UNIVERSITÉ DE NANTES

UFR SCIENCES ET TECHNIQUES DES ACTIVITES PHYSIQUES ET SPORTIVES

Habilitation à Diriger des Recherches

Analyse de la Fonction Motrice : des Signatures Révélatrices de notre Présent

Présentée le 8 mars 2017

THIBAULT DESCHAMPS
Maître de conférences

LABORATOIRE « MOTRICITE, INTERACTIONS, PERFORMANCE » (E.A. 4334)

ECOLE DOCTORALE « COGNITION, EDUCATION, INTERACTIONS» (ED 504)
SPECIALITE « SCIENCES ET TECHNIQUES DES ACTIVITES PHYSIQUES ET SPORTIVES » (SECTION CNU N°74)

Jury :

Michel AUDIFFREN (Professeur des Universités, Université de Poitiers, France)	**Rapporteur**
Christophe CORNU (Professeur des Universités, Université de Nantes, France)	**Examinateur**
Ludovic MARIN (Maître de Conférences – HDR, Université de Montpellier, France)	**Examinateur**
Thierry PAILLARD (Professeur des Universités, Université de Pau et des Pays de l'Adour, France)	**Rapporteur**
Jean-Jacques TEMPRADO (Professeur des Universités, Aix-Marseille Université, France)	**Rapporteur**

Annexes

Publications scientifiques associées *de près ou de loin* au mémoire d'Habilitation à Diriger des Recherches

Classées par date de publication, de la plus récente à la plus ancienne

Liste des publications

Daviaux, Y., Crémoux, S., Tallet, J., Amarantini, D., Cornu, C., & **Deschamps, T.** **(2016)**. I Can't Reach It! Focus on Theta Sensorimotor Rhythm Toward a Better Understanding of Impaired Action-Perception Coupling. *Neuroscience, 339,* 32-46. (**position: 6/6 - IF$_{2015}$ = 3.23**)

Deschamps, T., Sauvaget, A., Pichot, A., Valrivière, P., Maroulidès, M., Bois, A., Bulteau, S. & Thomas-Ollivier, V. **(2016)**. Posture-cognitive dual-tasking: a relevant marker of depression-related psychomotor retardation. An illustration of the positive impact of repetitive transcranial magnetic stimulation in patients with major depressive disorder. *Journal of Psychiatric Research, 83,* 86-93. (**position: 1/8 - IF$_{2015}$ = 4.46**)

Deschamps, T. **(2016)**. Let's programme exercise during haemodialysis (intradialytic exercise) into the care plan for patients, regardless of age! *British Journal of Sports Medicine, 50,* 1537-1538. (**position: 1/1 - IF$_{2015}$ = 6.72**)

Deschamps, T., Le Goff, C., Berrut, G., Cornu, C., & Mignardot, J-B **(2016)**. A decision model to predict the risk of the first fall onset. *Experimental Gerontology, 81,* 51-55. (**position: 1/5 - IF$_{2015}$ = 3.35**)

Deschamps, T., Magnard, J., Jubeau, M., Hug, F., & Tucker, K. **(2016)**. Altered Force-Generating Capacity Is Well Perceived Regardless of the Pain Presence. *Journal of Experimental Psychology: Human Perception and Performance, 42,* 1363-1371. (**position: 1/5 - IF$_{2015}$ = 2.42**)

Hristea D., **Deschamps T.***, Paris, A., Lefrançois, G., Volteau, C., Savoiu, C., Ozenne, S., Coupel, S., Testa, A., & Magnard, J. **(2016)**. Combining Intra-dialytic Exercise and Nutritional Supplementation in Malnourished Older Hemodialysis Patients: Towards Better Quality of Life and Autonomy. Results from the Pilot Randomized ACTINUT Trial. *Nephrology, 21(9)*, 785-790. (**position: co-1/10 - IF$_{2015}$ = 1.79**) (** 1er co-auteur*)

Thomas-Ollivier, V., **Deschamps, T.***, Bulteau, S., Le Gall, F., Pichot, A., Valrivière, P., Vachon, H., & Sauvaget, A. **(2016)**. Effect of Repetitive Transcranial Magnetic Stimulation on Psychomotor Retardation in Major Depression: A Pilot Feasibility Study. *The Journal of Neuropsychiatry & Clinical Neurosciences, 28(1),* 62-65. (**position: co-1/8 - IF$_{2015}$ = 2.43**) (** 1er co-auteur*)

Daviaux, Y., Crémoux, S., Tallet, J., Amarantini, D., Cornu, C., & **Deschamps, T.** **(2016)**. An enhanced experimental procedure to rationalize on the impairment of perception of action capabilities. *Psychological Research, 80*, 224-234. **(position: 6/6 - IF$_{2015}$ = 2.68)**

Deschamps, T., Thomas-Ollivier, V., Sauvaget, A., Bulteau S., Fortes-Bourbousson, M., & Vachon, H. **(2015)**. Balance characteristics in patients with major depression after a two-month walking exercise: A pilot study. *Gait & Posture, 42*, 590-593. (position: 1/6 - IF$_{2015}$ = 2.28)

Mignardot, J-B., **Deschamps, T.**, Le Goff, C., Roumier, F-X., Duclay, J., Martin, A., Sixt, M., Pousson, M. & Cornu, C. **(2015)**. Neuromuscular electrical Stimulation leads to physiological gains enhancing postural balance in the pre-frail elderly. *Physiological Reports* (**position: 2/9 - IF$_{2015}$ = N/A**)

Magnard J., Lardy, J., Testa, A., Hristea, D., & **Deschamps T.** **(2015)**. The effect of hemodialysis session on postural strategies in older end stage renal disease patients. *Hemodialysis International, 19*, 553–561. (position: 5/5 - IF$_{2015}$ = 1.49)

Magnard, J., Hristea, D., Lefrançois, G., Testa, A., Paris, A., & **Deschamps, T.** **(2014)**. Implicit postural control strategies in older hemodialysis patients: an objective hallmark feature for clinical balance assessment. *Gait & Posture, 40*, 723-726 **(position: 6/6 - IF$_{2015}$ = 2.28)**

Mignardot, J-B., Beauchet, O., Annweiler, C., Cornu, C., & **Deschamps, T.** **(2014)**. Postural sway, falls and cognitive status: a cross-sectional study among older adults. *Journal of Alzheimer's Disease, 41(2),* 431–439. **(position: 5/5 - IF$_{2015}$ = 3.92)**

Daviaux, Y., Mignardot, J-B., Cornu, C., & **Deschamps, T.** **(2014)**. The effects of total sleep deprivation on the perception of action capabilities. *Experimental Brain Research, 232 (7)* 2243-2253. **(position: 4/4 - IF$_{2015}$ = 2.05)**

Deschamps, T., Hug, F., Hodges, P., & Tucker, K. **(2014)**. Influence of experimental pain on the perception of action capabilities and performance of a maximal single leg hop. *The Journal of Pain, 15*, 271.e1-271.e7. **(position: 1/4 - IF$_{2015}$ = 4.46)**

Deschamps, T., Beauchet, O., Annweiler, C., Cornu, C., & Mignardot, J-B. **(2014)**. Postural control and cognitive decline in older adults: position versus velocity implicit motor strategy. *Gait & Posture, 39 (1)*, 628-630. **(position: 1/5 - IF$_{2015}$ = 2.28)**

Mignardot, J-B., **Deschamps, T.**, Barrey, E., Auvinet, B., Berrut, G., Cornu, C., Constans, T. & De Decker, L. **(2014)**. Gait disturbances as specific predictive markers of the first fall onset in elderly people: A two-year prospective observational study. *Frontiers in Aging Neuroscience,* 6:22. **(position: 2/8 - IF$_{2015}$ = 4.34)**

Magnard, J., **Deschamps, T.**, Cornu, C., Paris, A., & Hristea, D. **(2013)**. Effects of a six-month intradialytic physical ACTIvity program and adequate NUTritional support on protein-energy wasting, physical functioning and quality of life in chronic hemodialysis patients: ACTINUT study protocol for a randomised controlled trial. *BMC Nephrology,* 14:259. **(position: 2/5 - IF$_{2015}$ = 2.28)**

Neuroscience 339 (2016) 32–46

I CAN'T REACH IT! FOCUS ON THETA SENSORIMOTOR RHYTHM TOWARD A BETTER UNDERSTANDING OF IMPAIRED ACTION–PERCEPTION COUPLING

YANNICK DAVIAUX, [a] **SYLVAIN CREMOUX,** [b,c] **JESSICA TALLET,** [d] **DAVID AMARANTINI,** [d] **CHRISTOPHE CORNU** [a] **AND THIBAULT DESCHAMPS** [a]*

[a] *University of Nantes, Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), F-44000 Nantes, France*

[b] *University of Paul Sabatier Toulouse 3, Laboratory PRISSMH-LAPMA (EA 4651), F-31062 Toulouse, France*

[c] *LAMIH, UMR CNRS 8201, Université de Valenciennes et du Hainaut-Cambrésis, Valenciennes, France*

[d] *Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS, France*

Abstract—It is known that anxiety (ANX) impairs action–perception coupling. This study tests whether this impairment could be associated with an alteration of the sensorimotor function. To this aim, the cortical activities underlying the sensorimotor function were recorded in twelve volunteers in a reach-to-grasp paradigm, in which the level of ANX and the position of a glass were manipulated. The experimental manipulation of the ANX-related somatosensory state was expected to prompt participants to underestimate their reaching-to-grasp capabilities while the sensorimotor-related oscillatory brain activities around the 6-Hz (θ) frequency over motor-related and parietal regions were expected to be modulated. We also investigated the oscillatory brain dynamics around the 11.5-Hz (fast-α) frequency as a neural hallmark of ANX manipulation induced by the breath-restriction. Results indeed showed that participants underestimated their reaching-to-grasp maximal performance. Concomittantly, θ-EEG synchronization over the motor cortex contralateral to the dominant hand was higher during glass presentation under breath-restriction condition (+20.1%; $p < 0.05$), and when the glass was perceived as non-reachable (+20.0%; $p < 0.05$). Fast-α-EEG desynchronization was reduced under breath-restriction (−37.7%; $p < 0.05$). The results confirm that ANX-related impairment of action–perception coupling co-modulates with theta-sensorimotor rhythm. This finding is discussed as an altered "readiness state" in the reaching-related cortical network, while individuals are anxious.

Key words: action–perception coupling, sensorimotor function, motor region, parietal region, theta activity.

INTRODUCTION

It is widely accepted that the neuronal processes involved in action and perception interact, making the action–perception coupling a crucial component in achieving efficient visuomotor actions (Prinz and Hommel, 2002). These neural processes includes the encoding and association of visuospatial and somatosensory (including sensorimotor) afferences during the preparation and initiation phase of the movement, and their update when motor running until the action is achieved (Cruikshank et al., 2012).

But the action–perception processes occurring when the goal of the action is visually identified can be impaired with changes in somatosensory state, as reported under anxiety (ANX) state with misestimated reaching capabilities (Pijpers et al., 2006; Graydon et al., 2012; Daviaux et al., 2016). Despite the fact that action–perception coupling in reaching tasks is well investigated so far (e.g., Wamain et al., 2016), only few study focused on the cortical correlates for such an impaired action–perception coupling in the context of emotional valence (Valdés-Conroy et al., 2014). Yet this issue is crucial to understand and prevent movement disorders in the field of public health (*e.g.*, Lee et al., 2001; Higuchi et al., 2009; Guardia et al., 2010, 2012; Smith et al., 2011; Hackney and Cinelli, 2013; Sakurai et al., 2013). We thus examined the effect of ANX state on participants' perceived reach-to-grasp abilities while the electroencephalographic (EEG) brain activities were recorded.

To ease the understanding, we refer here to "action–perception coupling" as a perceptual occurrence, and "sensorimotor function" as the neurophysiological processing of motor- and body-representation-related afferences which is part of the processes underlying the action–perception coupling.

*Corresponding author at: University of Nantes, Laboratory «Motricité, Interactions, Performance» (EA 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. Fax: +33 (0) 2 51 83 72 10.

E-mail address: thibault.deschamps@univ-nantes.fr (T. Deschamps).

Abbreviations: actual-D_{max}, maximal actual reach-to-grasp performance; ANX, experimental breathing restriction (anxiety); CTL, experimental control condition; NON-REACH, non-reachable-to-be-grasped experimental condition; perceived-D_{max}, maximal perceived reach-to-grasp performance; REACH, reachable-to-be-grasped experimental condition.

http://dx.doi.org/10.1016/j.neuroscience.2016.09.033

ACTION–PERCEPTION COUPLING AND THE SENSORIMOTOR FUNCTION

Previous studies have shown that impaired action–perception coupling occurs in patients with conditions that encounter sensorimotor disorders (*e.g.*, body spatial awareness) such as Parkinson's disease (Lee et al., 2001; Smith et al., 2011) or anorexia nervosa (Guardia et al., 2010, 2012). The same applies in older healthy individuals who experience progressive regression of sensorimotor functions (Luyat et al., 2008; Noël et al., 2011; Hackney and Cinelli, 2013; Sakurai et al., 2013). These findings raised the question of whether the alteration of somatosensory state, such as under ANX, is associated with an alteration in sensorimotor function leading to the impairment of action–perception coupling (Graydon et al., 2012; Daviaux et al., 2016).

NEUROPHYSIOLOGICAL CONTEXT OF THE ACTION–PERCEPTION COUPLING

The reaching-to-grasp paradigm, which involved hand–object interactions, is the main task used in behavioral studies to investigate the relationship between ANX and action–perception coupling (*e.g.*, Pijpers et al., 2006; Graydon et al., 2012; Daviaux et al., 2016). Such a perceptual task potentiates visuomotor transformations partitioned in the brain into sub-sensorimotor-components (Ellis and Tucker, 2000; Borghi and Riggio, 2009). It specifically involves the fronto-parietal network and the motor-planning-related regions (Fogassi, 2007; Binkofski and Buxbaum, 2012; Bartolo et al., 2014). The exchanges of multimodal information between the premotor and posterior-parietal regions allow the sensorimotor representation of individuals' body and its awareness regarding the environment (Graziano and Botvinick, 2002; Thurm et al., 2011). In such a cortical network, modulations of the EEG activity ~6 Hz, so-called the theta (θ) rhythm, can be used to reflect the sensorimotor function as it was thought to allow the motor and sensory systems to update each other and coordinate their activities (Klimesch, 1999; Bland and Oddie, 2001; Caplan et al., 2003). In a motionless context where a to-be-reached target is visible, an increasing level of event-related θ-EEG activity spectral power over the motor and parietal regions is suggested to *"initiates a series of sensory transformation and activates cortical sensorimotor networks*" for motor planning (Cruikshank et al., 2012, p.69). Given that achieving reaching behaviors requires an efficient sensorimotor function, studies have particularly focused on the motor regions and the posterior-parietal regions to assess their involvement in pointing-reaching tasks when spatial cues were manipulated (Curtis et al., 2004; Praamstra et al., 2009; Tombini et al., 2009; Cruikshank et al., 2012; Rawle et al., 2012). Moreover, Bartolo et al. (2014) have shown that reachability judgements involve motor-related brain processing, with an involvement of fronto-parietal cortical network including the motor cortex and the cerebellum. Taken together, these findings provide evidences that judging reachability cannot be considered as a simple visual task, and rather requires to investigate the activity of the motor-related cortical regions to understand impairment in perception of reaching capabilities.

WORKING HYPOTHESIS

According to the aforementioned background, the present study examines the θ-EEG activities over the motor and posterior-parietal regions as a marker of altered sensorimotor function for impaired action–perception coupling. Participants were required to *estimate* whether a glass could be reached-and-grasped while their EEG brain activities was recorded. An underestimation of their reaching-to-grasp capabilities was expected when individuals were breathing-restricted, which corresponded to a validated situation to manipulate ANX (Graydon et al., 2012; Daviaux et al., 2016). As the main hypothesis of this work, we hypothesized that the underestimation of the reaching-to-grasp capabilities under ANX would be associated with altered sensorimotor functioning. This latter should be revealed by a co-modulation in θ-EEG synchronization over the motor-related and posterior-parietal regions. We also focused on contralateral and ipsilateral motor regions; previous studies have indeed found simultaneous activation during the preparation phase prior to reaching movement with the dominant hand (Tombini et al., 2009; Cruikshank et al., 2012).

Also, it has to be noted that ANX impairs the performance of the attentional system: the individuals' attentional resources can shift from a task-relevant stimulus to an eventual threat-relevant stimulus in stressful situations, or individuals can enhance the attentional effort to maintain their performance (Eysenck et al., 2007). The amplitude of the EEG activity ~10 Hz [alpha rhythm (α)] reflects the amount of the neural populations involved in the attentional processes (Niedermeyer and Lopes da Silva, 2005). Ascending level of α-EEG desynchronization accounts for ascending task-engagement due to the task's attentional demands (Stipacek et al., 2003). This α rhythm is classically divided into two sub-rhythms, namely slow-α and fast-α rhythms (Klimesch, 1999). The slow-α rhythm accounts for general, non-specific attention over broad regions of the brain, whether the fast-α rhythm is especially sensible to task-related attentional modulation over the parietal regions (Gevins et al., 1997; Klimesch, 1999; Stipacek et al., 2003). Thus, in complement to the main hypothesis regarding the sensorimotor θ-EEG activity, we also focused on the fast-α-EEG activity over the parietal regions as a task-related indication of the brain activity that could account for an effective manipulation of the brain ANX-network state – from the hypothalamic–pituitary adrenal axis to the activation of brainstem nuclei (Steimer, 2002) – related to the breathing restriction.

METHODS

In this study, we replicated the experimental setup, experimental conditions, and task procedure reported in Daviaux et al. (2016). The main features are briefly reported here in order to improve the readability of the present work while optimizing its understanding. Readers

are invited to refer to the methodological section of Daviaux et al.'s (2016) study for details.

Participants

Thirteen right-handed students at Paul Sabatier University of Toulouse, France, voluntarily participated in the experiment. One of the participants felt an excessive discomfort in the breath-restricted condition and could not complete the entire session. This volunteer was excluded from the statistical analyses. Thus, the analyses were conducted on the data collected from twelve volunteers (5 men, 7 women, mean age 21.2 ± 3.8 years, Edinburg Handedness test score +64.0 ± 21.3, Oldfield, 1971). None of the participants exhibited visual or physical impairment. They were not familiar with the experimental design procedures. They were clearly informed of the experimental breathing restriction (ANX) manipulation before providing their written consent. Participants were not paid for their participation. The experiment was conducted according to the Helsinki Statement (1964).

EXPERIMENTAL SETUP

Participants sat in a darkened room in front of modified Box for Interaction with Objects system (BIO system, Oliveira et al., 2012) synchronized with a computer running Presentation software 0.81 (Neurobehavioural Systems Inc., Albany, CA) (see Fig. 1c for an illustration). The surround-displaying inner box reflected a neutral and black uniform environment. The room's luminance was measured to be about 27-lx with a light meter (Luxmètre MS-1300, Voltcraft, Lomme, France). When the LEDs inside the BIO system were ignited, the luminance inside the box was about 52-lx while the luminance at the level of participants' eyes remained to be about 27-lx. The participants' position was standardized, as illustrated in Fig. 1c. They were instructed to maintain their right hand in a congruent anatomical configuration for glass grasping (Natraj et al., 2013). Participants could not see their arm, to prevent them capturing any feedback during the experimental task.

EXPERIMENTAL CONDITIONS

The perceptual task was performed in control (CTL) and ANX conditions (Fig. 1a).

In CTL condition, participants were asked to wear a nose clip (Nabaiji Pince Nez, Oxylane, Villeneuve-d'Ascq, France) and breath normally through their mouth when performing the experiment task.

In ANX condition, a device comprising a mouthpiece, a 2-mm-diameter pipe, and an air outlet (ProRhinel, Novartis Pharma SAS, France) was employed to induce ANX from breath restriction (Fig. 1b). Participants breathed through the breathing set while they wore the same nose clip as in CTL when performing the experiment task. An optimal strategy to keep the participants in a high but tolerable restricted breathing condition was applied prior to the experimental session to set the breath restriction level by filling the air outlet with cotton (Daviaux et al., 2016). During the experimental session, a 1 min of breathing restriction allowed conditioning the participants before each set of trials in ANX condition. They had to keep breathing with the breathing set throughout the ANX trials.

TASK PROCEDURE

For both CTL and ANX, the participants had to estimate whether the proximity of a glass was sufficient to allow them to reach it and grasp it with their right hand by extending their arm without torso anteroposterior flexion or sagittal rotation, i.e., in experimental restriction condition allowing only shoulder and elbow flexion–extension in the transverse plane. An experimenter's demonstration, performed on a table away from the BIO system, exemplified the instructions. Participants were advised to never extend their arms through the box to prevent them capturing any feedback on their reach-to-grasp capabilities. The glass was a white goblet with no handle, 8.5-cm high and 7-cm in diameter. It was placed on an invisible, dimension-matched trolley in the middle of the anteroposterior axis of the BIO system and moved from one location to the next along the anteroposterior axis by a wooden stick attached to the small trolley. During the trials, the wooden stick remained invisible to the participant.

For every estimation of the glass reachability, participants reported their breathing discomfort score both for CTL and ANX conditions. The discomfort scores accounted for a range from 0 = "calm enough to fall asleep" to 100 = "feeling as if you could have a panic attack".

Five CTL and five ANX sets of 30 trials were randomized, resulting in 300 trials. A minimum of 3 min of rest were systematically allocated to the participants between every set of trials (ANX and CTL).

RECORDINGS

Behavioral recording

Maximal perceived reach-to-grasp performance. The experimenter adjusted the Glass Position with the wooden stick while the BIO system was switched off. Participants thus remained unaware of the Glass Position until the BIO system was turned on again.

Prior each trial, participants gazed at a red fixation point displayed into the box on the rear panel, in the same horizontal plane than their eyes. The experimenter then switched on the inner LEDs of the BIO system: the Glass Position was shown for 300-ms after which the BIO system was switched off. The computer running Presentation software delivered a sound-trigger 1500-ms after the stimulus onset. It prompted the participants to report whether they felt able to reach-and-grasp the glass and to report their score on the breathing discomfort scale. Participants reported the perceived reachability verbally, to avoid any update of the perceived reaching-to-grasp capabilities when breath-restricted that could arise from "learning-by-doing" process (Franchak et al., 2010) and

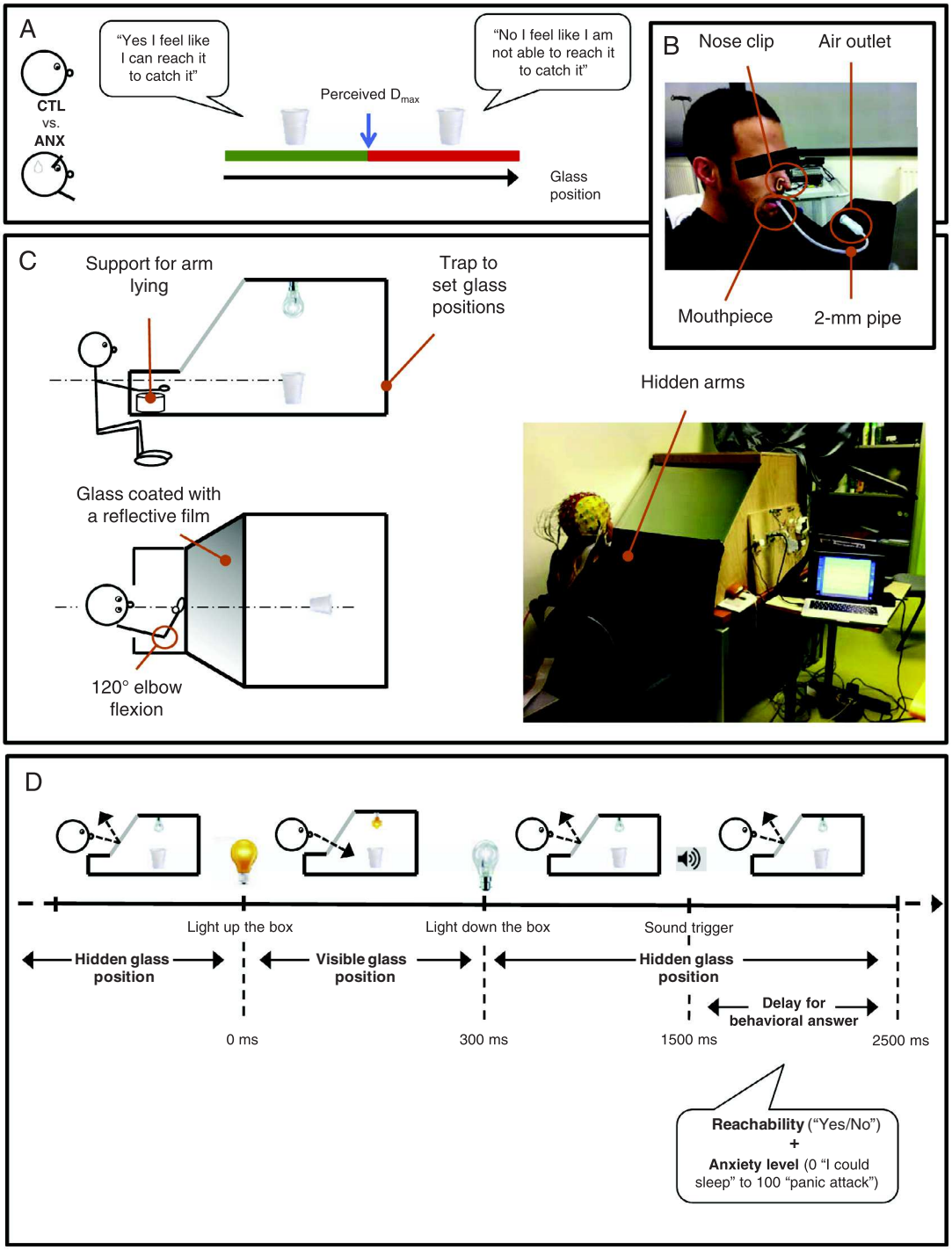

Fig. 1. Original paradigm of the experimentation. (a) *Perceived-D_{max}* is taken as the maximal distance that the participant judged to be able to reach-and-grasp the glass, and it was compared between a control condition (CTL) and a breath restriction condition (ANX). (b) The breathing set used to induce anxiety composed of a mouthpiece/a 2-mm pipe/an air outlet and a nose clip. Participants also wore nose clip during the control condition. (c) The BIO system, adapted from Oliveira et al. (2012). The participants' positions were standardized while they stood in front of the device. (d) Procedure for one trial. The same procedure was repeated for 300 trials, i.e., 150 trials in CTL and 150 trials in ANX.

during ongoing movement (Hackney and Cinelli, 2013). One trial procedure is depicted in Fig. 1d. Answers provided 2200-ms after the end of the stimulus onset were excluded from the data analysis. Less than 0.5% of all answers were excluded. No indication of the upcoming stimuli apparition was provided to magnify the visuomotor transformations elicited by the Glass Positions (for further explanations, see the method section in Daviaux et al., 2016). Participants were told trials were separated by 5-s to 10-s break.

The Glass Positions were presented according to the constant stimuli method (Kingdom and Prins, 2009). The

potential Glass Positions were randomized across 150 trials, i.e., 5 sets of 30 trials, for both CTL and ANX conditions to prevent order effects (Hirose and Nishio, 2001). Considering the inter-individual variability of perceptual capabilities (Kanai and Rees, 2011), ranges of displayed positions were individualized to enhance the robustness of the constant stimuli method (adapted from the recommendations of Kingdom and Prins, 2009). To do so, two ranges of 15 random positions (from 70-cm to 98-cm with a 2-cm discrete step) were presented prior to the experimental session. The lowest (highest) value of the individual ranges presented during the experiment was determined by subtracting (adding) 12-cm from (to) the lower (upper) distance at which the participants reported being (unable) able to reach-and-grasp the glass from these two ranges presented prior to the experiment. The individual ranges tested during the experimental sets of trials were 65.7 ± 5.0 cm to 101.3 ± 2.7 cm and all stimuli were presented 8.1 ± 0.5 times in average.

Maximal actual reach-to-grasp performance. At the end of the experiment, the distance between the right acromion and the fleshy part between the right thumb and the index at fully extended arm position was measured. It was considered as the maximal participants' reach-to-grasp distance (*actual-*D_{max}).

Electrophysiological recording. Participants wore a 64-channel EEG cap (ActiveII cap, Biosemi Inc., Amsterdam, The Netherlands) using the international 10–20 system to record neural activity with Ag/AgCl electrodes. The electro-oculogram (EOG) was recorded from the right-eye (one electrode beneath and one on the lateral side) to discern blinks. The electromyographic activity (EMG) of the main muscles promoting the extension-flexion movement around the participant's right elbow joint was also checked to ensure that the perceptual task was performed at rest and to rule out any interpretation of muscle activity in the neural firing (Holmes and Spence, 2004). The biceps brachii was chosen to represent the elbow flexors while the lateral head of the triceps brachii was chosen to represent the elbow extensors (Buchanan et al., 1989). EMG was collected using bipolar surface electrodes separated with a 2-cm inter-electrodes distance. The reference electrode for EMG data was positioned on the left earlobe. Skin was prepared following the SENIAM recommendations for EMG and EOG recordings (Hermens et al., 2000).

For all signals, impedance was kept below 20-kΩ. Signals were amplified with BioSemi Active-Two amplifiers (ActiveII, Biosemi Inc., Amsterdam, The Netherlands) sampled at 1024-Hz and recorded on a dedicated computer. Events depicted in Fig. 1d were triggered: the BIO system and computer running Presentation software were synchronized with electrophysiological recordings through a National-Instrument acquisition hardware (NI USB-6216, National Instrument, Austin, Texas, USA).

For later normalization purpose of EEG data, participants performed 30 trials prior to the experimentation while they remained naïve about grasping paradigm at this time, and the BIO system did not contain a glass inside.

The normalization of the EMG data required participants to perform 2 isometric 3-s maximal voluntary contractions (MVC) with a 1-min rest in flexion and in extension around the elbow joint. They were seated with their trunk and their right upper limb was maintained by the experimenter. The right arm was positioned along the trunk. The forearm was supinated, flexed at 90°, and positioned under or over a table depending on extension or flexion requirement. The beginning and the ending of contractions were verbally indicated. Encouragements were provided to ensure maximal effort.

DATA ANALYSIS

Behavioral data

Maximal perceived reach-to-grasp performance. For each participant, the perceived threshold for maximal grasping (*perceived-*D_{max}) was computed using a psychometric method. The proportion of positive grasping judgments (on the *y*-axis) was plotted as a function of glass distances (*x*-axis) and optimally fitted by a logistic function from the least-squares method. The *perceived-*D_{max} was defined as the value on the *x*-axis when the logistic function reached a proportion of 0.5 (Fig. 2) (*e.g.*, Guardia et al., 2010). It was computed as follows:

$$Answer = \frac{1}{1 + e^{-b \times (a - position)}}$$

where *b* is the slope of the curve at the point where *Answer* = 0.5, *a* is the perceived critical Glass Position (i.e., *perceived-*D_{max} in cm) with a 0.5 proportion of "yes" response, and "*position*" is the Glass Position.

The individual *perceived-*D_{max} in CTL condition was considered as the baseline perceptual performance of the participant. Note that in CTL condition, a systematic over- or underestimation is assumed to be derived from individuals' inability to account for experimental restrictions when assessing action capabilities (Rochat and Wraga, 1997; Fisher, 2000; Graydon et al., 2012), or from individual experience or features (e.g., Higuchi et al., 2011). That is, a systematic difference between *actual-*D_{max} and *perceived-*D_{max} in CTL condition is considered as a baseline misestimating. Consequently, this individual difference between *actual-*D_{max} and *perceived-*D_{max} in CTL condition was computed, and removed from CTL *perceived-*D_{max} and *perceived-*D_{max} ANX to account for this systematic baseline misestimating (see also in Daviaux et al., 2016).

Breathing-discomfort-related ANX state. Breathing discomfort scores were averaged for each set of 30 trials within both experimental conditions. Thus, five sets of averaged scores were compared between CTL and ANX.

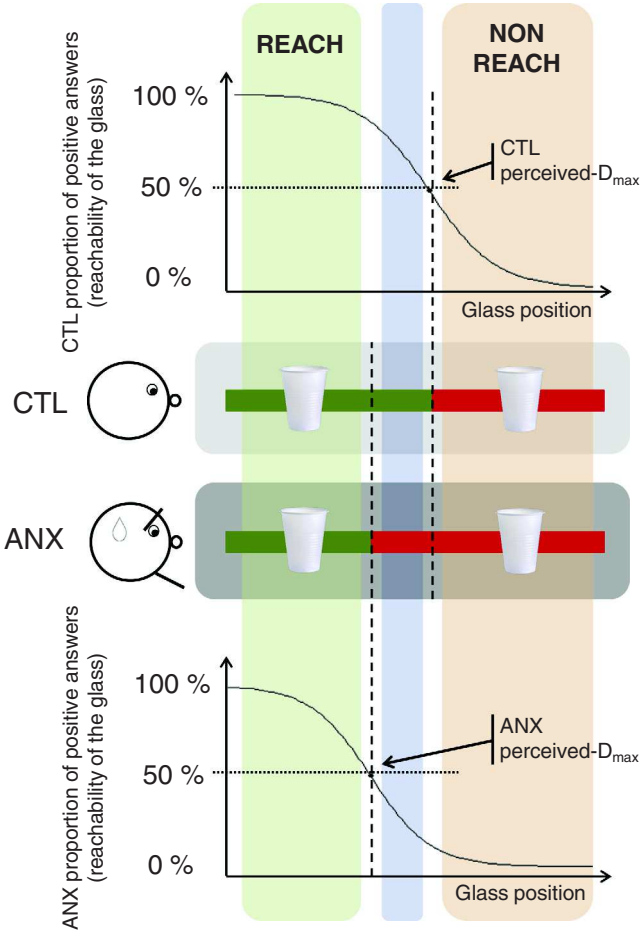

Fig. 2. Trials sorting for EEG analysis based on behavioral answers. When the psychometric function reached 50% of positive answers for reachability of the Glass Positions, the maximal perceived reach-to-grasp performance (*perceived-D*$_{max}$) was assessed for CTL and ANX. Light gray area includes CTL trials, and dark gray area includes ANX trials. Trials averaged for EEG data analysis were sorted based on behavioral analysis. For both CTL and ANX, all Glass Positions that were perceived as ''reachable-to-be-grasped" and remained closer to the participant compared ANX *perceived-D*$_{max}$ were included in the reachable-to-be-grasped condition (REACH) (i.e., all trials with positive answer in the green area); all Glass Positions perceived as ''non-reachable-to-be-grasped" and remained farther than CTL *perceived-D*$_{max}$ were included in the non-reachable-to-be-grasped condition (NON-REACH) (i.e., all trials with negative answer in the red area). Trials in the blue area were not considered in the analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Trials classification. For the analysis of electrophysiological data, trials were sorted according to the maximal perceived reaching performance as in Fig. 2. Following this, the number of averaged trials was respectively 58.8 ± 21.7, 52.0 ± 22.6, 63.6 ± 20.9 and 47.3 ± 21.2 in the CTL REACH, CTL NON-REACH, ANX REACH and ANX NON-REACH, without a significant difference between the conditions ($p < 0.05$).

Electrophysiological data

The processing of the electrophysiological dataset was performed using MATLAB (The MathWorks, Natick, MA, USA). EEGLAB toolbox (Delorme and Makeig, 2004) was used to sort and pre-process filtered EEG data. The time–frequency analysis of the EEG data was conducted using the WavCrossSpec package (Bigot et al., 2011) based on the wavelet package developed by Grinsted et al. (2004).

EEG, EOG and EMG data pre-processing. EEG and EOG data were down-sampled at 512 Hz, 1–100 Hz band-pass filtered, and 45–55 Hz notch filtered. EMG data were 10–400 Hz band-pass and 45–55 Hz notch filtered. Filters were fourth-order, zero-lag Butter-worth type filters.

Filtered EEG data were re-referenced to an averaged-electrodes reference excluding faulty electrodes (0.7 ± 1.2 faulty electrodes were visually detected then extrapolated). Signals were segmented into 1.3-s epochs so the dataset corresponded to a [−1; +0.3 s] window from the moment the Glass Position was revealed. An independent component analysis (ICA) was applied on epoched EEG and EOG dataset to correct blink and ocular movement artifacts (Delorme et al., 2007). A visual inspection of independent component scalp maps, power spectrum, and raw activity was performed to reject typical artifactual independent components. Finally, trials with residuals EEG artifacts were visually identified and rejected. 0.3% to 6% of trials were rejected across all participants.

Individualization of theta and alpha frequency bands. Theta (θ) and alpha (α) frequency bands within EEG data are conventionally introduced with fixed intervals, [4–7.5 Hz] and [8–13 Hz], respectively (Sanei and Chambers, 2007). However, in the current study, frequency bands were individualized, as θ-EEG and α-EEG rhythmic patterns showed inter-individual differences in their frequencies (Doppelmayr et al., 1998; Klimesch, 1999; Klimesch et al., 2000). Because θ and α bands share a common border, this procedure prevented data overlap between θ and α bands when fixed frequency limit is considered.

Individual frequency bands were computed with the channel reactivity based (CRB) method using CRB functions in Matlab environment (Goljahani et al., 2012, 2014). The choice of CRB method was motivated by the fact that the present increasing task demand relative to the baseline rest state have opposite effect on the power of θ and α rhythms, i.e., an increase (synchronization) of θ spectral power and a decrease (desynchronization) of α spectral power. The CRB procedure was applied to channels C3, FC3, C4, FC4, P3, P1, Pz, P2, and P4 for all trials. The [0 + 300 ms] window dataset was the test interval, and the [−600–100 ms] window dataset was the reference interval. To compute the power spectrum densities, Hanning window length was equal to full length of test dataset and full length of reference dataset, respectively. According to the guidelines for CRB analysis parameters (Goljahani et al., 2012), the parameters of shift and size of the scanning window on [8–13 Hz] frequency band were w_{shift} = 0.2 Hz and w_{size} = 2 Hz with a regularisation factor λ = 0.5 and a pre-located fraction for the threshold of local minima of difference between test and reference spectrums ε = 0.5. Individual α peak frequency (α_{IPF}) as well as lower (α_{low}) and upper (α_{upp}) limits for α band were computed using a minimum reactivity index equal to ρ_{min} = 0.15 μV^2/Hz, a percentile value p = 80 for the computation of sub threshold reactivity index ρ_{sub}, and a fraction of the maximum reactivity that renders an electrode out of range at r = 0.5. For all participants and the 9 electrodes of interest, 7.6 ± 1.1 electrodes were considered to compute the individual frequencies.

The lower threshold value of the θ frequency band (θ_{low}) was computed as $\theta_{low} = 0.4 \times \alpha_{IPF}$ (Doppelmayr et al., 1998). The upper threshold value of the θ frequency band (θ_{upp}) was taken as the lower value of the individual α band (α_{low}), i.e. $\theta_{upp} = \alpha_{low}$. The lower threshold value of the fast-α frequency band (fast-α_{low}) was taken as the individual peak frequency (α_{IPF}), i.e. fast-$\alpha_{low} = \alpha_{IPF}$ (Doppelmayr et al., 1998). The upper threshold value of the fast-α frequency band (fast-α_{upp}) was taken as upper value of the individual α band (α_{upp}), i.e. fast-$\alpha_{upp} = \alpha_{upp}$. According, frequency bands were individualized as θ_{low} = 4.4 ± 0.3 Hz, $\theta_{upp} = \alpha_{low}$ = 8.6 ± 0.8 Hz, fast-α_{low} = 10.9 ± 0.7, and fast-α_{upp} = 13.5 ± 0.7 Hz.

Event related spectrum power processing of cortical activity. For each experimental condition, the event-related spectrum power (ERSP) was computed following a full-epoch length single-trial baseline normalization and gain model procedure (Grandchamp and Delorme, 2011). First, the power spectrum for every trial was computed in the time–frequency domain. The number of wavelet cycles (n) to apply to the individualized θ and fast-α frequency bands were adjusted based on the processing of simulated data, respectively at n_θ = 3 and n_α = 9 (Fig. 3).

Then, for every trial, each time–frequency point value was divided by the average spectral power of the full epoch period with the same frequency. Trials were averaged within a given experimental condition and the ERSP was computed for θ and α frequency bands as

$$ERSP = 10 \times \log_{10}\left(\frac{Pow_{freq}}{Pow_{BLfreq}}\right).$$

where Pow_{freq} is the spectral power for a given frequency point, Pow_{BLfreq} is the mean spectral power for all baseline points at the same given frequency, and *ERSP* is expressed in dB. The baseline epoch was defined here as [−600–100 ms] from the moment the glass appeared in the box.

The increase and decrease in averaged ERSP in θ and fast-α bands during the [0; +300 ms] epoch refers to event-related synchronization (ERS_θ) and event-related desynchronization ($ERD_{fast\text{-}\alpha}$) (Fig. 4). Gain-modulation in sensory processing was shown to be a major regulation principle at a single neuron level and for a population of neurons (Brown and Friston, 2012; Serrano et al., 2013). Thus, the cortical activity related to the whole experimental task (*i.e.*, ERD and ERS) were divided by a non-task-related cortical reactivity (CoRea) to obtain normalized ERS_θ and $ERD_{fast\text{-}\alpha}$ ($Norm\_ERS_\theta$ and $Norm\_ERD_{fast\text{-}\alpha}$) that account for inter-individual variability of the perceptual processes and allow to consider the robustness of the task-related EEG modulations. The non-task-related cortical reactivity was assessed in θ band ($CoRea\_ERS_\theta$) and fast-α band ($CoRea\_ERD_{fast\text{-}\alpha}$) from 30 trials performed prior to the experimental session, while the BIO system did not contain a glass inside. EEG data were pre-processed identically as experimental trials. $CoRea\_ERS_\theta$ and $CoRea\_ERD_{fast\text{-}\alpha}$ were computed the same way as were ERS_θ and $ERD_{fast\text{-}\alpha}$ for those 30 trials, respectively. Within ROI, normalized ERS_θ and ERD_α were computed as follows:

$$Norm_{ERS_\theta} = \frac{ERS_\theta}{CoRea_{ERS_\theta}}$$

and

$$Norm_{ERD_{fast-\alpha}} = \frac{ERD_{fast-\alpha}}{CoRea_{ERD_{fast-\alpha}}}$$

where $Norm\_ERS_\theta$ and $Norm\_ERD_{fast\text{-}\alpha}$ are non-unit values, as they account for a proportion of ERS_θ and $ERD_{fast\text{-}\alpha}$, respectively.

We then focused (1) on ERS_θ and $Norm\_ERS_\theta$ activity over the contralateral-motor region and ipsilateral-motor region, and (2) on ERS_θ and $Norm\_ERS_\theta$ as well as $ERD_{fast\text{-}\alpha}$ and $Norm\_ERD_{fast\text{-}\alpha}$ over the posterior-parietal region.

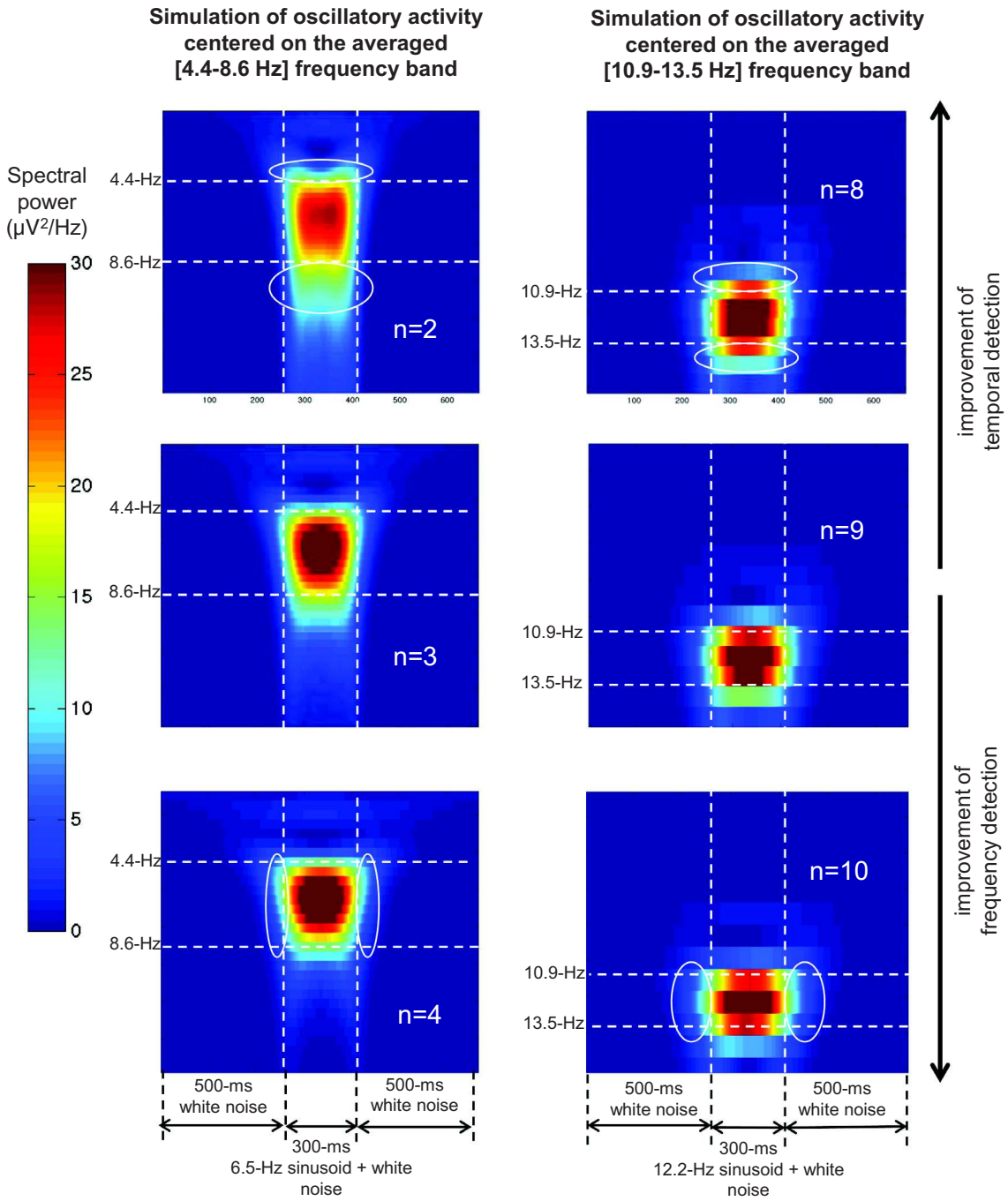

Fig. 3. Optimization of the number of wavelet cycles on simulated signals. The figure depicts simulated time–frequency charts of 6.5-Hz (median frequency of [4.4–8.6 Hz]) and 12.2-Hz (median frequency of [10.9–13.5 Hz]) sinusoid signal detection, with color code as an indicator of the spectral power at a given frequency and *n* the number of wavelet cycles used in the Morlet wavelets analysis. The qualitative analysis based on 30 simulated signals of 300-ms showed that wavelet cycles adjusted at $n = 3$ and $n = 9$ allow optimal detection of oscillatory activities for individual frequency bands around [4.4–8.6 Hz] and [10.1–13.5 Hz], respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Regions of interest. The topographic scalp maps of $ERS_{\theta\ and}$ $ERD_{fast\text{-}\alpha}$ activities were computed (Fig. 5). Driven by our hypothesis and these scalp maps, we focused on the motor region contralateral and ipsilateral to the dominant arm-hand as well as on the posterior-parietal region. ROIs were defined from sub-groups of electrodes according to Homan et al. (1987) consisting of electrodes C3-FC3, electrodes C4-FC4 and electrodes P3-P1-Pz-P2-P4, respectively. Within ROIs, the data were channel-averaged and the ERSP was computed based on the averaged signal.

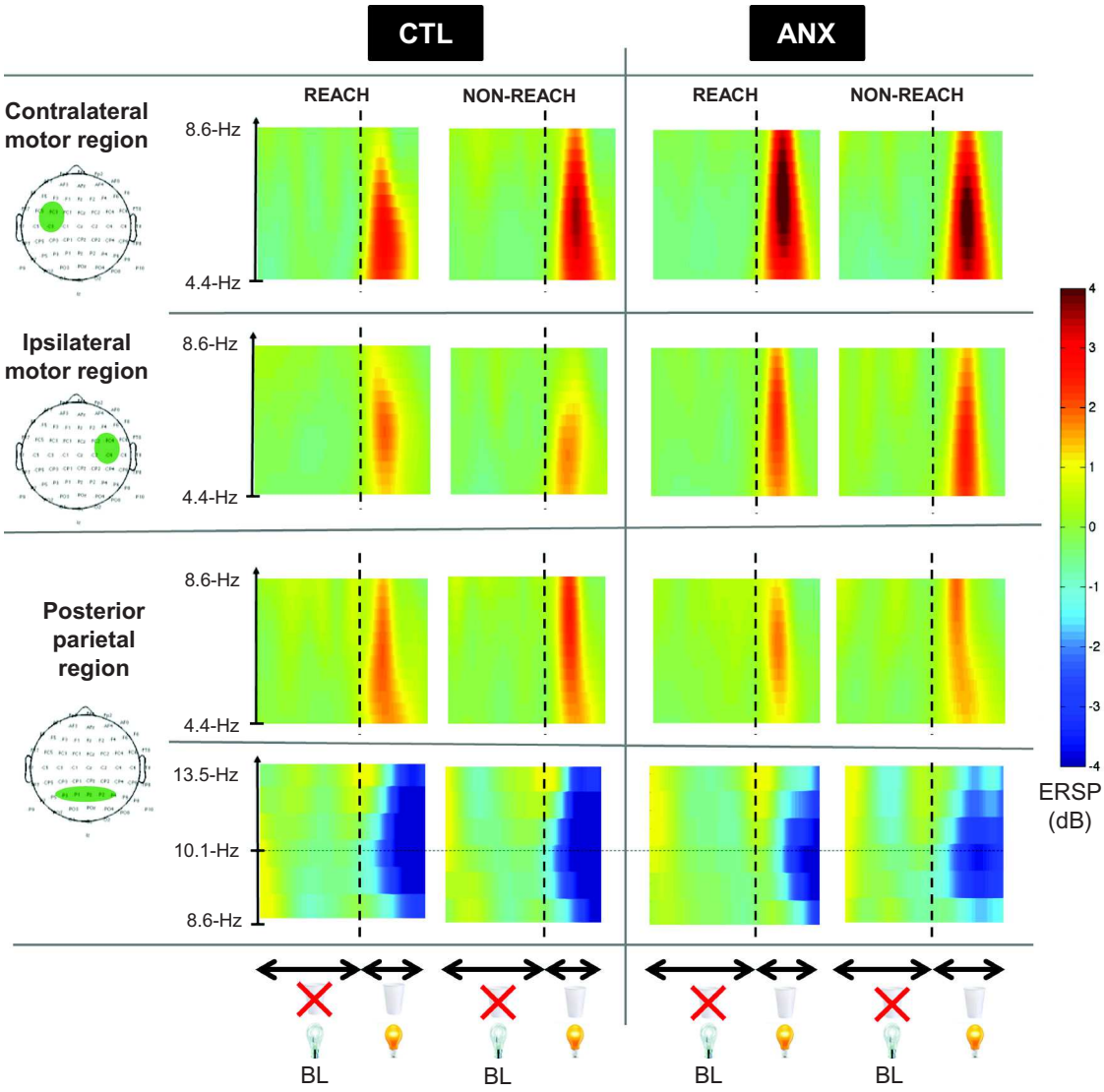

Fig. 4. Maps of the event related spectral perturbations per condition, for individualized θ-EEG ([4.4–8.6 Hz] frequency band) and fast-α-EEG ([10.1–13.5 Hz] frequency band ERSP averaged across the 12 participants, per ROI and for each condition. For each time–frequency figure, the horizontal axis is [−600 +400 ms] from the onset of glass apparition (vertical dashed line). The color code accounts for spectral power's variation relative to the baseline BL mean power, with warm colors (positive number) depict ERS event related synchronization whereas cold colors (negative number) depict ERD event related desynchronization, expressed in decibel (dB). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

EMG activation. The EMG activation was computed for the right arm biceps brachii and triceps brachii. The root mean square (RMS) value was computed for every trial at [−600; 0 ms] (PRIOR) and [0; + 300 ms] (DURING) time windows from the moment the glass appears. The values were normalized to their respective RMS from MVC for the biceps brachii and triceps brachii computed over a period of 500-ms centered on muscular onset-to-offset activation window.

STATISTICS

Statistical significance threshold was adjusted to $p < 0.05$. Following the significant effects, Bonferroni pairwise comparisons were used as post hoc tests. Partial eta-squared (hp^2) values are reported as measures of effect size, with $hp^2 \geqslant 0.07$ and $hp^2 \geqslant 0.14$ considered moderate and large effects, respectively (Cohen, 1988).

Behavioral data

Maximal perceived reach-to-grasp performance. A paired *t*-test was used to compare CTL and ANX in the *perceived-*D_{max}. The ratio of *perceived-*D_{max} ANX divided by *actual-*D_{max} was also reported to provide an informative estimation of the perceptual accuracy relative to CTL (as the normalization procedure accounts for a CTL ratio equal to 1).

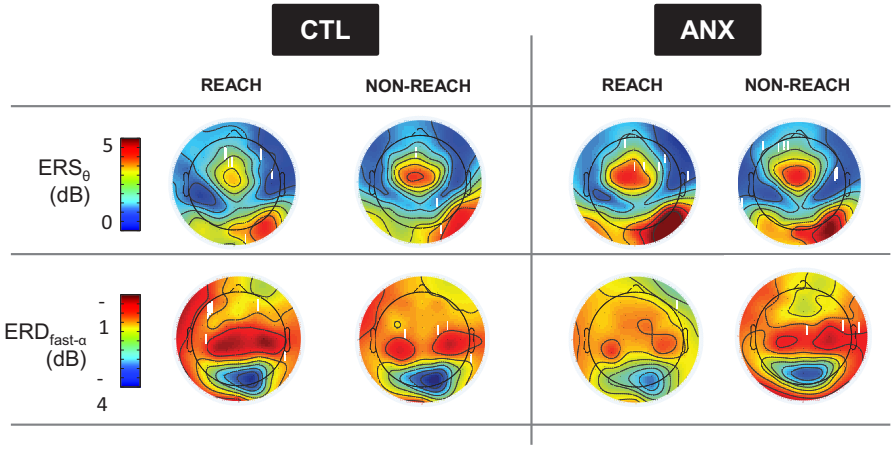

Fig. 5. Averaged scalp map of the topographic distribution of ERS_θ ([4.4–8.6 Hz] frequency band) and $ERD_{fast\text{-}\alpha}$ ([10.1–13.5 Hz] frequency band). Activities are reported for the [0 + 300 ms] time window from the onset of the glass apparition. The color code accounts for spectral power's variation relative to the baseline mean power. For the ERS_θ scalp map: the more the event-related synchronization is high in the theta band, the more the color code is warm, while cold colors account for moderate to no synchronization (all positive numbers). For the scalp $ERD_{fast\text{-}\alpha}$ map: the more the event-related desynchronization is high in the alpha band, the more the color code is cold, while warm colors account for moderate to no desynchronization (all negative numbers). Synchronization and desynchronization are expressed in decibel (dB). $ERD_{fast\text{-}\alpha}$ showed a maximal activity over the parietal region, and ERS_θ showed a maximal fronto-parieto-occipital activity. The later maximal activity over the occipital and frontal regions suggests that the present experimental task evokes strong visual ignition-related transformations. However, it must be emphasized that such a maximal activity can overshadow the moderate activity of the adjacent cortical regions involved in visuomotor task-related processing. Based on our hypothesis, we then focused on the contralateral and ipsilateral motor-related brain regions, as well as the posterior parietal brain region. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Breathing-discomfort-related ANX state. A 2 Condition (ANX vs. CTL) × 5 Sets of trials ANOVA was conducted using the mean discomfort score [0–100] as the dependent variable.

Electrophysiological data

Trials classification. To insure that Conditions were comparable according to the behavioral results after trials classification, a 2 Breathing Condition (ANX vs. CTL) × 2 Glass Position (REACH vs. NON-REACH) ANOVA was performed on averaged Glass Positions.

Event related spectrum power processing of cortical activity. An ANOVA with 2 Conditions (ANX *vs.* CTL) × 2 Glass Positions (REACH *vs.* NON-REACH, see Fig. 2) as repeated measures was conducted with 8 EEG dependent variables: (*i*) ERS_θ and $Norm\_ERS_\theta$ over the contralateral-motor region, (*ii*) ERS_θ and $Norm\_ERS_\theta$ over the ipsilateral-motor region, (*iii*) ERS_θ and $Norm\_ERS_\theta$ over the posterior-parietal region, and (*iv*) $ERD_{fast\text{-}\alpha}$ and $Norm\_ERD_{fast\text{-}\alpha}$ over the posterior-parietal region. ERS_θ and $Norm\_ERS_\theta$ are supposed to reflect the sensorimotor function while $ERD_{fast\text{-}\alpha}$ and $Norm\_ERD_{fast\text{-}\alpha}$ are supposed to reflect attentional processes.

Baseline power-spectrum. A paired samples *t*-test (ANX vs. CTL) was performed for the 4 EEG dependent variables: (*i*) $Pow_{BLfreq\text{-}\theta}$ over the contralateral-motor region, (*ii*) $Pow_{BLfreq\ \theta}$ over the ipsilateral-motor region, (*iii*) $Pow_{BLfreq\ \theta}$ over the parietal region and (*iii*) $Pow_{BLfreq\ fast\text{-}\alpha}$ over the parietal region.

Background EMG muscular activation. A repeated-measures ANOVA with 2 Conditions (ANX *vs.* CTL) × 2 Glass Positions (REACH *vs.* NON-REACH) × 2 Epochs (PRIOR *vs.* DURING the stimulus presentation) as repeated measures was conducted on background muscular activation data for both biceps brachii and triceps brachii.

RESULTS

Data distributions consistently passed the Kolmogorov–Smirnov normality test, and thus all data are reported as mean ± standard deviation (or standard error when indicated) throughout the text and figures.

Behavioral data

The *t*-test revealed a significant effect of Breathing Condition, with lower values of *perceived*-D_{max} in ANX compared to CTL for absolute values (mean distance 84.3 ± 7.9 cm *vs.* 85.7 ± 7.8 cm) [$t(1,11) = 6.277$, $p = 0.029$, $hp^2 = 0.363$] (Fig. 6a left). The participants underestimated their reaching-to-grasp capabilities in ANX condition, as evidenced by the mean ratio between *perceived*- and *actual*-D_{max} in ANX of 0.98 ± 0.03.

The ANOVA ensured that participants experienced discomfort and stress when breath restricted, as indicated by the main effect of Breathing Condition: participants reported significant higher discomfort scores in ANX than in CTL condition (mean score 71.9 ± 10.3 *vs.* 11.6 ± 7.8) [$F(1, 11) = 603.68$, $p < 0.001$, $hp^2 = 0.982$]. The effect of sets of trials [$F(4, 8) = 0.453$, $p = 0.769$, $hp^2 = 0.185$] and condition × sets of trials interaction [$F(4, 8) = 0.849$, $p = 0.532$, $hp^2 = 0.298$] were non-significant (Fig. 6a right).

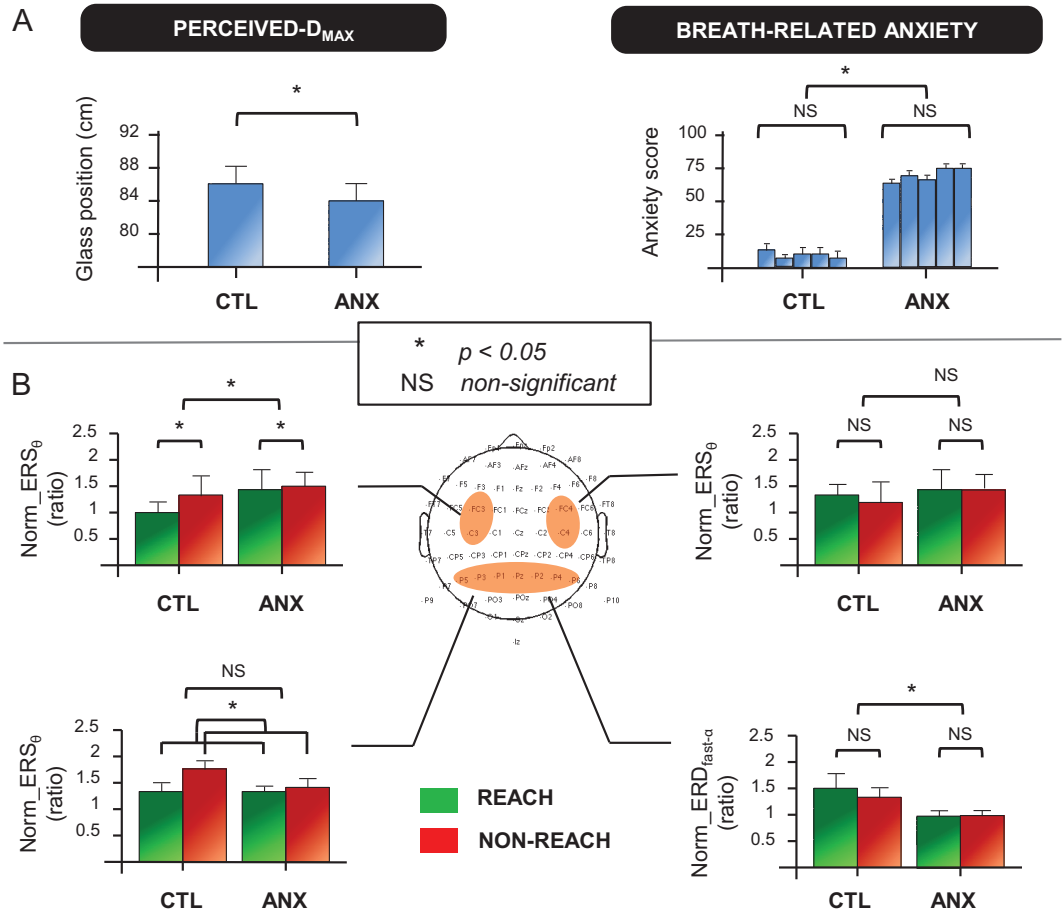

Fig. 6. Main findings for (a) behavioral and (b) electrophysiological data analysis. The vertical bars depict the standard error of the mean. (a) The left chart illustrates the results of the paired *t*-test used to compare the *perceived-D*$_{max}$ between CTL and ANX. The right chart shows the results of the 2 (Condition; ANX vs. CTL) × 5 (Sets of trials) ANOVA conducted using the breath-related anxiety score as the dependent variable. (b) The results of the ANOVA with 2 Conditions (ANX *vs.* CTL) × 2 Glass Positions (REACH *vs.* NON-REACH, see Fig. 2) conducted on NormERS$_\theta$ over the contralateral-motor area and the ipsilateral-motor area, and both NormERS$_\theta$ and NormERD$_{fast-\alpha}$ over the posterior-parietal area are reported here.

Electrophysiological data

Trials classification. The ANOVA revealed a main effect of Glass Position in that averaged Glass Position of trials sorted after the behavioral analysis were closer of the participants in REACH condition compared to NON-REACH condition (74.1 ± 6.0 cm vs. 94.3 ± 5.9 cm) [F(1, 11) = 819.06, $p < 0.001$, $hp^2 = 0.987$]. The main effect of Breathing Condition [F(1, 11) = 3.54, $p = 0.087$, $hp^2 = 0.243$] and Breathing Condition × Glass Position interaction [F(1, 11) = 2.84, $p = 0.120$, $hp^2 = 0.206$] were non-significant. Accordingly, as a methodological prerequisite, these results attest that the analysis of electrophysiological data was performed at comparable behavioral conditions after trials classification.

Contralateral-motor region. ERS$_\theta$. A main effect of Glass Position was revealed by the ANOVA, showing that the amplitude of ERS$_\theta$ was significantly smaller in REACH than in NON-REACH position (values 1.89 ± 0.97 dB *vs.* 2.22 ± 0.88 dB) [$F(1, 11) = 4.861$, $p = 0.048$, $hp^2 = 0.306$]. A main effect of Breathing Condition was also shown: the amplitude of ERS$_\theta$ was smaller in CTL than in ANX condition (value 1.86 ± 0.86 dB *vs.* 2.25 ± 0.97 dB) [$F(1, 11) = 6.188$, $p = 0.030$, $hp^2 = 0.360$]. The Breathing Condition × Glass Position interaction was not significant [$F(1, 11) = 0.271$, $p = 0.613$, $hp^2 = 0.024$].

Normalized ERS$_\theta$. The ANOVA revealed a main effect of Glass Position: the amplitude of NormERS$_\theta$ was significantly smaller in REACH than in NON-REACH position (ratio 1.18 ± 1.19 *vs.* 1.41 ± 1.30) [$F(1, 11) = 6.94$, $p = 0.023$, $hp^2 = 0.387$]. A main effect of Breathing Condition was also revealed, indicating that the amplitude of NormERS$_\theta$ was smaller in CTL than in ANX condition (ratio 1.18 ± 1.20 *vs.* 1.41 ± 1.29) [$F(1, 11) = 5.61$, $p = 0.037$, $hp^2 = 0.338$]. The condition × Glass Position interaction was not significant [$F(1, 11) = 1.265$, $p = 0.285$, $hp^2 = 0.103$] (Fig. 6b).

Pow$_{BLfreq-\theta}$. The *T*-test did not show statistical difference for *Pow*$_{BLfreq-\theta}$ over the contralateral motor region between CTL and ANX (values 1.01 ± 0.1 dB *vs.*

0.96 ± 0.1 dB) [$t(1, 11) = 2.204$, $p = 0.166$, $hp^2 = 0.167$].

Ipsilateral-motor region. ERS_{θ}. The effects of Breathing Condition [$F(1, 11) = 3.339$, $p = 0.095$, $hp^2 = 0.233$], Glass Position [$F(1, 11) = 0.239$, $p = 0.634$, $hp^2 = 0.021$], and Breathing Condition × Glass Position interaction [$F(1, 11) = 0.899$, $p = 0.363$, $hp^2 = 0.076$] were non-significant for ERS_{θ}.

Normalized ERS_{θ}. No effect of Breathing Condition [$F(1, 11) = 4.203$, $p = 0.075$, $hp^2 = 0.176$], Glass Position [$F(1, 11) = 0.190$, $p = 0.672$, $hp^2 = 0.017$], nor Breathing Condition × Glass Position interaction [$F(1, 11) = 0.464$, $p = 0.510$, $hp^2 = 0.040$] were revealed for $NormERS_{\theta}$.

$Pow_{BLfreq\text{-}\theta}$. No difference was revealed by the *T*-test when $Pow_{BLfreq\text{-}\theta}$ over the contralateral motor region was compared between CTL and ANX (values 1.01 ± 0.1 dB *vs.* 0.97 ± 0.1 dB) [$t(1, 11) = 2.327$, $p = 0.155$, $hp^2 = 0.175$].

Posterior-parietal region. ERS_{θ}. The ANOVA showed a significant main effect of Glass Position, with ERS_{θ} in REACH was significantly smaller than in NON-REACH (values 2.08 ± 0.72 *vs.* 2.38 ± 0.82) [$F(1, 11) = 11.720$, $p = 0.006$, $hp^2 = 0.516$]. No effect of Breathing Condition [$F(1, 11) = 1.265$, $p = 0.285$, $hp^2 = 0.103$] nor Breathing Condition × Glass Position interaction [$F(1, 11) = 3.717$, $p = 0.083$, $hp^2 = 0.253$] were significant.

Normalized ERS_{θ}. A main effect of Glass Position was significant, in that the amplitude of $NormERS_{\theta}$ in REACH was significantly smaller than in NON-REACH (ratio 1.36 ± 0.43 *vs.* 1.57 ± 0.58) [$F(1, 11) = 7.50$, $p = 0.019$, $hp^2 = 0.405$]. The effects of Breathing Condition [$F(1, 11) = 1.96$, $p = 0.189$, $hp^2 = 0.151$] and Breathing Condition × Glass Position interaction [$F(1, 11) = 2.80$, $p = 0.122$, $hp^2 = 0.203$] were non-significant (Fig. 6b).

$Pow_{BLfreq\text{-}\theta}$. No difference was shown by the *T*-test when $Pow_{BLfreq\text{-}\theta}$ over the posterior-parietal region was compared between CTL and ANX (values 1.02 ± 0.1 dB *vs.* 0.99 ± 0.1 dB) [$t(1, 11) = 1.188$, $p = 0.229$, $hp^2 = 0.097$].

$ERD_{fast\text{-}\alpha}$. The ANOVA showed a main effect of Breathing Condition: the amplitude of $ERD_{fast\text{-}\alpha}$ was significantly smaller in ANX than in CTL condition (values −1.31 ± 0.88 dB *vs.* −1.75 ± 0.79 dB) [$F(1, 11) = 6.742$, $p = 0.016$, $hp^2 = 0.426$]. No effect of Glass Position [$F(1, 11) = 1.459$, $p = 0.449$, $hp^2 = 0.053$] nor Condition × Glass Position interaction [$F(1, 11) = 1.035$, $p = 0.551$, $hp^2 = 0.033$] were significant.

Normalized $ERD_{fast\text{-}\alpha}$. The ANOVA showed a main effect of condition indicating that the amplitude of $NormERD_{fast\text{-}\alpha}$ was significantly smaller in ANX than in CTL (ratio 0.89 ± 0.41 *vs.* 1.43 ± 0.96) [$F(1, 11) = 6.55$, $p = 0.027$, $hp^2 = 0.373$]. The effect of Glass Position [$F(1, 11) = 1.25$, $p = 0.287$, $hp^2 = 0.102$] and Condition × Glass Position interaction [$F(1, 11) = 0.52$, $p = 0.486$, $hp^2 = 0.045$] were non-significant (Fig. 6b).

$Pow_{BLfast\text{-}\alpha}$. The *T*-test did not show statistical difference for $Pow_{BLfast\text{-}\alpha}$ over the contralateral motor region between CTL and ANX (values 1.35 ± 0.2 dB *vs.* 1.25 ± 0.2 dB) [$t(1, 11) = 2.247$, $p = 0.084$, $hp^2 = 0.247$].

Background EMG muscle activation. For biceps brachii and triceps brachii muscles, the ANOVA revealed no effect of Breathing Condition [$F(1, 11 = 3.93$, $p = 0.172$, $hp^2 = 0.197$, and $F(1, 11) = 1.449$, $p = 0.259$, $hp^2 = 0.139$, respectively], no effect of Glass Position [$F(1, 11) = 0.075$, $p = 0.790$, $hp^2 = 0.008$, and $F(1, 11) = 1.57$, $p = 0.241$, $hp^2 = 0.149$, respectively], and no effect of epoch for pre- vs. post- stimuli epochs [$F(1, 11) = 3.925$, $p = 0.079$, $hp^2 = 0.304$, and $F(1, 11) = 2.10$, $p = 0.181$, $hp^2 = 0.189$, respectively].

Moreover, none of the following interactions were significant: Condition × Glass Position [$F(1, 11) = 0.17$, $p = 0.688$, $hp^2 = 0.019$, and $F(1, 11) = 2.84$, $p = 0.126$, $hp^2 = 0.240$, respectively], Condition × Epoch from time to stimuli presentation [$F(1, 11) = 2.90$, $p = 0.123$, $hp^2 = 0.183$, and $F(1, 11) = 1.79$, $p = 0.214$, $hp^2 = 0.166$, respectively], Glass Position × epoch from time to stimuli presentation [$F(1, 11) = 2.09$, $p = 0.182$, $hp^2 = 0.188$, and $F(1, 11) = 0.73$, $p = 0.414$, $hp^2 = 0.075$, respectively], and Breathing Condition × Glass Position × Epoch from time to stimuli presentation [$F(1, 11) = 0.21$, $p = 0.662$, $hp^2 = 0.022$, and $F(1, 11) = 0.97$, $p = 0.350$, $hp^2 = 0.097$, respectively].

The grand averages of the level of activation for biceps brachii and triceps brachii were 1.0 ± 0.6% and 0.9 ± 0.6% of the EMG activation level during MVC, respectively.

DISCUSSION

The aim of the present study was to bring new insights into cortical correlates of impaired action–perception coupling, when the ANX level was experimentally manipulated. Former behavioral results have suggested that alterations in the sensorimotor function account for impaired action–perception coupling (Lee et al., 2001; Guardia et al., 2010; Smith et al., 2011), but such consideration for cortical activities related to sensorimotor function was never challenged. Our EEG study revealed that the θ-EEG activity (i.e., the cortical activity related to sensorimotor function) co-modulates with impaired action–perception coupling in a context, where participants in state of breathing-restriction under-estimated their reaching-to-grasp capabilities.

Before discussing the changes of EEG activities, it should be noted that a lower fast-α-EEG desynchronization was found over the posterior-parietal region when participants were breath-restricted, suggesting a shift in task-specific attentional resources (Gevins et al., 1997; Klimesch, 1999; Stipacek et al.,

2003). Given that an attentional shift would not be the cause of the underestimation of reaching-to-grasp performance (see Daviaux et al., 2016), the modulation of fast-α-EEG over the parietal region is reasonably considered as a task-related indication of the brain activity that account for an effective manipulation of the brain ANX-network state with breathing restriction.

That being said, a modulation in θ-EEG synchronization over the contralateral-motor region was observed in line with our main hypothesis, i.e. when participants underestimated their reaching-to-grasp performance during ANX condition. Furthermore, the θ-EEG activity measured over the contralateral-motor region depended on the glass proximity. No change in θ-EEG was found over the ipsilateral motor region. Though, θ-EEG activity was previously shown to be similar over contralateral and ipsilateral motor regions in the preparation phase of efficient reaching action (Tombini et al., 2009; Cruikshank et al., 2012). The absence of changes over the ipsilateral-motor region in the present study suggests the effects over the contralateral-motor region to be task-specific.

The effects observed over the contralateral region seem to be consistent with the conservative behavior of participants; the motor region was indeed shown to be involved concomitantly in the encoding of action–related body parts and target's position necessary for the movement execution (e.g. Hoshi and Tanji, 2000; Praamstra et al., 2009). Considering the main effects of Condition and Glass Position on θ-EEG over the contralateral-motor region, the synchronization was higher for the "*non-reach*" Glass Positions than for the "*reach*" Glass Positions, and was higher for the ANX than for the CTL condition. These two concomitant main effects then suggest that any Glass Position challenges a visuomotor transformation inducing a 'farther-to-be-reached' representation of the Glass Position in ANX compared to CTL. The analysis of EMG activity recordings showed that the muscular activation remained comparable during rest and during the glass presentation. The low average level of muscle activation suggested that participants remained close to a completely passive situation, as conventionally taken at 1% of the EMG maximal activation level (*e.g.*, Nordez et al., 2008). Then the 'farther-to-be-reached' assumption is consistent with the role assigned to the θ-EEG synchronization within a motionless context, considered as representative of a *readiness state* of the motor system (type-2 theta activity, Bland and Oddie, 2001). As such, it could be reasonably hypothesized that θ-EEG synchronization over the contralateral-motor region supported the processes of integration of relevant sensorimotor inputs for a goal-directed action while there is no intention to act (see in Cruikshank et al., 2012 and in Rawle et al., 2012). Accordingly, the present θ-EEG synchronization over the contralateral-motor region is assumed to have carried all the sensorimotor and visuomotor information underlying the consistency with which a movement should be initiated. In summary, for a given Glass Position, a rising amount of θ-EEG activity over the motor region can be thought to have supported a less congruent visuomotor context for reaching-and-grasp behavior. In other words, along the reachable-to-non-reachable continuum of Glass Positions, the "too-far-to-be-reached" θ-EEG readiness state would be evoked for closer Glass Position in ANX condition compared to CTL condition. This could explain why participants were underestimating their reaching-to-grasp performances.

An effect of breathing restriction was also expected over the posterior-parietal region for θ-EEG activity, due to the reciprocal relationship between the motor and parietal region in the sensorimotor function dedicated to reaching and pointing behavior (Praamstra et al., 2009; Cruikshank et al., 2012; Rawle et al., 2012). However, θ-EEG activity over the posterior-parietal region was only sensitive to the glass distance. This is consistent with previous studies highlighting the role of the posterior-parietal region in encoding the spatial localization of a target and the control for action (Culham and Kanwisher, 2001; Binkofski and Buxbaum, 2012). To be noted are results in Rawle et al. (2012), where identical θ-EEG responses of the parietal region where found whatever the visual target load. Accordingly, in our study, the posterior-parietal region appeared to promote the encoding of the Glass Position representation (Culham and Kanwisher, 2001; Curtis et al., 2004) regardless of the complexity of its motor-related representation (Rawle et al., 2012).

The statistical analysis applied to θ-ERS and fast-α-ERD revealed equivalent significant effects compared to the analysis applied to the normalized values of θ-ERS and fast-α-ERD, for every cortical regions of interests. It confirms how robust are the present task-related EEG modulations, while the statistical values slightly differ as the normalization procedure allow to take into account the inter-individual variability of the perceptual processes.

As a limit of this study, one could assume that the breathing restriction would have changed the oxygen concentrations and modified the EEG activity (Pastena et al., 2015) within the baseline period. Consequently, the power spectrum of the baseline periods were checked and compared across conditions. As shown by the absence of difference, the power spectrums remained equals in CTL and ANX: it corroborates that the actual effects were not due to oxygen-corrupted cortical activities within the baseline periods but rather to cortical activities during the glass presentation.

Finally, a traditional, well accepted point of view about the theta and alpha EEG oscillations was adopted to introduce the study and debate our results. It should be emphasized that the observed modulations of EEG theta and alpha oscillations might also have been introduced and debated through more contemporary view on the functional interpretations of these oscillations. This particularly includes positions about the cross-frequency coupling of theta and alpha oscillations with gamma oscillations (e.g., Jiang et al., 2015) in which a reduction in theta/alpha activities would be a signature of task-engaged cortical areas (see Lisman and Jensen, 2013 for an extensive discussion), and also a position in which both theta and alpha oscillatory activities would support a facilitatory effect for

corticostriatal interactions for visual – but non necessarily motor-related - stimuli processing (Horschig et al., 2015).

CONCLUSION

To conclude, the actual changes of θ-EEG activity over the contralateral-motor region provides the first evidence of a co-modulation of the sensorimotor cortical activities with impaired action–perception coupling under stressful state. From these results, we look forward to future studies that can illustrate a ‘‘narrower” construction of the sensorimotor body representation acting as a reference to judge action capacities, as suggested by Guardia et al. (2010). Future research works might also address the changes in peripersonal space’s properties that have already been shown to be altered consistently in various forms of ANX conditions (Lourenco et al., 2011; Sambo and Iannetti, 2013; see De Vignemont, 2010 4 for discussion). Finally, impaired action–perception coupling within action–scaled paradigms remains a challenge given that the predictive consequence of action may be involved in the perception of the action capabilities, e.g., changes in energetic aspects of action–perception coupling (Witt and Riley, 2014).

Acknowledgment—The research was supported by grants from the Region of Pays de la Loire (France).

REFERENCES

Bartolo A, Coello Y, Edwards MG, Delepoulle S, Endo S, Wing AM (2014) Contribution of the motor system to the perception of reachable space: an fMRI study. Eur J Neurosci 40:3807–3817.

Bigot J, Longcamp M, DalMaso F, Amarantini D (2011) A new statistical test based on the wavelet cross-spectrum to detect time–frequency dependence between non-stationary signals: application to the analysis of cortico-muscular interactions. NeuroImage 55:1504–1518.

Binkofski F, Buxbaum LJ (2012) Two action systems in the human brain. Brain Lang.

Bland BH, Oddie SD (2001) Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. Behav Brain Res 127:119–136.

Borghi AM, Riggio L (2009) Sentence comprehension and simulation of object temporary canonical and stable affordances. Brain Res 1253:117–128.

Brown HR, Friston KJ (2012) Dynamic causal modeling of precision and synaptic gain in visual perception - an EEG study. NeuroImage 63:223–231.

Buchanan TS, Roval GP, Zev Rymer W (1989) Strategies for muscle activation during isometric torque generation at the human elbow. J Neurophysiol 62:1201–1212.

Caplan JB, Madsen JR, Schulze-Bonhage A, Aschenbrenner-Scheibe R, Newman EL, Kahana MJ (2003) Human theta oscillations related to sensorimotor integration and spatial learning. J Neurosci 23:4726–4736.

Cohen J (1988) Statistical power analysis for the behavioural sciences. New-York: Academic press.

Cruikshank LC, Singhal A, Hueppelsheuser M, Caplan JB (2012) Theta oscillations reflect a putative neural mechanism for human sensorimotor integration. J Neurophysiol 107:65–77.

Culham JC, Kanwisher NG (2001) Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 11:157–163.

Curtis CE, Rao VY, D’Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944–3952.

Daviaux Y, Cremoux S, Tallet J, Amarantini D, Cornu C, Deschamps T (2016) An enhanced experimental procedure to rationalize on the impairment of perception of action capabilities. Psychol Res 80:224–234.

De Vignemont F (2010) Body schema and body image–pros and cons. Neuropsychologia 48:669–680.

Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9–21.

Delorme A, Westerfield M, Makeig S (2007) Medial prefrontal theta bursts precede rapid motor responses during visual selective attention. J Neurosci 27:11949–11959.

Doppelmayr M, Klimesch W, Pachinger T, Ripper B (1998) Individual differences in brain dynamics: important implications for the calculation of event-related band power. Biol Cybern 79: 49–57.

Ellis R, Tucker M (2000) Micro-affordance: the potentiation of components of action by seen objects. Brit J Psychol 91:451–471.

Eysenck MW, Derakshan N, Santos R, Galvo MG (2007) Anxiety and cognitive performance: attentional control theory. Emotion 7:336–353.

Fisher MH (2000) Estimating reachability: whole body engagement or postural stability? Hum Movement Sci 19:297–318.

Fogassi L (2007) Action representation in the cerebral cortex and the cognitive functions of the motor system. In: Funahashi S, editor. Representation and brain. Tokyo: Springer. p. 123–151.

Franchak JM, van der Zalm DJ, Adolph KE (2010) Learning by doing: action performance facilitates affordance perception. Vision Res 50:2758–2765.

Gevins A, Smith ME, McEvoy L, Yu D (1997) High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty type of processing and practice. Cereb Cortex 7:374–385.

Goljahani A, D’Avanzo C, Schiff S, Amodio P, Bisiacchi P, Sparacino G (2012) A novel method for the determination of the EEG individual alpha frequency. NeuroImage 60:774–786.

Goljahani A, Bisiacchi P, Sparacino G (2014) An EEGLAB plugin to analyze individual EEG alpha rhythms using the ‘‘channel reactivity-based method. Comput Meth Prog Bio 113:853–861.

Grandchamp R, Delorme A (2011) Single-trial normalization for event-related spectral decomposition reduces sensitivity to noisy trials. Front Psychol:1–14.

Graydon MM, Linkenauger SA, Teachman BA, Proffitt DR (2012) Scared stiff: the influence of anxiety on the perception of action capabilities. Cogn Emot 26:1301–1315.

Graziano MSA, Botvinick MM (2002) How the brain represents the body: insights from neurophysiology and psychology. In: Prinz W, Hommel B, editors. Common mechanisms in perception and action: attention and performance, vol. 19. Oxford: Oxford University Press. p. 136–157.

Grinsted A, Moore JC, Jevrejeva S (2004) Application of the cross wavelet transform and wavelet coherence to geophysical time series. Nonlinear Proc Geophys 11:561–566.

Guardia D, Lafargue G, Thomas P, Dodin V, Cottencin O, Luyat M (2010) Anticipation of body-scaled action is modified in anorexia nervosa. Neuropsychologia 48:3961–3966.

Guardia D, Conversy L, Jardri R, Lafargue G, Thomas P, Dodin V, Cottencin O, Luyat M (2012) Imagining one’s own and someone else’s body actions: dissociation in anorexia nervosa. PLoS One: e43241.

Hackney AL, Cinelli ME (2013) Young and older adults use body-scaled information during a non-confined aperture crossing task. Exp Brain Res 225:419–429.

Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G (2000) Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol 10:361–374.

Higuchi T, Hatano N, Soma K, Imanaka K (2009) Perception of spatial requirements for wheelchair locomotion in experienced users with Tetraplegia. J Physiol Anthropo 28:15–21.
Higuchi T, Murai G, Kijima A, Seya Y, Wagman JB, Imanaka K (2011) Athletic experience influences shoulder rotations when running through apertures. Hum Mov Sci 30:534–549.
Hirose N, Nishio A (2001) The process of adaptation to perceiving new action capabilities. Ecol Psychol 13:49–69.
Holmes NP, Spence C (2004) The body schema and the multisensory representation(s) of peripersonal space. Cogn Process 5:94–105.
Homan RW, Herman J, Purdy P (1987) Cerebral location of international 10–20 system electrode placement. Electroencephalogr Clin Neurophysiol 66:376–382.
Horschig JM, Smolders R, Bonnefond M, Schoffelen JM, van den Munckhof P, Schuurman PR, Cools R, Denys D, Jensen O (2015) Directed communication between nucleus accumbens and neocortex in humans is differentially supported by synchronization in the theta and alpha band. PLoS One 10: e0138685.
Hoshi E, Tanji J (2000) Integration of target and body-part information in the premotor cortex when planning action. Nature 408:466–470.
Jiang H, Bahramisharif A, van Gerven MA, Jensen O (2015) Measuring directionality between neuronal oscillations of different frequencies. NeuroImage 118:359–367.
Kanai R, Rees G (2011) The structural basis of interindividual differences in human behaviour and cognition. Nature Rev Neurosci 12:231–242.
Kingdom FAA, Prins N (2009) Psychophysics: a practical introduction. San Diego: Elsevier.
Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev 29:169–195.
Klimesch W, Vogt F, Doppelmayr M (2000) Interindividual differences in alpha and theta power reflect memory performance. Intelligence 27:347–362.
Lee AC, Harris JP, Atkinson EA, Fowler MS (2001) Disruption of estimation of body-scaled aperture width in Hemiparkinson's disease. Neuropsychologia 39:1097–1104.
Lisman JE, Jensen O (2013) The theta-gamma neural code. Neuron 77:1002–1016.
Lourenco SF, Longo MR, Pathman T (2011) Near space and its relationship to claustrophobic fear. Cognition 119:448–453.
Luyat M, Domino D, Noël M (2008) Can overestimating one's own capacities of action lead to fall? A study on the perception of affordance in the elderly? Geriatr Psychol Neuropsychiatr Vieil 6:287–297.
Natraj N, Poole V, Mizelle JC, Flumini A, Borghi AM, Wheaton LA (2013) Context and hand posture modulate the neural dynamics of tool-object perception. Neuropsychologia 51:506–519.
Niedermeyer E, Lopes da Silva F (2005) Electroencephalography: basic principles clinical applications and related fields. Lippincott Williams and Wilkins Philadelphia.
Noël M, Bernard A, Luyat M (2011) The overestimation of performance: a specific bias of aging? Geriatr Psychol Neuropsychiatr Vieil 9:287–294.
Nordez A, Gennisson JL, Casari P, Catheline S, Cornu C (2008) Characterization of muscle belly elastic properties during passive stretching using transient elastography. J Biomech 41:2305–2311.
Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.
Oliveira JM, Volchan E, Vargas CD, Gleiser S, David IA (2012) Box for interaction with objects (BIO): a new device to synchronize the presentation of objects with electrophysiological recordings. Behav Res Meth 44:1115–1120.
Pastena L, Formaggio E, Storti SF, Faralli F, Melucci M, Gagliardi R, Ricciardi L, Ruffino G (2015) Tracking EEG changes during the exposure to hyperbaric oxygen. Clin Neurophysiol 136:339–347.
Pijpers JR, Oudejans R, Bakker FC, Beek PJ (2006) The role of anxiety in perceiving and realizing affordances. Ecol Psychol 18:131–161.
Praamstra P, Kourtis D, Nazarpour K (2009) Simultaneous preparation of multiple potential movements: opposing effects of spatial proximity mediated by premotor and parietal cortex. J Neurophysiol 102:2084–2095.
Prinz W, Hommel B (2002) Common mechanisms in perception and action: introductory remarks. In: Prinz W, Homme B, editors. Attention and performance XIX: common mechanisms in perception and action. NY: Oxford University Press. p. 1–3.
Rawle CJ, Miall RC, Praamstra P (2012) Frontoparietal theta activity supports behavioral decisions in movement-target selection. Front Hum Neurosci.
Rochat P, Wraga M (1997) An account of the systematic error in judging what is reachable. J Exp Psychol Hum Percept Perform 23:199–212.
Sakurai R, Fujiwara Y, Ishihara M, Higuchi T, Uchida H, Imanaka K (2013) Age-related self-overestimation of step-over ability in healthy older adults and its relationship to fall risk. BMC Geriatrics:13–44.
Sambo CF, Iannetti GD (2013) Better safe than sorry? The safety margin surrounding the body is increased by anxiety. J Neurosci 33:14225–14230.
Sanei S, Chambers JA (2007) EEG signal processing. Chichester England: JohnWiley Sons Ltd.
Serrano E, Nowotny T, Levi R, Smith BH, Huerta R (2013) Gain control network conditions in early sensory coding. PLoS Comput Biol:e1003133.
Smith JG, Harris JP, Khan S, Atkinson EA, Fowler MS, Ewins D, D'Souza S, Gregory RP, Kean RJ (2011) Motor asymmetry and estimation of body-scaled aperture width in Parkinson's disease. Neuropsychologia 49:3002–3010.
Steimer T (2002) The biology of fear and anxiety-related behaviors. Dialogues Clin Neurosci 4:231–249.
Stipacek A, Grabner RH, Neuper C, Fink A, Neubauer AC (2003) Sensitivity of human EEG alpha band desynchronization to different working memory components and increasing levels of memory load. Neurosci Lett 353:193–196.
Thurm BE, Pereira ES, Fonseca CC, Cagno MJS, Gama EF (2011) Neuroanatomical aspects of the body awareness. J Morphol Sci 28:296–299.
Tombini M, Zappasodi F, Zollo L, di Pellegrino G, Cavallo G, Tecchio F, Guglielmelli E, Rossini PM (2009) Brain activity preceding a 2D manual catching task. NeuroImage 47:1735–1746.
Valdés-Conroy B, Sebastián M, Hinojosa JA, Román FJ, Santaniello G (2014) A close look into the near/far space division: a real-distance ERP study. Neuropsychologia 59:27–34.
Wamain Y, Gabrielli F, Coello Y (2016) EEG μ rhythm in virtual reality reveals that motor coding of visual objects in peripersonal space is task dependent. Cortex 74:20–30.
Witt J, Riley MA (2014) Discovering your inner Gibson: reconciling action–specific and ecological approaches to perception–action. Psychon Bull Rev 21:1353–1357.

(Accepted 20 September 2016)
(Available online 28 September 2016)

Journal of Psychiatric Research 83 (2016) 86–93

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Posture-cognitive dual-tasking: A relevant marker of depression-related psychomotor retardation. An illustration of the positive impact of repetitive transcranial magnetic stimulation in patients with major depressive disorder

Thibault Deschamps [a, *], Anne Sauvaget [b, c], Anne Pichot [b], Pierre Valrivière [b], Maxime Maroulidès [a], Aurore Bois [a], Samuel Bulteau [b], Véronique Thomas-Ollivier [a]

[a] Laboratory "Movement, Interactions, Performance" (E.A. 4334), University of Nantes, France
[b] CHU de Nantes, Service d'Addictologie et Psychiatrie de liaison, France
[c] EA SPHERE 4275 Methods for Patients-centered outcomes and Health Research, University of Nantes, Nantes, France

ARTICLE INFO

Article history:
Received 23 May 2016
Received in revised form
14 August 2016
Accepted 18 August 2016

Keywords:
Depression
rTMS
Psychomotor retardation
Posture

ABSTRACT

This study examined whether postural control variables, particularly the center-of-pressure (COP) velocity-based parameters, could be a relevant hallmark of depression-related psychomotor retardation (PMR). We first aimed at investigating the interplay between the PMR scores and the COP performance in patients with major depressive disorder (MDD), as compared to age-matched healthy controls; secondly, we focused on the impact of a repetitive transcranial magnetic stimulation (rTMS) treatment on depression, PMR scores and postural performance. 16 MDD patients, and a control group of 16 healthy adults, were asked to maintain quiet standing balance during two trials with or without vision, and while backward counting (dual task). All the position and velocity-based COP variables were computed. Before and after the rTMS session (*n* eligible MDD = 10), we assessed the depression level with the Montgomery –Asberg Depression Rating Scale (MADRS), the PMR scores with the French Retardation Rating Scale for Depression (ERD), and postural performance. Before the treatment, significant positive partial correlations were found between the pre-ERD scores and the velocity-based COP variables, especially in the dual-task conditions ($p < 0.05$). In contrast, there was no significant correlation between the post-ERD scores and any postural parameter after the treatment. The MADRS and ERD scores showed a significant decrease between before and after the rTMS intervention. For the first time, the findings clearly validated the view that the assessment of postural performance - easy to envisage in clinical settings- constitutes a reliable and objective marker of PMR in MDD patients.

1. Introduction

By considering a two-month walking exercise program as an effective intervention for improving depression related psychomotor disorders, we recently showed that patients with major depressive disorder (MDD) improved their postural control by decreasing essentially center-of-pressure (COP) velocity-based parameters (Deschamps et al., 2015). In addition to confirming the impaired balance performance in MDD in comparison to healthy controls (Bolbecker et al., 2011; Doumas et al., 2012), we support the idea that significant changes in these COP-velocity variables while assessing balance in depressed people could be a relevant hallmark of depression-related psychomotor retardation (PMR). As a core symptom of depression, which includes motor and cognitive impairments, this PMR actually has become the subject of increasing interest in recent studies on its diagnostic, prognostic, and therapeutic relevance in MDD (Beheydt et al., 2015; Bennabi et al., 2013; Schrijvers et al., 2008; Thomas-Ollivier et al., 2016). Conventionally, most studies have used interviewer-rated scales based on observations of behavior, such as the retardation item of the Hamilton Depression Rating Scale (Hamilton, 1960) and the

* Corresponding author. University of Nantes, Laboratory «Movement, Interactions, Performance» (E.A. 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France.
E-mail address: thibault.deschamps@univ-nantes.fr (T. Deschamps).

http://dx.doi.org/10.1016/j.jpsychires.2016.08.013
0022-3956/

Salpêtrière Retardation Rating Scale (SRRS) (Montgomery and Åsberg, 1979; Widlöcher, 1983). However we recently showed that administering a comprehensive PMR battery of tests (e.g. 3-Meter Timed Up and Go test, dual-tasking postural control assessments, the handgrip strength test or verbal fluency tasks) during a repetitive transcranial magnetic stimulation (rTMS) treatment was feasible, free of adverse effects, and well tolerated by the MD patients in naturalistic conditions before or after the three-week rTMS protocol (see Thomas-Ollivier et al., 2016 for details). Beyond the confirmation of significant effects of rTMS treatment on depression (e.g., Aleman, 2013; Brunelin et al., 2014; Dell'Osso et al., 2011), another interesting finding was the positive changes in psychomotor outcome measures following the intervention, especially in balance performance.

Thus, the characterization of implicit postural control strategies in MDD patients emerged as one relevant and objective hallmark feature for clinical PMR assessment. In fact, we demonstrated an improvement in postural performance (when assessed in a dual task, namely standing balanced with eyes open or eyes closed while counting backward), evidenced by a significant decrease in COP velocity variables (e.g. mean velocity in mm/s) (Thomas-Ollivier et al., 2016). Although these results are in line with recent studies that support the clinical interest for characterizing postural instability in MDD adults or older healthy individuals with cognitive impairment (Deschamps et al., 2014; Mignardot et al., 2014), no specific PMR scale was used in this feasibility study (Thomas-Ollivier et al., 2016) to link depression-related postural sway with respect to a validated scale.

Thus, the purposes of the present study are twofold: first, it aims to take a clear look at the interplay between the PMR scores and the impaired balance performance in MDD patients, as compared to age-matched healthy controls (Deschamps et al., 2015; Bolbecker et al., 2011; Doumas et al., 2012); the exploratory nature of our second aim focuses on the impact of rTMS treatment on depression, PMR and balance assessments. In this regard, only a few studies about the neurostimulation-related effects on PMR are available in the literature, with divergent results (Baeken et al., 2010; Höppner et al., 2003; Ullrich et al., 2012). But some neurophysiological mechanisms underlying the significant effects of rTMS treatment on depression-related PMR and the disbalanced control in MDD patients make clear our expectations (Walther et al., 2012).

Changes in PMR probably arise from the alterations of limbic signals, at the interface of emotion, volition, higher-order cognitive functions, and movement. For example, a recent review on the functional neuroanatomy of PMR suggests the involvement of fronto-striatal neurocircuitry, and monoaminergic pathways and metabolism; this functional anatomical specificity of PMR "*could be improved by the use of objective measurements of motor performance*" (see Liberg and Rahm, 2015, p. 5). In the same way, the rTMS-induced activity has a positive effect on the limbic system and causes changes in functionally connected remote areas (Paus et al., 2001); it is also likely to facilitate the striatal dopamine release (Strafella et al., 2003) and reduce the attentional and cognitive deficits related to PMR in MDD patients (De Raedt et al., 2015), with positive impact on their postural control (Doumas et al., 2012; Thomas-Ollivier et al., 2016). Put all together, solid assumptions can be made. A significant improvement of PMR is expected following the 3-week rTMS protocol in which eligible MDD patients were stimulated to the left or right add-on to continued psychopharmacological treatment in a naturalistic clinical setting. In either left or right rTMS protocols, it has been shown that both rTMS method were equally effective therapies for MDD patients (Chen et al., 2013). This positive change in PMR may be associated with a decrease in essentially COP velocity-based parameters, as a relevant index of better postural control.

2. Methods

2.1. Participants

Sixteen patients with major depression at Nantes University Hospital (mean age 57.9 ± 13.9 years, range 28–78 years; 9 females) were compared to 16 healthy controls (HC), adults (mean age 60.7 ± 9.6 years, range 36–69 years; 12 females) who volunteered to participate in this open unblinded study. Inclusion criteria were: diagnosis of MDD according to DSM-IV; the patients had to have failed to respond to at least two previous adequate courses of antidepressants; no neurological, psychotic or addictive disorders; and a Montgomery–Asberg Depression Rating Scale (MADRS;/60; Montgomery and Åsberg, 1979) score $\geq$ 20. Exclusion criteria included contraindication to rTMS and any change in psychoactive drugs during the rTMS therapy. Thus eligible MDD patients ($n = 10$) were stimulated to the left or right add-on to a continued psychopharmacological treatment in a naturalistic clinical setting. All eligible patients provided a signed consent form for participation. Note that none of the participants had previous experience with the experimental tasks. The study was carried out according to the fifth revision of the Declaration of Helsinki.

Clinical Ratings. Prior to the first TMS session, the MDD patients completed the MADRS, and the French Retardation Rating Scale for Depression (ERD:/60 (Widlöcher, 1983; Hardy et al., 1984); - a validated 15-item rating instrument to assess the severity of psychomotor retardation in depressed populations -, was completed by the same trained rater before and one week after the last rTMS session. Table 1 summarizes patients' characteristics.

2.2. Experimental conditions and procedures

Postural assessments. For data collection of postural sway, all participants (MDD *vs*. HC) were asked to maintain standing position on a Kistler force platform (model 9286BA) for two trials of quiet standing balance with eyes open (EO) or eyes closed (EC), and two trials (EO *vs*. EC) while backward counting by two from a random number around 100. The counting of numbers was tape-recorded. The participants were asked to stand quietly while barefoot with the head in a straight ahead position, their arms along the body, and each foot positioned on the platform plate that maintained the distance between the medial sides of the heel at 8.4 cm with an external rotation angle of 9°. During the EO conditions, the participants were also instructed to look straight ahead, and focus on a visual reference mark (2 cm in diameter) placed on a white wall in front of them at a 200-cm distance. For a trial of 60-s duration (sampling frequency of 100 Hz), the system was linked to BioWare® 5.2.2 software (Kistler Group, Winterthur, Switzerland), thus providing COP series on the anteroposterior (AP) and mediolateral (ML) axes. The postural conditions [EO *vs*. EC; single task (ST) *vs*. dual task (DT)] were presented in randomized order among participants.

rTMS treatment for ten eligible MDD patients. Similar to our pilot feasibility study (Thomas-Ollivier et al., 2016), a pre-post study design was set up in which the postural stability in MDD patients was assessed in naturalistic conditions before and after 15 sessions of active rTMS that were conducted over a three-week period. For the rTMS, the intensity was 110% of the individual's motor threshold (i.e. the minimum stimulus required to induce contraction of the right thumb at least 5 of 10 times). Six patients underwent a high frequency rTMS on the left dorsolateral prefrontal cortex (10 Hz, 40 trains of 4 s with 28-sec intertrain intervals, providing a total of 1600 pulses over 20 min); Four patients underwent a low frequency rTMS on the

right dorsolateral prefrontal cortex (1 Hz, 12 trains of 60 s with 30-sec intertrain intervals, providing a total of 720 pulses over 17 min). It also is particularly important to note that no structured individualized psychotherapy treatment, such as hypnosis, cognitive-behavioral therapy, or psychoanalysis started during the study period or the preceding month. Likewise, no change in medication occurred one month before and during the study.

2.3. Data analysis

The dependent variables computed from the analysis of COP trajectories included mean range (in millimeters) and 95% confidence intervals (CI) of COP excursion in the AP and ML directions, standard deviation (SD) of position, area (95% confidence ellipse), and mean and SD of COP velocity in AP and ML directions. The average absolute maximal velocity (AAMV in mm/s) was also computed from the COP velocity series by extracting the maximum and minimum values of series within non-overlapping 2-s windows. Then the absolute values of these extremes were averaged. In fact, in recent studies, this AAMV that bounds the COP velocity dynamics of postural sway has been identified as the most sensitive dependent variable for characterization of postural control performance, as a function of cognitive impairment (Deschamps et al., 2014), fall history (Mignardot et al., 2014), and depressive disorder (Deschamps et al., 2015).

2.4. Statistical analysis

Most data failed to pass the normality Shapiro-Wilk tests (appropriate for small sample sizes). For testing the effects of Group (MDD vs. HC) on the postural control, Mann-Whitney U tests were carried out for each aforesaid dependent variable. Then between group comparisons were performed using 2 (Group) × 2 (Vision: EO *vs.* EC) × 2 (Condition: ST *vs.* DT) ANOVAs to test the effects of visual information processing and attentional demands on the postural control.

To explore changes in depression and PMR after three weeks of rTMS intervention, a Wilcoxon test was used (before *vs.* after) for MADRS and ERD scores. Likewise, for testing the effect of the rTMS treatment on postural control in MDD, we conducted a doubly-multivariate, 2 (Session: before *vs.* after) × 2 (Vision: EO *vs.* EC) × 2 (Condition: ST *vs.* DT) repeated measures with time-varying covariates (i.e., depression symptoms) and then univariate repeated-measures analyses of covariance (ANCOVAs). Partial eta square ($p\eta^2$) values are reported as measures of effect size, with $p\eta^2 > 0.14$ considered a very large effect (Cohen, 1988). Finally, in line with our primary purpose, partial correlation analyses were conducted to relate individual ERD scores in MDD patients to balance measures before and after the treatment. These partial correlations were used to remove the effects of age and the MADRS scores.

3. Results

All statistical results are summarized in Tables 1–5.

Postural balance in HC vs. MDD. Firstly, there were significant differences between the groups for almost all the aforesaid position-based variables or velocity-based variables (Mann-Whitney U tests: all p values < 0.02). These findings are in accordance with the ANOVA, revealing an effect of Group [all F values > 9.6; p values < 0.01], with altered postural sway in MDD: higher COP velocity/position values were systematically found for the MDD group (Tables 2 and 3). There were significant main effects of Vision [all F values > 9.5; p values < 0.01] and Condition [all F values > 9.3; p values < 0.01] for all velocity-based variables. Note that there was no significant interaction considering the Group factor (all Fs < 3.75, Ps > 0.06).

Changes in depression and PMR. Notably, the MADRS scores showed a significant decrease between before (30.2 ± 7.2) and after the rTMS intervention (18.9 ± 10.1) [paired sample Wilcoxon test: $p = 0.005$, large Cohen's $d = 1.28$]. Likewise, the PMR values collected at visit 1 (25.7 ± 8.4) were significantly different from the PMR at visit 15 (13.2 ± 8.9) [paired sample Wilcoxon test: $p = 0.005$, large Cohen's $d = 1.44$] (Table 1).

Effects of rTMS treatment on postural balance. The doubly-multivariate ANCOVA revealed significant effects of Session and Condition (Table 4). The Session effect highlights an overall decrease after the rTMS intervention in all COP variables. The univariate ANCOVAs of COP position-/velocity-based variables confirmed these positive changes in postural sway over time. Precisely, significant effects of Session and Condition were systematically observed for most COP velocity-based variables, except for the mean velocity in ML axis (see Fig. 1). Note also that there was no significant interaction considering the Session factor (Table 4), indicating a more efficient postural control after the treatment whatever the complexity task. No difference was found between the sessions in the number of enumerated figures or errors while counting backward (pre vs. post rTMS intervention).

Partial correlations between balance and the ERD scores within each of the four postural conditions. Before the treatment ($n = 16$), significant positive correlations were found between the pre-ERD scores and some velocity-based COP variables in the four postural conditions (Table 5). Note that no correlation was found between the ERD scores and position-based variables. In contrast, there was no significant correlation between the post-ERD scores and any postural parameter after the treatment ($n = 10$) (all Pearson's $r < 0.67$; all p values > 0.07).

4. Discussion

The present study aimed at contributing to a deeper understanding of the motor performance that characterizes objectively the depression-related PMR. More specifically, we investigated the expected relationships between postural performance and PMR

Table 1
Baseline characteristics of healthy control participants (HC) ($n = 16$) and the major depressive disorder participants (MDD) before ($n = 16$) and after 15 sessions of active rTMS within a 3-week period ($n = 10$).

	HC (n = 16)	MDD (n = 16)	Eligible MDD before treatment (n = 10)	Eligible MDD after treatment (n = 10)	% Evolution
Age (years), mean ± SD	60.7 ± 9.6	57.9 ± 13.9	60 ± 11.5		
Female gender, n (%)	12 (75)	9 (56.25)	7 (70)		
MADRS score (/60), mean (min-max)	N/A	30.2 (20–43)	32.7 (20–43)	18.9 (2–33)	−42.2[a]
ERD score (/60), mean (min-max)	N/A	25.7 ± 8.4	23.8 (9–37)	13.2 (1–28)	−44.5[a]

Note. MADRS: Montgomery–Asberg Depression Rating Scale (Montgomery and Åsberg, 1979); ERD: French Retardation Rating Scale for Depression (Widlöcher, 1983).
[a] Significant evolutions from paired sample Wilcoxon tests (see text).

Table 2
Descriptive statistics (mean ± standard deviation) for the COP measures for the major depressive disorder patients (MDD) in comparison to healthy controls (HC) at t_0 (before the rTMS treatment).

COP measures	HC (n = 16)				MDD (n = 16)			
	Single task		Dual task		Single task		Dual task	
	Eyes open	Eyes closed	Eyes open	Eyes closed	Eyes open	Eyes closed	Eyes open	Eyes closed
1. *COP position-based variables*								
Range_AP (mm)	18.3 ± 4.5	25.6 ± 7.1	18.5 ± 8.5	25.3 ± 8.1	40.4 ± 20.4	57.9 ± 26.8	42.9 ± 23.6	50.3 ± 22.1
Range_ML (mm)	10.1 ± 2.4	13.6 ± 7.3	16.6 ± 16.4	17 ± 10.2	21.5 ± 9.2	34.9 ± 32.7	25.3 ± 13.2	29.9 ± 18.4
SD position_AP (mm)	3.4 ± 0.9	4.5 ± 1.7	3.3 ± 1.5	4.3 ± 1.5	7.8 ± 4.6	10.5 ± 5.5	8 ± 4.5	9.1 ± 4.2
SD position_ML (mm)	1.9 ± 0.7	2.1 ± 1.2	2.7 ± 2.7	2.5 ± 1.3	4.3 ± 1.8	5.2 ± 3.3	4.5 ± 2.5	4.4 ± 2.1
Area (95% ellipse)	133.6 ± 61.7	205 ± 194.7	230.7 ± 337.6	226.6 ± 165.4	773.3 ± 720	1264.8 ± 1345.8	903.2 ± 874.1	900.2 ± 728.3
2. *COP velocity-based variables*								
Mean velocity (mm/s)	6.3 ± 2.7	10.2 ± 6.6	9.2 ± 4	13.9 ± 8.5	12.2 ± 6.5	21.6 ± 13.3	17.8 ± 8.9	24.9 ± 14.3
Mean velocity_AP (mm/s)	5.1 ± 2.3	8.7 ± 5.1	6.9 ± 2.1	11.4 ± 6.9	9.5 ± 5.4	17.6 ± 10.8	14.3 ± 7.3	20.9 ± 12.5
SD velocity_AP (mm/s)	6.7 ± 2.9	11.4 ± 6.6	6.9 ± 2.1	15.2 ± 8.8	18.8 ± 11.2	31.2 ± 16.2	23.7 ± 10.8	32.2 ± 17.6
AAMV_AP (mm/s)	10.4 ± 4.7	17.1 ± 11.7	14.3 ± 4.6	24.5 ± 14.6	22.7 ± 15.3	43.3 ± 32.9	32.8 ± 18.4	51.4 ± 38.1
Mean velocity_ML (mm/s)	2.6 ± 1.1	3.8 ± 3.2	4.5 ± 3.2	5.6 ± 4.1	5.7 ± 2.9	9.1 ± 6.2	8 ± 4.2	9.8 ± 5.2
SD velocity_ML (mm/s)	3.4 ± 1.5	5.1 ± 4.2	6.8 ± 6	8.1 ± 6	8.7 ± 4.3	15.2 ± 13	12.9 ± 6.7	15.7 ± 8.7
AAMV_ML (mm/s)	5.5 ± 2.3	7.8 ± 6.5	8.5 ± 6.6	12.4 ± 8.5	13.7 ± 7.7	22.6 ± 18.3	18.6 ± 10.5	23 ± 14.4

Note. COP: center of pressure; AP: anteroposterieur; ML: mediolateral.

Table 3
Analysis of variance results (F values) for the COP measures for the major depressive disorder patients in comparison to healthy controls at t_0 (before the rTMS treatment).

COP measures	G	C	V	G × C	G × V	C × V	G × C × V
	(1, 30)	(1, 30)	(1, 30)	(1, 30)	(1, 30)	(1, 30)	(1, 30)
1. *COP position-based variables*							
Range_AP (mm)	**23.8*****	0.38	**37.9*****	0.46	3.1	2.68	2.5
Range_ML (mm)	**9.6****	1.1	**4.8***	1.7	2.0	2.7	0.6
SD position_AP (mm)	**19.6*****	1.1	**24.7*****	0.4	1.8	1.9	1.8
SD position_ML (mm)	**15.2*****	0.34	0.7	2.1	0.8	1.6	0.5
Area (95% ellipse)	**14.1****	0.2	1.9	1.8	1.1	**5.0***	2.7
2. *COP velocity-based variables*							
Mean velocity (mm/s)	**11.4****	**22.1*****	**25.1*****	0.5	2.5	0.4	1.7
Mean velocity_AP (mm/s)	**10.9****	**23.8*****	**30.0*****	1.7	2.6	0.1	1.9
SD velocity_AP (mm/s)	**21.7*****	**9.6****	**35.5*****	0.01	3.7	0.6	2.5
AAMV_AP (mm/s)	**10.5****	**21.8*****	**21.1*****	1.2	3.3	0.1	1.7
Mean velocity_ML (mm/s)	**11.3****	**12.2****	**11.2****	0.2	1.6	1.4	1.2
SD velocity_ML (mm/s)	**13.4****	**9.3****	**9.5****	0.2	2.5	1.9	1.1
AAMV_ML (mm/s)	**12.6****	**8.5****	**10.3****	0.3	1.4	0.6	2.8

Note. Factors were Group, G, Condition, C, and Vision, V. Degrees of freedom are shown in parentheses. COP: center of pressure; AP: anteroposterieur; ML: mediolateral.
$^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$. Statistically significant results are indicated in bold.

scores often used in a clinical setting, and the positive effects of three weeks of rTMS treatment on depression and the balance performance in MDD patients. The main finding in this study was that postural sway was associated with the ERD scores collected before the rTMS treatment in MDD under well-defined conditions. In particular, all velocity-based COP variables were significantly correlated with the ERD scores for the dual task with eyes closed condition (see Table 5). Interestingly, the ERD scores were not found to be significantly correlated with postural sway under any condition after the rTMS intervention. The implications of these results will be discussed in more detail below.

4.1. The dual postural performance: an objective marker of PMR

These results suggest that the implicit motor strategy supported by velocity-based control of posture is a good and reliable marker of PMR in MDD patients. In line with our pilot studies (Deschamps et al., 2015; Thomas-Ollivier et al., 2016), the eyes closed condition makes the visual information unreliable, and therefore proprioceptive inputs must be predominantly used for an effective "automatic" postural control. When associated with impaired balance related to deficits in integration of proprioceptive inputs in MDD (Bolbecker et al., 2011), the essential "proprioceptive reweighting" process for postural control (Peterka, 2002; Peterka and Loughlin, 2004) is adversely influenced by the dual-task condition. These findings are in line with Doumas et al. (2012), who showed greater postural instability in dual-task performance in MDD patients compared to healthy controls. Based on our results, the dual postural performance while increasing the reliance on proprioceptive information appears to characterize – at least to a significant extent – the PMR, as assessed by a validated scale (Widlöcher, 1983). Before the rTMS intervention (n = 16), the highest correlations while accounting for age and pre-MADRS score were systematically found when visual information was removed in the dual-task condition (r = 0.57 in average). Note that these correlations between ERD score and postural instability were significant only for the COP velocity variables. The more PMR is impaired, the higher are the values of the thresholds that bound the dynamics of COP movement speed (i.e. the AAMV). It not only corroborates the assumption of a velocity-based postural control assessment as a robust marker of early cognitive dysfunction (Deschamps et al., 2014), it also objectively validates and quantifies the motor and cognitive components of PMR in MDD patients (Bennabi et al., 2013). It does this by capturing the cognitive cost expended by the central nervous system for maintaining a stable/unstable dual postural performance (see Boisgontier et al., 2013, for

Table 4
Doubly-multivariate and -univariate analysis of covariance results (main effects of factors) for all the COP measures for the major depressive disorder patients.

Factors effects	F values	*p*-value	$_p\eta 2$
Session (pre *vs.* post treatment)	**3.46**	**0.001**	**0.41**
Condition (ST *vs.* DT)	**2.07**	**0.04**	**0.3**
Vision (EO *vs.* EC)	1.44	0.17	0.22
Session × Condition	0.93	0.51	0.16
Session × Vision	0.64	0.8	0.11
Condition × Vision	0.9	0.56	0.15
Session × Condition × Vision	0.78	0.67	0.14
Time-varying covariates (depression symptoms)			
Pre-MADRS scores	**2.2**	**0.03**	**0.31**
Post-MADRS scores	1.6	0.11	0.25

Univariate ANCOVA *p*-value ($_p\eta 2$) COP measures	Session (pre *vs.* post)	Condition (ST *vs.* DT)	Vision (EO *vs.* EC)	Covariant *Pre-MADRS scores*	Covariant *Post-MADRS scores*
1. *COP position-based variables*					
Range_AP (mm)	**0.008 (0.10)**	**0.01 (0.1)**	0.71 (0.01)	**0.01 (0.08)**	0.41 (0.001)
Range_ML (mm)	0.98 (0.00)	0.26 (0.02)	0.38 (0.01)	**0.03 (0.07)**	0.45 (0.008)
SD position_AP (mm)	**0.01 (0.10)**	**0.02 (0.07)**	0.53 (0.01)	0.2 (0.04)	0.72 (0.002)
SD position_ML (mm)	0.06 (0.05)	0.63 (0.00)	0.96 (0.00)	**0.001 (0.14)**	0.46 (0.008)
Area (95% ellipse)	0.1 (0.09)	0.15 (0.03)	0.87 (0.00)	**0.03 (0.07)**	0.47 (0.007)
2. *COP velocity-based variables*					
Mean velocity (mm/s)	**0.03 (0.06)**	**0.006 (0.11)**	0.20 (0.02)	0.32 (0.01)	0.09 (0.04)
Mean velocity_AP (mm/s)	**0.04 (0.06)**	**0.003 (0.12)**	0.21 (0.02)	0.49 (0.01)	0.06 (0.05)
SD velocity_AP (mm/s)	**0.005 (0.11)**	**0.003 (0.12)**	0.45 (0.01)	0.19 (0.02)	0.31 (0.02)
AAMV_AP (mm/s)	**0.03 (0.07)**	**0.006 (0.10)**	0.47 (0.01)	0.6 (0.004)	0.08 (0.04)
Mean velocity_ML (mm/s)	**0.04 (0.06)**	**0.04 (0.05)**	0.21 (0.02)	0.09 (0.04)	0.33 (0.01)
SD velocity_ML (mm/s)	0.10 (0.04)	0.10 (0.04)	0.33 (0.01)	**0.03 (0.06)**	0.85 (0.00)
AAMV_ML (mm/s)	**0.01 (0.09)**	**0.04 (0.05)**	0.52 (0.01)	0.23 (0.02)	0.30 (0.01)

Note. Factors were Session, Condition (ST: single task *vs.* DT: dual task) and Vision (EO: Eyes open *vs.* EC: Eyes closed). COP: center of pressure; AP: anteroposterieur; ML: mediolateral. $_p\eta 2$: partial eta squared. Significant results are indicated in bold.

Table 5
Partial correlation analyses between the COP variables and individual ERD score within each of the four postural conditions in the major depressive disorder patients (n = 16) *before* the rTMS treatment.

COP measures *vs.* ERD scores Pearson's *r*	Postural conditions			
	ST/EO	ST/EC	DT/EO	DT/EC
1. *COP position-based variables*				
Range_AP (mm)	0.36	0.31	0.47	0.36
Range_ML (mm)	0.37	0.24	0.47	0.35
SD position_AP (mm)	0.34	0.22	0.45	0.39
SD position_ML (mm)	0.39	0.32	0.52	0.49
Area (95% ellipse)	0.40	0.15	**0.55***	0.38
2. *COP velocity-based variables*				
Mean velocity (mm/s)	**0.54***	**0.63***	0.51	**0.59***
Mean velocity_AP (mm/s)	0.53	**0.63***	0.50	**0.59***
SD velocity_AP (mm/s)	**0.54***	**0.61***	**0.61***	**0.61***
AAMV_AP (mm/s)	0.53	**0.57***	0.52	**0.57***
Mean velocity_ML (mm/s)	0.53	**0.56***	0.49	**0.54***
SD velocity_ML (mm/s)	0.49	0.38	**0.62***	**0.56***
AAMV_ML (mm/s)	0.53	0.48	0.49	**0.54***

Note. Age and pre-MADRS scores were used as control factors. ST: single task; DT: dual task. EO: Eyes open; EC: Eyes closed. Significant results are indicated in bold (*$p < 0.05$).

a review on attention and dual-task postural performance]. In addition, clinically, this initial postural instability (and the associated risk of falls, Launay et al., 2013) may be a consistent hallmark that could predict positive outcomes in MDD patients after a rTMS treatment.

4.2. The rTMS treatment of depression and "postural retardation"

By focusing on stability and processing of posture in MDD patients more precisely, this exploratory part of the current study showed significant positive effects of rTMS intervention on postural instability, PMR and depression (as evidenced by a statistically significant decrease in MADRS scores). This apparent effectiveness of multi-session rTMS in reducing depressive symptoms seems to be consistent with the previous literature (Aleman, 2013; Berlim et al., 2013a, 2013b; George et al., 2010; Lefaucheur et al., 2014). Likewise, and in an original way, the current improvement of PMR (significant drop in ERD scores, see Table 1) after 15 sessions of rTMS is associated with a quantitative improvement of balance. But it is true that any natural course of the illness that improves depression severity may change psychomotor behavior along with postural stability (see below for a methodological discussion of this point as a limitation). Regardless of the true reason, the MDD patients essentially reduced their postural instability by decreasing most COP velocity-based variables after the rTMS intervention (e.g. pre mean velocity: 21.3 mm/s [95% CI 17.7–24.9 mm/s] *vs.* post mean velocity: 15.9 mm/s [95% CI 12.4–19.5 mm/s], that is −21.1%; pre AAMV in AP axis: 42.3 mm/s [95% CI 33.9–50.7 mm/s] *vs.* post AAMV: 28.8 mm/s [95% CI 20.4–37.2 mm/s], that is −31.9%) (Fig. 1). Therefore, these findings from the doubly-multivariate analysis of covariance with time-varying covariates (i.e., depression symptoms) confirm the importance of velocity information to optimize postural sway (Jeka et al., 2004), and as a variable of specific interest for characterizing PMR in populations with MDD. Here, two major findings are as follows. First, the bounding limits of COP velocity dynamics decreased after three weeks of rTMS intervention, regardless of the initial MADRS scores, as an index of positive changes in intermittent velocity-based control of posture (Delignières et al., 2011). Second, since no session (pre *vs.* post) × condition (single *vs.* dual task) interaction was found, identical positive effects of rTMS (or any natural course of the illness) were observed, whatever the condition. This indicates that MDD patients showed significant improvement in postural control to the same extent regardless of the associated dual cost, which is consistent with our previous pilot study (Thomas-Ollivier et al., 2016). After the intervention, a more efficient postural control appears to mark substantively the motor component of PMR, even if an improved dual task performance probably marks improvement in cognitive efficiency (i.e. lower attentional demands). Nevertheless, the mental slowing specific to PMR such as changes in fluency and prosody (Flint et al., 1993; Szabadi et al., 1976), in decision-making (Bonin-Guillaume et al., 2008) or in task-switching performance (Smith et al., 1995), require further investigations for a comprehensive and quantitative assessment of PMR. These perspectives are in line with the improvement in selective cognitive functions after 20 sessions of rTMS in patients with MDD (e.g., Kedzior et al., 2012).

While no neuroanatomical substrates have been investigated to highlight the observed effects of rTMS treatment on postural control and depression, some neurophysiological mechanisms underlying the disbalanced motor control in MDD provide a relevant starting point for discussion. For example, Walther et al. (2012) found that MDD patients (on antidepressant medication) displayed associations between resting state cerebral blood flow and activity level in the right orbito-frontal cortex and left

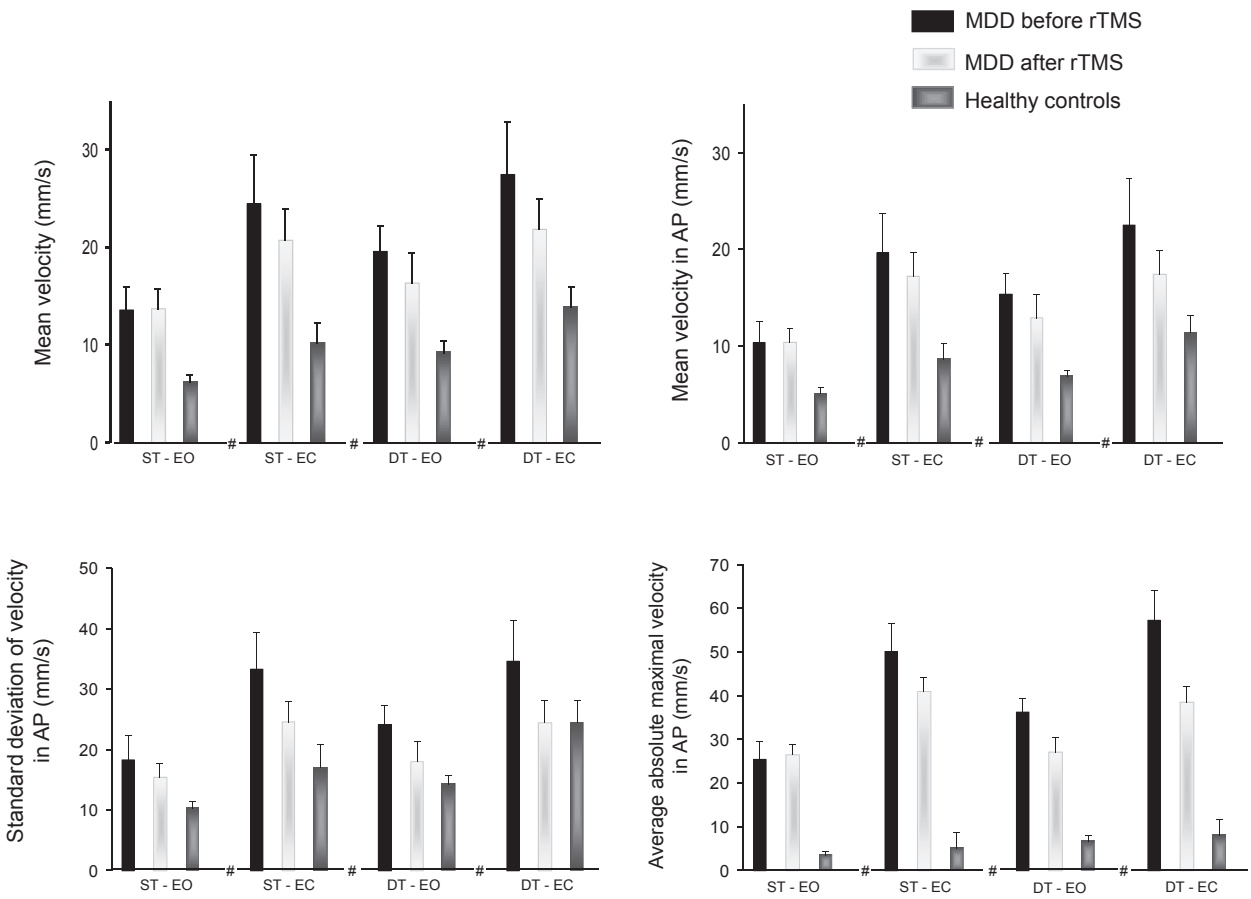

Fig. 1. Changes in some velocity-based COP variables before and after rTMS intervention in ten patients with major depressive disorder (MDD), as a function of postural conditions (ST-EO: single task with eyes open; ST-EC: single task with eyes closed; DT-EO: dual task with eyes open; DT-EC: dual task with eyes closed). Note: The histograms in grey display the reference values of the healthy controls. Errors bars correspond to the standard errors.

supplemental motor area (SMA). While this is a little outside the scope of the current study, it is interesting to note because the orbitofrontal hypometabolism and abnormalities of activation in SMA were also found in patients with catatonia and obsessive-compulsive disorders, that are characterized by behavioral and motor alterations (Walther, 2015).

The current findings are also consistent with the assumption that hypodopaminergic states contribute to altered motor control in MDD patients (Sobin and Sackeim, 1997). Against the role of the prefrontal cortex and SMA in human balance control (Mihara et al., 2008), the DLPFC neurostimulation may have influenced the psychomotor symptoms via mesolimbic and mesostriatal dopaminergic pathways (Strafella et al., 2003). Moreover, the connectivity of DLPFC with areas such as the dorsal regions of the anterior cingulate cortex could lead to reduce the PMR-related attentional and cognitive deficits in MDD patients (De Raedt et al., 2015). This assumption is in line with the positive effects of rTMS on physical function and motor signs (e.g. improvement of gait velocity) in Parkinson's Disease (see Chung and Mak, 2016 for details).

4.3. Methodological considerations

We acknowledge that there are some methodological limitations in our protocol. Despite the abundant literature (e.g. Brunelin et al., 2014), it is somewhat difficult to make a robust conclusion about the possible effectiveness of rTMS intervention in treating depression and the associated psychomotor retardation and balance deficits, since a comparative MMD control group us lacking. Thus there is no reliable way to know whether the improvement in the balance task in MDD was due to repetition of the same tasks or due to stimulation. In addition, it is well known that a natural course to depression exists in the acute phase. So the current positive effects of rTMS intervention on depression, PMR and postural stability need to be described and interpreted with caution. Any intervention or even natural course of the illness that improved depression severity may have changed psychomotor behavior along with postural stability. This major point requires further investigation in a larger population in a double-blind, sham-controlled trial protocol to establish a solid knowledge for the current promising results.

In summary, these findings, through significant correlations between body posture and depression-related psychomotor retardation, validate the view that the assessment of postural performance in challenging conditions (e.g. eyes closed in dual task) constitutes an objective marker of PMR in MDD patients (Thomas-Ollivier et al., 2016). Note that this postural hallmark is easy to envisage being used in clinical settings (i.e., safe test, short duration, and low cost). In current perspective, these positive results lead to a trial protocol for administering rTMS treatment among depressed patients with appropriate sample size (Browne, 1995), and for testing its predictive power while considering the baseline postural performance, as an objective and sensitive marker of PMR.

Financial support

This research received no specific grand from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

The authors report no conflicts of interest.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals.

Note also that in this study, no change in our current clinical practice and no randomization were performed. As it was an observational study, according to the French legislation (articles L.1121-1 paragraph 1 and R1121-2, Public Health Code), no approval of the ethics committee was needed to use data for an epidemiologic study.

Author contributions

TD has full access to all of the data in the study, takes responsibility for the data, the analyses and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsor.

All authors meet all of the following criteria: (1) contributing to the conception and design, or analyzing and interpreting data; (2) drafting the article or revising it critically for important intellectual content; and (3) approving the final version to be published.

References

Aleman, A., 2013. Use of repetitive transcranial magnetic stimulation for treatment in psychiatry. Clin. Psychopharmacol. Neurosci. 11, 53–59.
Baeken, C., De Raedt, R., Santermans, L., Zeeuws, D., Vanderhasselt, M.A., Meers, M., et al., 2010. HF-rTMS treatment decreases psychomotor retardation in medicationresistant melancholic depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 34, 684–687.
Beheydt, L.L., Schrijvers, D., Docx, L., Bouckaert, F., Hulstijn, W., Sabbe, B., 2015. Psychomotor retardation in elderly untreated depressed patients. Front. Psychiatry 5, 196.
Bennabi, J., Vandel, P., Papaxanthis, C., Pozzo, T., Haffen, E., 2013. Psychomotor retardation in depression: a systematic review of diagnostic, pathophysiologic, and therapeutic implications. Biomed. Res. Int. 158746.
Berlim, M.T., Neufeld, N.H., Van den Eynde, F., 2013a. Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. J. Psychiatr. Res. 47, 999–1006.
Berlim, M.T., Van den Eynde, F., Daskalakis, Z.J., 2013b. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol. Med. 43, 2245–2254.
Boisgontier, M.P., Beets, I.A., Duysens, J., Nieuwboer, A., Krampe, R.T., Swinnen, S.P., 2013. Age-related differences in attentional cost associated with postural dual tasks: increased recruitment of generic cognitive resources in older adults. Neurosci. Biobehav. Rev. 37, 1824–1837.
Bolbecker, A.R., Hong, S.L., Kent, J.S., Klaunig, M.J., O'Donnell, B.F., Hetrick, W.P., 2011. Postural control in bipolar disorder: increased sway area and decreased dynamical complexity. PLoS One 6, e19824.
Bonin-Guillaume, S., Hasbroucq, T., Blin, O., 2008. Psychomotor retardation associated to depression differs from that of normal aging. Psychol. Neuropsychiatr. Vieil. 6, 137–144.
Browne, R.H., 1995. On the use of a pilot sample for sample size determination. Stat. Med. 14, 1933–1940.
Brunelin, J., Jalenques, I., Trojak, B., Attal, J., Szekely, D., Gay, A., et al., 2014. The efficacy and safety of low frequency repetitive transcranial magnetic stimulation for treatment-resistant depression: the results from a large multicenter french RCT. Brain Stimul. 7, 855–863.
Chen, J., Zhou, C., Wu, B., Wang, Y., Li, Q., Wei, Y., et al., 2013. Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. Psychiatry Res. 210, 1260–1264.
Chung, C.L., Mak, M.K., 2016. Effect of repetitive transcranial magnetic stimulation on physical function and motor signs in Parkinson's Disease: a systematic review and meta-analysis. Brain Stimul. 9, 475–487.
Cohen, J., 1988. Statistical Power Analysis for the Behavioural Sciences, third ed. Academic Press, New York.
De Raedt, R., Vanderhasselt, M.A., Baeken, C., 2015. Neurostimulation as an intervention for treatment resistant depression: from research on mechanisms towards targeted neurocognitive strategies. Clin. Psychol. Rev. 41, 61–69.
Delignières, D., Torre, K., Bernard, P.-L., 2011. Transition from persistent to antipersistent correlations in postural sway indicates velocity-based control. PLoS Comput. Biol. 7, 2.
Dell'Osso, B., Camuri, G., Castellano, P., Vecchi, V., Benedetti, M., Bortolussi, S., et al., 2011. Meta-review of metanalytic studies with repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression. Clin. Pract. Epidemiol. Ment. Health 7, 167–177.
Deschamps, T., Beauchet, O., Annweiler, C., Cornu, C., Mignardot, J.-B., 2014. Postural control and cognitive decline in older adults: position versus velocity implicit motor strategy. Gait Posture 39, 628–630.
Deschamps, T., Thomas-Ollivier, V., Sauvaget, A., Bulteau, S., Fortes-Bourbousson, M., Vachon, H., 2015. Balance characteristics in patients with major depression after a two-month walking exercise program: a pilot study. Gait Posture 42, 590–593.
Doumas, M., Smolders, C., Brunfaut, E., Bouckaert, F., Krampe, R.T., 2012. Dual task performance of working memory and postural control in major depressive disorder. Neuropsychology 26, 110–118.
Flint, A.J., Black, S.E., Campbell-Taylor, I., Gailey, G.F., Levinton, C., 1993. Abnormal speech articulation, psychomotor retardation, and subcortical dysfunction in major depression. J. Psychiatr. Res. 27, 309–319.
George, M.S., Lisanby, S.H., Avery, D., McDonald, W.M., Durkalski, V., Pavlicova, M., et al., 2010. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch. Gen. Psychiatry 67, 507–516.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hardy, P., Jouvent, R., Widlöcher, D., 1984. Speech pause time and the retardation rating scale for depression (ERD). Towards a reciprocal validation. J. Affect. Disord. 61, 123–127.
Höppner, J., Schulz, M., Irmisch, G., Mau, R., Schläfke, D., Richter, J., 2003. Antidepressant efficacy of two different rTMS procedures: high frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. Eur. Arch. Psychiatry Clin. Neurosci. 253, 103–109.
Jeka, J., Kiemel, T., Creath, R., Horak, F., Peterka, R., 2004. Controlling human upright posture: velocity information is more accurate than position or acceleration. J. Neurophysiol. 92, 2368–2379.
Kedzior, K.K., Rajput, V., Price, G., Lee, J., Martin-Iverson, M., 2012. Cognitive correlates of repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant depression- a pilot study. BMC Psychiatry 12, 163.
Launay, C., De Decker, L., Annweiler, C., Kabeshova, A., Fantino, B., Beauchet, O., 2013. Association of depressive symptoms with recurrent falls: a cross-sectional elderly population based study and a systematic review. J. Nutr. Health Aging 17, 152–157.
Lefaucheur, J.P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., et al., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150–2206.
Liberg, B., Rahm, C., 2015. The functional anatomy of psychomotor disturbances in major depressive disorder. Front. Psychiatry 6, 34.
Mignardot, J.-B., Beauchet, O., Annweiler, C., Cornu, C., Deschamps, T., 2014. Postural sway, falls and cognitive status: a cross-sectional study among older adults. J. Alzheimers Dis. 41, 431–439.
Mihara, M., Miyai, I., Hatakenaka, M., Kubota, K., Sakoda, S., 2008. Role of the prefrontal cortex in human balance control. NeuroImage 43, 329–336.
Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Paus, T., Castro-Alamancos, M.A., Petrides, M., 2001. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur. J. Neurosci. 14, 1405–1411.
Peterka, R.J., 2002. Sensorimotor integration in human postural control. J. Neurophysiol. 88, 1097–1118.
Peterka, R.J., Loughlin, P.J., 2004. Dynamic regulation of sensorimotor integration in human postural control. J. Neurophysiol. 1, 410–423.
Schrijvers, D., Hulstijn, W., Sabbe, B.C.G., 2008. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. J. Affect. Disord. 109, 1–20.
Smith, M.J., Brébion, G., Banquet, J.P., Cohen, L., 1995. Retardation of mentation in depressives: posner's covert orientation of visual attention test. J. Affect. Disord. 35, 107–115.
Sobin, C., Sackeim, H.A., 1997. Psychomotor symptoms of depression. Am. J. Psychiatry 154, 4–17.
Strafella, A., Paus, T., Fraracciio, M., Dagher, A., 2003. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126, 2609–2615.

Szabadi, E., Bradshaw, C.M., Besson, J.A.O., 1976. Elongation of pause time in speech: a simple, objective measure of motor retardation in depression. Br. J. Psychiatry 129, 592–597.
Thomas-Ollivier, V., Deschamps, T., Bulteau, S., Le Gall, F., Pichot, A., Valrivière, P., Vachon, H., Sauvaget, A., 2016. Effect of repetitive transcranial magnetic stimulation on psychomotor retardation in major depression: a pilot feasibility study. J. Neuropsychiatry Clin. Neurosci. 28, 62–65.
Ullrich, H., Kranaster, L., Sigges, E., Andrich, J., Sartorius, A., 2012. Ultra-high-frequency left prefrontal transcranial magnetic stimulation as augmentation in severely ill patients with depression: a naturalistic sham-controlled, double-blind, randomized trial. Neuropsychobiology 66, 141–148.
Walther, S., 2015. Psychomotor symptoms of schizophrenia map on the cerebral motor circuit. Psychiatry Res. 233, 293–298.
Walther, S., Höfle, O., Federspiel, A., Horn, H., Hügli, S., Wiest, R., et al., 2012. Neural correlates of disbalanced motor control in major depression. J. Affect. Disord. 136, 124–133.
Widlöcher, D., 1983. Psychomotor retardation: clinical, theoretical and psychometric aspects. Psychiatr. Clin. North Am. 6, 27–40.

BJSM Online First, published on July 15, 2016 as 10.1136/bjsports-2016-096356

Let's programme exercise during haemodialysis (intradialytic exercise) into the care plan for patients, regardless of age

Thibault Deschamps

Exercise programmes have been called for in routine care plans for patients with chronic kidney disease,[1 2] but nephrologists still hesitate to prescribe exercise during haemodialysis,[3] especially for patients with end-stage renal disease (ESRD). One reason may be the age of patients with ESRD, a vulnerable population at high risk of mortality. Now more than ever, whether for paediatric patients[4] or older patients (>65 years of age),[5] let's challenge this intrinsic reluctance by advocating intradialytic exercise programmes as part of the standard care for patients receiving dialysis.

EXERCISE WORKS!

Exercise is effective for patients with ESRD[6]—it increases maximal oxygen uptake capacity, improves blood-pressure control, decreases arterial stiffness, decreases systemic inflammation, improves solute removal by dialysis, increases muscle force, and augments perceived quality of life (QoL). Beyond outstanding issues regarding the precise exercise prescription (endurance vs resistance training), the critical question is not whether to include exercise programmes in the standard care of haemodialysis patients with ESRD, but why you would not. Therefore, I invite all nephrologists and medical professionals to promote, prescribe and, especially, plan long-term, intradialytic exercise programmes in their units, regardless of patient age. Here are some arguments for adequate exercise training in patients with ESRD, with a special focus on children and malnourished older adults.

ADDRESSING MAJOR MISCONCEPTIONS ABOUT THE YOUNG AND THE OLD

A major misconception is the issue of the feasibility, acceptability and safety of an intradialytic cycling programme in a population of children or older adults on haemodialysis. A recent study showed that a 3-month exercise programme of intradialytic cycling (30 min sessions, 2–3 times a week) is feasible, free from adverse effects, and well tolerated by paediatric patients (age range 9.1–24.2 years).[4] Considering the challenge of providing optimal haemodialysis to children with ESRD,[7] their positive feedback on the intradialytic cycling programme has interesting implications, starting with an increase in the acceptance of haemodialysis therapy and a possible means of improving their long-term outcomes.[4 7] Similar conclusions can be drawn from studies of frail older haemodialysis patients, especially those with protein–energy wasting (PEW), for whom prevention and treatment aim to replenish protein and energy stores and stimulate anabolic processes. Few dialysis centres currently offer exercise training programmes to older patients (over-represented in the dialysis population)[6] as a new therapeutic complement. Yet, robust arguments support the fundamental and clinical value of prescribing exercise to patients with PEW, along with nutritional interventions, to enhance the anabolic effects of nutrition and thereby reverse this high-risk state. A recent randomised controlled trial (RCT) showed that a 6-month intradialytic exercise programme, combined with nutritional support, was safe, free from noticeable adverse effects, well tolerated, and accepted by older patients with PEW (mean age 69.7 ±14.2 years). In addition, the nutrition and exercise group (vs the nutrition group) showed an improvement in the 6 min walk test (+22%), an absence of decline in balance mechanisms (unlike the nutrition group), and a noteworthy increase in self-reported physical health dimensions of QoL (+53%).[5]

Interestingly, another advantage of intradialytic exercise is the excellent compliance (87.7% of realised sessions). Effective improvements in physical function contribute to prevention of some clinical and functional disabilities. QoL scores accurately predict hospitalisations and mortality.[8] Similarly, a significant bimonthly progression of the training parameters, such as distance covered when cycling (~103.8 ±46.74 km/month) and cycling duration (~355.03±95.95 min/month), provides other convincing evidence of better physical autonomy in these older patients. Importantly, all patients in the exercise group said that they hoped to continue cycling after the end of the study. They reported a feeling of well-being and that dialysis sessions were less boring and a better experience. An unexpected but encouraging consequence was the demand for similar interventions from the control group, and even from other older haemodialysis patients that were not eligible for the RCT.

A CALL TO ACTION

When combined, these modest findings indicate the effectiveness of exercise training for haemodialysis patients, whether children or young or older adults. Exercise training should be standard practice in the care of haemodialysis patients. Beyond the feasibility of implementing exercise programmes for these specific populations, the beneficial effects are clinically crucial. They offer a more attractive bridge to someone awaiting a future transplant.

Collectively, let us not hesitate to change our routines and programme intradialytic exercise for haemodialysis patients, regardless of age! For future RCTs necessary to provide the main outcome measures, a reasonable and reasoned ambitious Big Data Clinical Trial will reshape the profiles of clinical research in nephrology.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Deschamps T. *Br J Sports Med* Published Online First: [*please include* Day Month Year] doi:10.1136/bjsports-2016-096356

Accepted 1 July 2016

Br J Sports Med 2016;**0**:1–2. doi:10.1136/bjsports-2016-096356

Correspondence to Dr Thibault Deschamps, University of Nantes, Laboratory 'Movement, Interactions, Performance' (UPRES-E.A. 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France; thibault.deschamps@univ-nantes.fr

REFERENCES

1 Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2011;(10):CD003236.
2 Smart NA, Williams AD, Levinger I, *et al*. Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease. *J Sci Med Sport* 2013;16:406–11.
3 Silva LC, Marinho PÉ. Knowledge among nephrologists about the importance of exercise in the intradialytic period. *J Phys Ther Sci* 2015;27:2991–4.
4 Paglialonga F, Lopopolo A, Scarfia RV, *et al*. Intradialytic cycling in children and young adults on chronic hemodialysis. *Pediatr Nephrol* 2014;29:431–8.

5 Hristea D, Deschamps T, Paris A, *et al*. Combining intra-dialytic exercise and nutritional supplementation in malnourished older hemodialysis patients: Towards better quality of life and autonomy. Results from the pilot randomized ACTINUT trial. *Nephrology* 2016; in press.
6 Wang Y, Jardine MJ. Benefits of exercise training in patients receiving haemodialysis: a systematic review and meta-analysis. *Br J Sports Med* 2011;45:1165–6.
7 Müller D, Goldstein SL. Hemodialysis in children with end-stage renal disease. *Nat Rev Nephrolo* 2011;7:650–8.
8 Kalantar-Zadeh K, Kopple JD, Block G, *et al*. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am Soc Nephrol* 2001;12:2797–806.

Let's programme exercise during haemodialysis (intradialytic exercise) into the care plan for patients, regardless of age

Thibault Deschamps

Br J Sports Med published online July 15, 2016

Experimental Gerontology 81 (2016) 51–55

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

A decision model to predict the risk of the first fall onset

Thibault Deschamps [a,*,1], Camille G. Le Goff [b,1], Gilles Berrut [a,c], Christophe Cornu [a], Jean-Baptiste Mignardot [a,b,*,2]

[a] Laboratory MIP (UPRES-EA4334), University of Nantes, France
[b] Laboratory Courtine, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland
[c] Centre Hospitalier Universitaire de Nantes, Pole de Gérontologie Clinique, Hôpital Bellier, Nantes, France

ARTICLE INFO

Article history:
Received 15 December 2015
Received in revised form 18 March 2016
Accepted 21 April 2016
Available online 23 April 2016

Section Editor: Diana Van Heemst

Keywords:
Risk of fall
Machine learning
Prediction model
Prospective follow-up
Posture

ABSTRACT

Background: Miscellaneous features from various domains are accepted to be associated with the risk of falling in the elderly. However, only few studies have focused on establishing clinical tools to predict the risk of the first fall onset. A model that would objectively and easily evaluate the risk of a first fall occurrence in the coming year still needs to be built.
Objectives: We developed a model based on machine learning, which might help the medical staff predict the risk of the first fall onset in a one-year time window.
Participants/measurements: Overall, 426 older adults who had never fallen were assessed on 73 variables, comprising medical, social and physical outcomes, at *t0*. Each fall was recorded at a prospective 1-year follow-up. A decision tree was built on a randomly selected training subset of the cohort (80% of the full-set) and validated on an independent test set.
Results: 82 participants experienced a first fall during the follow-up. The machine learning process independently extracted 13 powerful parameters and built a model showing 89% of accuracy for the overall classification with 83%–82% of true positive fallers and 96%–61% of true negative non-fallers (training set vs. independent test set).
Conclusion: This study provides a pilot tool that could easily help the gerontologists refine the evaluation of the risk of the first fall onset and prioritize the effective prevention strategies. The study also offers a transparent framework for future, related investigation that would validate the clinical relevance of the established model by independently testing its accuracy on larger cohort.

1. Introduction

Approximately 30% of seniors aged 65 and older experience one or more falls annually (Tinetti et al., 1988). Hence, in view of the dramatic consequences of falls in older adults in various domains, including impaired mobility (Dai et al., 2012), quality of life (Davis et al., 2015), or the overall economic cost (Davis et al., 2010), the capacity to predict a future fall constitutes a clinical target, which continually needs to be refined. Even if numerous parameters associated with the risk of falling have already been identified (e.g., (Bloch et al., 2013; Gillespie et al., 2012)), the medical community still lacks an easy-to-use tool that could accurately predict the risk of the first fall onset. Indeed, falls in the elderly result from intricate interactions between extrinsic and intrinsic risk factors related to iatrogenic component, medical histories, or physical characteristics (for a detailed review (Bloch et al., 2013)). Many studies reported models that can predict the risk of falling in the elderly (Ivziku et al., 2011; Kojima et al., 2015; Schoene et al., 2013; Verghese et al., 2009). However, most of them were based on large cohorts of heterogeneous elderly population without specifying whether participants had ever fallen before their enrolment in the study (for notable exceptions see Beauchet et al. (2008), Mignardot et al. (2014)).

Up to now, no studies have identified a subset of relevant parameters and the way in which they should interact (hierarchical sorting) to develop a powerful model. Yet, many studies have proposed fall prediction models using risk-scoring system (Stalenhoef et al., 2002; Whitney et al., 2012; Yoo et al., 2015). However, the statistical properties of a prediction model of falls, such as the trade-off between sensitivity and specificity, determine how the prediction model can be effectively used. Hence, the false positive and false negative rates in many models question their clinical application. Finally, as another pitfall, the lack of control associated with independent testing sets is of overriding importance in health care practice.

* Corresponding authors at: Laboratory MIP (UPRES-EA4334), University of Nantes, France.
E-mail addresses: thibault.deschamps@univ-nantes.fr (T. Deschamps), mignardot.jb@gmail.com (J.-B. Mignardot).
[1] Equal contribution.
[2] Ecole Polytechnique Fédérale de Lausanne, Laboratoire UP-COURTINE - station 19, CH-1015 Lausanne, Switzerland.

http://dx.doi.org/10.1016/j.exger.2016.04.016
0531-5565/

We seek to alleviate these issues by performing data mining on a database that contains most of relevant parameters associated with the risk of fall (neurologic, cardiovascular, cognitive, anthropometric, motor function, and socio-educational assessments). We built a predictive model for the occurrence of a first fall from a cohort comprising 426 older adults who were followed prospectively over one year. The machine learning technique we used has generated a decision tree with a set of simple classification rules. We were also concerned about the validity of these extracted rules; thus, we performed a blind control on an independent set to evidence its clinical relevance.

2. Methods

2.1. Participants

A cohort of 426 older adults (mean age 69.5 ± 2.6 years; 61.5% women) who never experienced a fall experience were recruited for a prospective observational multicenter study designed to identify the risk factors for the first fall in elderly community-dwellers. The Local Ethical Committee of the Region of Pays de la Loire (France) approved this study (ref: no. 2004/05). The data collection procedure has been described elsewhere in detail (Mignardot et al., 2014). In summary, eligibility criteria were age between 66 and 75 years, living at home, never fallen, and an ability to walk without assistance for at least 30 s. For the present analysis, exclusion criteria were refusal to give consent or lack capacity to give consent or if the participant was hospitalized at the time of screening. Participants were included after having given their written informed consent for research.

2.2. Screening of falls and prospective follow-up

Before the enrolment in the study, the faller status in older participants was evaluated during the first information meeting, where they were questioned about their past. A geriatric doctor explained the WHO definition of a fall (WHO, 2007) to the participants using case examples. Subjects were excluded if they already experienced a fall. Of note, the non-faller status of healthy adults was double-checked at the inclusion visit. During this same visit, all baseline characteristics described in the following "data collection" section were collected. The research medical staff designed a standard phone call that aimed to prospectively monitor any fall onset (date, circumstances, causes and consequences) and/or major events each month for one year. Trained interviewers performed the phone calls, similar to the procedure used in the literature (Stalenhoef et al., 2002). At the end of the follow-up period, a committee of geriatric doctors analyzed the circumstances of each fall recorded during the prospective follow-up in order to verify and, if appropriate, validate that the fall occurred during usual living conditions and in line with the WHO definition-related criteria of a fall (WHO, 2007). The expert committee rejected 5% of collected falls. During the 12-month follow-up period, 82 subjects (19.2%) reported falling at least once. Note also that the committee kept blind for the results as the geriatric M.D. met, and none of them has been involved in the construction of the decision tree.

2.3. Data collection

Medical staff screened each participant at t_0 for various baseline characteristics that have been found to be predictors of falls: gender, taking medications, impaired cognition (e.g., Frontal Assessment Battery "FAB"), postural sway during upright quiet standing with eyes open and eyes closed (51.2 s.), the body composition associated with anthropometrical measures, the functional autonomy and physical lifestyle, and various systemic domains, such as vision, hearing, cardiovascular, sensory features and executive functions (see Table 1).

2.4. Decision tree learning procedure

The final database comprised 426 subjects providing 31,098 values and 73 variables divided into 50 unordered categorical and 23 continuous variables describing the status of each older adult (see Table 1). Based on those input variables, the outcome variable was the occurrence of the first fall in the next 12 months. Considering the status of each subject and categorical nature of the data, a decision tree revealed to be the most adequate supervised machine learning algorithm to develop a direct and easy-to-use tool (for details about decision trees definition and implementation see Kotsiantis (2007)). A classification tree is created by splitting the initial training set (called the root node) into two subsets based on the most discriminative variable. This process is then recursively repeated on the new subsets until the splitting no longer brings value to the prediction. The final subsets are called leaves while the intermediate ones are named internal nodes.

2.4.1. Random attribution of the data for the training or testing sets

Among the 426 subjects, 82 experienced the first fall onset within 12 months and formed the faller group (F group). Overall, 344 subjects have not shown any sign of fall onset, and they were considered as control non-faller subjects (NF group). To respect the assumption of samples equality in both groups (Breiman et al., 1984), we have randomly and blindly selected 25% of the subjects from the NF group (86 subjects) to balance the number of subjects in both groups (F and NF groups). Then, the reduced database was split into training and test sets. Overall, 80% of the subjects from F group were blindly assigned to the training set (65 subjects); the remaining subjects were assigned to the test set (17 subjects). Identically, 80% of the subjects from the NF group were assigned to the training set (68 subjects) while the others were assigned to the test set (18 subjects).

2.4.2. Model accuracy assessment

The decision tree was implemented in Matlab® using the Statistics toolbox with the *classregtree* function to perform classification (Breiman et al., 1984). The parameters of this function have been adjusted to obtain the highest accuracy (subsets must have at least 10 training samples to be split, the Gini's diversity index (Raileanu and Stoffel, 2004) was used as the split criterion, all variables were assigned the same weight, and prior probabilities belonging to one class were equal). Subjects with missing values were retained, as long as the algorithm was able to handle them. The optimal tree, as determined by the algorithm on the training set, was then tested on the test set. Confusion matrices and the area under the receiver operating characteristics curves (AUC) on both sets were used to determine the accuracy of the model.

3. Results

All statistical results are summarized in Table 1, with mean ± standard deviations representing baseline continuous variables and number of subjects in percentages representing categorical variables. No significant differences in baseline characteristics were found between F and NF groups, except for gender. Overall, no significant differences emerged between groups, regardless of the baseline characteristics (postural balance, body composition and anthropometry, physical lifestyle and autonomy, hearing, vision, cardiovascular, orthopedy, neurology, executive functions).

The decision tree was built on the training set (comprising 9709 values), and 2555 values have been used for the independent evaluation of model accuracy. Fig. 1A displays the final decision tree with its 15 internal nodes and 17 leaves. For each internal node, the split criterion is indicated. The tree demonstrates that the two first levels of splitting are related to nutrition and anthropometry. The root of the tree starts by the mini nutritional assessment, followed by the body mass index (BMI) and the lean body mass at the second level. The field of sensory disabilities, including the ankle hypoesthesia, the visual acuity, and the

Table 1
Baseline characteristics of the studied sample (n = 426) according to their faller status (faller vs. non-faller). $p < 0.05$: *.

	Fallers ($n = 82$)	Non-fallers ($n = 344$)	Total ($n = 426$)
Baseline characteristics			
Female gender, n (%)*	**41 (50.0)**	**224 (65.1)**	**265 (62.2)**
Age (years), mean ± SD [a (1, 2, 3)]	69.5 ± 2.8	69.5 ± 2.6	69.5 ± 2.6
Taking medications (yes), n (%)	72 (87.8)	267 (77.6)	339 (79.6)
Family status (in couple vs. single), n (%)	65 (79.3)	283 (82.3)	348 (81.7)
Postural balance			
Eyes open			
Area (95% confidence ellipse) (mm^2)	167 ± 135.6	152 ± 106	154.8 ± 112.3
COP mediolateral length (mm)	240.6 ± 85.2	241 ± 92.3	240.9 ± 90.9
COP antero-posterior length (mm)	270.3 ± 93.3	274.2 ± 103	273.4 ± 101.1
Eyes closed			
Area (95% confidence ellipse) (mm^2)	285.3 ± 296.1	247.4 ± 176.2	254.7 ± 204.9
COP mediolateral length (mm)	344.5 ± 160.5	347.3 ± 158.3	346.8 ± 158.6
COP antero-posterior length (mm)	448.7 ± 210.3	454.3 ± 218	453.2 ± 216.3
Body composition and anthropometry			
Body mass index (kg/m^2), mean ± SD	26.4 ± 4	26 ± 3.7	26.1 ± 3.7
Weight (kg), mean ± SD	70.2 ± 12	70.9 ± 12.4	70.7 ± 12.3
Height (cm), mean ± SD	162.9 ± 9.5	164.6 ± 8.6	164.3 ± 8.8
Right brachial circumference, mean ± SD	28.9 ± 3.3	29 ± 3.3	29 ± 3.3
Calf brachial circumference, mean ± SD	36.1 ± 3.3	35.9 ± 3.1	36 ± 3.1
Mini-nutritional assessment score (/30 points), mean ± SD	27.5 ± 1.7	28 ± 4.2	27.9 ± 3.9
Fat mass (kg), mean ± SD	21.4 ± 7	20.3 ± 6.6	20.5 ± 6.7
Lean mass (kg), mean ± SD	48.4 ± 9.7	50.4 ± 9.7	50 ± 9.7
Total body water (kg), mean ± SD	35.7 ± 6.9	37.2 ± 7.1	36.9 ± 7.1
Physical lifestyle and autonomy			
Index of independence in activities of daily living (Katz index/6), mean ± SD	5.8 ± 0.4	5.9 ± 0.3	5.9 ± 0.3
Daily life activities (/27 = without aid), mean ± SD	26.6 ± 1	26.7 ± 1.1	26.7 ± 1.1
Physical activity (walk) > = 30 min/day, n (%)	64 (78.0)	280 (81.4)	344 (80.8)
One leg standing >5 s (yes), n (%)	75 (91.5)	323 (93.9)	398 (93.4)
Vision			
Visual Object and Space Perception Battery, (/10 points), mean ± SD	8.8 ± 1.5	8.6 ± 1.8	8.7 ± 1.7
Distance visual acuity (right eye) (/10), mean ± SD	8.2 ± 3.2	8.3 ± 2.5	8.3 ± 2.6
Distance visual acuity (left eye) (/10), mean ± SD	8.1 ± 3	8.2 ± 2.5	8.2 ± 2.6
Near visual acuity (right eye) (/10), mean ± SD	23.6 ± 36.6	20.1 ± 17.8	20.8 ± 22.6
Near visual acuity (left eye) (/10), mean ± SD	17.5 ± 7.3	18.4 ± 9	18.2 ± 8.7
Vision with glasses (yes), n (%)	81 (98.8)	343 (99.7)	424 (99.5)
Glasses (bifocal/progressive lenses), n (%)	70 (85.4)	303 (88.1)	373 (87.6)
Cataract (yes), n (%)	18 (22.0)	86 (25.0)	104 (24.4)
Hearing			
Hearing surgery (yes), n (%)	2 (2.4)	16 (4.7)	18 (4.2)
Hearing aid (right ear), n (%)	3 (3.7)	10 (2.9)	13 (3.1)
Hearing aid (left ear), n (%)	4 (4.9)	12 (3.5)	16 (3.8)
Hearing deficiency (>30 dB) (yes), n (%)	69 (84.1)	275 (79.9)	344 (80.8)
Presbycusis (yes), n (%)	68 (82.9)	274 (79.7)	342 (80.3)
Cardiovascular			
Normal electrocardiogram (yes), n (%)	69 (84.1)	289 (84.0)	358 (84.0)
Systolic blood pressures (supine/standing ratio), mean ± SD	0.99 ± 0.09	0.9 ± 0.08	0.9 ± 0.08
Orthopedy			
Orthopedic surgery of lower limbs, n (%)	15 (18.3)	55 (16.0)	70 (16.4)
Spinal surgery, n (%)	8 (9.8)	14 (4.1)	22 (5.2)
Paralyzing sciatica, n (%)	5 (6.1)	15 (4.4)	20 (4.7)
Herniated disc, n (%)	10 (12.2)	35 (10.2)	45 (10.6)
Coxarthrosis, n (%)	6 (7.3)	35 (10.2)	41 (9.6)
Knee osteoarthritis, n (%)	10 (12.2)	38 (11.0)	48 (11.3)
Limited hip range of motion, n (%)	8 (9.8)	21 (6.1)	29 (6.8)
Limited knee range of motion, n (%)	1 (1.2)	19 (5.5)	20 (4.7)
Frozen ankles, n (%)	3 (3.7)	2 (0.6)	5 (1.2)
Orthopedic shoes, n (%)	3 (3.7)	5 (1.5)	8 (1.9)
Feet pathology, n (%)	30 (36.6)	108 (31.4)	138 (32.4)
Neurology			
Sensory features			
Stroke, n (%)	3 (3.7)	8 (2.3)	11 (2.6)
Diziness, n (%)	9 (11.0)	32 (9.3)	41 (9.6)
Romberg's test (positive result), n (%)	27 (32.9)	100 (29.1)	127 (29.8)
Left distal hypopallesthesia of medial malleolus, n (%)	4 (8.5)	42 (12.2)	46 (11.5)
Left distal hypopallesthesia of lateral malleolus, n (%)	12 (14.6)	42 (12.2)	54 (12.7)
Left distal hypopallesthesia of heel, n (%)	18 (22.0)	55 (16.0)	73 (17.1)
Left distal hypopallesthesia of foot arch, n (%)	10 (12.2)	40 (11.6)	50 (11.7)
Right distal hypopallesthesia of medial malleolus, n (%)	9 (11.0)	57 (16.6)	66 (15.5)
Right distal hypopallesthesia of lateral malleolus, n (%)	5 (6.1)	51 (14.8)	56 (13.1)
Right distal hypopallesthesia of heel, n (%)	17 (20.7)	61 (17.7)	78 (18.3)
Right distal hypopallesthesia of foot arch, n (%)	10 (12.2)	51 (14.8)	61 (14.3)
Left distal hypoesthesia of medial malleolus, n (%)	3 (3.7)	10 (2.9)	13 (3.1)
Left distal hypoesthesia of lateral malleolus, n (%)	3 (3.7)	8 (2.3)	11 (2.6)

(continued on next page)

Table 1 (*continued*)

	Fallers ($n = 82$)	Non-fallers ($n = 344$)	Total ($n = 426$)
Neurology			
Sensory features			
Left distal hypoesthesia of heel, n (%)	3 (3.7)	34 (9.9)	37 (8.7)
Left distal hypoesthesia of foot arch, n (%)	4 (4.9)	17 (4.9)	21 (4.9)
Right distal hypoesthesia of medial malleolus, n (%)	1 (1.2)	8 (2.3)	9 (2.1)
Right distal hypoesthesia of lateral malleolus, n (%)	1 (1.2)	9 (2.6)	10 (2.3)
Right distal hypoesthesia of heel, n (%)	3 (3.7)	33 (9.6)	36 (8.5)
Right distal hypoesthesia of foot arch, n (%)	3 (3.7)	20 (5.8)	23 (5.4)
Executive functions			
Frontal assessment battery (Score/18 ± *SD*)	14.8 ± 2.3	14.6 ± 2.4	14.7 ± 2.4
Gear wheel test, (yes), n (%)	0 (0.0)	2 (0.6)	2 (0.5)
Repeat three words ("lemon, key, balloon"), (yes), n (%)	82 (100.0)	343 (99.7)	425 (99.8)
Spell the word "world" backwards, (yes), n (%)	76 (92.7)	328 (95.3)	404 (94.8)
Recall the three words ("lemon, key, balloon") without aid			
0 word, n (%)	1 (1.2)	3 (0.9)	4 (0.9)
1 word, n (%)	10 (12.2)	39 (11.3)	49 (11.5)
2 words, n (%)	25 (30.5)	87 (25.3)	112 (26.3)
3 words, n (%)	46 (56.1)	215 (62.5)	261 (61.3)

presbycusis, and the variables related to quiet standing postural control, both during eyes opened and eyes closed conditions, contributes strongly to the decision tree (Fig. 1A–B). Finally, the disabilities at the distal part of the lower limbs also represent an important part of the tree. Indeed, in addition to the hypoesthesia at the ankle level, an overall pathology at the foot level and/or a limited range of motion at the knee level need to be diagnosed to complete the model.

The detailed prediction results of the training and test datasets are presented in the form of confusion matrixes and ROC curves (Fig. 1C–D). In the training set, the overall classification accuracy was 89% (AUC = 0.89), with accuracy rate of 83% for fallers and 96% for non-fallers. Further, for older adults classified by the decision tree as fallers, 54 cases (95%) were actually fallers. For the 18 non-fallers in the test dataset, the decision tree correctly classified 11 older adults (61%). The prediction model accurately identified older adults at high risk for first fall with an accuracy rate of 82% for the 17 fallers (AUC = 0.72 for both curves).

4. Discussion

Considering the WHO recommendations (WHO, 2007), the development of long term targeted fall-prevention programs to prevent falls in older adults as soon as possible is a health priority. Thus, the early identification of people at high risk of falls should be based on an "easy to use"

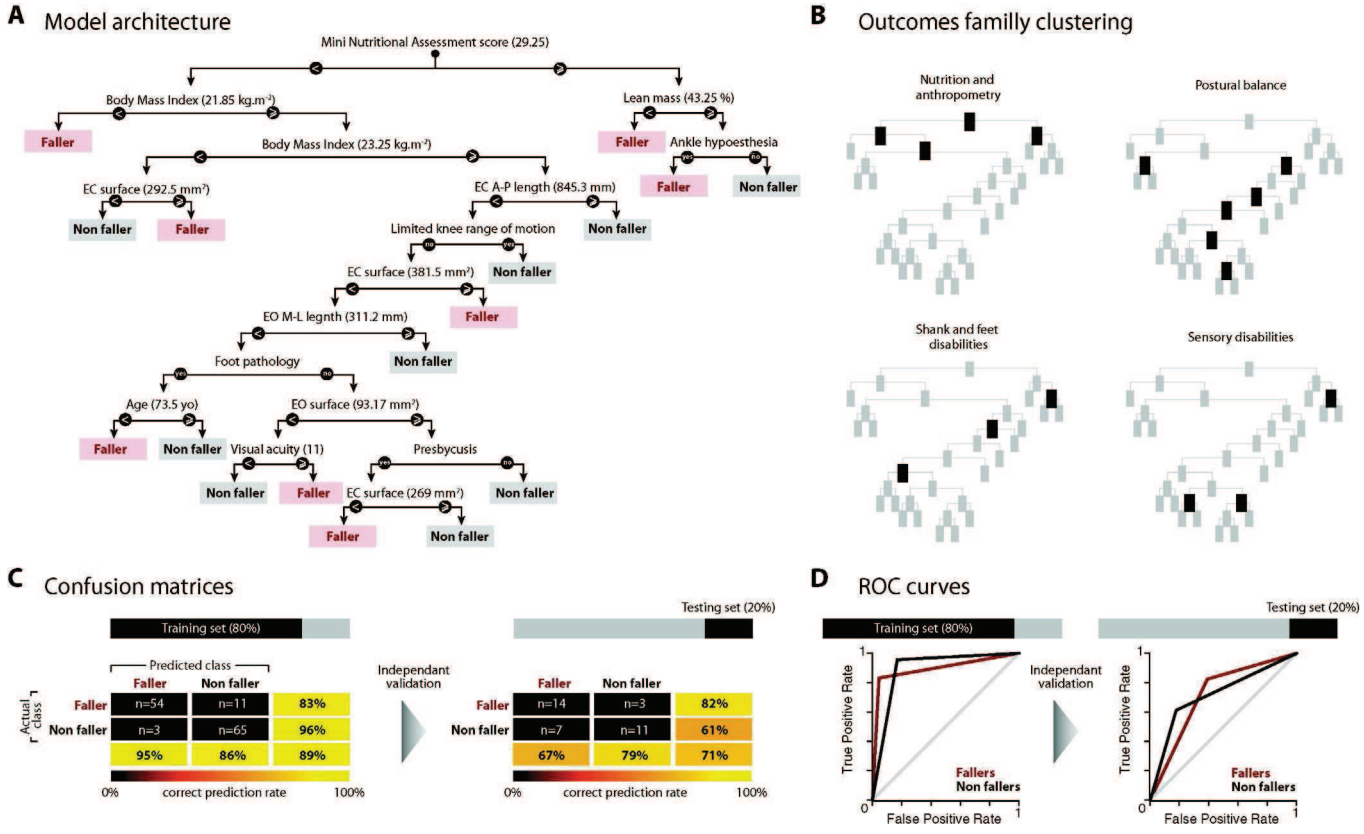

Fig. 1. Decision tree architecture, which objectively shows the '*If*'-'*Then*' *rules* (A), the clustering of the selected parameters to enhance understanding (B) and the accuracy of the model both for the training set and the independent testing set through confusion matrices (C) and receiver operating characteristics (ROC) curves (D). *Note*. EC: eyes closed; EO: eyes open; A-P: antero-posterior axis; M-L: mediolateral axis.

predictive models built on a randomly selected training subset of the cohort and validated on an independent test set. These objectives guided this pilot study conducted with a very original cohort (namely home-dwelling older adults who had never fallen). We developed the first algorithm using machine-learning technique leading to a set of simple rules to estimate the probability of the risk of the first fall onset in the coming year. As a striking result, we found a high classification accuracy of true fallers in the training dataset (83%), which was consistently confirmed by the decision tree analysis in the independent test set (82%).

The model extracted a restricted amount of relevant parameters, which includes anthropometric, sensory-motor, and postural balance parameters, from an initial set of 73 variables. These variables constituted a subset of the determinants already known to be associated with the risk of falls in significant meta-analyses (Bloch et al., 2013; Gillespie et al., 2012). Abnormal balance test [OddsRatio = 2.26 (1.79–2.85)], low body mass index [*OR* = 2.05 (1.70–2.48)], fracture history [*OR* = 1.89 (1.53–2.34)], hearing impairment [*OR* = 1.37 (1.27–1.48)], vision impairment [*OR* = 1.49 (1.39–1.59)], sensory disorders [*OR* = 2.2 (1.56–3.11)] or lower extremity disability [*OR* = 1.89 (1.65–2.17)] are important intrinsic predictors of falls. They are consistent with the parameters used by our algorithm, which include the mini nutritional assessment score (/30 points) (Rubenstein et al., 2001), body mass index, lean body mass, clinical balance measures (the surface and the path length of the COP during quiet stance trials with eyes open or eyes closed), presbycusis or visual acuity impairment, and shank/ft disabilities (ankle hypoesthesia, limited knee range of motion or foot pathology such as hallux valgus). Overall to be an older adult, with nutritional disturbances, limited knee range of motion or ankle hypoesthesia, and hearing and visual deficits tend to impair the postural, indicative of an increased risk of the first fall. Other things being equal, this might be the first insights in pathophysiological mechanisms underlying the phenotype of fallers.

The clustering of these parameters in four families (Fig. 1B) illustrates the importance of considering simultaneously the fields of nutrition/body composition, the sensory-motor features at the lower limb level, and the control of postural balance for an optimized integrative prevention strategy. Indeed, both the morphological states (i.e., overweight and restricted joint range of motion), the muscle strength at the ankle joint, and the feet sensitivity strongly influence the postural control skills and *in fine* the risk of fall. (Cattagni et al., 2014; Mignardot et al., 2013; Perry, 2006)

One of key aspects of this pilot regression tree analysis is the simple conversion of main findings into a collection of '*If*'-'*Then*' rules easily useable in clinical setting (Fig. 1A). Beyond the high classification accuracy of the current prediction model of the first fall, further analyses are needed to increase the visibility of these rules because of limited sample size associated with those nodes. Thus further statistic validity of the current prediction model on a larger and truly independent cohort is still required to guarantee the clinical relevance of the current prediction model. One of the key results is indeed relatively moderate accuracy rate for non-fallers in the test set (61%) compared to the accuracy rate of 96% in the training dataset. The possibility that this drop is a sign of impaired robustness of the model needs to be considered as a limitation of the present study. However, we assume that the accuracy of this prediction model for *future fallers* may help medical professional prescribe an intervention early enough to effectively prevent the first fall onset. From a clinical viewpoint, although this new guide reliably identifies older adults at high risk for fall, diagnosing older individuals who are really not at risk as being at high risk is much less dramatic.

To conclude, using few routine clinical, anthropometric, and metrologic measurements, this pilot study tested a reliable prognostic model to predict the first fall onset in older adults. The model may offer a simple and easy tool to use in the clinical settings and medical field."

Conflict of interest

The authors report no conflicts of interest.

Author contribution

Conception and design of the cohort study: GB.
Collection, assembly, analysis and interpretation of data: CLG, JBM, TD.
Drafting the article or revising it critically for important intellectual content: TD, CLG, JBM, CC, GB.

Sponsor's role

The study was sponsored by grants from the Region of Pays de la Loire (#2011-05457 & #2011-05455), France, for the projects "RP3AP" and "LMA". The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

References

Beauchet, O., Allali, G., Annweiler, C., et al., 2008. Does change in gait while counting backward predict the occurrence of a first fall in older adults? Gerontology 54, 217–223.
Bloch, F., Thibaud, M., Tournoux-Facon, C., et al., 2013. Estimation of the risk factors for falls in the elderly: can meta-analysis provide a valid answer? Geriatr. Gerontol. Int. 13, 250–263.
Breiman, L., Friedman, J.H., Olshen, R.A., Stone, C.J., 1984. Classification and Regression Trees. Wadsworth, Belmont, California.
Cattagni, T., Scaglioni, G., Laroche, D., et al., 2014. Ankle muscle strength discriminates fallers from non-fallers. Front. Aging Neurosci. 6, 336.
Dai, B., Ware, W.B., Giuliani, C.A., 2012. A structural equation model relating physical function, pain, impaired mobility (IM), and falls in older adults. Arch. Gerontol. Geriatr. 55, 645–652.
Davis, J.C., Robertson, M.C., Ashe, M.C., et al., 2010. International comparison of cost of falls in older adults living in the community: a systematic review. Osteoporos. Int. 21, 1295–1306.
Davis, J.C., Bryan, S., Best, J.R., et al., 2015. Mobility predicts change in older adults' health-related quality of life: evidence from a Vancouver falls prevention prospective cohort study. Health Qual. Life Outcomes 13, 101.
Gillespie, L.D., Robertson, M.C., Gillespie, W.J., et al., 2012. Interventions for preventing falls in older people living in the community. Cochrane Database Syst. Rev. 9, CD007146.
Ivziku, D., Matarese, M., Pedone, C., 2011. Predictive validity of the Hendrich fall risk model II in an acute geriatric unit. Int. J. Nurs. Stud. 48, 468–474.
Kojima, G., Masud, T., Kendrick, D., et al., 2015. Does the timed up and go test predict future falls among British community-dwelling older people? Prospective cohort study nested within a randomised controlled trial. BMC Geriatr. 3 (15), 38.
Kotsiantis, S.B., 2007. Supervised machine learning: a review of classification techniques. Informatica 31, 249–268.
Mignardot, J.B., Olivier, I., Promayon, E., et al., 2013. Origins of balance disorders during a daily living movement in obese: can biomechanical factors explain everything? PLoS One 8, e60491.
Mignardot, J.-B., Deschamps, T., Barrey, E., et al., 2014. Gait disturbances as specific predictive markers of the first fall onset in elderly people: a two-year prospective observational study. Front. Aging Neurosci. 6, 22.
Perry, S.D., 2006. Evaluation of age-related plantar-surface insensitivity and onset age of advanced insensitivity in older adults using vibratory and touch sensation tests. Neurosci. Lett. 392, 62–67.
Raileanu, L.E., Stoffel, K., 2004. Theoretical comparison between the Gini index and information gain criteria. Ann. Math. Artif. Intell. 41, 77–93.
Rubenstein, L.Z., Harker, J.O., Salvà, A., et al., 2001. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J. Gerontol. A Biol. Sci. Med. Sci. 56, M366–M372.
Schoene, D., Wu, S.M., Mikolaizak, A.S., et al., 2013. Discriminative ability and predictive validity of the timed up and go test in identifying older people who fall: systematic review and meta-analysis. J. Am. Geriatr. Soc. 61, 202–208.
Stalenhoef, P.A., Diederiks, J.P.M., Knottnerus, J.A., et al., 2002. A risk model for the prediction of recurrent falls in community-dwelling elderly: a prospective cohort study. J. Clin. Epidemiol. 55, 1088–1094.
Tinetti, M., Speechley, M., Ginter, S.F., 1988. Risk factors for falls among elderly persons living in the community. N. Engl. J. Med. 319, 1701–1707.
Verghese, J., Holtzer, R., Lipton, R.B., et al., 2009. Quantitative gait markers and incident fall risk in older adults. J. Gerontol. A Biol. Sci. Med. Sci. 64, 896–901.
Whitney, J., Close, J.C.T., Lord, S.R., et al., 2012. Identification of high risk fallers among older people living in residential care facilities: a simple screen based on easily collectable measures. Arch. Gerontol. Geriatr. 55, 690–695.
WHO, 2007. World Health Organization report/WHO Global Report on Falls Prevention in Older Age (47 pp.).
Yoo, S.H., Kim, S.R., Shin, Y.S., 2015. A prediction model of falls for patients with neurological disorder in acute care hospital. J. Neurol. Sci. 356, 113–117.

Journal of Experimental Psychology:
Human Perception and Performance
2016, Vol. 42, No. 9, 1363–1371

0096-1523/16/$12.00 http://dx.doi.org/10.1037/xhp0000232

Altered Force-Generating Capacity is Well-Perceived Regardless of the Pain Presence

Thibault Deschamps, Justine Magnard, and Marc Jubeau
University of Nantes

François Hug
University of Nantes and The University of Queensland

Kylie Tucker
The University of Queensland

An inability to perceive changes in action capabilities may result in increased risk of injury and/or reduced performance. We investigated whether the perception of ability to perform a maximal single-leg hop was updated when the actual ability to perform the task was reduced due to experimentally altered force-generating capacity and associated pain. Twenty-five healthy volunteers performed a series of maximal isometric voluntary knee extensions (MVC), performance estimates and actual performances of a maximal single-leg hop. The motor tasks were completed for each leg, before (t_{0_pre}), and immediately (t_{0_post}), 48 hr (t_{+48hr}) and 1 month ($t_{+1month}$) after, a neuromuscular electrical stimulation (NMES) protocol was used to decrease the force generating capacity of the quadriceps muscle of 1 leg. MVC torque decreased by ~30% after the NMES protocol for the stimulated leg at t_{0_post} and t_{+48hr} ($p < .001$). This reduction was associated with a significant decrease in estimation of performance and actual performance of the maximal single-leg hop at t_{0_post} and t_{+48hr} for the test leg ($p < .001$). The reduction in performance ability was associated with low-level pain immediately after NMES, and moderate pain and an increase in the belief that everyday motor tasks would be harmful 48 hours after NMES. Participants accurately estimated their performance capabilities during each testing period. This study provides a critical step toward understanding the potential for decreased force-generating capacity and muscle pain to modify the relationship between motor performance and perceived abilities.

Keywords: motor performance, perceived capability, single-leg hop, pain

Catching-to-lifting a heavy weight (Bleuse, Delval, & Defebvre, 2014) such as a pack of bottles, walking through apertures or jumping over a gap are common tasks that require an accurate perception of one's own action capabilities to efficiently achieve the goal. Healthy individuals generally underestimate their action capabilities by ~8% to 10%, which is thought to provide a safety margin, to reduce the risk of task failure and potential for injury (Hackney & Cinelli, 2013; Linkenauger, Witt, & Proffitt, 2011). The ability to perceive action capabilities is affected by changes in physiological potential, for example, general fatigue (Pijpers, Oudejans, & Bakker, 2007), fitness level (Bhalla & Proffitt, 1999), athletic expertise (Weast, Shockley, & Riley, 2011), and aging (Hackney & Cinelli, 2013). Underestimating a reduction in performance ability could lead to risky behavioral responses, accident, or injury as has been observed in the elderly population who are at greater risk of falls (Comalli, Franchak, Char, & Adolph, 2013). In contrast, overestimating a reduction in performance ability may be associated with decreased physical activity (Sakurai, Fujiwara, Ishihara, Higuchi, Uchida, & Imanaka, 2013) as observed in older people with pain (Patel, Guralnik, Dansie, & Turk, 2013). In line with these empirical studies and the "action-specific paradigm," which postulates that people experience the world in terms of their action capabilities (Witt & Riley, 2014), we aim to determine if the estimation of performance capabilities is updated when a muscle's force-generating capacity is impaired that is, following muscle damage and associated pain.

We have recently demonstrated that local unilateral acute muscle pain reduces performance ability and perception of performance ability of a maximal single-leg hop (Deschamps, Hug, Hodges, & Tucker, 2014). Interestingly, this reduction occurred

This article was published Online First April 28, 2016.

Thibault Deschamps, Justine Magnard, and Marc Jubeau, Laboratory MIP (EA 4334), University of Nantes; François Hug, Laboratory MIP (EA 4334), University of Nantes; The Centre for Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, University of Queensland; Kylie Tucker, School of Biomedical Sciences, The University of Queensland.

The authors report no conflicts of interest. The authors thank Dr René Faynot for performing the medical examination. The authors thank Jean Hug for drawing Figure 1. The research was supported by grants from the Region of Pays de la Loire, France, for the projects "RP3AP," "ANOPACy," and "QUETE." The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data or in the preparation, review, or approval of the manuscript.

Correspondence concerning this article should be addressed to Thibault Deschamps, University of Nantes Laboratory « Movement, Interactions, Performance » (E.A. 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. E-mail: thibault.deschamps@univ-nantes.fr

bilaterally even though pain was induced unilaterally in a knee extensor muscle. We concluded that the reduction in performance and perception of performance ability during acute pain was consistent with protecting the painful region. In the case of contralateral pain, participants likely reduced their maximal hop distance to reduce the chance that they would need to use their painful leg for balance. This is consistent with the proposition that people change how they perceive their action capabilities when anticipating the pain induced by future actions (Tabor et al., 2015; Witt, Linkenauger, Bakdash, Augustyn, Cook, & Proffitt, 2009).

The injection of hypertonic saline into muscle (as performed in the aforementioned study) is an effective technique used to induce acute nociceptive stimulation (Graven-Nielsen, Arendt-Nielsen, Svensson, & Jensen, 1997; Graven-Nielsen et al., 1997) that is experienced for ~5 to 10 min. However, this pain model is not necessarily associated with a decrease in muscle force-generating capacity (e.g., Slater, Arendt-Nielsen, Wright, & Graven-Nielsen, 2003), which is commonly observed after strenuous exercise as a result of fatigue (Kennedy, Hug, Sveistrup, & Guével, 2013) and/or muscle damage (Brown, Howatson, Keane, & Stevenson, 2015). Further, pain induced with hypertonic saline can reduce in intensity with muscle contraction (Tsao, Tucker, Coppieters, & Hodges, 2010). Therefore, this acute pain model does not replicate many aspects of clinical pain/injury. It remains unclear if the estimation of performance capabilities is updated when a muscle's force-generating capacity is impaired that is, following muscle damage. Further, it is unclear whether the perception of a reduction in performance ability (resulting from the muscle damage) may be enhanced by the presence of local persistent nociceptive feedback (pain).

This study aimed to investigate the effects of muscle damage and associated pain on the perception of action capabilities and maximal performance of a single-leg hop. To minimize the occurrence of central fatigue (Zory, Boërio, Jubeau, & Maffiuletti, 2005), we used neuromuscular electrical stimulation (NMES) rather than eccentric exercise to decrease the force generating capacity of the quadriceps muscle of one leg of otherwise healthy volunteers. The presence of muscle damage is systematically reported after a NMES protocol, with the development of delayed muscle soreness that peaks 48 hr after NMES (Aldayel, Jubeau, McGuigan, & Nosaka, 2010; Jubeau et al., 2008). Thus participants performed a series of estimations and then performances of a maximal single-leg hop before, immediately after, 48 hr after and 1 month after NMES-induced muscle damage. This protocol allowed us to differentially consider if the perception of action capabilities is altered by (1) muscle fatigue/damage (Jubeau et al., 2008; Zory et al., 2005), immediately after the NMES protocol when mild pain is possible during the hop but is unlikely during the estimation of hop distance performed in quiet single-leg standing; and (2) muscle damage with moderate pain that is present during activities of daily living and peaks 48 hr after NMES protocol (Crameri et al., 2007). Consistent with reduced performance ability during isometric maximal voluntary contractions following NMES (Graven-Nielsen, Lund, Arendt-Nielsen, Danneskiold-Samsøe, & Bliddal, 2002), we hypothesize that maximal single-leg hop distance will be lower immediately and 48 hr after NMES. Further, given the presence of pain during everyday motor tasks, that peaks 48 hr following NMES, we hypothesize that participants will better perceive their reduction in performance ability 48 hr after NMES than immediately after. Finally, consistent with protecting the painful or injured region (Deschamps et al., 2014), we hypothesize that the reduction in performance ability and perception of performance ability will be observed bilaterally. As force-generating capacity and associated muscle soreness recover to their baseline values 3 weeks after the damaging exercise (Lacourpaille, Nordez, Hug, Couturier, Dibie, & Guilhem, 2014), we expect all outcome measures to have returned to baseline levels by the 1-month follow up session.

Method

Participants

Twenty-five healthy participants (21 men, 4 women; mean age 22.4 ± 3.7 years, height 174.9 ± 7.4 cm, body mass 68.2 ± 11.3 kg) volunteered to participate in the study. All participants were engaged in regular physical activity (e.g., cycling, running, judo, swimming) but none had previous experience with the maximal single-leg hop task. Twenty-one participants indicated a preference to kick a ball with their right leg. Exclusion criteria included visual or physical impairments, psychiatric or neurologic disorders, any long-term medication use or any pain in the lower limbs within the previous 12 months that had resulted in time off work or attendance to a medical doctor. Participants were informed of the experimental tasks, associated risks and the discomfort expected due to the NMES protocol before providing written consent. The experimental design of the study was approved by the Ethical Committee of Nantes Ouest IV (reference: CPP-MIP-004P) and was conducted in accordance with the Declaration of Helsinki.

Experimental Apparatus

A rigid floor mat (4 cm thick, 7 m long, 1 m wide) was laid in a room with minimal possible visual cues that could be used to assist the estimation of maximal hopping distance. A white line of masking tape was placed along the midline of the floor mat. Participants were asked to focus on and aim for the midline when estimating their hop performance and when performing the single-leg hop task, respectively.

The estimated and actual hop distance was evaluated using a 4-camera OptiTrack 3D motion analysis system (Natural Point, Corvallis, Oregon) with data acquired at 100 Hz (see Figure 1). An infrared emitting diode (IRED) was placed bilaterally on the participant's big toe, and another two IREDs were placed on the extremities of the estimation stick (see see the following single leg hop estimations and performances protocol). All data were filtered using a fourth-order Butterworth, zero-phase low pass at 5 Hz.

Experimental Protocol

Test sessions. All participants attended the laboratory on three separate days. Data (i.e., single-leg hop estimations and actual performances, and quadriceps maximal voluntary contractions) were recorded twice on Day 1, immediately before (t_{0_pre}) and after (t_{0_post}) NMES, and 48 hr (t_{+48hr}) and 1 month ($t_{+1month}$) after the initial testing session.

General pain cognitions, maximal pain, and mobility experience. To consider general pain cognitions, the French version of the Pain Catastrophizing Scale (PCS) (French et al., 2005) was completed once at the beginning of the t_0 session.

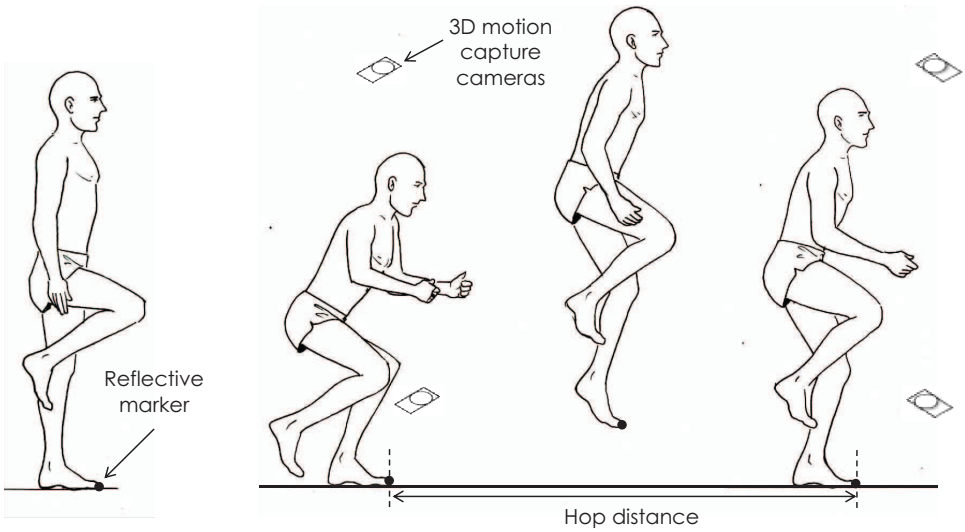

Figure 1. Sagittal view of the experimental setup for measuring single-leg hop distance.

To consider pain experience at the time of testing, participants completed a 7-point Likert scale at the beginning of each experimental session (t_0, t_{+48hr}, $t_{+1month}$). Participants were asked to qualify their pain using the following indicators (translated from French): 0 = *a complete absence of pain/soreness*, 1 = *slight pain and soreness only perceived with touch*, 2 = *moderate pain and soreness only perceived with touch*, 3 = *pain and soreness when lifting/carrying objects*, 4 = *slight pain and soreness and/or stiffness when you use your leg*, 5 = *moderate pain and soreness and/or stiffness when you use your leg*, and 6 = *severe muscle soreness/pain, high stiffness that limits your ability to move*.

Finally, participants were asked to qualify their maximal perceived harmfulness of common daily activities (such as squatting, bending, walking a dog) using the Photograph Series of Daily Activities (PHODA; Leeuw, Goossens, van Breukelen, Boersma, & Vlaeyen, 2007) at the beginning of each experimental session (t_0, t_{+48hrr}, $t_{+1month}$). This questionnaire requires participants to indicate the perceived harmfulness of each task on a standardized visual analogue scale (scored/10) that is anchored with "not harmful at all" and "very harmful." The PHODA includes 40 common daily activities, and scores from the items are averaged to provide a perceived harmfulness rating (/10).

Warm up. After completion of the pain and mobility questionnaires, participants performed ~5 min of free warm-up (cycling, running, and jumping). Then, they were instructed on how to perform the maximal single-leg hop (stand on one leg, hop maximally while maintaining the ability to balance on the hopping leg upon landing), and then immediately performed 3 practice hops on each leg.

Single-leg hop estimations and performances. To assess the participant's ability to estimate their maximal hop distance participants were asked to stand on the test leg and "estimate the maximum distance that you could hop and then maintain balance upon landing." Participants indicated this distance by saying "stop" as the experimenter moved the estimation stick (placed transversely across the width of the carpet and with a 120-cm handle) away from the starting position at ~20 cm/s. To optimize this estimation of maximal single-leg hop performance, participants could give instructions "further" or "closer" to the experimenter to make minor adjustments to the stick's position. To limit potential distance cues, the starting position was changed for each trial (within an interval of about 1 m). Following each estimation, participants were asked to close their eyes and turn away while the experimenter returned to a new starting position.

The maximal hop performance was defined as the maximal distance hopped during the single-leg hop test, without using the opposite leg for stability before the jump and successfully landing on that same leg without losing balance (Munro & Herrington, 2011). To limit the potential for any distance cues to affect performance the starting position was altered (within ~ 1m) between trials.

For all trials, the estimation of performance was conducted prior to the actual performance. In total, six estimates (three per leg, alternating between legs, and with the first leg counterbalanced between participants) were recorded. Participants then performed 6 maximal single-leg hops (three per leg, alternating between legs, and with their first leg counterbalanced between participants) with at least 40 s of recovery between trials of the same leg to minimize fatigue (Reid, Birmingham, Stratford, Alcock, & Giffin, 2007).

Maximum voluntary contractions (MVC). To determine whether the maximal quadriceps muscle function of the test leg was affected by the NMES protocol (described subsequently), maximal knee extension force was measured for each leg during each experimental session (after completion of all performance estimates and actual hop performance). Participant was seated on the ergometer with a 100° angle at the knee and hip joints (0° being full knee extension). The maximal quadriceps force was assessed for both legs independently. For each leg two maximal isometric voluntary knee-extensions were performed for 5 s, with a 90-s rest interspersed between contractions. A third maximal isometric torque was recorded if the first two measurements differed by more than 5%. To minimize changes in posture during MVC's, participants' hips and shoulders were fixed with belts attached to the ergometer. During MVC assessment, participants positioned

their arms across the chest with each hand clasping the opposite shoulder. The force generated during muscle contraction was measured using a strain gauge (PT1 Scaime®, Annemasse, France) mounted on the ergometer. The force signal was digitized at a sampling rate of 50 Hz (MP36, BIOPAC Systems, Goleta, CA). The peak force amplitude was used for further analysis.

NMES protocol. Neuromuscular electrical stimulation (Jubeau et al., 2008) was used to induce local muscle damage (and associated delayed onset muscle soreness, DOMS) immediately after completion of the $t_{0\text{-}pre}$ experiential session. Participants were seated on the ergometer chair with a knee angle of 100°. Electrically evoked contractions were induced in the test leg ($n = 13$ right leg, $n = 12$ left leg, randomly allocated to the participant) by a portable electrical stimulator (Compex Mi Sport, Medicompex, Ecublens, Switzerland). Three self-adhesive electrodes were placed over the anterior aspect of the tested thigh with two positive electrodes (5 cm × 5 cm) positioned over the motor points of the vastus lateralis and vastus medialis muscles which were individually identified as the sites on the skin where the smallest intensity of stimulation was required to produce muscle contraction (Botter et al., 2011) and one negative electrode (10 cm × 5 cm) placed about 5 cm below the inguinal ligament (see Figure 2). According to previous studies (e.g., Jubeau et al., 2008), this stimulator was programmed to deliver biphasic symmetric rectangular pulses with the following characteristics: frequency 75 Hz, pulse duration 380 μs, on-off ratio 6.25–19 s (rise time 1.5 s, fall time 0.75 s). Each participant underwent a warm-up, consisting of 5-min low-frequency (5 Hz) and submaximal electrically evoked contractions. Then the protocol consisted of 40 electrically evoked contractions at the maximal NMES intensity tolerated (total duration: 18 min). During the first five contractions, the intensity was increased until the maximal tolerable level of electrical stimulation was reached. The participants were regularly asked if the intensity of the electrical stimulus remained at their "maximal tolerable level." In the case that a participant indicated that they could tolerate a higher stimulus intensity, the intensity was further increased.

The mean level of isometric force evoked during NMES (40 contractions) was 28.9 ± 9.7% (range: 11.3–48%) of the t_{0_pre} MVC.

Task- and NMES-related pain experience. Immediately after each estimate and performance of the single-leg hop, participants were asked to report their task-related pain on an 11-point numerical rating scale, ranging from 0 (*no pain*) and 10 (*most extreme pain imaginable*). Note that no pain (i.e., 0/10) was reported at $t_{0\text{-}pre}$ and $t_{+1month}$. Following completion of the testing session at t_{+48hr}, participants drew the region of pain experienced on their own leg, and a photograph was taken.

Data and Statistical Analysis

Data distributions consistently passed the Kolmogorov–Smirnov normality test, and thus all data are reported as means ± standard deviation. As the results were the same with the average and the maximum performance estimates and actual hopping performance, only the statistical analyses with the maximum performance as the dependant variable are presented.

To quantify the effect of NMES on muscle function, quadriceps MVC (in N) were compared using a two-way repeated-measures ANOVA with leg (control vs. test) and session (t_{0_pre}, t_{0_post}, t_{+48hr}, vs. $t_{+1month}$) as within-participant variables.

The general pain and mobility experience prior to the testing session was determined from the aforementioned 7-point Likert scale and the PHODA, respectively. These outcome measures were compared between testing days using repeated-measures ANOVAs with session (t_0, t_{+48hr} and $t_{+1month}$) as the within participant variable. Pain in the leg that was stimulated with NMES was reported during the t_{0_post} and t_{+48hr} sessions only. Subsequently, a repeated-measures ANOVA was used to determine whether a difference in pain intensity was observed between session (t_{0_post} vs. t_{+48hr}) and/or measure (estimate vs. performance).

A single analysis of covariance (ANCOVA) with repeated measures was used to determine if the NMES protocol (and subsequent muscle soreness) affected the maximal single-leg hop distance, with session (× 4: t_{0_pre}, t_{0_post}, t_{+48hr}, vs. $t_{+1month}$), measure (× 2: estimates vs. performance) and leg (× 2: control vs. tested) as within participant variables and PCS score and PHODA score at t_{+48hr} as potential confounding factors (covariates). Precisely, this ANCOVA was conducted to examine a possible confounding effect of pain related cognitions to participants' performance estimation and actual performance.

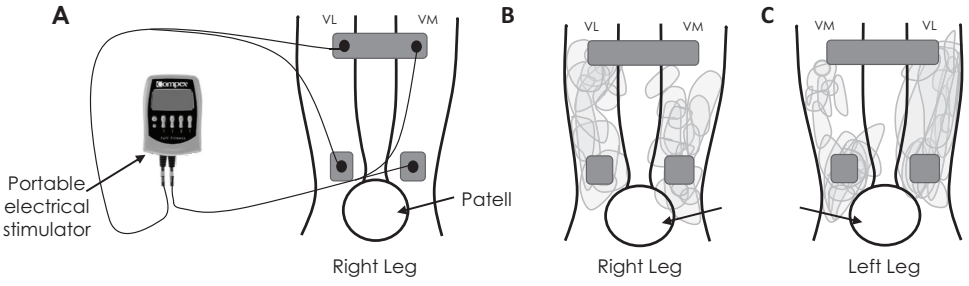

Figure 2. Neuromuscular electrical stimulation (NMES) protocol and induced pain location. Approximated regions for the, vastus lateralis (VL); vastus medialis (VM) and patella are shown in each panel. Panel A: Placement of the stimulating electrodes for the NMES protocol (example of a right leg shown, however note that $n = 13$ participants received NMES to their right leg, and $n = 12$ participants received NMES to their left leg; Panels B−C: The area of pain (gray circles) reported by each participant t_{+48hr} after NMES was applied (to the right leg (Panel B); and to the left leg (Panel C) are shown overlaid on a representative image of the distal thigh and knee cap (patella).

The level of significance was set at $p < .05$. For all analyses, effect sizes were quantified as partial eta square (η_p^2), with moderate and large effects considered for $\eta_p^2 = 0.07$ and $\eta_p^2 \geq 0.14$, respectively (Cohen, 1988). Bonferroni post hoc tests were performed following significant main effects (adjusted p values are reported).

Results

Maximal Knee Extension

Maximal knee extension torque was influenced by a main effect of session, $F(3, 72) = 37.03$, $p < .001$, $\eta_p^2 = .61$, and leg, $F(3, 72) = 20.48$, $p < .001$, $\eta_p^2 = .46$), and a Session × Leg interaction, $F(3, 72) = 50.54$, $p < .001$, $\eta_p^2 = .68$. MVC of the test leg was reduced at t_{0_post} (1189 ± 325.6 N, −30.6 ± 14.1%, $p < .001$) and t_{+48hr} (1171.3 ± 395.3 N; −31.8 ± 19.4%, $p < .001$) compared to t_{0_pre} (1765 ± 495.4 N) and $t_{+1month}$ (1778.5 ± 514 N). In contrast, MVC remained similar (1710.9 ± 567 N) over time for the control leg (all post hoc time comparisons $p > .9$). Finally, the MVC was significantly lower in test leg compared to the control leg at t_{0_post} ($p < .001$) and t_{+48hr} ($p < .001$; see Figure 3).

Pain Cognitions, Pain Intensity, and Mobility Index

Prior to beginning the experiment participants scored 6.4 ± 3.5 (/16), 3.5 ± 2.5 (/12) and 5.1 ± 3.1 (/24), respectively, in the rumination, magnification, and helplessness subscales of the French PCS.

There was a main effect of session, $F(2, 48) = 314.6$, $p < .001$, $\eta_p^2 = .92$, on the participants general pain intensity rating measured using the 7-point Likert scale. Participants rated their general pain as higher at t_{+48hr} (4.7 ± 1) than at t_{0_pre} (0.4 ± 0.7; $p < .001$) and at $t_{+1month}$ (0.2 ± 0.4; $p < .001$). There was also a main effect of session, $F(2, 48) = 85.7$, $p < .001$, $\eta_p^2 = .78$] on PHODA score. Participants reported that the common lower limb movement tasks would be more harmful at t_{+48hr} (3 ± 1.5/10) than t_0 (0.8 ± 0.7/10; $p < .001$) and $t_{+1month}$ (0.3 ± 0.4/10; $p < .001$). The perception of everyday activities being harmful (PHODA) and the 7-point Likert pain scale were highly correlated at t_{+48hr} ($r = .69$; $p < .001$).

Pain During Performance

No pain was reported during estimation or performance of the single-leg hops at t_{0_pre} or $t_{+1month}$. When considering the t_{0_post} and t_{+48hr} testing sessions, there was a main effect of session, $F(1, 24) = 9.44$, $p = .005$, $\eta_p^2 = .28$, and measure, $F(1, 24) = 51.4$, $p < .001$, $\eta_p^2 = .68$, and a Session × Measure interaction, $F(1, 24) = 6.4$, $p = .02$, $\eta_p^2 = .21$, on the pain intensity reported during the hop task. Greater pain intensity was reported during the actual performance (4.3 ± 2/10) than the estimates (1.6 ± 1.6/10) at t_{+48hr} ($p < .001$). No difference in pain level was reported at t_{0_post} between performance estimates (1 ± 1.4/10; 3/25 participants rated their pain >2/10 with a maximum = 6/10) and actual performance (2.5 ± 2.1/10; 10/25 participants rated their pain >2/10 with a maximum = 6/10) ($p = .33$). Figure 2 depicts the diffuse regions of pain reported by participants immediately following the experimental session at t_{+48hr}.

Estimates and Actual Performance (ANCOVA)

Before NMES (t_{0_pre}), participants estimated their maximal single-leg hop distance to be 194.1 ± 33.9 cm, and they performed their maximal single-leg hop at 203.4 ± 24.8 cm (on average for both legs). There was no significant main effect of measure, $F(1, 22) = 0.56$, $p = .46$, $\eta_p^2 = .03$, or significant interaction considering this factorf(all Fs <2.02, p values > .12; all $\eta_p^2 < .02$ (see Figure 3). Likewise, no significant effect of leg was found, $F(1, 22) = 1.94$, $p = .18$, $\eta_p^2 = .08$. However, there was a main effect of session, $F(3,66) = 3.1$, $p = .03$, $\eta_p^2 = .13$, and a Session × Leg interaction, $F(3,66) = 4.13$, $p = .01$, $\eta_p^2 = .17$. Post hoc analysis revealed a significant reduction in both estimation and performance for hops using the tested leg at t_{0_post} (178.5 ± 28.8 cm) and t_{+48hr} (180.6 ± 33.1 cm), in comparison with both t_{0_pre} (198.9 ± 28.7 cm; both p values < .001) and $t_{+1month}$ (202.6 ± 30.7 cm; both p values < .001). No significant change in estimation of performance or actual performance was observed between sessions for the control leg (all p values = 1).

There was no significant effect of the covariates, PCS score, $F(1, 22) = 0.38$, $p = .54$, $\eta_p^2 = .02$, or PHODA_t_{+48hr}, $F(1, 22) = 0.43$, $p = .52$, $\eta_p^2 = .02$, on either the estimate or actual performance measures.

Discussion

The present study was designed to determine whether a decrease in maximal performance ability accompanied by a low to moderate level of pain is associated with an updating of perception of action capabilities (i.e., performance estimates) when performing a single-leg hop. Consistent with the observed reduction in MVC force, maximal hop performance was significantly reduced immediately after and 48 hr after NMES of the quadriceps muscles. This reduction in performance ability was associated with low-level pain (in some participants) immediately after NMES, and moderate pain and an increase in the belief that everyday motor tasks would be harmful 48 hours after NMES. Performance ability, pain and harmfulness cognitions were all fully recovered by the third testing session, 1 month post NMES. In contrast to our second hypothesis (i.e., improved participants' perception of reduction in performance ability at t_{+48hr} than at t_{0_post}), participants accurately perceived their performance capabilities during each testing period, irrespective of the reduced performance ability induced by NMES and/or peak pain experienced as a result of NMES. In contrast to our third hypothesis, the reduction in performance ability and perception of performance ability was only observed for the test leg. This contrasts previous work that demonstrated bilateral changes in performance ability and perception of performance ability during dynamic tasks with acute unilateral experimental pain (Deschamps et al., 2014; see potential explanations in the following text).

NMES Reduces Performance Ability During Dynamic Tasks

The NMES protocol used in our current investigation aimed to reduce the maximal force generating capacity of the vastii

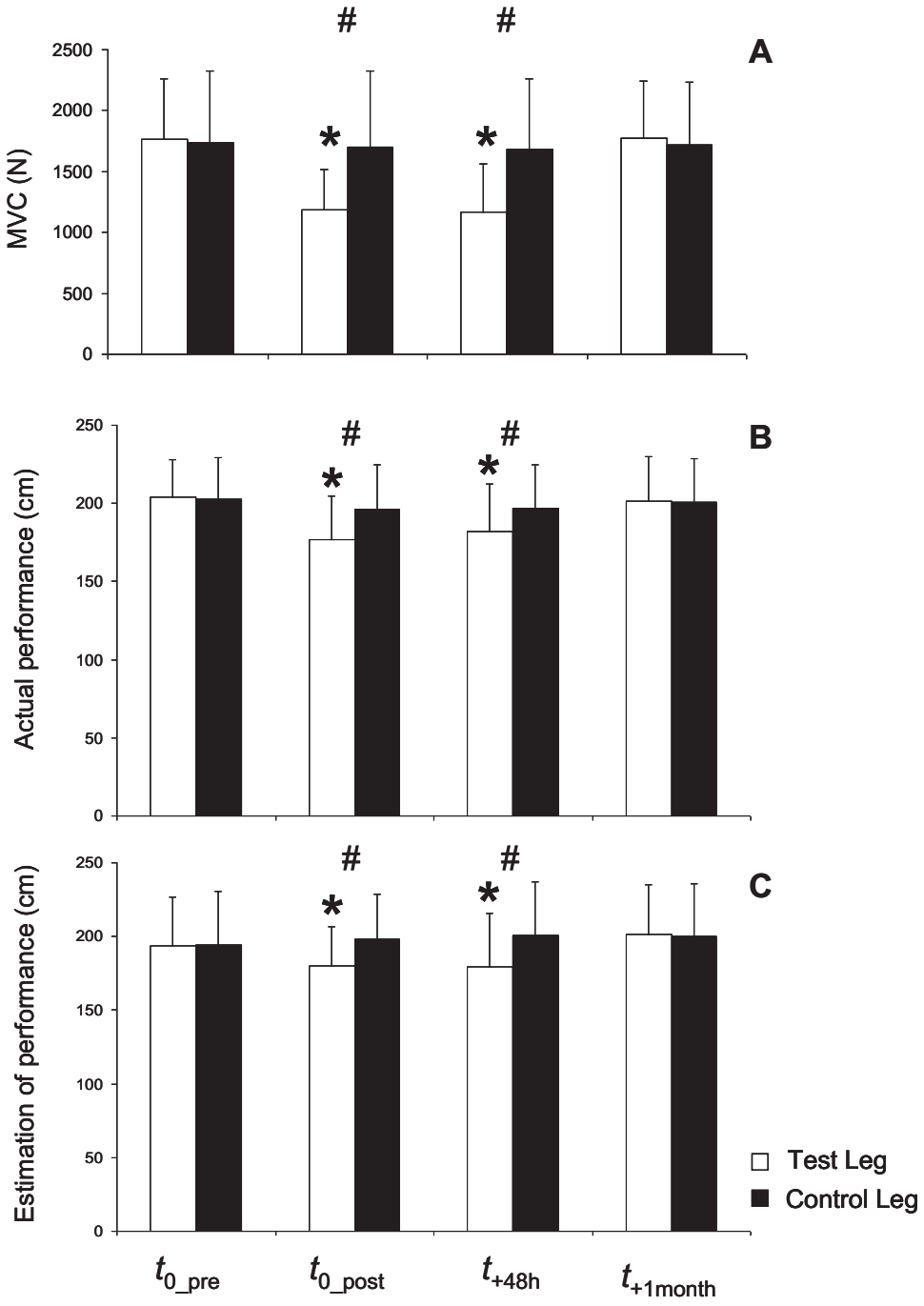

Figure 3. A significant reduction in isometric quadriceps maximum voluntary contractions (MVC) (*N*; Panel A), actual performance (cm; Panel B), and performance estimates (cm; Panel C) was observed for the test leg at t_{0_post} and t_{+48hr} compared with assessments at t_{0_pre} and 1 month ($t_{+1month}$). * Significant difference between t_{0_post} *or* t_{+48hr}, and t_{0_pre} or $t_{+1month}$ for the test leg. # Significant difference between legs at t_{0_post} and t_{+48hr}. Error bars correspond to the standard deviations.

muscles of one leg. We have demonstrated that a ~31 ± 14% and 32 ± 19% reduction in ipsilateral MVC induced by NMES at t_{0_post} and t_{+48hr} respectively, occurs concurrently with a 13.9 ± 8% and 11 ± 10.3% reduction in ipsilateral maximal single-leg hop performance at t_{0_post} and t_{+48hr} respectively. This decrease in maximal force generating capacity occurred simultaneously with higher pain intensity at t_{+48hr} than at t_{0_post}. No change in MVC or hop performance was observed in the contralateral leg following NMES (consistent with Aldayel et al., 2010). Overall, these results demonstrate that our proto-

col effectively decreased the force-generating capacity of the vastii muscles of the test leg.

Pain Cognitions, Pain Intensity, and Mobility Index

Participant's pain related cognitions were as expected for a healthy population (Sullivan, Bishop, & Pivik, 1995). The presence of pain is generally minor (and not reported) immediately after NMES. In accordance with this, only 3/25 participants rated their pain >2/10 during the estimations (group average: 1.0 ± 1.4/10, maximum 6/10) and 10/25 participants rated their pain >2/10 when performing the hopping task on the test leg (group average 2.5 ± 2.0/10, maximum 6/10) at t_{0_post}. Of note, when asked following completion of the hopping task, participants reported that the pain experienced during the hopping task was associated with the landing phase of the hop when the knee extensors were eccentrically contracting. As expected, pain experienced when performing the hopping task on the test side increased further (to 4.3 ± 2/10) by $t_{+48hr.}$ At $t_{+48hr,}$ general pain experience was moderate (4.7 ± 1.1 on the 7-point Likert scale), and everyday movement tasks were perceived as moderately harmful on the PHODA scale (3 ± 1.5/10). We are therefore confident that sufficient decreased force-generating capacity and associated pain occurred due to the NMES protocol to test our hypotheses.

Unilateral Changes With Unilateral Muscle Damage and Pain

The unilateral reduction in maximal hop distance is somewhat surprising given the results of our earlier study (Deschamps et al., 2014). We have previously shown that maximal single-leg hop distance was reduced bilaterally when acute pain was induced by injection of hypertonic saline into one knee extensor muscle. Similarly, Bonifazi, Ciccarone, della Volpe, Spidalieri, and Rossi (2004) demonstrated that pain induced in either the ipsilateral or contralateral prime mover (i.e., the biceps) affects maximal unilateral bench press performance. As the NMES protocol was associated with local pain and reduced performance ability of the knee extensor muscles, we hypothesized a similar bilateral reduction in hop performance. We have previously argued that the bilateral reduction in performance was associated with a protective mechanism, that is, reduced performance on the contralateral side lessens the chance of balance loss upon landing, and thus reduces the possibility to need to use the painful region for balance. The intensity of pain cannot account for the differences in our own results as similar pain intensities were reported in this study at t_{+48} (4.3 ± 2.0/10) and our previous work (4.7 ± 0.4/10) (Deschamps et al., 2014). We propose two potential explanations for the differences in results. First, the onset of pain induced by hypertonic saline is rapid (within ~20s), and the maximum pain intensity is often reported within ~ 1 min of the injection (e.g., Graven-Nielsen et al., 1997). In contrast, pain following NMES increases gradually over 48 hr. As such, the motor adaptation to a similar pain intensity may be very different given other contributors to the pain experience. Second, pain induced by hypertonic saline is continuous for 5 to 10 min, which contrasts to the pain following NMES that peaks on muscle contraction (during landing for the hopping task). It is therefore possible that participants did not adopt the previously observed protective strategy, as pain was not present when they performed the hop with their contralateral leg.

The Perception of Action Capabilities

Participants in our study accurately estimated their performance ability during all experimental sessions. This finding contrasts some previous work (including our own) which shows that most people underestimate their performance ability by ~8% to 10%, and is thought to provide a safety margin, to reduce the risk of task failure and potential for injury. Our current results may be explained by the high level of physical fitness of our participants. For example, it is well understood that physically fit participants or highly trained individuals are less likely to underestimate their performance ability (Bhalla & Proffitt, 1999; Higuchi et al., 2011), and exhibit faster learning to estimate successfully their action capabilities (Ramenzoni, Davis, Riley, & Shockley, 2011).

NMES is well known to induce local peripheral muscle fatigue (Zory et al., 2005) and local muscle damage (Aldayel et al., 2010; Jubeau et al., 2008; Malatesta, Cattaneo, Dugnani, & Maffiuletti, 2003). Our NMES protocol induced low to moderate pain immediately after and 48 hours after stimulation, respectively, and the belief that everyday motor tasks would be moderately harmful 48 hr after stimulation. Further, our NMES protocol reduced maximal hop distance in the test leg immediately after and 48 hr after stimulation. Despite these effects of NMES, we have shown that participants accurately estimated their performance ability during each testing session. This ability to quickly update the perception of our action capability is consistent with our previous study that considered the same maximal single-leg hop task when acute pain was induced by injection of hypertonic saline in the leg (Deschamps et al., 2014). However, in contrast to our second hypothesis, the presence of moderate pain was not necessary to assist in updating the perception of action capabilities. It appears that there was sufficient afferent information (potentially indicators of muscle fatigue/damage but not necessarily nociception) at t_{0_post} to assist with the update of estimation of action capability.

The perception of action capabilities is altered in people with chronic pain (Witt et al., 2009) when estimating distance to walk, but has not been considered in a similar maximal hopping task. Further, we are unaware of other studies that have considered the perception of action capabilities during clinical/chronic musculoskeletal pain condition. We therefore contend that any potential change in perception of action capabilities in people with chronic pain (Witt et al., 2009) is not likely due to a direct effect of nociception, local fatigue and local muscle damage alone. It is possible that the updated perception of action capabilities as observed in our study might be driven by changes in self-efficacy, which is known to influence physical performance (Bandura, 1998; Maly, Costigan, & Olney, 2006). In other words, participants may have interpreted the fatigue and pain that they experienced as signs of vulnerability to poor performance. Self-efficacy was not assessed in the current study, but will be an important consideration in future studies which include people with clinical pain and/or injury.

Further, the present study demonstrates that a change in belief of harmfulness of everyday motor tasks due to experimentally induced pain and muscle damage does not influence the accurate perception of action capabilities in young healthy adults. This is consistent with young sports participants smoothly calibrating the continually evolving relationships between action capabilities and environmental properties (Fajen, Riley, & Turvey, 2009).

In combination with our previous work, this study provides a critical step toward understanding the potential for musculoskeletal pain, local muscle fatigue, and muscle injury to modify the relationship between motor performance and perceived abilities in healthy individuals. It is now important to determine if the process of estimating action capabilities is updated in a similar way in diverse samples of people living with clinical pain with differing pain (and self-efficacy) related cognitions as little it known about the relationship between perception of ability and actual ability in clinical populations.

References

Aldayel, A., Jubeau, M., McGuigan, M. R., & Nosaka, K. (2010). Less indication of muscle damage in the second than initial electrical muscle stimulation bout consisting of isometric contractions of the knee extensors. *European Journal of Applied Physiology, 108,* 709–717. http://dx.doi.org/10.1007/s00421-009-1278-0

Bandura, A. (1998). Health promotion from the perspective of social cognitive theory. *Psychology & Health, 13,* 623–649. http://dx.doi.org/10.1080/08870449808407422

Bhalla, M., & Proffitt, D. R. (1999). Visual-motor recalibration in geographical slant perception. *Journal of Experimental Psychology: Human Perception and Performance, 25,* 1076–1096. http://dx.doi.org/10.1037/0096-1523.25.4.1076

Bleuse, S., Delval, A., & Defebvre, L. (2014). Does overestimation of an object's mass during arm-raising modify postural adjustments? *Neuroscience Letters, 578,* 12–16. http://dx.doi.org/10.1016/j.neulet.2014.06.016

Bonifazi, M., Ciccarone, G., della Volpe, R., Spidalieri, R., & Rossi, A. (2004). Influences of chemically-induced muscle pain on power output of ballistic upper limb movements. *Clinical Neurophysiology, 115,* 1779–1785. http://dx.doi.org/10.1016/j.clinph.2004.03.014

Botter, A., Oprandi, G., Lanfranco, F., Allasia, S., Maffiuletti, N. A., & Minetto, M. A. (2011). Atlas of the muscle motor points for the lower limb: Implications for electrical stimulation procedures and electrode positioning. *European Journal of Applied Physiology, 111,* 2461–2471. http://dx.doi.org/10.1007/s00421-011-2093-y

Brown, M. A., Howatson, G., Keane, K., & Stevenson, E. J. (2015). Exercise-induced muscle damage following dance and sprint specific exercise in females. *The Journal of Sports Medicine and Physical Fitness*. Advance online publication.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum.

Comalli, D., Franchak, J., Char, A., & Adolph, K. (2013). Ledge and wedge: Younger and older adults' perception of action possibilities. *Experimental Brain Research, 228,* 183–192. http://dx.doi.org/10.1007/s00221-013-3550-0

Crameri, R. M., Aagaard, P., Qvortrup, K., Langberg, H., Olesen, J., & Kjaer, M. (2007). Myofibre damage in human skeletal muscle: Effects of electrical stimulation versus voluntary contraction. *The Journal of Physiology, 583,* 365–380. http://dx.doi.org/10.1113/jphysiol.2007.128827

Deschamps, T., Hug, F., Hodges, P. W., & Tucker, K. (2014). Influence of experimental pain on the perception of action capabilities and performance of a maximal single-leg hop. *The Journal of Pain, 15,* 271.e1–271.e7. http://dx.doi.org/10.1016/j.jpain.2013.10.016

Fajen, B. R., Riley, M. A., & Turvey, M. T. (2009). Information, affordances, and control of action in sports. *International Journal of Sport Psychology, 40,* 79–107.

French, D. J., Noël, M., Vigneau, F., French, J. A., Cyr, C. P., & Evans, R. T. (2005). PCS-CF: A French-language, French-Canadian adaptation of the Pain Catastrophizing Scale. *Canadian Journal of Behavioural Science, 37,* 181–192. http://dx.doi.org/10.1037/h0087255

Graven-Nielsen, T., Arendt-Nielsen, L., Svensson, P., & Jensen, T. S. (1997). Experimental muscle pain: A quantitative study of local and referred pain in humans following injection of hypertonic saline. *Journal of Musculoskeletal Pain, 5,* 49–69. http://dx.doi.org/10.1300/J094v05n01_04

Graven-Nielsen, T., Lund, H., Arendt-Nielsen, L., Danneskiold-Samsøe, B., & Bliddal, H. (2002). Inhibition of maximal voluntary contraction force by experimental muscle pain: A centrally mediated mechanism. *Muscle & Nerve, 26,* 708–712. http://dx.doi.org/10.1002/mus.10225

Graven-Nielsen, T., McArdle, A., Phoenix, J., Arendt-Nielsen, L., Jensen, T. S., Jackson, M. J., & Edwards, R. H. (1997). In vivo model of muscle pain: Quantification of intramuscular chemical, electrical, and pressure changes associated with saline-induced muscle pain in humans. *Pain, 69,* 137–143. http://dx.doi.org/10.1016/S0304-3959(96)03270-8

Hackney, A. L., & Cinelli, M. E. (2013). Older adults are guided by their dynamic perceptions during aperture crossing. *Gait & Posture, 37,* 93–97. http://dx.doi.org/10.1016/j.gaitpost.2012.06.020

Higuchi, T., Murai, G., Kijima, A., Seya, Y., Wagman, J. B., & Imanaka, K. (2011). Athletic experience influences shoulder rotations when running through apertures. *Human Movement Science, 30,* 534–549. http://dx.doi.org/10.1016/j.humov.2010.08.003

Jiang, Y., & Mark, L. S. (1994). The effect of gap depth on the perception of whether a gap is crossable. *Perception & Psychophysics, 56,* 691–700. http://dx.doi.org/10.3758/BF03208362

Jubeau, M., Sartorio, A., Marinone, P. G., Agosti, F., Van Hoecke, J., Nosaka, K., & Maffiuletti, N. A. (2008). Comparison between voluntary and stimulated contractions of the quadriceps femoris for growth hormone response and muscle damage. *Journal of Applied Physiology, 104,* 75–81. http://dx.doi.org/10.1152/japplphysiol.00335.2007

Kennedy, A., Hug, F., Sveistrup, H., & Guével, A. (2013). Fatiguing handgrip exercise alters maximal force-generating capacity of plantarflexors. *European Journal of Applied Physiology, 113,* 559–566. http://dx.doi.org/10.1007/s00421-012-2462-1

Lacourpaille, L., Nordez, A., Hug, F., Couturier, A., Dibie, C., & Guilhem, G. (2014). Time-course effect of exercise-induced muscle damage on localized muscle mechanical properties assessed using elastography. *Acta Physiologica (Oxford, England), 211,* 135–146. http://dx.doi.org/10.1111/apha.12272

Leeuw, M., Goossens, M. E., van Breukelen, G. J., Boersma, K., & Vlaeyen, J. W. (2007). Measuring perceived harmfulness of physical activities in patients with chronic low back pain: The Photograph Series of Daily Activities—Short electronic version. *The Journal of Pain, 8,* 840–849. http://dx.doi.org/10.1016/j.jpain.2007.05.013

Linkenauger, S. A., Witt, J. K., & Proffitt, D. R. (2011). Taking a hands-on approach: Apparent grasping ability scales the perception of object size. *Journal of Experimental Psychology: Human Perception and Performance, 37,* 1432–1441. http://dx.doi.org/10.1037/a0024248

Malatesta, D., Cattaneo, F., Dugnani, S., & Maffiuletti, N. A. (2003). Effects of electromyostimulation training and volleyball practice on jumping ability. *Journal of Strength and Conditioning Research, 17,* 573–579.

Maly, M. R., Costigan, P. A., & Olney, S. J. (2006). Determinants of self-efficacy for physical tasks in people with knee osteoarthritis. *Arthritis and Rheumatism, 55,* 94–101. http://dx.doi.org/10.1002/art.21701

Munro, A. G., & Herrington, L. C. (2011). Between-session reliability of four hop tests and the agility T-test. *Journal of Strength and Conditioning Research, 25,* 1470–1477. http://dx.doi.org/10.1519/JSC.0b013e3181d83335

Patel, K. V., Guralnik, J. M., Dansie, E. J., & Turk, D. C. (2013). Prevalence and impact of pain among older adults in the United States: Findings from the 2011 National Health and Aging Trends Study. *Pain, 154,* 2649–2657. http://dx.doi.org/10.1016/j.pain.2013.07.029

Pijpers, J. R., Oudejans, R. R. D., & Bakker, F. C. (2007). Changes in the perception of action possibilities while climbing to fatigue on a climbing

wall. *Journal of Sports Sciences, 25,* 97–110. http://dx.doi.org/10.1080/02640410600630894

Ramenzoni, V. C., Davis, T. J., Riley, M. A., & Shockley, K. (2010). Perceiving action boundaries: Learning effects in perceiving maximum jumping-reach affordances. *Attention, Perception & Psychophysics, 72,* 1110–1119. http://dx.doi.org/10.3758/APP.72.4.1110

Reid, A., Birmingham, T. B., Stratford, P. W., Alcock, G. K., & Giffin, J. R. (2007). Hop testing provides a reliable and valid outcome measure during rehabilitation after anterior cruciate ligament reconstruction. *Physical Therapy, 87,* 337–349. http://dx.doi.org/10.2522/ptj.20060143

Sakurai, R., Fujiwara, Y., Ishihara, M., Higuchi, T., Uchida, H., & Imanaka, K. (2013). Age-related self-overestimation of step-over ability in healthy older adults and its relationship to fall risk. *BMC Geriatrics, 13,* 44. http://dx.doi.org/10.1186/1471-2318-13-44

Slater, H., Arendt-Nielsen, L., Wright, A., & Graven-Nielsen, T. (2003). Experimental deep tissue pain in wrist extensors—A model of lateral epicondylalgia. *European Journal of Pain (London, England), 7,* 277–288. http://dx.doi.org/10.1016/S1090-3801(02)00141-6

Sullivan, M. J. L., Bishop, S., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment, 7,* 432–524. http://dx.doi.org/10.1037/1040-3590.7.4.524

Tabor, A., Catley, M. J., Gandevia, S. C., Thacker, M. A., Spence, C., & Moseley, G. L. (2015). The close proximity of threat: Altered distance perception in the anticipation of pain. *Frontiers in Psychology, 6,* 626. http://dx.doi.org/10.3389/fpsyg.2015.00626

Tsao, H., Tucker, K. J., Coppieters, M. W., & Hodges, P. W. (2010). Experimentally induced low back pain from hypertonic saline injections into lumbar interspinous ligament and erector spinae muscle. *Pain, 150,* 167–172. http://dx.doi.org/10.1016/j.pain.2010.04.023

Weast, J. A., Shockley, K., & Riley, M. A. (2011). The influence of athletic experience and kinematic information on skill-relevant affordance perception. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 64,* 689–706. http://dx.doi.org/10.1080/17470218.2010.523474

Witt, J. K., Linkenauger, S. A., Bakdash, J. Z., Augustyn, J. S., Cook, A., & Proffitt, D. R. (2009). The long road of pain: Chronic pain increases perceived distance. *Experimental Brain Research, 192,* 145–148. http://dx.doi.org/10.1007/s00221-008-1594-3

Witt, J. K., & Riley, M. A. (2014). Discovering your inner Gibson: Reconciling action-specific and ecological approaches to perception-action. *Psychonomic Bulletin & Review, 21,* 1353–70. http://dx.doi.org/10.3758/s13423-014-0623-4

Zory, R., Boërio, D., Jubeau, M., & Maffiuletti, N. A. (2005). Central and peripheral fatigue of the knee extensor muscles induced by electromyostimulation. *International Journal of Sports Medicine, 26,* 847–853. http://dx.doi.org/10.1055/s-2005-837459

Received September 30, 2015
Revision received February 23, 2016
Accepted March 7, 2016 ■

Nephrology •• (2016) ••–••

Brief Communication

Combining intra-dialytic exercise and nutritional supplementation in malnourished older haemodialysis patients: Towards better quality of life and autonomy

DAN HRISTEA,[1†] THIBAULT DESCHAMPS,[2†] ANNE PARIS,[1] GAËLLE LEFRANÇOIS,[3] VALÉRIE COLLET,[4] CORNELIU SAVOIU,[1] SOPHIE OZENNE,[1] STÉPHANIE COUPEL,[3] ANGELO TESTA[3] and JUSTINE MAGNARD[2†]

[1]Dialysis Unit Laënnec, ECHO Association, [2]Laboratory MIP (UPRESEA4334) University of Nantes France, [3]Dialysis Unit Confluent, ECHO Association, [4]Biometrics, CHU Nantes, Nantes, France

KEY WORDS:
aging, intra-dialytic exercise, nutrition, protein energy wasting, quality of life.

Correspondence:
Dan HRISTEA (MD), Expansion des centres de dialyse de l'Ouest « ECHO » Nantes, 23, rue des Piliers de la Chauvinière, 448000 Saint Herblain, FRANCE. Email: dhristea@echo-sante.com

Accepted for publication 14 February 2016.

doi: 10.1111/nep.12752

Declaration: There is no conflict of interest in the preparation of this manuscript.

†HD and TD contributed equally and both are considered first-authors.

ABSTRACT:

Protein-energy wasting (PEW), defined as a loss of body protein mass and fuel reserves, is a powerful predictor of adverse outcomes in haemodialysis (HD) patients. Robust arguments suggest that intra-dialytic exercise, combined with oral/parenteral nutrition, enhances the effect of nutritional interventions in HD patients. This pilot randomized controlled trial investigated the feasibility and the effects of a 6 month intra-dialytic cycling program combined to a nutritional support on PEW, physical functioning (gait, balance, muscle strength) and quality of life (QoL) in older HD patients (mean age 69.7 ± 14.2 years). Twenty-one patients fulfilling diagnostic criteria of PEW were randomly assigned to Nutrition-Exercise group (GN-Ex, $n = 10$) or Nutrition group (GN, $n = 11$). Both groups received nutritional supplements in order to reach recommended protein and energy intake goals. In addition GN-Ex completed a cycling program. No significant difference between groups was found in the number of patients having reached remission of PEW. Likewise, no change was observed in serum-albumin, -prealbumin, C-reactive protein, body mass index, lean- and fat-tissue index, or quadriceps force. Interestingly, we found positive effects of exercise on physical function and QoL for the GN-Ex, as evidenced by a significant improvement in the 6-min walk test (+22%), the absence of decline in balance (unlike the GN), and a noteworthy increase in QoL (+53%). Combining intra-dialytic exercise and nutrition in HD patients is feasible, and well accepted, improves physical function and QoL but it appears not to have the potential to reverse PEW.

Protein-energy wasting (PEW) is an insidious complication in haemodialysis (HD) patients,[1] defined as the loss of body protein mass and fuel reserves.[2] The mechanisms causing PEW are complex: low nutrient intake, loss of nutrients in dialysate, and abnormalities that stimulate protein degradation and/or decrease protein synthesis. Accordingly, prevention and treatment of PEW aim to replenish protein and energy stores and stimulate anabolic processes. Traditional management of PEW consists of dietary counselling, oral nutritional supplements (ONC), enteral feeding, and in severe cases, the use of intra-dialytic or total parenteral nutrition.[3]

Multiple studies have pointed out anabolic effects of physical activity in HD patients.[4] Both resistance and endurance training induce transcriptional changes in genes, which stimulate anabolic signalling pathways.[5] Thus intra-dialytic exercise, combined with oral or parenteral nutrition, enhances amino acid uptake and protein accretion in the muscles.[6] Programming exercise training during the HD session has important advantages, particularly better adherence by patients who feel safer[7] and increased dialysis efficiency through improved removal of solutes.[8]

In sum, there are robust arguments suggesting a clinical interest in prescribing intra-dialytic exercise combined with nutritional interventions to PEW patients. However, no randomized controlled open-label trial has investigated the effect of such an intervention on PEW (see[9] for details). This pilot trial aimed to determine whether an intra-dialytic exercise program combined with nutritional support is able to safely reverse PEW

and induce favourable effects on functional performances (gait, postural control and muscular strength), body composition, and quality of life (QoL) in older HD patients.

METHODS

The Ethical Committee of Nantes Ouest IV (ref: n°2012-A01662-41) approved the study. The study protocol is described in detail elsewhere,[14] and was registered at http://clinicaltrials.gov/:NCT01813851.

In sum, all 210 patients of two units treated by haemodialysis or online haemo-diafiltration were screened for serum albumin, serum prealbumin, C-reactive protein (CRP) levels, body mass index (BMI), and the presence of weight loss according to the PEW criteria. Eligibility criteria were age > 18 years, minimum haemodialysis vintage of 3 months, and satisfying the criteria for PEW[2] (three out of the four listed categories and at least one test in each of selected category): (i) *Serum chemistry criteria*: Serum albumin level < 3.8 g d/L (Bromcresol Green), or serum prealbumin < 300 mg/L); (ii) *Body mass criteria:* BCI < 23 kg/m^2, or unintentional weight loss > 5% over 3 months or > 10 % over 6 months); (iii) *Muscle mass criteria*: lean body mass (LBM) estimated by bioimpedance spectroscopy (Body Composition Monitor (BCM) Fresenius, Bad Homburg, Germany) lower than the 10th percentile of an aged-matched normal population; and (iv) *Dietary intake criteria*: Unintentional low dietary protein intake < 1 g/kg of ideal weight/day for at least 2 months, unintentional low dietary energy intake < 30 kcal/kg of ideal weight /day for at least 2 months.

Twenty-one HD patients were randomly assigned to Nutrition-Exercise group (GN-Ex) (mean age 68.5 ± 14 years; $n = 10$) or Nutrition group (GN) (mean age 70.8 ± 15.2 years; $n = 11$). Seven patients in GN-Ex and nine patients in GN completed the 6 months of the study (Table 1). Causes of dropout were death due to comorbidities and not related to the interventions (1 of GN; 1 of GN-Ex), undercurrent disease (2 of GN-Ex), and withdrawal of consent (1 GN) (Fig. 1).

Nutritional intervention

All patients received dietary counselling by a dietician. The prescription of ONC or intra-dialytic parenteral nutrition (IDPN) (if ONC intolerance) was adapted to patient needs according to the dietary record to attain goals set by the EBP guidelines (see[9] for details). No changes in the dialysis prescription were allowed except modification of dry weight.

Exercise program

Patients in GN-Ex completed a 6-month training program, which consisted of a progressive submaximal individualized cycling exercise using a cycloergometer at the beginning of each of the three weekly dialysis sessions at an intensity perceived as moderate. We aimed at reaching 30 min duration of continuous cycling at intensity, corresponding to the level "3 – moderate" on the Borg Rating Perceived Exertion (RPE) scale (see[9] for details).

Primary outcome

The number of patients who no longer were in a state of PEW was compared at study end. Remission of PEW was defined as normalization of albumin, prealbumin and of the lean tissue index.

Biological measures

Serum albumin and -prealbumin were measured monthly. All patients had a monthly routine serum chemistry follow-up, including serum electrolytes, -bicarbonate, -urea and -creatinine, urea reduction rate KT/V.

Body composition

Body-composition (lean tissue index, (LTI, kg/m^2) and fat tissue index (FTI, kg/m^2) were measured using the Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany) every 2 months.

Assessment of physical capacity, balance and muscle strength

Gait was assessed using the 6-min walk test (6MWT), which is a reliable measure of physical capacity. Muscle strength was measured using a manual dynamometer (Metil Industry, Belgium) and the balance performance was measured using a Kistler force platform using a protocol described elsewhere.[9] In sum, for all data collection of postural sway, the system was linked to BioWare 5.2.2 software thus providing centre-of-pressure (COP) parameters, such as area (95% confidence ellipse).

Quality of life

The generic self-reported Medical Outcome Study Short Form 36 (SF-36) was used as a valid assessment of health-related QoL in dialysis patients.[10]

Statistics

To test the effects of exercise program on all outcome measures, univariate two (Group: GN-Ex *vs.* GN) × 4 (Time: ***t*0**, ***t*+2m**, ***t*+4m** and ***t*+6m**) ANOVAs were performed for each dependent variable, with Newman-Keuls post-hoc tests. Partial eta square ($p\eta 2$) values are reported, with $p\eta 2 = 0.07$ and $p\eta 2 \geq 0.14$ considered moderate and large effects, respectively.

Table 1 Clinical characteristics of eligible haemodialysis (HD) patients at the onset of the study ($n = 16$) and secondary outcomes as a function of time.

	GN-Ex ($n = 7$)				GN ($n = 9$)			
Clinical characteristics at *t*0 *								
Age (years) (mean ± SD)	68.5 ± 13.97				70.8 ± 15.18			
Dry weight (kg) (mean ± SD)	53.61 ± 9.73				59.44 ± 10.04			
BMI (kg/m^2) (mean ± SD)	20.51 ± 3.53				20.81 ± 2.76			
LTI (kg/m^2) (mean ± SD)	11.01 ± 1.88				12.35 ± 2.15			
FTI (kg/m^2) (mean ± SD)	9.16 ± 4.00				8.18 ± 3.95			
Duration of HD (months) median (interquartile range)	139 (255.5)				96 (86)			
	*t*0	*t*+2m	*t*+4m	*t*+6m	*t*0	*t*+2m	*t*+4m	*t*+6m
Biological parameters								
Serum albumin (*g/L*) c	38.31 ± 2.88	39.96 ± 3.45	39.88 ± 2.96	39.33 ± 2.51	39.64 ± 3.72	37.82 ± 4.55	38.81 ± 3.25	39.12 ± 3.67
Serum prealbumin (*mg/L*)	225.71 ± 44.67	236.67 ± 58.88	252.86 ± 42.31	231.67 ± 27.14	251.11 ± 68.45	242.22 ± 73.11	242.22 ± 46.04	226.67 ± 55.90
C-reactive protein (*mg/L*)	5.71 ± 8.16	3.03 ± 2.67	5.79 ± 5.98	1.75 ± 1.62	6.22 ± 5.78	10.51 ± 23.91	2.21 ± 2.49	4.99 ± 5.96
Haemoglobin (*g/L*)	11.16 ± 1.12	11.3 ± 1.19	11.26 ± 0.92	10.92 ± 0.69	10.68 ± 0.69	11.12 ± 0.68	11.06 ± 0.75	11.21 ± 0.66
Urea (*mmol/L*)	18.6 ± 4.88	20.65 ± 6.74	20.84 ± 5.13	16.36 ± 6.49	21.68 ± 7.51	19.39 ± 4.45	18.31 ± 5.14	21.74 ± 6.35
Serum Creatinine (*umol/L*)	489.43 ± 195.76	538.86 ± 208.16	529.36 ± 161.14	484.97 ± 142.86	689 ± 180.02	709.56 ± 176.09	673.79 ± 160.44	724.76 ± 177.81
Kt/V	2.02 ± 0.38	1.99 ± 0.26	1.94 ± 0.45	1.97 ± 0.52	1.73 ± 0.38	1.77 ± 0.50	1.75 ± 0.41	1.73 ± 0.40
Normalized protein catabolic rate (*g/kg per day*)	1.21 ± 0.32	1.29 ± 0.41	1.25 ± 0.34	1 ± 0.24	1.22 ± 0.43	1.13 ± 0.35	1.05 ± 0.35	1.28 ± 0.35
Serum Phosphate (mmol/L)	1.47 ± 0.59	1.69 ± 0.59	1.39 ± 0.35	1.32 ± 0.42	1.65 ± 0.56	1.78 ± 0.67	1.46 ± 0.33	1.59 ± 0.42
Serum bicarbonate (mmol/L)	22.57 ± 2.15	21.43 ± 1.99	21.29 ± 1.11	22.43 ± 3.98	20.44 ± 1.74	20.40 ± 2.79	20.75 ± 2.61	21.11 ± 3.02
Serum calcium (mmol/L)	2.26 ± 0.16	2.25 ± 0.15	2.30 ± 0.13	2.25 ± 0.12	2.34 ± 0.21	2.16 ± 0.07	2.25 ± 0.09	2.29 ± 0.12
Nutritional parameters								
Total energy intake (*kcal/kg*) a	26.56 ± 3.92	30.30 ± 6.83	30.18 ± 5.31	30.09 ± 6.64	21.20 ± 4.25	23.16 ± 5.77	25.14 ± 6.51	27.53 ± 8.42
Total protein intake (*g/kg*) b	1.05 ± 0.23	1.37 ± 0.44	1.23 ± 0.28	1.17 ± 0.26	0.93 ± 0.16	1.20 ± 0.23	1.09 ± 0.30	1.17 ± 0.38
Body composition								
Body mass index (*kg/m^2*)	20.51 ± 3.53	20.53 ± 3.65	21.61 ± 2.57	20.89 ± 1.19	20.81 ± 2.76	20.77 ± 2.58	20.98 ± 2.49	20.93 ± 2.57
LTI (*kg/m^2*)	11.01 ± 1.88	11.17 ± 1.75	11.22 ± 1.83	11.15 ± 1.75	12.35 ± 2.15	12.16 ± 2.30	12.34 ± 2.61	12.51 ± 2.85
FTI (*kg/m^2*)	9.16 ± 4.00	9.12 ± 4.86	10.51 ± 3.59	11.05 ± 3.55	8.18 ± 3.95	8.2 ± 4.20	8.26 ± 4.74	8.06 ± 4.58
Functional Measures								
6 min walk (*m*) b	284 ± 166.60	332.85 ± 132.52	342.28 ± 133.78	346.28 ± 134.88	319.66 ± 109.83	315.66 ± 124.43	304.66 ± 117.89	295.77 ± 121.07
Knee extension maximal strength (*kg*)b	10.22 ± 4.95	10.23 ± 3.32	10.09 ± 3.3	10.56 ± 3.49	9.97 ± 4.41	9.38 ± 4.00	8.14 ± 2.01	7.87 ± 2.19
COP Area (*mm^2*) c	405.19 ± 223.47	395.07 ± 297.26	474.77 ± 357.09	307.4 ± 143.74	505.54 ± 341.37	658.18 ± 369.14	525.36 ± 276.77	892.40 ± 845.95
SF-36 Scale Scores								
SF36 Physical dimension (%) c	60.52 ± 19.7	77.13 ± 15.43	81.49 ± 15.16	84.7 ± 13.32	65.62 ± 16.91	56.6 ± 27.14	65.44 ± 15.43	59.87 ± 21.37
SF36 Mental dimension (%) b	43.41 ± 26.71	58.46 ± 19.47	69.99 ± 10.6	74.3 ± 10.61	60.94 ± 20.12	47.65 ± 17.15	56.73 ± 15.11	52.07 ± 16.11

*Note that no significant differences for all baseline characteristics were found between groups (independent *t*-tests, Mann–Whitney test or χ^2 as appropriate) aMain effect of Group bMain effect of Time cGroup × Time interaction Values are expressed as means (± standard deviation). GN-Ex, nutrition and exercise group, GN, nutrition group, *t*+2m, 8th week, *t*+4m, 16th week, *t*+6m, 24th week of the 6 month adapted rehabilitation program. BMI, body mass index; COP, centre of pressure; FTI, fat tissue index; HD, haemodialysis; LTI, lean tissue index; SF-36, short form 36.

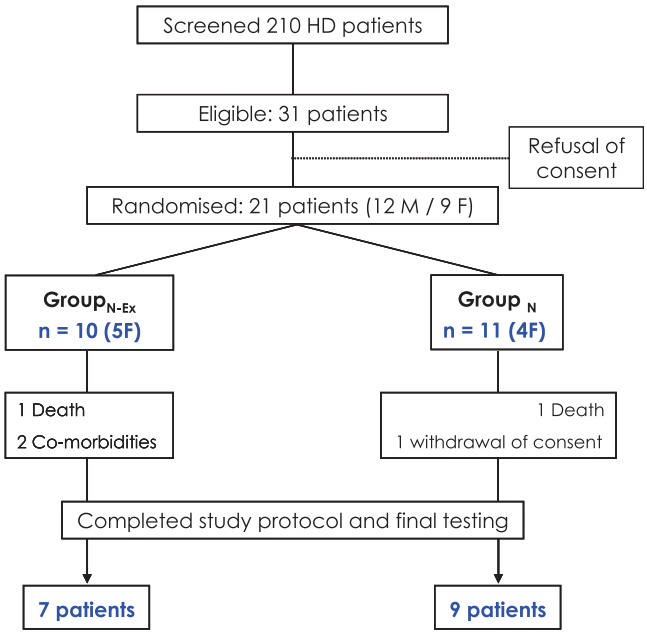

Fig. 1 Consort statement.

RESULTS

All statistics are summarized in Table 1. Note that no differences between final groups at ***t*0** were found for all baseline characteristics.

Total energy and protein intake

The analyses showed a main Group effect ($P = 0.03$, $p\eta 2 = 0.3$), with a higher total energy intake for the GN-Ex as compared to GN. For the total protein intake, only a Time effect was observed ($P = 0.01$, $p\eta 2 = 0.2$), with post-hoc differences between ***t*0** and ***t*+2m** (+39.8%) and ***t*+2m** and ***t*+4m** (−10.8%).

Compliance, tolerance and volume training

Compliance to the cycling sessions was 87.7 ± 17.1%, with tiredness and hypotension as main reasons for not training. Overall, the exercise program was well tolerated. One patient with a history of cardiac arrhythmia and frequent hyperkalaemia presented an episode of hypotension and tachyarrhythmia after a cycling session. The investigator decided to stop the study in this patient. No other exercise-related serious adverse events were reported.

A significant bimonthly progression of the training parameters, such as cycling covered distance (~103.8 ± 46.74 km/month) and cycling duration (~355.03 ± 95.95 min/month) ($P < 0.01$, $p\eta 2 > 0.6$) was observed. The total mean virtual distance travelled by each patient was 622.9 ± 261.3 km.

Primary outcome

No difference emerged between groups in the number of patients having reached remission of PEW ($\chi 2 = 0.14$, $P = 0.7$). At study end, two patients in GN-Ex and four in GN no longer met all PEW criteria.

Secondary outcomes (Table 1)

Biological markers of nutrition

Concerning albumin level, only a Time × Group interaction ($P = 0.03$, $p\eta 2 = 0.2$) was found, with an increase for GN-Ex and a decrease in the GN between ***t*0** and ***t*+2m**. For prealbumin, no effect was observed.

Body composition

The BMI, LTI, and FTI did not significantly differ as a function of Group or Time (all $P > 0.1$). No interaction was observed ($P > 0.7$).

6MWT performance

A Time × Group interaction was identified ($P < 0.001$, $p\eta 2 = 0.4$). The covered distance increased between ***t*0** and ***t*+2m** and between ***t*+4m** and ***t*+6m** only for the GN-Ex ($P < 0.01$). No progression was observed for the GN (Fig. 2A).

Postural control

The ANOVAs revealed a Group × Time interaction only for Area, revealing a higher postural instability between ***t*0** and ***t*+6m** for GN patients whereas no change was observed for GN-Ex ($P < 0.01$, $p\eta 2 = 0.2$).

Muscle strength

The analysis showed a small decrease over Time ($P = 0.02$, $p\eta 2 = 0.2$), with differences between ***t*0** and ***t*+2m**, and ***t*+4m** and ***t*+6m**.

Quality of life

Physical health. Only a Time × Group interaction was identified ($P < 0.01$, $p\eta 2 = 0.2$), with an increase in QoL for GN-Ex between ***t*0** and ***t*+2m** and between ***t*+4m** and ***t*+6m**, and a decline between ***t*0** and ***t*+2m** for GN ($P < 0.03$). Significant differences were found between groups from ***t*+4m** to ***t*+6m** (Fig. 2B). *Mental health.* A Time × Group interaction was also identified ($P = 0.001$, $p\eta 2 = 0.4$), demonstrating that the mental health QoL increased between ***t*0** and ***t*+2m** and between ***t*+4m** and ***t*+6m** but only for the GN-Ex. Finally, groups differed in the mental scores at ***t*+6m**.

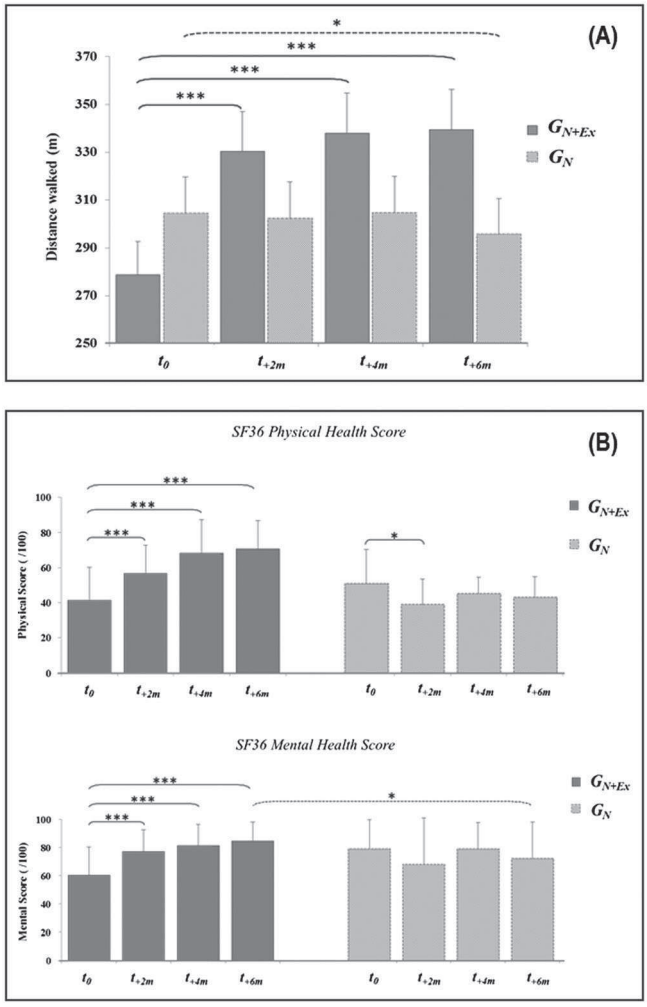

Fig. 2 (A). Evolution of the distance covered during the 6-min walk test throughout 6 months of study. (B) Evolution of the SF36 "physical health" score (*top*) and the "mental health" score (*bottom*) throughout 6 months of study. The vertical bars indicate the standard deviation. *t*+2m, eighth week, *t* +4m, sixteenth week, *t*+6m, twenty-fourth week of the 6 month adapted rehabilitation program. * $P < 0.05$, *** $P < 0.001$

DISCUSSION

To our knowledge, ACTINUT is the first pilot trial to investigate the primary effects of a 6 month adapted exercise program, combined with nutritional support, on PEW in severely malnourished older HD patients. Our results showed that GN-Ex patients started with a higher intake, but changed their intake to a similar extent as the GN. However, contrary to our expectations,[9] no significant difference between groups emerged in PEW reversal. Interestingly, the exercise program had positive effects on physical function and QoL in the GN-Ex, as evidenced by an improvement in the 6MWT (+22%), the absence of decline in balance (unlike the GN), and a noteworthy increase in QoL (+53%). Overall, these results indicate clear benefits of exercise on physical capacity and QoL for HD patients.[11] Overall, the exercise program was free of noticeable adverse effects, well tolerated and accepted by patients (87.7% of compliance). The death of one patient in each group, unrelated to the study intervention, is not surprising in this population at high risk of mortality.

Clinically, the most relevant effects of this intervention are the increase in the 6MWT performance, which has been traditionally used as a measure of physical function in numerous exercise programs in the HD population.[12–14] These studies also found significant increases in 6MWT following an exercise training, but in younger HD patients.[14,15] However, in older individuals, it has been shown that impairments in motor function, such as gait speed, are highly predictive of subsequent disability in performing activities of daily living,[16] nursing home admissions, and mortality.[17] The observed improvement in physical capabilities might contribute, over time, to delay patients' physical deconditioning and maintain their autonomy. The balance assessment reinforced this key point. The GN patients have higher postural sway and therefore potentially higher risk of falls with consequent morbidity and disability.[18] Finally, the increase in both physical (+72%) and mental dimensions (+40%) of QoL observed in GN-Ex is consistent with Painter's study,[17] which demonstrated that the frailest patients experienced the greatest improvement in QoL following exercise. The QoL scores are highly predictive of hospitalizations and mortality[19]; thus, the improvement obtained in GN-Ex patients is even more interesting, satisfactory, and fully positive, given the specific characteristics of the studied population.

The trial's strengths are the randomized design and the 6 months follow up. The principal limitation of this pilot study is the relatively low number of patients. In our population, the prevalence of PEW seemed to be lower compared to those reported by recent studies which found a prevalence of 40 % of PEW at baseline and after 12 months of follow up.[20] Currently, only about 15% of the screened 210 patients fulfilled the required criteria of PEW. Finally, due to medical considerations, 21 (10%) of all patients were eligible and only 16 patients completed the study. The regular nutritional counselling and support started early in the course of ESRD in our establishment might explain this low prevalence. Our experience highlights the difficulty of recruiting HD patients for exercise studies and to maintain them over a longer period of time.

Although the trial was underpowered to detect differences between groups with regard to the primary outcome, the reported effect sizes were large, supporting herby the positive effects of exercise on QoL and functional autonomy. These findings, which require confirmation in a larger population, offer new arguments for integrating exercise programs in multimodal interventional trials aimed at preventing PEW and maintaining patients' autonomy and well-being.

ACKNOWLEDGEMENTS

The study was sponsored by the University Hospital of Nantes. The research is also sponsored in part by the ACTICLAN prize provided by Fresenius Kabi France, and by grants from the

Region of Pays de la Loire, France, for the projects "RP3AP" and "LMA". We thank all of the study subjects and for their participation. We thank Mrs Marie Claude Legall, Mrs Isabelle Bertho, dieticians for performing the nutritional records and counselling, the dialysis nurses for their invaluable help in performing the exercise program and Mrs Angelique Colin for her important role in data collection.

AUTHOR CONTRIBUTIONS

Conception and design of the experiments: DH, AP, TD, JM.

Collection, assembly, analysis and interpretation of data: DH, TD, JM, AP, GL, VC.

Drafting the article or revising it critically for important intellectual content: DH, TD, JM, AT, CS, SO, SC.

TRIAL REGISTRATION

The protocol for this study is registered at http://clinicaltrials.gov/: NCT01813851

REFERENCES

1. Segall L, Moscalu M, Hogaş S *et al.* Protein-energy wasting, as well as overweight and obesity, is a long-term risk factor for mortality in chronic hemodialysis patients. *Int. Urol. Nephrol.* 2014; **46**: 615–21.
2. Fouque D, Kalantar-Zadeh K, Kopple J *et al.* A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* 2008; **73**: 391–8.
3. Fouque D, Vennegoor M, ter Wee P *et al.* EBPG guideline on nutrition. *Nephrol. Dial. Transplant.* 2007; **22**: ii45–87.
4. Smart N, Steele M. Exercise training in haemodialysis patients: a systematic review and meta-analysis. *Nephrology* 2011; **16**: 626–32.
5. Kopple JD, Wang H, Casaburi R *et al.* Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. *J. Am. Soc. Nephrol.* 2007; **8**: 2975–86.
6. Majchrzak KM, Pupim LB, Flakoll PJ, Ikizler TA. Resistance exercise augments the acute anabolic effects of intradialytic oral nutritional supplementation. *Nephrol. Dial. Transplant.* 2008; **23**: 1362–9.
7. Konstantinidou E, Koukouvou G, Kouidi E, Deligiannis A, Tourkantonis A. Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. *J. Rehabil. Med.* 2002; **34**: 40–45.
8. Kong CH, Tattersall JE, Greenwood RN, Farrington K. The effect of exercise during haemodialysis on solute removal. *Nephrol. Dial. Transplant.* 1999; **14**: 2927–31.
9. Magnard J, Deschamps T, Cornu C, Paris A, Hristea D. Effects of a six-month intradialytic physical ACTIvity program and adequate NUTritional support on protein-energy wasting, physical functioning and quality of life in chronic hemodialysis patients: ACTINUT study protocol for a randomised controlled trial. *BMC Nephrol.* 2013; **14**: 259.
10. Mingardi G, Cornalba L, Cortinovis E *et al.* Health-related quality of life in dialysis patients: a report from an Italian study using the SF-36 health survey: DIA-QOL group. *Nephrol. Dial. Transplant.* 1999; **14**: 1503–10.
11. Esteve Simó V, Junqué A, Fulquet M *et al.* Complete Low-Intensity Endurance Training Programme in Haemodialysis Patients: Improving the Care of Renal Patients. *Nephron Clin. Pract.* 2014; **128**.
12. Headley S, Germain M, Mailloux P *et al.* Resistance training improves strength and functional measures in patients with end stage renal disease. *Am. J. Kidney Dis.* 2002; **40**: 355–64.
13. Painter P, Carlson L, Carey S, Paul SM, Myll J. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. *Am. J. Kidney Dis.* 2000; **35**: 482–92.
14. Johansen K, Painter P, Sakkas G *et al.* Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized controlled trial. *J. Am. Soc. Nephrol.* 2006; **17**: 2307–14.
15. Painter P, Carlson L, Carey S, Paul SM, Myll J. Low-functioning hemodialysis patients improve with exercise training. *Am. J. Kidney Dis.* 2000; **36**: 600–8.
16. Guralnik J, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 as a predictor of subsequent disability. *New Engl. J. Med.* 1995; **43**: 845–54.
17. Painter PL, Stewart AL, Carey S. Physical functioning: Definitions, measurement, and expectations. *Adv. Ren. Replace. Ther.* 1999; **6**: 110–23.
18. Magnard J, Lardy J, Testa A, Hristea D, Deschamps T. The effect of hemodialysis session on postural strategies in older end stage renal disease patients. *Hemodial. Int.* 2015; **19**: 553–61.
19. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J. Am. Soc. Nephrol.* 2001; **12**: 2797–806.
20. Gracia-Iguacel C, González-Parra E, Pérez-Gómez MV *et al.* Prevalence of protein-energy wasting syndrome and its association with mortality in haemodialysis patients in a centre in Spain. *Nefrologia* 2013; **33**: 495–505.

Effect of Repetitive Transcranial Magnetic Stimulation on Psychomotor Retardation in Major Depression: A Pilot Feasibility Study

Véronique Thomas-Ollivier, Ph.D., Thibault Deschamps, Ph.D., Samuel Bulteau, M.D., Flora Le Gall, Anne Pichot, Pierre Valriviere, Hugo Vachon, Anne Sauvaget, M.D.

This pilot study investigated the feasibility of a comprehensive battery of tests assessing psychomotor retardation after a 3-week protocol of repetitive transcranial magnetic stimulation for depression. In addition to the beneficial effect of this treatment on depression, the results showed positive changes in psychomotor retardation.

JNP in Advance (doi: 10.1176/appi.neuropsych.15030068)

Psychomotor retardation is an important symptom of major depression and is characterized by an adverse reduction in many behavioral components, such as speech, facial expression, ideation, and fine and gross motor skills.[1,2] Although clinical rating scales are often included in the diagnostic process, they do not provide information about psychomotor functioning. Moreover, psychomotor retardation has been associated with alterations in the dorsolateral prefrontal cortex and abnormalities in the basal ganglia and dopaminergic pathways.[2–7] Modulating dorsolateral prefrontal cortex activity with noninvasive brain stimulation may improve psychomotor retardation in depression.

Repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex has been proposed as an alternative, effective, and safe therapeutic strategy for major depression.[8,9] Although its positive neurostimulation-related effects on changes in depressive symptomatology are well documented,[10] currently very few studies have investigated whether rTMS changed psychomotor retardation in major depression. Some studies have suggested that rTMS significantly decreased psychomotor retardation,[11–13] whereas others have found that rTMS did not influence this symptom.[14] In these studies, psychomotor retardation was assessed either with one specific scale or with only one item of a specific depression scale, but no detailed information about psychomotor functioning was provided. Accordingly, we hypothesized that an objective detailed assessment of psychomotor retardation was necessary to examine the effects of rTMS, applied to the dorsolateral prefrontal cortex, on this key symptom. Thus, we investigated the feasibility and acceptability of a comprehensive battery of tests for psychomotor retardation (i.e., assessing its main motor and cognitive components) in naturalistic conditions before and after a 3-week rTMS protocol for major depression.

METHODS

Participants

Seven patients with major depression participated in this open, unblinded study at Nantes University Hospital. Inclusion criteria were ages 18–75 years, diagnosis of major depression according to *DSM-IV*, partial medication resistance or low tolerance, a Montgomery-Åsberg Depression Rating Scale score ≥20, and no neurological, psychotic, or addictive disorders. Exclusion criteria included contraindication to rTMS and any change in psychoactive drugs during rTMS therapy. Patients were stimulated to the left or right add-on to continued psychopharmacological treatment in a naturalistic clinical setting. All eligible patients provided a signed form for participation. Table 1 summarizes patients' characteristics.

Study Design

A pre–post study design was adopted in which the participants underwent a battery of psychomotor tests before and after 15 sessions of active rTMS, which were conducted within a 3-week period. For rTMS, the intensity was 110% of the individual's motor threshold, which was the minimum stimulus required to induce contraction of the right thumb at least five of 10 times. Five patients underwent high-frequency rTMS on the left dorsolateral prefrontal cortex (10 Hz, 40 trains of 4 seconds with 28-second intertrain intervals,

TABLE 1. Baseline Characteristics of Seven Patients With Major Depressive Disorder and Main Results Before and After 15 Sessions of Active rTMS Within a 3-Week Period[a]

Characteristic	Baseline Value	Before rTMS Treatment	After rTMS Treatment	% Evolution	p Value
Age	54 (9.2);(45–71)				
Gender					
Men	2				
Women	5				
Tests assessing psychomotor retardation					
MADRS	32.28 (20–41)	32.28 (20–41)	18.14 (2–34)	−43.8	0.02[b]
3-Meter Timed Up and Go test (seconds)		8.18 (5.7–13.3)	7.7 (5.7–10.1)	−3.2	0.40
Balance (COP mean velocity in millimeters per second)					
Simple task					
Eyes open		12.48 (5.83)	10.68 (5.11)	−16.86	0.07
Eyes closed		16.61 (6.43)	14.80 (5.70)	−12.17	0.07
Dual task					
Eyes open		14.75 (7.50)	12.62 (6.07)	−20.74	0.04[b]
Eyes closed		18.49 (5.46)	14.91 (3.11)	−24.04	0.04[b]
Finger-tapping test (no. of taps)					
Left		51.14 (2–62)	54.42 (44–67)	+3.86	0.09
Right		54.85 (45–71)	57 (38–73)	+6.97	0.03[b]
Handgrip test (kg)					
Left		22.27 (16.66–35.03)	22.73 (11.03–37.3)	+8.09	0.23
Right		22.38 (14.16–36.44)	23.3 (16.51–36.37)	+4.62	0.73
Letter fluency task		16.60 (4.32–31)	16.57 (8–22)	−0.19	0.86
Category fluency task		19.7 (7.8–27.75)	22.14 (8–36)	+12.37	0.61
Subtest WAIS-IV symbol search		24.57 (9–36)	24.42 (8–42)	−0.61	0.90
DP-15		1.28 (0–3)	2.28 (0–5)	+10.0	0.17
RPE		4.57 (2–8)	3.42 (0–7)	−7.61	0.39

[a] Data are presented as means with standard deviations or minimum to maximum values. Maximum scores were 60, for the MADRS and WAIS-IV symbol search test, 15 for the DP-15, and 10 for the RPE. COP, center of pressure; DP-15, perceived difficulty 15-point category scale; MADRS, Montgomery-Åsberg Depression Rating Scale; RPE, ratings of perceived exertion; rTMS, repetitive transcranial magnetic stimulation.
[b] Significant evolutions (p values from paired-sample Wilcoxon tests).

providing a total of 1,600 pulses over 20 minutes). Two patients underwent low-frequency rTMS on the right dorsolateral prefrontal cortex (1 Hz, 12 trains of 60 seconds with 30-second intertrain intervals, providing a total of 720 pulses over 17 minutes). Both sessions (before and after rTMS) lasted 45 minutes and included seven psychomotor tests.

Assessments

To examine gait speed and balance, the patients performed the Timed Up and Go test. Balance was measured using a force platform to record the center-of-pressure–based parameters such as the mean velocity (in millimeters per second). Four conditions were tested (random order): two trials of standing balance with eyes open or eyes closed and two trials (eyes open versus eyes closed) of counting backward (dual task; the enumerated figures were recorded with a tape recorder). The trial duration was 60 seconds, followed by a short rest period. A finger-tapping test examined motor speed. Participants were asked to tap their right and left index finger on a lever as quickly as possible within a 10-second time interval. Finally, manual strength was measured with a handheld dynamometer and repeated with both hands three times with 30 seconds of recovery between each effort. Verbal fluency tasks were proposed to test clustering and shifting ability. Participants were required to say as many words as possible within 1 minute, which began with a given letter (R or P) and belonged to a specified semantic category (fruit or clothes). The symbol subtest of the WAIS symbol search was performed as a processing speed index. The order of the tests was randomly counterbalanced within sessions. The perceived difficulty 15-point category scale[15] assessing the perceived difficulty of performing the tasks and the 10-point Borg scale of perceived exertion[16] provided feedback regarding the feasibility and acceptability of psychomotor assessments.

RESULTS

All participants complied with the protocol. None of the participants withdrew from the study. Participants reported no adverse effects of the intervention associated with completion of the battery. The low 15-point categorical scale scores and ratings of perceived exertion suggest that psychomotor assessments are highly acceptable. Notably, the Montgomery-Åsberg Depression Rating Scale scores showed a significant decrease after the rTMS intervention (paired-sample Wilcoxon test: $p=0.02$, large Cohen's $d=1.42$). Moreover, t tests revealed positive effects of the rTMS intervention

on postural control, with a significant decrease in center-of-pressure mean velocity at post-rTMS evaluation compared with baseline assessment in a dual-task condition (eyes open condition: –20.74%, p=0.04, medium Cohen's d=0.42; eyes closed condition: –24.04%, p=0.04, large Cohen's d=1.04). Note that no change in the number of enumerated figures or errors while counting backward aloud was found. A positive effect was also found for the dominant right finger–tapping performance (+6.97%, p=0.03, small Cohen's d=0.21). All results are summarized in Table 1.

DISCUSSION

Our study showed that administering a comprehensive psychomotor battery of tests during rTMS is feasible, free of adverse effects, and well tolerated by the patients in naturalistic conditions before or after the treatment. Moreover, this pilot study—despite the limited sample—showed a significant effect of rTMS treatment on depression, which is consistent with the previous literature.[17] In addition, after the intervention, participants showed positive changes in psychomotor impairment, and they were able to perform more functional motor activities (e.g., more efficient postural control) associated with probable improvement in cognitive efficiency (e.g., improved dual postural performance). Accordingly, a better reweighting of velocity information, as indicated by lower mean velocity values after rTMS treatment, appears to be a meaningful objective index of an effective adaptive process, given the baseline characteristics related to psychomotor retardation (Mignardot et al.[18] arrived at similar conclusions in patients with Alzheimer's disease). This point is also of special interest for clinical balance assessment and the risk for falls in major depression.[19] Overall, our findings are in line with previous studies that reported improvements in the Depressive Retardation Rating Scale scores, a subjective scale validated to assess the severity of psychomotor retardation.[11] In support of our expectations, these present objective and motoric markers are likely sensitive to improvement of psychomotor retardation in depressed patients after 3 weeks of rTMS intervention.[13] However, two studies reported that psychomotor retardation significantly improved only after 10 sessions of rTMS,[11,12] yet another study with 15 sessions did not report any improvements.[14] The features of the assessment tools for psychomotor retardation may thus influence the results of the studies, regardless of rTMS duration or other parameters, such as frequency and laterality of stimulation site.[12] Concerning the underlying neurophysiological mechanisms, two different but not exclusive processes may have induced improvement of psychomotor retardation. First, such improvement is probably attributable to an effect of rTMS on dopamine release in the caudate nucleus and mesolimbic and mesostriatal systems.[20] Second, rTMS, when applied to the dorsolateral prefrontal cortex, is known to have remote effects on other dorsal regions, such as the anterior cingulate cortex, which is implicated in attentional and cognitive control. Thus, the rTMS probably reduced the attentional and cognitive deficits related to psychomotor retardation in patients with major depression.[21]

In summary, our study shows that our comprehensive battery of tests assessing psychomotor retardation is feasible, safe, and well accepted in rTMS routine practice for patients with major depression, and it allows us to identify motor and cognitive dimensions of the RPM. However, this clinical study has a number of limitations. First, a psychomotor retardation scale was not included in this feasibility study to link to the current objective tests with respect to a validated scale. We nevertheless assume that the comprehensive battery of tests we used constitutes a reliable tool for the assessment of psychomotor retardation. In addition, it might be more sensitive to positive effects of rTMS intervention compared with the psychomotor retardation scale. Second, the pilot study reported here involved a small group of participants. Nevertheless, if the reported effects are large (see the Cohen's d values as measures of effect size), supporting the consistency of the significant findings, they need to be confirmed in a larger population. These positive results would then help guide the feasible development of a large, double-blind, sham-controlled trial protocol for administering rTMS treatment in appropriate sample sizes[22] of patients with depression and for testing its predictive efficiency while accounting for the objective RPM baseline assessment.

AUTHOR AND ARTICLE INFORMATION

From the Motricité, Interactions, and Performance Laboratory (UPRES-E.A.4334), University of Nantes, Nantes, France (VT-O, TD, FLG, HV); and the Addictology and Liaison Psychiatry Dept. and the BALANCED (Behavioral Addictions and Complex Affective Disorders) Clinical Investigation Unit (UIC 18), University Hospital, Nantes, France (SB, AP, PV, AS).

Send correspondence to Dr. Thomas-Ollivier; e-mail: veronique.thomas-ollivier@univ-nantes.fr

Drs. Thomas-Ollivier and Deschamps are co-first authors.

The authors report no financial relationships with commercial interests.

Received March 25, 2015; revised June 19, 2015; accepted August 16, 2015.

REFERENCES

1. Bennabi D, Vandel P, Papaxanthis C, et al: Psychomotor retardation in depression: a systematic review of diagnostic, pathophysiologic, and therapeutic implications. Biomed Res Int 2013; 2013: 158746
2. Buyukdura JS, McClintock SM, Croarkin PE: Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35:395–409
3. Bench CJ, Friston KJ, Brown RG, et al: Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychol Med 1993; 23: 579–590
4. Bracht T, Federspiel A, Schnell S, et al: Cortico-cortical white matter motor pathway microstructure is related to psychomotor retardation in major depressive disorder. PLoS One 2012; 7:e52238
5. Martinot M, Bragulat V, Artiges E, et al: Decreased presynaptic dopamine function in the left caudate of depressed patients with

affective flattening and psychomotor retardation. Am J Psychiatry 2001; 158:314–316
6. Meyer JH, McNeely HE, Sagrati S, et al: Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. Am J Psychiatry 2006; 163:1594–1602
7. Walther S, Hügli S, Höfle O, et al: Frontal white matter integrity is related to psychomotor retardation in major depression. Neurobiol Dis 2012; 47:13–19
8. Berlim MT, Van den Eynde F, Daskalakis ZJ: A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med 2013; 43:2245–2254
9. Lefaucheur JP, André-Obadia N, Antal A, et al: Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014; 125:2150–2206
10. Dell'osso B, Camuri G, Castellano F, et al: Meta-review of metanalytic studies with repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression. Clin Pract Epidemol Ment Health 2011; 7:167–177
11. Baeken C, De Raedt R, Santermans L, et al: HF-rTMS treatment decreases psychomotor retardation in medication-resistant melancholic depression. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34:684–687
12. Höppner J, Schulz M, Irmisch G, et al: Antidepressant efficacy of two different rTMS procedures. High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. Eur Arch Psychiatry Clin Neurosci 2003; 253:103–109
13. Ullrich H, Kranaster L, Sigges E, et al: Ultra-high-frequency left prefrontal transcranial magnetic stimulation as augmentation in severely ill patients with depression: a naturalistic sham-controlled, double-blind, randomized trial. Neuropsychobiology 2012; 66: 141–148
14. Hoeppner J, Padberg F, Domes G, et al: Influence of repetitive transcranial magnetic stimulation on psychomotor symptoms in major depression. Eur Arch Psychiatry Clin Neurosci 2010; 260: 197–202
15. Delignières D: Perceived difficulty and resources investment in motor tasks. Eur Yearbook Sport Psychol 1998; 2:33–54
16. Borg G: Borg's Perceived Exertion and Pain Scales. Champaign, IL, Human Kinetics, 1998
17. Aleman A: Use of repetitive transcranial magnetic stimulation for treatment in psychiatry. Clin Psychopharmacol Neurosci 2013; 11: 53–59
18. Mignardot JB, Beauchet O, Annweiler C, et al: Postural sway, falls, and cognitive status: a cross-sectional study among older adults. J Alzheimers Dis 2014; 41:431–439
19. Launay C, De Decker L, Annweiler C, et al: Association of depressive symptoms with recurrent falls: a cross-sectional elderly population based study and a systematic review. J Nutr Health Aging 2013; 17:152–157
20. Strafella AP, Paus T, Fraraccio M, et al: Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 2003; 126:2609–2615
21. De Raedt R, Vanderhasselt MA, Baeken C: Neurostimulation as an intervention for treatment resistant depression: from research on mechanisms towards targeted neurocognitive strategies. Clin Psychol Rev (Epub ahead of print, Nov. 4, 2014)
22. Browne RH: On the use of a pilot sample for sample size determination. Stat Med 1995; 14:1933–1940

ORIGINAL ARTICLE

An enhanced experimental procedure to rationalize on the impairment of perception of action capabilities

Yannick Daviaux · Sylvain Cremoux · Jessica Tallet · David Amarantini · Christophe Cornu · Thibault Deschamps

Received: 12 January 2015 / Accepted: 13 February 2015 / Published online: 22 February 2015

Abstract It is well documented that changes in the physiological states of the perceiver–actor influence the perception of action capabilities. However, because experimental procedures of most studies involved a limitless availability for stimuli visual encoding and perceptual strategies, it remains difficult to adopt a single position among the large range of alternative interpretations for impaired perception. A reaching-to-grasp paradigm under breathing restriction was adapted from Graydon et al. (Cogn Emot 26:1301–1305, 2012) to standardize the time for encoding of stimuli information and narrowed the involvement of perceptual strategies. In the present study, we propose a highly controlled environment where the discrete information is presented during 300 ms, congruently with neurophysiological studies focused on visuomotor transformation. An underestimation of the perception of action capabilities is found under breath restriction, suggesting that 300 ms for stimuli encoding is sufficient to induce altered visuomotor brain transformations when limiting the involvement of perceptual strategies. This result suggests that such behavior could refer to an impaired brain potentiation of the perceptual occurrence, providing strong hypotheses on the brain dynamics of sensorimotor integration that underlie impaired perception of action capabilities in stressful situations.

Y. Daviaux (✉) · C. Cornu · T. Deschamps
Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), University of Nantes, 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France
e-mail: yannick.daviaux@univ-nantes.fr

T. Deschamps
e-mail: thibault.deschamps@univ-nantes.fr

S. Cremoux · J. Tallet
Laboratory "PRISSMH" (EA 4651), University of Paul Sabatier Toulouse 3, 31062 Toulouse, France

S. Cremoux
LAMIH, UMR CNRS 8201, Université de Valenciennes et du Hainaut-Cambrésis, Valenciennes, France

D. Amarantini
Inserm, Imagerie cérébrale et handicaps neurologiques UMR 825, Toulouse, France

D. Amarantini
UPS, Imagerie cérébrale et handicaps neurologiques UMR 825, Université de Toulouse, Toulouse, France

Introduction

Most behavioral studies have demonstrated that healthy humans successfully perceive their action capabilities in various tasks, such as stair climbing, reaching and grasping, or running through apertures (Higuchi et al., 2011; Linkenauger, Witt, Stefanucci, Bakdash & Proffitt, 2009; Linkenauger, Witt & Proffitt, 2011; Warren, 1984). In these situations, the perceiver's estimations were consistent and accurate with respect to their actual state. But, a wealth of empirical studies has shown that the perception of action capabilities is compromised during periods of individual's altered physiological states, e.g., fitness level, fatigue, pain, age or anxiety (Bhalla & Proffitt, 1999; Deschamps, Hug, Hodges & Tucker, 2014; Graydon, Linkenauger, Teachman & Proffitt, 2012; Hackney & Cinelli, 2013; Sakurai et al., 2013). However, the classic experimental procedures do not offer a clear conclusion about how physiological changes alter the perception of action capabilities.

Encoding and maintenance of stimuli are not dissociated in classic experimental procedures

It is worth noting that classic experimental procedures gave participants the opportunity for perceptual adjustments and

strategies while their physiological properties were experimentally manipulated, or were altered by disease or maturation. Several experimental procedures involved a limitless presentation/availability of "discrete" stimuli and an unrestricted latency for behavioral answer, e.g., when one focus on the 'passability' width of an aperture width or on the 'crossability' height of a bar height (Daviaux, Mignardot, Cornu & Deschamps, 2014; Guardia et al., 2010; Higuchi, Hatano, Soma & Imanaka, 2009; Lee, Harris, Atkinson & Fowler, 2001; Noël, Bernard & Luyat, 2011; Sakurai et al., 2013). Despite the care taken in the experimental designs, these open experimental procedures might have left room for participants to interpret ambiguous cues about their own physical properties and/or about the environment's properties during the period of compromised physiological state (Daviaux et al., 2014). Moreover, metacognitive adjustments accounting for error detection and correction, conflict resolution and emotional control (Fernandez-Duque, Baird & Posner, 2000) might have involved inferential strategies, especially given that metacognitive processes benefit from extending evaluation time to reach maximum quality (see artificial grammar-learning paradigm in Mealor & Dienes, 2013). Hence, an extensive period for perceptual judgement might have lessened or enhanced the effect of changes in a participant's physiological properties. Finally, considering the interplay between cognitive load and perceptual-motor performance (e.g., Temprado, Zanone, Monno & Laurent, 1999), poor perception of action capabilities can be interpreted in terms of higher cognitive load demands from a dual-task situation (e.g., the main perceptual task + the breath restriction task in the present experiment).

Altogether, it seems difficult to adopt a single position among the alternative interpretations accounting for altered perception of action capabilities. In particular, the factors that can alter perception can exist simultaneously and interplay with each other. This was demonstrated by one of our recent findings, in which the perceived stepping-over performance became underestimated after 24 h of sleep deprivation, while the actual performance remained unchanged (Daviaux et al., 2014). Since we used an open experimental design, it was quite challenging to establish whether the participants' underestimation involved an inability to successfully update the internal (i.e., the kinaesthetic and motor features of participants) and/or the external (i.e., the environmental properties) inputs that affected the estimated consequence for motor action. Likewise, we were not able to ascertain whether this underestimation came from—or was smoothed/enhanced by—a concomitant, strategically conservative interpretation of these cues resulting from their sleep deprivation (see also Deschamps et al., 2014 for a similar discussion about these potential alternative explanations). Note that *conservative* refers here to a systematic, directional bias that causes the perceiver to underestimate his or her capabilities.

To specify the interpretations of how participants' altered physiological state affects their self-perceived capabilities for motor action, we have propounded a new methodological paradigm. Particularly, we extend the experimental procedure by enforcing the time window for stimulus availability and minimizing the latency for behavioral answer delivery following the stimulus presentation. Thus, the prevention of information encoding (i.e., how information is gathered from the environment and from the organismic properties) averted possible metacognitive adjustments.

Standardized latencies of visual stimuli availability and behavioral answers

The issue of latency for stimuli availability was set in accordance with neurophysiological studies, which use an up-to-date definition of the *affordance* concept, and encompass the notion of perception of action capabilities. The notion of *affordance* was originally introduced by Gibson, (1966, 1977) to reflect the task-specific fit between the properties of the environment and the individual's anthropometric and dynamic features. It supports individuals' perceptions of their capabilities for motor interaction within their environment. The identification of visuomotor neurons (di Pellegrino, Fadiga, Fogassi, Gallese & Rizzolatti, 1992) led to a refinement of the original affordance concept (Garbarini & Adenzate, 2004). For example, Thill, Caligiore, Borghi, Ziemke and Baldassarre, (2013) recently reviewed studies that evidenced the implication of specific neuronal pathways and the involvement of visuomotor neurons in affordance selection. By "selection", it must be understood that the integration of perceptual inputs gather to the potentiation of multiple affordances, which are selected among the neuronal system in the basis of the hierarchical key aspects of actions (Hamilton & Grafton, 2007; Kilner, Friston & Frith, 2007). Within this visuomotor context, the unique sight of a graspable object is assumed to potentiate a whole action, partitioned in the brain into sub-sensorimotor components—even in case of any intention to act—defined as *stable* and *temporary affordances* (Borghi & Riggio, 2009; see also Ellis & Tucker, 2000 and the concept of *micro-affordances*). Stable affordances account for the constant features elicited by the graspable object, regardless of the environment, supporting the cortical representation of its functional possibilities (e.g., the shape of a typical glass or a tool). In contrast, temporary affordances account for the sporadic features of an object (e.g., the distance and the spatial orientation of a glass). Temporary affordance is considered as the

perception of action capabilities per se in behavioral studies aiming at disentangling impaired perception for action.

In the case of stable affordance, most studies reported that such *affordance effect* arose very early in motor-related brain regions (Franca et al., 2012; Makris, Hadar & Yarrow, 2011; Proverbio, Adorni & D'Aniello, 2011; Proverbio, 2012). Atypical cortical events revealed the cortical access to the distinction between the perception of manipulable and non-manipulable objects, i.e., the perception of their motoric properties. For example, a time–frequency analysis of electroencephalographic data disclosed a stronger mu frequency desynchronization over the somatosensory area within a 140- to 175-ms window after the presentation of manipulable objects (Proverbio, 2012), followed by the triggering of larger cortical event-related potentials in a 210- to 270-ms time window (Proverbio et al., 2011). Transcranial magnetic stimulations applied to the motor cortex also revealed an increasing corticospinal excitability of the synergist's hand muscles around 120 and 300 ms after the onset of a grip-congruent stimuli delivery, even though the exact time course is still debated due to differences in experimental procedures (Franca et al., 2012; Makris et al., 2011). Altogether, those results support that stable affordance is encoded within the first 300 ms after the onset of stimuli presentation. Because the identification of stable and temporary affordances is supported by the identification of respective but overlapping neural pathways (Binkofski & Buxbaum, 2013; Thill et al., 2013), the stimuli availability was then narrowed to a 300-ms time window.

An adaptation of Graydon et al.'s (2012) paradigm

To test whether altered perception of action capabilities is detected when the involvement of perceptual strategies is narrowed, we adapted the paradigm developed by Graydon et al. (2012) in their study 1. Originally, participants had to report their perceived reaching capabilities after being breath restricted for 1 min. The evaluation of perceived reaching-to-grasp capabilities was examined by moving a poker chip towards and away from the participants while the chip's displacement and the distance to the participants' initial seating position was always visually available (continuous stimuli presentation). Breath restriction is known to induce anxiety (Teachman, Smith-Janik & Saporito, 2007; Teachman & Gordon, 2009) that interacts with various aspects of perceptual-motor performances (Nieuwenhuys, Pijpers, Oudejans & Bakker, 2008; Nieuwenhuys & Oudejans, 2012; Pijpers, Oudejans, Bakker & Beek, 2006; Pijpers, Oudejans & Bakker, 2007). As a result, the participants who experienced anxiety manipulation underestimated their reaching ability. The authors interpreted this to mean that participants who felt more vulnerable to adverse conditions attempted to reduce the perceived dangerous situation by becoming conservative. However, there are other plausible interpretations, such as ambiguous perception, i.e., encoding of internal and external information, accompanied by extra cognitive load; and metacognitive and/or other cognitive strategies, such as hysteresis and enhanced contrast mechanisms (Hirose & Nishio, 2001; Lopresti-Goodman, Richardson, Baron, Carello & Marsh, 2009; Mark, 1987; Sweller, 2011).

In an attempt to distinguish among these different alternatives, we first adapted Graydon et al.'s (2012) design to involve a discrete and randomized presentation of glass position to be reached-and-grasped, using a Box for Interaction with Object system (BIO) similar to that recently developed by Oliveira, Volchan, Vargas, Gleiser and David (2012). This device was especially designed to look at an object, e.g., a glass, while displaying the object during very brief (300 ms) but manifold time windows, in a highly standardized surrounding. Behavioral answers were still reported verbally because an update of perceived reaching-to-grasp capabilities can be expected when the task-related sensorimotor network is recruited, as illustrated with "learning-by-doing" process (Franchak, van der Zalm & Adolph, 2010) and during ongoing movement (Hackney & Cinelli, 2013), or as it could be expected from transcranial magnetic stimulation (e.g., Franca et al., 2012).

Aims and hypotheses of the study

The present study owes its originality to the comparison of control and anxiety conditions in a perceptual task of reaching to grasp, using a restricted breathing task, with a very short presentation of available information necessary for the appropriate action-specific scaling of distance perception. The delay for the behavioral answer was set to a [1200–2200 ms] time window to minimize the duration of information maintenance and to prevent a reaction time task. Because we hypothesized that (1) altered visuomotor transformation of reaching-to-grasp capabilities can explain the conservative behavior since (2) a 300-ms latency is sufficient for task-related visuomotor transformation while narrowing the involvement of perceptual strategies, we expected an underestimate of the reaching-to-grasp ability in anxiety-inducing conditions (in line with Graydon et al.,'s 2012).

Methods

Participants

Fifteen right-handed students from the University of Toulouse (France) volunteered to participate in the present

study, without compensation. One of the participants felt an excessive discomfort in the ANX condition; thus, this individual could not complete the entire session. This volunteer was excluded from the statistical analyses. Thus, fourteen participants were retained for the analyses (mean age 20.9 ± 3.4 years, 60 % females, Edinburg Handedness test score 60.9 ± 21.3, Oldfield, 1971). None of the participants exhibited visual or physical impairment. None of them had previous experience with the experimental design. The experiment was undertaken with the understanding and written consent of each participant, and it was conducted according to the Helsinki Statement (last modified in 2004).

Experimental setup

In a darkened room, participants sat in front of the slightly modified BIO system (Oliveira et al., 2012) synchronized with a computer running Presentation software (Presentation, Neurobehavioral Systems, Berkeley, California) (see Fig. 1a for an illustration). The neutral and black uniform surround-displaying environment of the inner box restrained the availability of visual landmarks. The room's luminance was measured around 27 lx with a light meter (Luxmètre MS-1300, Voltcraft, Lomme, France). When the LEDs inside the BIO system are ignited, the luminance inside the box was 52 lx while the luminance at the level of participants' eyes remained around 27 lx. The participants' position was standardized, with their right arm lying on a support at 120° elbow extension. The left arm rested along the transversal edge of the box. The right acromion fitted the same transverse plane as the right hand, and both were aligned with the glass along the anteroposterior axis. Throughout the session, the participants could not see their arms/hands (inside or outside the box). Finally, participants were instructed to maintain their right hand in an anatomical configuration congruent with glass grasping, as if they held a fictitious glass (Natraj et al., 2013).

Procedure

Control and breathing restricted conditions

The participants had to estimate whether they were able to reach-and-grasp a glass with their right hand if they had to perform an arm extension without torso anteroposterior flexion or sagittal rotation, namely from a position allowing only shoulder and elbow flexion–extension in the transverse plane. It is noteworthy that the length of full arm extension matched the actual maximal reach-to-grasp performance with those degrees of freedom restrictions. Nonetheless, participants were not informed that their arm's length corresponded to their reaching-to-grasp capabilities within the experimental restriction paradigm. Instructions were accompanied by an experimenter's demonstration on a table apart from the BIO system. Participants were instructed never to extend their arms through the box, to prevent them receiving any feedback on their reach-to-grasp capabilities. The glass was a white goblet with no handle, 8.5-cm high and 7-cm in diameter. It was positioned on a small invisible trolley in the middle of the anteroposterior axis of the BIO system, and moved from one location to the next along the anteroposterior axis by a wooden stick attached to the small trolley. The inside floor of the box was draped with a soft, fluffy fabric, and the trolley was equipped with frictionless slick plastic wheels so that participants cannot hear the trolley when moving.

The estimation task was performed in control (CTL) and anxiety (ANX) conditions (see Fig. 1c). For ANX, we adapted the restricted breathing task used by Graydon et al. (2012). Participants breathed through a device composed of a mouthpiece, a 2 mm-diameter pipe and an air outlet normally used as a baby nasal aspirator (ProRhinel, Novartis Pharma SAS, France), while they wore a nose clip (Nabaiji Pince Nez, Oxylane, Villeneuve-d'Ascq, France) (see Fig. 1b). Pilot tests identified the optimal strategy to keep the participants in a high but tolerable restricted breathing condition (more than 50 points on a discomfort scale with 0 = "calm enough to fall asleep" and 100 = "feeling as if they may have a panic attack").

Prior to the experimental session, the individuals' optimal restriction flow was determined from a limit time procedure. To this end, the air outlet was filled with cotton, the quantity of which was adjusted in successive trials until the participants achieved a breathing restricted limit time between 2 and 3 min while reaching at least a 70 discomfort score. Participants required 2.9 ± 0.6 trials to reach a 2.34 ± 0.23 min breathing limit time with a 77.1 ± 7.5 breathing discomfort score.

During the experiment, the participants were conditioned by a 1 min breathing restriction before each set of trials in ANX condition. They were instructed to keep breathing with the breathing set throughout the ANX trials. Note that 3-min rests were systematically provided to participants between every set of trials (ANX and CTL). Participants were allowed to breath for three inspiration–expiration cycles outside of the straw each time they reached 80 points on the discomfort scale in ANX.

Perceptual reach-to-grasp performance

Five CTL and five ANX sets of 30 trials were randomized, resulting in 300 trials. The experimenter was positioned behind the BIO system where a trap allowed him to reach the trolley to adjust position of the glass. Importantly, the glass position was set while the BIO system was switched

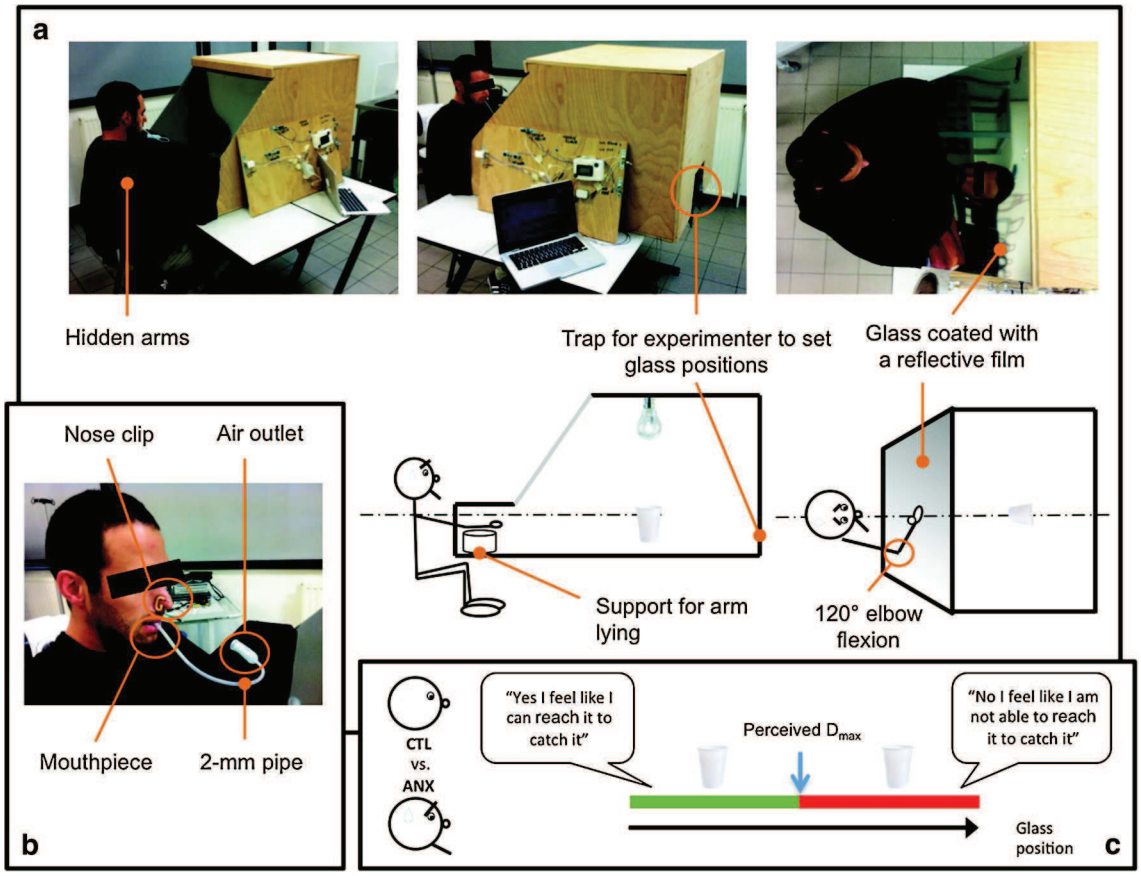

Fig. 1 **a** The participants' position was standardized while they stood in front of our modified BIO system (from Oliveira et al., 2012). **b** To induce anxiety, participants had to keep breathing through a mouthpiece/2-mm pipe/air outlet while they wore a nose clip. **c** Perceived D_{max} is taken as the maximal distance the participant judged to be able to reach-and-grasp the glass, and is compared between the control condition (CTL) and the breathing restriction condition (ANX)

off and the glass was invisible, keeping participants unaware of the glass distance until the BIO system ignition. Prior to the trial, participants were required to gaze at a red fixation point displayed at the bottom of the box shown at eye level. As the experimenter switched on the inner LEDs of the BIO system, the glass position was visible for 300-ms; then the BIO system switched off. The computer running Presentation software delivered a sound trigger 1500-ms after the stimuli onset to allow the participants to verbally report whether yes or no they self-estimate their ability to reach-and-grasp the glass, and their score on the breathing discomfort scale. Answers given more than 2200-ms after the end of stimuli delivery were not considered for data analysis. Eleven answers apportioned between five volunteers were excluded, i.e., less than 1 % of the total answers. One trial procedure is depicted in Fig. 2 for illustration purposes. Note that objects potentiating for functional motor actions (i.e., *stable affordance*) draw the visual attention of participants only when cortical regions involved in visually guided action and planning are activated (Handy, Grafton, Shroff, Ketay & Gazzaniga, 2003). In other word, the "attentional drawing effect" facilitates the motor potentiation for object manipulation by also drawing the visual attention to the object location. Then no pre-cue of stimuli apparition was delivered, in order to magnify the visuomotor transformations elicited by the glass positions. Participants were nevertheless aware that about 5–10-s separated the end of one trial to the beginning of the next one.

The glass positions were presented according to the constant stimuli method (Kingdom & Prins, 2009). All potential positions were randomized across 150 trials (i.e., 5 sets of 30 trials) for both CTL and ANX conditions to prevent hysteresis and retuning effects (Lopresti-Goodman et al., 2009; Lopresti-Goodman, Turvey & Frank, 2013; Mark, 1987; Hirose & Nishio, 2001). Considering the inter-individual variability of perceptual capabilities (Kanai & Rees, 2011), ranges of displayed positions were individualized to enhance the robustness of the constant stimuli method (adapted from the recommendations of Kingdom & Prins, 2009). Thus, two ranges of 15 random positions (from 70 to 98-cm with a 2-cm discrete step) were

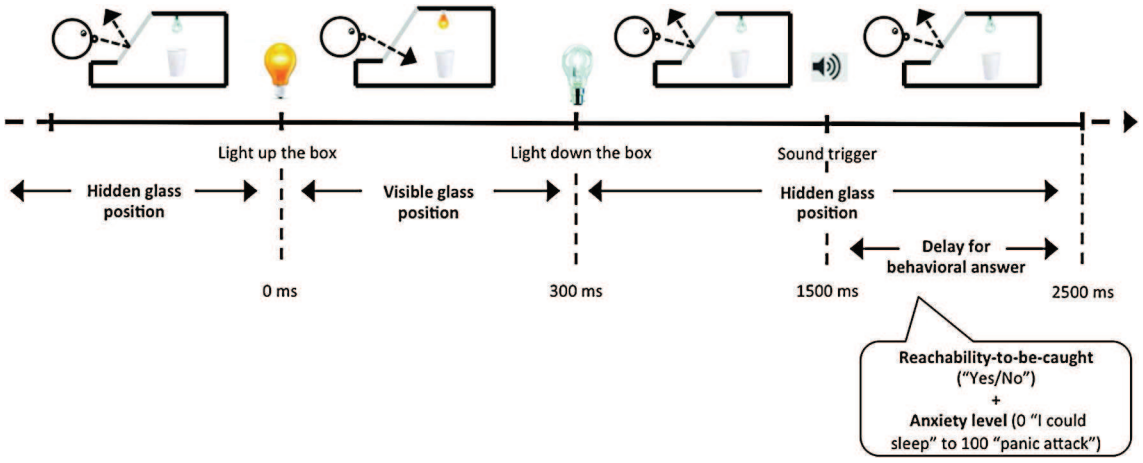

Fig. 2 Procedure for one trial. This procedure was repeated for 300 trials, i.e., 150 trials in CTL and 150 trials in ANX

presented first. The lowest (highest) value of individual ranges was determined by subtracting (adding) 12-cm from (to) the lower (upper) distance at which the participants reported being (unable) able to reach-and-grasp the glass. The individual ranges tested during the experimental sets of trials were 64.1 ± 6.3–99.8 ± 4.8 cm and each stimuli were presented stimuli 8 ± 0.8 times.

Actual reach-to-grasp performance

At fully extended arm position, the distance between the right acromion and the fleshy part between the right thumb and the index was considered as the maximal actual distance for the reach-to-grasp capability (*actual* D_{max}).

Data analysis and statistics

All data were normally distributed; thus, values are reported as mean ± standard deviation (or standard error) throughout the text and the figures. Statistical significance threshold was adjusted to $p < 0.05$. Partial eta square ($_p\eta^2$) values are reported as measures of the effect size, with $_p\eta^2 \geq 0.07$ and $_p\eta^2 \geq 0.14$ considered as moderate and large effects, respectively (Cohen, 1988).

Breathing discomfort state

Breathing discomfort scores were averaged for each set of 30 trials. Thus, a 2 (condition; ANX vs. CTL) × 5 (sets of trials) ANOVA was conducted using the mean discomfort score [0–100] as the dependent variable.

Perceptual threshold for reach-to-grasp capabilities

The perceived threshold for maximal reach-to-grasp capabilities was defined as *perceived* D_{max}. For each participant, *perceived* D_{max} was computed by using a psychometric method. The proportion of positive reach-to-grasp judgments (y-axis) was plotted as a function of glass distances (x-axis) and was optimally fitted by a logistic function of the least-squares method. The *perceived* D_{max} was defined as the value on the x-axis when the logistic function reached a proportion of 0.5 (e.g., Guardia et al., 2010). It was computed as follow:

$$\text{Answer} = \frac{1}{1 + e^{-b \times (a - \text{position})}}$$

where b is the slope of the curve at the point where Answer = 0.5, a is the perceived critical glass position (i.e., *perceived* D_{max} in cm) with a 0.5 proportion of "yes" response, and "position" is the glass position.

Note that individuals' *perceived* D_{max} in CTL was considered as the baseline performance of participants. We assumed that the systematic baseline of over- or underestimation, i.e., difference between perceived and actual reach-to-grasp capabilities, can be derived from individuals' inability to account for experimental restrictions when assessing action capabilities (Fischer, 2000; Graydon et al., 2012) and/or from individual characteristics, such as expertise or fitness level (Bhalla & Proffitt, 1999; Higuchi et al., 2011; Weast, Shockley & Riley, 2011). As a result, the individual difference between *actual* D_{max} and *perceived* D_{max} in CTL was removed from *perceived* D_{max} in both CTL and ANX (see Daviaux et al., 2014 for a similar normalization procedure). Finally, the slope of the psychometric curve (i.e., b in the aforementioned equation) in CTL and ANX was computed to provide additional information about the performance of discriminability of distances (e.g., Guardia et al., 2010). The shallower the slope, the weaker the discrimination.

A paired t test was used to compare CTL and ANX in terms of the *perceived* D_{max} and the slope. The ratio

between *perceived* D_{max} ANX and *actual* D_{max} was also reported to provide an informative estimation of the perceptual accuracy relative to CTL (as the normalization procedure accounts for a CTL ratio equal to 1).

Results

Breathing discomfort state

The ANOVA revealed a significant main effect of Condition, with higher discomfort scores for ANX (mean score 70.0 ± 1.68) compared to CTL (mean 10.7 ± 0.7) [$F(1, 13) = 526.33$, $p < 0.001$, ${}_{p}\eta^2 = 0.976$]. No effects of block [$F(4, 10) = 0.640$, $p = 0.646$, ${}_{p}\eta^2 = 0.204$] or condition × sets of trials interaction [$F(4, 10) = 1.039$, $p = 0.434$, ${}_{p}\eta^2 = 0.294$] were found (Fig. 3a, left side).

Perceptual threshold for reach-to-grasp capabilities

Perceived D_{max} was significantly lower in ANX condition (mean 82.4 ± 8.8 cm) compared to CTL (mean 83.6 ± 9.1 cm) in absolute values [$t(1,13) = 2.29$, $p = 0.038$, ${}_{p}\eta^2 = 0.287$]. The mean ratio between *perceived* and *actual* D_{max} in ANX was 0.98 ± 0.03: participants underestimated their reach-to-grasp capabilities in ANX (Fig. 3a, middle side).

Performance of discrimination

The slope in ANX (mean slope −0.24 ± 0.11) was significantly flatter than in CTL (mean slope-0.29 ± 0.10) [$t(1,13) = 5.376$, $p = 0.037$, ${}_{p}\eta^2 = 0.293$]; suggesting that the discrimination performance is poorer in ANX (Fig. 3a, right side).

Discussion

This study aimed to investigate the effects of a breath restriction task to induce anxiety on the perception of reaching-to-grasp capabilities, by examining the perceptual and behavioral performance of participants (*perceived* and *actual* D_{max}) in an experimental procedure were the involvement of cognitive strategies was narrowed. In our new approach, we did not aim at manipulating the time for stimulus display or the delay to make the 'yes/no' decision. Rather, these experimental features were deliberately fixed to ensure a standardized involvement of the first stage of the working memory process, namely the stimuli information encoding of stimuli information (Jonides et al., 2008), between CTL and ANX conditions. We enforced the duration of stimuli availability to potentiate the action-specific brain transformation of reaching-to-grasp capabilities, in accordance with neurophysiological studies focused on the 'affordance effect' time course (Franca et al., 2012; Makris et al., 2011; Proverbio, 2012; Proverbio et al., 2011).

Underestimated reaching-to-grasp capabilities

As the main result, participants underestimated their reaching-to-grasp capabilities in ANX condition while the stimuli availability was limited to a 300-ms time window. Considering Lopresti-Goodman et al. (2009), "[…] with increasing constraints on the perceiving–acting system, the less likely it is for an individual to engage in analytic processes and the more likely it is for an individual's behavior to be constrained by the direct detection of affordances" (p. 81). The update of perception for action capabilities from perceptual strategies is thus possible only in some conditions, namely when the participant 'has the opportunity to' perform it. Considering the current original experimental design and findings, we argue that participants likely had less or no opportunity to engage in ongoing perceptual strategies while the time for stimuli availability was sufficient to potentiate the entire visuomotor transformation leading to impaired perception. Moreover, Graydon's et al. (2012) findings were replicated in an intra-group comparison. The effect of anxiety is ascribing to breathing restriction-related changes rather than a potential initial mismatching of perceived reaching-to-grasp capabilities between two independent groups. Consequently, the current findings extend the hypothesis of conservative estimates of action capabilities by participants for the affordances in near space, evidencing their vulnerability to adverse conditions when matching visual and sensorimotor information (Daviaux et al., 2014).

Anxiety, visual strategies and working memory load

It is well documented that gaze behavior tendencies and attentional detection of non-threat-related stimuli are reliably altered when performers are anxious, leading to inefficient and often ineffective visual strategies (Eysenck & Derakshan, 2011; Eysenck, Derakshan, Santos & Galvo, 2007; Janelle, 2002). The amount of information that must be processed in the same time during the perceptual task may also alter the working memory capacities (Sweller, 2011) because of a somewhat dual-task situation, i.e., when participants remained engaged in the breathing task while they encode the stimuli information. But considering inefficiency in gaze behavior, altered attentional detection and extra working memory load is not entirely satisfactory from our view. Those altered perceptual features should have produced a unique, 'blurry' perception causing more

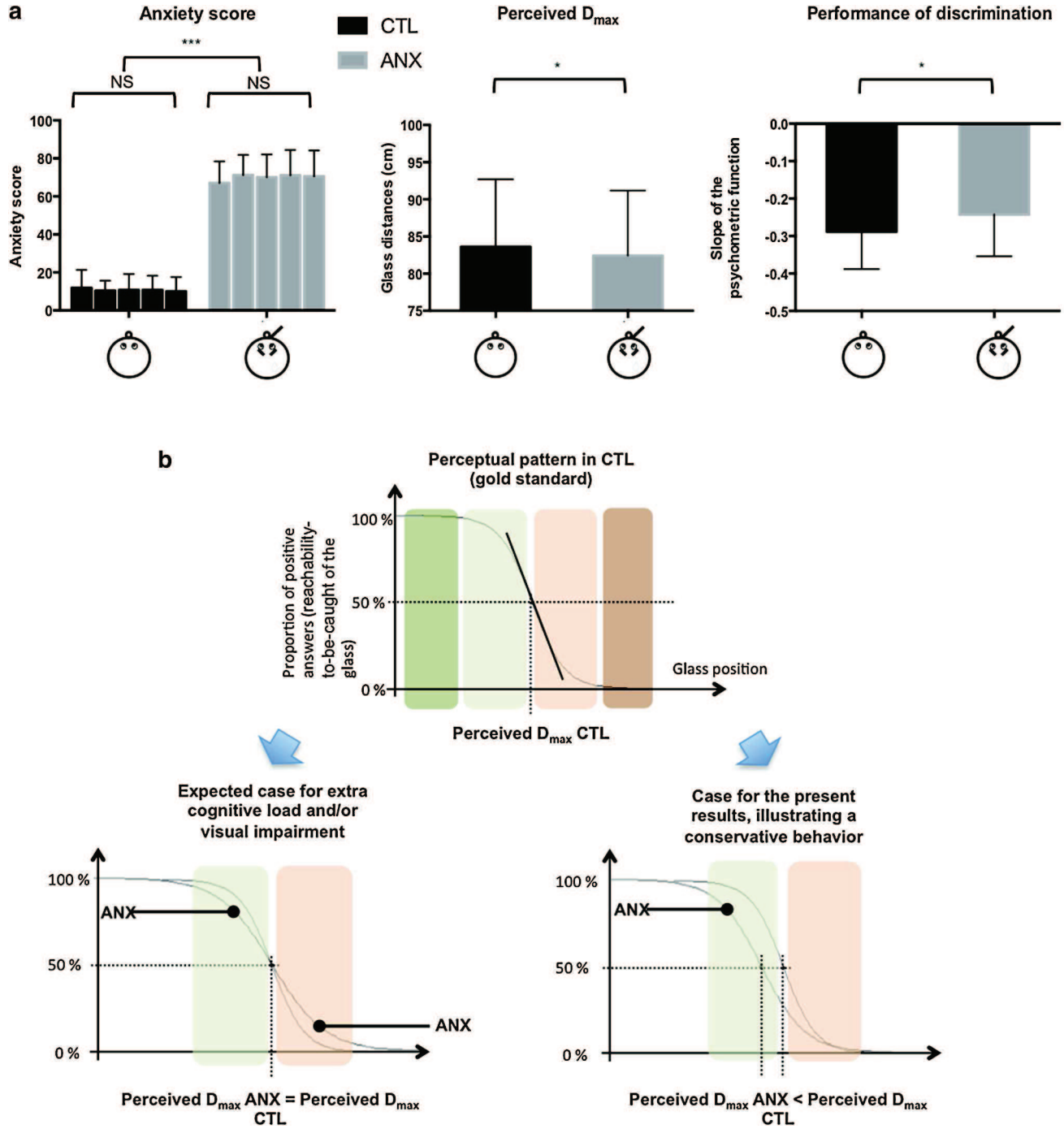

Fig. 3 **a** Results for statistical analysis of anxiety score (ANOVA condition × set of trials), perceived D_{max} and performance of discrimination (*t* test Condition). $*p < 0.05$, $***p < 0.001$. **b** Psychometric functions are used to evaluate perceived D_{max} in CTL and ANX. *Green areas* depict the glass position perceived as graspable in CTL. In the *upper graph*, the proportion of positive judgments for graspability is 100 % in the *dark green area* and between 50 and 100 % in the *light green area*. The *light green area* includes false negative judgments (i.e., glass position perceived as non-graspable while it remains closer than CTL *perceived* D_{max}). Inversely, the *orange areas* depict glass positions perceived as non-graspable in CTL. The proportion of positive judgments for graspability is 0 % in the *dark orange area* and between 0 and 50 % in the *light orange area*. The *light green area* includes false positive judgments (i.e., glass position perceived as graspable while it remains beyond CTL *perceived* D_{max}). In case of extra attentional load and/or visual impairment, it is expected that the number of false negative and positive judgments will be equal, and lead to shallower slope in ANX, but no changes in perceived D_{max} as illustrated in the *lower left figure*. However, our results show that perceived D_{max} in ANX is smaller than in CTL, with a shallower slope. It indicates that more false negative than false positive judgments are reported, as illustrated in the *lower right figure*, and indicates a conservative behavior

variability in answers, that is, more wrong estimates (to perceive not being able/being able to reach-and-grasp the glass while the glass was perceived closer to/beyond the CTL *perceived* D_{max}). This behavioral pattern, classically encountered in an anxiety state (Janelle, 2002), can be defined as an erratic behavior that is a non-directional bias of estimation, unlike conservative behavior. Contrary to threat-related reach-to-grasp task such as climbing (Pijpers et al., 2006, 2007), the current participants had no reason here to engage a systematic, conservative-oriented processes from inefficient gaze behavior, altered attentional detection and extra working memory load.

Did the underestimation reflect a conservative encoding of visuomotor information?

Participants estimated their reaching-to-grasp capabilities several times for every glass position due to the discretized procedure. This procedure assumes that a shallower logistic regression slope indicates an increase in the variability of estimates around the (gold standard) perceptual threshold (Guardia et al., 2010). Since an erratic behavior supposes the participants will produce more wrong judgments, whatever the glass position, it should have produced an equal amount of false negative and false positive estimates. Such perceptual pattern cannot led to underestimated capabilities because the shallower slope in ANX can cross the same transition point as in CTL condition (Fig. 3b, bottom left). As our findings exhibited a lower transition point, we can argue that ANX led mostly to more conservative estimates, i.e., a larger amount of false negative than false positive estimates (bottom right Fig. 3b) (Nieuwenhuys & Oudejans, 2012; Wilson, 2008; Graydon et al., 2012). In this new methodological paradigm, in which the duration of stimuli encoding was restricted, altered visuomotor transformation of reaching-to-grasp capabilities then takes place beside the major hypothesis formed by the involvement of perceptual strategies traditionally supported to account for a conservative behavior (Nieuwenhuys et al., 2008; Nieuwenhuys & Oudejans, 2012; Pijpers et al., 2006, 2007). Indeed, the conservative behavior can also be the result of a non-intentional, impaired brain representation of external (i.e., glass position encoded as closer) and/or internal information (i.e., anthropometric and dynamic features of the right upper limb encoded as lower) during the stimuli encoding in ANX. Indirect evidences slightly support this assumption in a context where individuals experiencing a distorted representation of their body schema exhibited impaired perception of their crossing-aperture capabilities, e.g., in patients with right-sided symptoms of Parkinson's disease and individuals experiencing anorexia nervosa (Guardia et al., 2010, 2012; Lee et al., 2001; Smith et al., 2011).

Conclusion

Changes in physiological states were found to alter estimates for action by manipulating specific constraints on the perceiving–acting system. The present work was particularly focused on the modulation of brain potentiation for reach-to-grasp capabilities during stimuli presentation, i.e., whether the cortical visuomotor transformations were altered during the scaling between the glass distance and anthropometric/dynamic properties of the participants' right limb. It notably raises the question whether the (anthropometric and dynamic) brain representation of the right upper limb of the participants might have been altered per se, to produce a new reference to estimate reaching-to-grasp capabilities.

The results are in line with the recent findings evidencing that respiration (as manipulated in a breath-holding situation) is a critical factor in explaining the link between specific brain networks, including parietal, posterior midline, and frontal regions, and successful cognitive performance (Huijbers et al., 2014). Future research on specific cortical assumptions should provide further neurophysiological support for the failure to update the perception of action capabilities in stressful-inducing conditions. From a relevant perspective, investigating brain dynamics using the same original experimental design while recording electroencephalographic (EEG) activity should improve our understanding of the underlying integration of external (i.e., encoding of glass location) or internal (i.e., the subject's representation of sensorimotor state) inputs in stressful conditions.

References

Bhalla, M., & Proffitt, D. R. (1999). Visual-motor recalibration in geographical slant perception. *Journal of Experimental Psychology: Human Perception and Performance, 25*, 1076–1096.

Binkofski, F., & Buxbaum, L. J. (2013). Two action systems in the human brain. *Brain and Language,*. doi:10.1016/j.bandl.2012.07.007.

Borghi, A. M., & Riggio, L. (2009). Sentence comprehension and simulation of object temporary, canonical and stable affordances. *Brain Research, 1253*, 117–128. doi:10.1016/j.brainres.2008.11.064.

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences*. New-York: Academic press.

Daviaux, Y., Mignardot, J.-B., Cornu, C., & Deschamps, T. (2014). Effects of total sleep deprivation on the perception of action capabilities. *Experimental Brain Research, 232*, 2243–2253.

Deschamps, T., Hug, F., Hodges, P. W., & Tucker, K. (2014). Influence of experimental pain on the perception of action capabilities and performance of a maximal single leg hop. *The Journal of Pain, 15*, 271.e1–271.e7.

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Experimental Brain Research, 91*, 176–180.

Ellis, R., & Tucker, M. (2000). Micro-affordance: the potentiation of components of action by seen objects. *British Journal of Psychology, 91*, 451–471.

Eysenck, M. W., & Derakshan, N. (2011). New perspectives in attentional control theory. *Personality and Individual Differences, 50*, 955–960.

Eysenck, M. W., Derakshan, N., Santos, R., & Galvo, M. G. (2007). Anxiety and cognitive performance: attentional Control Theory. *Emotion, 7*, 336–353.

Fernandez-Duque, D., Baird, J. A., & Posner, M. I. (2000). Executive attention and metacognitive regulation. *Consciousness and Cognition, 9*, 288–307. doi:10.1006/ccog.2000.0447.Frern.

Fischer, M. H. (2000). Estimating reachability: whole body engagement or postural stability? *Human Movement Science, 19*(297), 318.

Franca, M., Turella, L., Canto, R., Brunelli, N., Allione, L., Andreasi, N. G., & Fadiga, L. (2012). Corticospinal facilitation during observation of graspable objects: a transcranial magnetic stimulation study. *PLoS One, 7*, e49025.

Franchak, J. M., van der Zalm, D. J., & Adolph, K. E. (2010). Learning by doing: action performance facilitates affordance perception. *Vision Research, 50*, 2758–2765.

Garbarini, F., & Adenzato, M. (2004). At the root of embodied cognition: cognitive science meets neurophysiology. *Brain and Cognition, 56*, 100–106. doi:10.1016/j.bandc.2004.06.003.

Gibson, J. J. (1966). *The senses considered as perceptual systems*. Boston: Houghton Mifflin.

Gibson, J. J. (1977). *The theory of affordances. Perceiving, acting, and knowing: toward an ecological psychology*. Hillsdale: Erlbaum Associates, Inc.

Graydon, M. M., Linkenauger, S. A., Teachman, B. A., & Proffitt, D. R. (2012). Scared stiff: the influence of anxiety on the perception of action capabilities. *Cognition and Emotion, 26*(1301–1315), 1–16.

Guardia, D., Conversy, L., Jardri, R., Lafargue, G., Thomas, P., Dodin, V., et al. (2012). Imagining one's won and someone else's body actions: dissociation in anorexia nervosa. *PLoS One, 7*, e43241. doi:10.1371/journal.pone.0043241.

Guardia, D., Lafargue, G., Thomas, P., Dodin, V., Cottencin, O., & Luyat, M. (2010). Anticipation of body-scaled action is modified in anorexia nervosa. *Neuropsychologia, 48*, 3961–3966.

Hackney, A. L., & Cinelli, M. E. (2013). Young and older adults use body-scaled information during a non-confined aperture crossing task. *Experimental Brain Research, 225*, 419–429.

Hamilton, A.F., & Grafton, S.T. (2007). The motor hierarchy: from kinematics to goals and intentions. In Rosetti,Y., Kawato, M., Haggard, P. (eds.), Attention and performance.

Handy, T. C., Grafton, S. T., Shroff, N. M., Ketay, S., & Gazzaniga, M. S. (2003). Graspable objects grasp attention when the potential for action is recognized. *Nature Neuroscience, 6*, 421–427.

Higuchi, T., Hatano, N., Soma, K., & Imanaka, K. (2009). Perception of spatial requirements for wheelchair locomotion in experienced users with Tetraplegia. *Journal of Physiological Anthropology, 28*, 15–21. doi:10.2114/jpa2.28.15.

Higuchi, T., Murai, G., Kijima, A., Seya, Y., Wagman, J. B., & Imanaka, K. (2011). Athletic experience influences shoulder rotations when running through apertures. *Human Movement Science, 30*, 534–549.

Hirose, N., & Nishio, A. (2001). The process of adaptation to perceiving new action capabilities. *Ecological Psychology, 13*, 49–69.

Huijbers, W., Pennartz, C. M., Beldzik, E., Domagalik, A., Vinck, M., Hofman, W. F., & Daselaar, S. M. (2014). Respiration phase-locks to fast stimulus presentations: implications for the interpretation of posterior midline "deactivations". *Humain Brain Mapping, 35*, 4932–4943. doi:10.1002/hbm.22523.

Janelle, C. M. (2002). Anxiety, arousal and visual attention: a mechanistic account of performance variability. *Journal of Sport Sciences, 20*, 237–251.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Sledge Moore, K. (2008). The mind and brain of short-term memory. *Annual Review of Psychology, 59*, 193–224. doi:10.1146/annurev.psych.59.103006.093615.

Kanai, R., & Rees, G. (2011). The structural basis of interindividual differences in human behaviour and cognition. *Nature Reviews Neuroscience, 12*, 231–242.

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. *Cognitive Processing, 8*, 159–166.

Kingdom, F. A. A., & Prins, N. (2009). *Psychophysics: a practical introduction*. San Diego: Elsevier.

Lee, A. C., Harris, J. P., Atkinson, E. A., & Fowler, M. S. (2001). Disruption of estimation of body-scaled aperture width in Hemiparkinson's disease. *Neuropsychologia, 39*, 1097–1104.

Linkenauger, S. A., Witt, J. K., & Proffitt, D. R. (2011). Taking a hands-on approach: apparent grasping ability scales the perception of perceived object size. *Journal of Experimental Psychology: Human Perception and Performance, 37*, 1432–1441.

Linkenauger, S. A., Witt, J. K., Stefanucci, J. K., Bakdash, J. Z., & Proffitt, D. R. (2009). The effects of handedness and reachability on perceived distance. *Journal of Experimental Psychology: Human Perception and Performance, 35*, 1649–1660.

Lopresti-Goodman, S. M., Richardson, M. J., Baron, R. M., Carello, C., & Marsh, K. L. (2009). Task constraints on affordance boundaries. *Motor Control, 13*, 69–83.

Lopresti-Goodman, S. M., Turvey, M. T., & Frank, T. D. (2013). Negative hysteresis in the behavioral dynamics of the affordance "graspable". *Attention, Perception, and Psychophysics, 75*, 1075–1091.

Makris, S., Hadar, A. A., & Yarrow, K. (2011). Viewing objects and planning actions: on the potentiation of grasping behaviours by visual objects. *Brain and Cognition,*. doi:10.1016/j.bandc.2011.08.002.

Mark, L. S. (1987). Eyeheight-scaled information about affordances: a study of sitting and stair climbing. *Journal of Experimental Psychology: Human Perception and Performance, 13*, 361–370.

Mealor, A. D., & Dienes, Z. (2013). The speed of metacognition: taking time to get to know one's structural knowledge. *Consciousness and Cognition, 22*, 123–136. doi:10.1016/j.concog.2012.11.009.

Natraj, N., Poole, V., Mizelle, J. C., Flumini, A., Borghi, A. M., & Wheaton, L. A. (2013). Context and hand posture modulate the neural dynamics of tool-object perception. *Neuropsychologia, 51*, 506–519.

Nieuwenhuys, A., & Oudejans, R. R. D. (2012). Anxiety and perceptual-motor performance: toward an integrated model of concepts, mechanisms, and process. *Psychological Research, 76*, 747–759.

Nieuwenhuys, A., Pijpers, J. R., Oudejans, R. R. D., & Bakker, F. C. (2008). The influence of anxiety on visual attention in climbing. *Journal of Sport and Exercise Psychology, 30*(171), 185.

Noël, M., Bernard, A., & Luyat, M. (2011). The overestimation of performance: a specific bias of aging? *Gériatrie et psychologie neuropsychiatrie du vieillissement, 9*, 287–294. doi:10.1684/pnv.2011.0290.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97–113.

Oliveira, J. M., Volchan, E., Vargas, C. D., Gleiser, S., & David, I. A. (2012). Box for interaction with objects (BIO): a new device to

synchronize the presentation of objects with electrophysiological recordings. *Behavior Research Methods, 44*, 1115–1120.

Pijpers, J. R., Oudejans, R. R. D., & Bakker, F. C. (2007). Changes in the perception of action possibilities while climbing to fatigue on a climbing wall. *Journal of Sports Sciences, 25*, 97–110.

Pijpers, J. R., Oudejans, R. R. D., Bakker, F. C., & Beek, P. J. (2006). The Role of anxiety in perceiving and realizing affordances. *Ecological Psychology, 18*, 131–161.

Proverbio, A. M. (2012). Tool perception suppresses 10–12 Hz μ rhythm of EEG over the somatosensory area. *Biological Psychology, 91*, 1–7.

Proverbio, A. M., Adorni, R., & D'Aniello, G. E. (2011). 250 ms to code for action affordance during observation of manipulable objects. *Neuropsychologia, 49*, 2711–2717.

Sakurai, R., Fujiwara, Y., Ishihara, M., Higuchi, T., Uchida, H., & Imanaka, K. (2013). Age-related self-overestimation of step-over ability in healthy older adults and its relationship to fall risk. *BMC Geriatrics*, *13*, 44. doi:10.1186/1471-2318-13-44.

Smith, J. G., Harris, J. P., Khan, S., Atkinson, E. A., Fowler, M. S., Ewins, D., et al. (2011). Motor asymmetry and estimation of body-scaled aperture width in Parkinson's disease. *Neuropsychologia, 49*, 3002–3010. doi:10.1016/j.neuropsychologia.2011.06.025.

Sweller, J. (2011). Cognitive Load Theory. In J. P. Mestre & B. H. Ross (Eds.), *The pscyhology of learning and motivation* (pp. 37–76). San Diego: Elsevier.

Teachman, B. A., & Gordon, T. L. (2009). Age differences in anxious responding: older and calmer, unless the trigger is physical. *Psychology and Aging, 24*, 703–714.

Teachman, B. A., Smith-Janik, S. B., & Saporito, J. (2007). Information processing biases and panic disorder: relationships among cognitive and symptom measures. *Behaviour Research and Therapy, 45*, 1791–1811.

Temprado, J.-J., Zanone, P. G., Monno, A., & Laurent, M. (1999). Attentional load associated with performing and stabilizing preferred bimanual patterns. *Journal of Experimental Psychology: Human Perception and Performance, 25*, 1579–1594.

Thill, S., Caligiore, D., Borghi, A. M., Ziemke, T., & Baldassarre, G. (2013). Theories and computational models of affordance and mirror systems: an Integrative Review. *Neuroscience and Biobehavioral Reviews, 37*, 421–491.

Warren, W. H. (1984). Perceiving affordances: visual guidance of stair climbing. *Journal of Experimental Psychology: Human Perception and Performance, 10*, 683–703.

Weast, J. A., Shockley, K., & Riley, M. A. (2011). The influence of athletic experience and kinematic information on skill-relevant affordance perception. *The Quarterly Journal of Experimental Psychology, 64*, 689–706.

Wilson, M. (2008). From processing efficiency to attentional control: a mechanistic account of the anxiety-performance relationship. *International Review of Sport and Exercise Psychology, 1*, 184–201.

Gait & Posture 42 (2015) 590–593

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Short Communication

Balance characteristics in patients with major depression after a two-month walking exercise program: A pilot study

Thibault Deschamps [a,*], Véronique Thomas-Ollivier [a], Anne Sauvaget [b], Samuel Bulteau [b], Marina Fortes-Bourbousson [a], Hugo Vachon [a]

[a] University of Nantes, Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), F-44000, University of Nantes, France
[b] Service «Addictologie et Psychiatrie de liaison, Pôle Hospitalo-Universitaire de Psychiatrie et de Santé Mentale», CHU de Nantes, France

ARTICLE INFO

Article history:
Received 13 February 2015
Received in revised form 22 July 2015
Accepted 23 July 2015

Keywords:
Posture
Walking program
Velocity control hypothesis
Depression

ABSTRACT

Recent studies have demonstrated impaired balance performance in patients with major depressive disorder (MDD) in comparison to healthy controls (HC), which is likely to be related to deficits in integration of visual and proprioceptive inputs necessary for efficient postural control. In parallel, considerable literature supports the positive effects of a walking program on depressive symptoms. Thus this study aimed to determine the effects of a two-month walking program on implicit postural control strategies in MDD. Compared with twelve age- and body mass index-matched non-psychiatric HC (mean age 50.41 ± 6.93 years; five women), nine MDD (mean age 51.88 ± 10.01 years; five women) performed two sessions of standing postural control assessment, separated by eight weeks of the walking program, while the HC were only assessed at t_0. The walking program included one-hour supervised walking sessions, three times a week over a two-month period. Postural performance was assessed by various center of pressure (COP) parameters, in particular those that bound the COP velocity of postural sway. The primary findings were that MDD patients exhibited positive physical activity-related changes in postural performance, with a decrease in body sway in the most difficult condition (with a foam surface). The real impact of the walking program on COP velocity-based variables suggests that MDD patients improved their ability to make more efficient postural corrections, which is useful for daily activities and autonomy. A balance assessment in the clinical screening routine might be used as a new index of the effectiveness of walking programs recommended for people with depression.

Trial registration: This study is registered at http://clinicaltrials.gov/: NCT01995422.

1. Introduction

Psychomotor disorders are more prevalent in depression than in healthy controls, and are often related to the severity of clinical state [1]. Numerous studies have described a strong association between motor disorders and early depressive symptoms (and associated cognitive decline) [2,3], and this association is supported by (depressed) state-related balance impairment. For example, Bolbecker et al. [4] demonstrated impaired balance in individuals with mood disorders in comparison to healthy controls (HC), which is often related to deficits in integration of visual and proprioceptive inputs. These findings are in line with Doumas et al. [5], who showed greater postural instability in dual-task performance in patients with major depressive disorder (MDD) compared to HC.

Depression is commonly treated with antidepressants and/or psychotherapy, but there is strong evidence that physical activity improves depressive symptoms in MDD [6,7]. Thus we postulate that the postural control strategies in MDD might also be positively modified after a walking program. Recent studies have demonstrated a key role for center-of-pressure (COP) velocity-based variables in postural sway in healthy individuals and in patients with cognitive impairment [8,9]. Specifically, velocity series appear to be bounded between upper and lower limits, underlining an intermittent corrective control process. These findings highlighted new variables of interest, such as the average absolute maximal velocity (AAMV). On that basis, a better reweighting of velocity information, revealed by lower AAMV values, might be an

* Corresponding author at: University of Nantes Laboratory «Interactions, Performance» (EA 4334) 25 bis boulevard Guy Mollet, BP 72206 44322 Nantes Cedex 3, France. Tel.: +33 02 51 83 72 14; fax: +33 02 51 83 72 10.
E-mail address: thibault.deschamps@univ-nantes.fr (T. Deschamps).

http://dx.doi.org/10.1016/j.gaitpost.2015.07.057
0966-6362/

Table 1
Baseline characteristics of participants according to their diagnostic status ($n = 21$), and detailed list of scheduled psychotropic medications for major depressive disorder participants (MDD).

	Total	Healthy controls ($n = 12$)	MDD ($n = 9$)
Age (years), mean ± SD	51.04 ± 8.19	50.41 ± 6.93	51.88 ± 10.01
Female gender, *n* (%)	10 (47.61)	5 (41.66)	5 (55.55)
Body Mass Index (kg/m^2), mean ± SD	25.95 ± 4.80	24.6 ± 3.75	27.76 ± 5.64
Medications (yes), *n* (%)	9 (42.85)	–	9 (100)
MDD Patients Medications			
1 Venlafaxine (75 mg) QD, Amitriptyline (25 mg) D, Prazepam (30 mg) TD, Cyamémazine (5 mg) D, Zopiclone (7,5 mg) D			
2 Venlafaxine (75 mg) TD, Cyamémazine (5 mg) BID, Alprazolam (1 mg) BID, Naltrexone (50 mg) D			
3 Sodic levothyroxine (75 μg) D, Melatonine (25 mg) D			
4 Divalproate Sodium (500 mg) BID, Escitalopram (25 mg) D, Venlafaxine (75 mg) BID, Quetiapine (400 mg) D, Loprazolam (1 mg) D			
5 Paroxetine (20 mg) D, Amitriptiline (50 mg) D, Alprazolam (0,5 mg) D			
6 Fluoxetine (20 mg) BID, Alprazolam (0,25 mg) BID			
7 Sertraline (50 mg) BID			
8 Divalproate Sodium (500 mg) BID, Clomipramine (75 mg) D			
9 Agomelatine (25 mg) BID, Mianserine (30 mg) D, Amoxapine (100 mg) BID, Aripiprazole (10 mg) D, Bromazepam (6 mg) D			

index of an effective adaptive control process of balance in MDD. Thus we conducted this nonrandomized clinical study to examine the effects of a walking program on velocity-based control of posture.

2. Methods

2.1. Participants

Nine MDD outpatients were compared with twelve age- and BMI-matched HC (see Table 1 for participants' characteristics). Notably, the HC were used as a *reference* non trained group, formed of adults living at home. Patients presenting co-morbid psychotic or addictive disorders were excluded. Only physically inactive patients were included (IPAQ scores <600). Diagnosis was done by a clinical interview; all MDD met criteria for a current major depressive episode [10]. A clinical two-month follow-up monitored the persistence of depression. Patients completed the Beck Depression Inventory II (BDI) [11] before (t_0) and after ($t_{+8weeks}$) the walking program. Lastly, patients were taking various combinations of antidepressant and anxiolytic medication (Table 1). No change of medication occurred during the preceding month or during the study.

2.2. Protocol

MDD performed two sessions of postural assessment, separated by eight weeks. Geurts et al. [12] found that balance parameters do not vary across multiple testing sessions in HC, therefore, the HC were only assessed at t_0. All sessions included postural measurements at 10 a.m. ± 30 min, using a Kistler force platform (sampling frequency of 100 Hz). Each test included four conditions: stance on a firm surface with eyes open (EO) or eyes closed (EC); stance on a foam surface (thickness 7 cm) with eyes open (FEO) or eyes closed (FEC). Participants stood barefoot, with the head in a straight-ahead position and arms along the body, and focused on a visual reference mark in front of at a 200 cm distance. Two trials (each of 51.2 s duration) were performed for each condition. The results were averaged across trials.

2.3. Walking program

The MDD group performed a walking program with one-hour supervised (by H.V) sessions, three times a week, over two months. The exercise intensity was based on the Metabolic Equivalent of Task (MET), where moderate intensity corresponds to a speed between 4.8 km/h and 5.4 km/h (3.3-3.6 MET). Participants maintained their walking speed by using a Global Positioning System. The adherence rate to exercise was 0.66 (±0.27) (patients averaged 15.84/24 sessions).

2.4. Data analysis

The COP parameters were the mean and standard deviation (SD) of amplitude, mean velocity and SD of velocity in antero-posterior (AP) and medio-lateral (ML) directions, and area. The AAMV was computed from the COP velocity series by extracting the maximum and minimum values of the series within non-overlapping windows (of a length of 2 s). Then the absolute values of these extremes were averaged [8,9].

2.5. Statistics

A Wilcoxon test was used (t_0 *vs.* $t_{+8weeks}$) for BDI scores. First, a 2 (Group: HC *vs.* MDD) × 2 (Condition: firm *vs.* compliant) × 2 (Vision: EO *vs.* EC) ANOVA was performed. For testing the effect of the walking program on velocity-based postural control in MDD, we conducted a doubly-multivariate, 2 (Session: t_0 *vs.* $t_{+8weeks}$) ×2 (Condition) ×2 (Vision) repeated measures with time-varying covariates (*i.e.*, depression symptoms) and then univariate repeated-measures analyses of covariance (ANCOVAs). Partial eta square ($p^{\eta 2}$) values are reported as measures of effect size, with large effects considered for $p^{\eta 2} \geq 0.14$.

3. Results

All statistical results are summarized in Tables 2 and 3. Firstly, the BDI scores at t_0 (mean 24.75 ± 11.02) were similar to those at $t_{+8weeks}$ (mean 19 ± 12.31), showing no change in depression severity after the program [$z(8) = 1.52$, $p = 0.12$] (effect size = 0.189). Secondly, the ANOVA revealed an effect of Group, with altered postural sway in MDD: higher COP velocity values were systematically found for the MDD group (Table 2).

The doubly-multivariate ANCOVA revealed significant effects of Session, Condition and Vision (Table 3). The Session effect highlights a decrease at $t_{+8weeks}$ in mean velocity [-50.39%], the SD velocity [−34.90%] or the AAMV [−43.41%]. The univariate ANCOVAs of COP position variables showed that postural sway remains similar over time. Rather, significant effects of Session and Condition were systematically observed for all COP velocity-based variables.

4. Discussion

Supporting our hypothesis, this study confirmed that a two-month walking program allows MDD adults to improve their

Table 2
Analysis of variance results (*F* values) for the COP measures for the major depressive disorder patients in comparison to healthy controls at t_0 (before the walking program). Note. Factors were Group, G, Condition, C, and Vision, V. Degrees of freedom are shown in parentheses. COP: center of pressure; AP: anteroposterieur; ML: mediolateral.

	G	C	V	G × C	G × V	C × V	G × C × V
COP measures	(1, 19)	(1, 19)	(1, 19)	(1, 19)	(1, 19)	(1, 19)	(1, 19)
1. COP position-based variables							
Mean position_AP (mm)	0.16	0.23	6.75	**0.00***	**12.37****	0.3	1.53
SD position_AP (mm)	4	**118.3*****	**58.7*****	2.8	0.3	**25.9*****	0.1
Mean position_ML (mm)	1.54	1.07	0.01	0.09	1.03	0.25	0.18
SD position_ML (mm)	**11.4****	**106.9*****	3.6	2.2	0.1	**4.7***	0.6
Area (95% ellipse)	**9.92****	**71.02*****	**10.51****	**7.09***	0.02	**11.75****	0.58
2. COP velocity-based variables							
Mean velocity_AP (mm/s)	**20.20*****	**36.93*****	**26.24*****	0.1	0.82	**11.26****	0.19
SD velocity_AP (mm/s)	**14.08*****	**67.1*****	**18.06*****	0.03	2.16	**22.08*****	0.16
AAMV_AP (mm/s)	**20.44*****	**44.78*****	**22.79*****	0.26	2.87	**13.28****	0.79
Mean velocity_ML (mm/s)	**48.83*****	**8.8****	0.02	1.24	2.53	0.2	1.67
SD velocity_ML (mm/s)	**27.06*****	**33.87*****	0.09	0.56	1.91	0.21	1.22
AAMV_ML (mm/s)	**41.3*****	**18.5*****	0.03	2.28	1.93	0.01	1.146

Significant results are indicated in bold.
* $p < 05$
** $p < .01$
*** $p < .001$.

Table 3
Doubly-multivariate and -univariate analysis of covariance results (main effects of factors) for all the COP measures for the major depressive disorder patients. Note. Factors were Session, S, Condition, C, and Vision, V. Degrees of freedom are shown in parentheses. COP: center of pressure; AP: anteroposterieur; ML: mediolateral. EO: Eyes open; EC: Eyes closed. $p^{\eta 2}$: partial eta squared. Significant results are indicated in bold.

Factors effects	*F* values	*p*-value	$p^{\eta 2}$
Session (t_0 *vs.* $t_{+8weeks}$)	**18.160**	**0.000**	**0.819**
Condition (firm *vs.* compliant)	**21.797**	**0.000**	**0.845**
Vision (EO *vs.* EC)	**5.952**	**0.000**	**0.598**
Session × Condition	**2.188**	**0.033**	**0.354**
Session × Vision	0.875	0.570	0.180
Condition × Vision	**3.725**	**0.001**	**0.482**
Session × Condition × Vision	0.658	0.769	0.141
Time-varying covariates (depression symptoms)			
Pre-BDI scores	1.837	0.076	0.315
Post-BDI scores	**2.387**	**0.020**	**0.374**

Univariate ANCOVA *p*-value ($p^{\eta 2}$)	Session (t_0 *vs.* $t_{+8weeks}$)	Condition (firm *vs.* compliant)	Vision (EO *vs.* EC)	Covariant *Pre-BDI scores*	Covariant *Post-BDI scores*
COP measures					
1. COP position-based variables					
Mean position_AP (mm)	0.542 (0.007)	0.248 (0.025)	0.454 (0.010)	0.519 (0.008)	0.133 (0.041)
SD position_AP (mm)	0.140 (0.040)	**0.000 (0.732)**	0.000 (0.362)	0.193 (0.031)	0.637 (0.004)
Mean position_ML (mm)	**0.030 (0.084)**	0.435 (0.011)	0.533 (0.007)	0.484 (0.009)	0.248 (0.025)
SD position_ML (mm)	0.882 (0.000)	**0.000 (0.405)**	0.015 (0.105)	**0.001 (0.176)**	0.876 (0.000)
Area (95% ellipse)	0.827 (0.001)	**0.000 (0.433)**	0.001 (0.179)	**0.036 (0.079)**	0.667 (0.003)
2. COP velocity-based variables					
Mean velocity_AP (mm/s)	**0.000 (0.335)**	**0.000 (0.409)**	**0.001 (0.197)**	0.806 (0.001)	**0.001 (0.191)**
SD velocity_AP (mm/s)	**0.000 (0.240)**	**0.000 (0.396)**	**0.004 (0.142)**	**0.005 (0.140)**	**0.014 (0.107)**
AAMV_AP (mm/s)	**0.000 (0.334)**	**0.000 (0.356)**	**0.013 (0.110)**	**0.009 (0.120)**	**0.040 (0.076)**
Mean velocity_ML (mm/s)	**0.000 (0.442)**	**0.003 (0.151)**	0.819 (0.001)	0.543 (0.007)	**0.023 (0.092)**
SD velocity_ML (mm/s)	**0.000 (0.375)**	**0.017 (0.101)**	0.936 (0.000)	**0.001 (0.176)**	0.075 (0.057)
AAMV_ML (mm/s)	**0.000 (0.484)**	**0.006 (0.132)**	0.998 (0.000)	**0.003 (0.156)**	0.074 (0.058)

balance by decreasing essentially COP velocity-based parameters. These findings corroborate current studies showing the high sensitivity of velocity-based variables for characterizing balance control in adults with cognitive/mood disorders [8,9]. Additionally, MDD patients improved their postural responses at $t_{+8weeks}$ for the most challenging conditions (with foam surface in EC). Therefore, we argue that a walking program would allow patients to acquire safe balance even in the case of modified sensory context (for example, medication use).

Little is known about the neurophysiological mechanisms underlying the disbalanced control in MDD. Walther et al. [13] recently found that MDD patients displayed associations between resting state cerebral blood flow and activity level in the right orbito-frontal cortex and left supplemental motor area (SMA). These findings are consistent with the assumption of dopamine deficiency responsible for the motor retardation in MDD patients [1]. Against the role of the prefrontal cortex and SMA in human balance control, physical activity influences brain-related function and outcomes, through effects on the striatal dopamine system [14]. Precisely, physical activity benefits behavioral performance in MDD by increasing the functional activity of monoamines related to mood (*e.g.*, dopamine, epinephrine/norepinephrine, serotonin) [15].

In addition to pharmacotherapies and psychological interventions, we support the idea of prescribing an exercise program in MDD patients as an effective intervention for improving depression-related psychomotor disorders, such as impaired balance and fall risks [2,5]. Thus, a balance assessment in the clinical screening routine might be used as an index of the effectiveness of walking programs recommended for depressive people. It may also be

possible that these COP-velocity variables could be a relevant hallmark of depressive disorder; however, these two points require further investigation in larger population.

Acknowledgements

Financial & competing interests disclosure

The research was supported by grants from the Region of Pays de la Loire, France, for the project "2DPAP". This study received also support from Research Mission of Directorate for Research Studies, Evaluation and Statistics (Direction de la recherche, des études, de l'évaluation et des statistiques–MiRe-DRESS) and IRePS (French public health research institute). The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

References

[1] Lohr JB, May T, Caligiuri MP. Quantitative assessment of motor abnormalities in untreated patients with major depressive disorder. J Affect Disord 2013;146:84–90.
[2] Hausdorff JM, Peng C-K, Goldberger AL, et al. Gait unsteadiness and fall risk in two affective disorders: a preliminary study. BMC Psychiatry 2004;24:4–39.
[3] Paterniti S, Verdier-Taillefer MH, Dufouil C, et al. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. Br J Psychiatry 2002;181:406–10.
[4] Bolbecker AR, Hong SL, Kent JS, et al. Postural control in bipolar disorder: increased sway area and decreased dynamical complexity. PLoS ONE 2001;6:e19824.
[5] Doumas M, Smolders C, Brunfaut E, et al. Dual task performance of working memory and postural control in major depressive disorder. Neuropsychology 2012;26:110–8.
[6] de la Cerda P, Cervelló E, Cocca A, et al. Effect of an aerobic training program as complementary therapy in patients with moderate depression. Percept Mot Skills 2011;112:761–9.
[7] Rimer J, Dwan K, Lawlor DA, et al. Exercise for depression. Cochrane Database Syst Rev 2012;11:7–4366.
[8] Deschamps T, Beauchet O, Annweiler C, et al. Postural control and cognitive decline in older adults: position versus velocity implicit motor strategy. Gait Posture 2014;39:628–30.
[9] Mignardot J-B, Beauchet O, Annweiler C, et al. Postural sway, falls and cognitive status: a cross-sectional study among older adults. J Alzheimers Dis 2014;41:431–9.
[10] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–33.
[11] Beck AT, Steer RA, Brown GK. Manual for Beck Depression Inventory II (BDII). San Antonio: TX, Psychology Corporation; 1996.
[12] Geurts ACH, Nienhuis B, Mulder TW. Intrasubject variability of selected force-platform parameters in the quantification of postural control. Arch Phys Med Rehabil 1993;74:1144–50.
[13] Walther S, Höfle O, Federspiel A, et al. Neural correlates of disbalanced motor control in major depression. J Affect Disord 2012;136:124–33.
[14] Loprinzi PD, Herod SM, Cardinal BJ, Noakes TD. Physical activity and the brain: a review of this dynamic, bi-directional relationship. Brain Res 2013;1539:95–104.
[15] Loprinzi PD, Cardinal BJ. Interrelationships among physical activity, depression, homocysteine, and metabolic syndrome with special considerations by sex. Prev Med 2012;54:388–92.

Physiological Reports

Open Access

Physiological Reports ISSN 2051-817X

ORIGINAL RESEARCH

Neuromuscular electrical stimulation leads to physiological gains enhancing postural balance in the pre-frail elderly

Jean-Baptiste Mignardot[1,2], Thibault Deschamps[2], Camille G. Le Goff[1], François-Xavier Roumier[3], Julien Duclay[3,4], Alain Martin[3], Marc Sixt[5], Michel Pousson[3] & Christophe Cornu[2]

1 Laboratory up-Courtine, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland
2 Laboratory MIP (UPRES-EA4334), University of Nantes, Nantes, France
3 Laboratory CASP (INSERM-U1093), University of Burgundy, Burgundy, France
4 Laboratory PRISSMH, team LAPMA (EA 4561), University of Tolouse III, Tolouse, France
5 Geriatric Department, Hospital of Beaune (Burgundy), Beaune, France

Keywords
Muscle-tendon unit, neuromuscular electrical stimulation, postural balance.

Correspondence
Jean-Baptiste Mignardot, Ecole Polytechnique Fédérale de Lausanne, Laboratoire UP-COURTINE – station 19, CH-1015 Lausanne, Switzerland.
Tel: +41 21 693 72 70
Fax: +33 2 51 83 72 10
E-mail: mignardot.jb@gmail.com

Deschamps, Le Goff, Pousson and Cornu contributed equally to this work.

Funding Information
The research was supported by grants from the Region of Pays de la Loire, France, for the project "RP3AP". The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Received: 15 April 2015; Revised: 25 June 2015; Accepted: 26 June 2015

doi: 10.14814/phy2.12471

Physiol Rep, 3 (7), 2015, e12471, doi: 10.14814/phy2.12471

Abstract

Physiological aging leads to a progressive weakening of muscles and tendons, thereby disturbing the ability to control postural balance and consequently increasing exposure to the risks of falls. Here, we introduce a simple and easy-to-use neuromuscular electrical stimulation (NMES) training paradigm designed to alleviate the postural control deficit in the elderly, the first hallmarks of which present as functional impairment. Nine pre-frail older women living in a long-term care facility performed 4 weeks of NMES training on their plantarflexor muscles, and seven nontrained, non-frail older women living at home participated in this study as controls. Participants were asked to perform maximal voluntary contractions (MVC) during isometric plantarflexion in a lying position. Musculo-tendinous (MT) stiffness was assessed before and after the NMES training by measuring the displacement of the MT junction and related tendon force during MVC. In a standing position, the limit of stability (LoS) performance was determined through the maximal forward displacement of the center of foot pressure, and related postural sway parameters were computed around the LoS time gap, a high force requiring task. The NMES training induced an increase in MVC, MT stiffness, and LoS. It significantly changed the dynamics of postural balance as a function of the tendon property changes. The study outcomes, together with a multivariate analysis of investigated variables, highlighted the benefits of NMES as a potential tool in combating neuromuscular weakening in the elderly. The presented training-based strategy is valuable in alleviating some of the adverse functional consequences of aging by directly acting on intrinsic biomechanical and muscular properties whose improvements are immediately transferable into a functional context.

Introduction

Sarcopenia is a common aging process that leads to a set of neuromuscular alterations, which contribute to the reduction in functional capacities and autonomy levels (Hill 2001; Wroblewski et al. 2011; Rom et al. 2012). The recent definition of sarcopenia (Report of the European Working Group on Sarcopenia in Older People 2010) in relation to age suggests not only a decline in muscle mass (Rosenberg 1997) but also a decline in muscle functions

(i.e., the force, the force control, and the force transmission) that disturb balance and motor control. The sarcopenia process is known to particularly affect muscles that are strongly involved in postural control, such as the knee and ankle extensor muscles (i.e., quadriceps and triceps surae muscles).

Triceps surae and postural control

The triceps surae (TS) is of paramount importance for the control of standing and walking (Sutherland et al. 1980; Schieppati et al. 1994; Loram et al. 2004). Its activation leads to ankle extension (or plantarflexion [PF]) and therefore to the forward displacement of the center of plantar pressure (CoP) within the base of support (BoS) (Winter 1995; Loram et al. 2004). Consequently, it plays a central role in the adjustment of the anteroposterior (A-P) position of CoP, depending on the actual A-P position of the center of mass (CoM), in order to maintain the postural balance. In contrast, it can also generate a mismatch between the A-P position of CoP and CoM to create an imbalance or initiate movement, for example, during a body-reaching task or the transition from standing to walking (Winter 1995; Polcyn et al. 1998; Stapley et al. 2000).

In this context, the ability to fully and accurately mobilize CoP within BoS is conditioned by the torque produced by the muscles crossing the joint and their force transmission to the external environment through the tendon (Winter et al. 1998; Loram et al. 2004; Onambele et al. 2006; Melzer et al. 2009) from a strictly biomechanical point of view. Any alteration in these properties (force and transmission of force) could lead to adverse changes in postural balance in older adults (Onambele et al. 2006; Billot et al. 2010; Sarabon et al. 2013) and increase the risk of a fall.

Postural control disorders with aging

Aging is associated with a decline in postural balance (Maki et al. 1994; Horak 2006) and in the control required for reaching, tilting, or goal-directed movements starting from a standing position (Darling et al. 1989; Paizis et al. 2008), which results in a greater likelihood of falls (Nachreiner et al. 2007; Robinovitch et al. 2013). Yet, the ability to amply move and finely control the position of CoP within the BoS is a prerequisite for performing daily movements, such as using a step or stool to reach higher places or stoop to pick up an object from the floor (Melzer et al. 2009). This capacity can be assessed by measuring the forward limit of stability (LoS), which is also reduced with aging (Cavanaugh et al. 1999; Kozak et al. 2003). Melzer et al. (2009) have shown that the reduction in the distance covered by CoP during a forward LoS task in older people is explained by a lack of force of the plantarflexor muscles (TS). This could explain, at least in part, falls that occur during dynamical reaching tasks. This point is consistent with the authors' suggestion that the training of TS among older people should be considered in long-term-targeted fall-prevention programs.

Neuromuscular damages with aging and activity-dependent plasticity

Physiological aging induces several musculo-tendinous (MT) damages, which can dramatically affect motor skills, including controlling postural balance (e.g., Lexell et al. 1983; Onambele et al. 2006; Lichtwark and Wilson 2008). The consequences of the overall damage can be summarized through three main outcomes: a reduction in the maximal force production (1), a decrease in fine control of force (2), and a lack of efficiency in force transmission from the muscle to the external environment through the tendon (3). The translation of these points is evidenced particularly by sarcopenia (Doherty 2003; Narici and Maffulli 2010) and by an increase in MT compliance (Lexell et al. 1983; Onambele et al. 2006; Narici et al. 2008). Several studies have demonstrated the exacerbated age-dependent MT damage in TS muscle (Simoneau et al. 2005; Onambele et al. 2006). These adverse effects can be slowed down by maintaining a sufficient level of physical activity (Hill 2001; Wroblewski et al. 2011) or through the physical therapy training protocols involving voluntary muscle contraction (Ferri et al. 2003; Simoneau et al. 2007). However, even if the activity-dependent muscle plasticity is still effective despite age (Hill 2001; Wroblewski et al. 2011), several constraints, which complicate the implementation of the muscle training protocol, must be considered to make it effective.

Neuromuscular electrical stimulation in older adults

From a practical point of view, the physical training that targets the recovery of the muscle capacity requires the supervision of a qualified person and several appropriate devices that are space-consuming, expensive and, for most of them, joint-specific. From a clinical point of view, the use of these devices also requires dynamic muscular contractions, which may be unsuitable for people suffering from joint disorders. The neuromuscular electrical stimulation (NMES) method which is increasingly used by physiotherapists (de Oliveira Melo et al. 2013; Papadopoulos et al. 2013) enables to alleviate these aforementioned constraints and can be performed at home,

provided specific cautionary advice is given (Quittan et al. 2001).

Depending on the characteristics of the training program, NMES has identical or even greater benefits compared to voluntary muscle training (Maffiuletti 2010). For example, as pointed out by the author, when compared to voluntary training and conventional rehabilitation procedures, NMES (regardless of whether it is combined with voluntary exercise) is more effective in preserving muscle function during a phase of reduced activity/immobilization (Bax et al. 2005; Vivodtzev et al. 2006; Glinsky et al. 2007) and is equally effective in recovering muscle function after an immobilization period (Bax et al. 2005). Although the muscle structure and functional gains generated by NMES are largely described in healthy individuals and some pathological conditions, such as cardiac disease or people with chronic obstructive pulmonary disorder (for a review, see Maffiuletti 2010), only a few studies have investigated this technique in older people (Caggiano et al. 1994; Amiridis et al. 2005; Paillard et al. 2005; Kern et al. 2014). Furthermore, the effect of NMES on the muscle-tendon properties remains poorly documented in all populations. A recent study by Gorgey and Khalil (2015) has shown preliminary results on a small group comprising four spinal cord injured individuals, who were trained with a 30 Hz NMES protocol on knee extensor muscles over 12 weeks. The training leads to a nonsignificant increase in cross-sectional area of the patellar tendon (+8%, $P = 0.14$). Another study by Grosset et al. (2014) has shown that 4 weeks of high-frequency NMES training in TS muscle of young sedentary participants induced positive changes in the contractile and elastic properties of the muscle-tendon complex. They hypothesized that a fiber-type transition to fast fibers is a more likely scenario compared to slow fibers without any change in passive (i.e., tendon) stiffness. Nevertheless, fiber-type transition toward faster fiber type after NMES still requires clarification as some results were in agreement with those previous findings (Perez et al. 2002; Kern et al. 2014) whereas others showed a fiber-type transition toward slower fibers (Maffiuletti et al. 2006; Gondin et al. 2011). Finally, Grosset et al. (2014) suggested that high-frequency NMES training could lead to functional changes of particular interest in older adults. It is known that the stiffness of the muscle-tendon complex involved in the transmission of forces between the skeleton and muscles is related to the activation of proprioceptive organs during sudden stretching or significant postural sway (Woollacott et al. 1986). This point is in line with the onset latency of the postural TS muscle noted in response to a body sway in older adults when compared to younger adults, suggesting a longer proprioceptive processing time (Amiridis et al. 2005).

Most of the time, the NMES training is passive without voluntary participation. Contrary to voluntary muscle training where postural balance control is required, the NMES training is widely conducted in a sitting or lying position with very low involvement of postural control. However, it is still unclear whether the NMES-trained participants can take full advantage of expected improvements in muscle-tendon properties during ecological situations where the postural balance is engaged.

Study aims and experimental setup

The present study targeted pre-frail people recently admitted to a long-term care facility. Due to their environmental changes and the related full daily life assistance, this population is of particular interest, as the transitional period potentially leads to a loss of autonomy, which is a hallmark of impairment in motor-balance control.

This study aimed to (1) evaluate the potential MT changes and the associated postural control improvement induced by NMES training in pre-frail older adults, (2) evaluate the ability of NMES-trained participants to transfer the force and force transmission gains into functional performance through a challenging postural task and finally, (3) determine whether these systemic changes affect the postural sway in a demanding low-force standing task.

Two main experimental setups were designed to meet this aim. First, the force level and force transmission characteristics of the trained muscle were assessed during maximal voluntary contraction (MVC) of the subject in lying position. This measure was achieved with an ergometer synchronized to an ultrasonography device. Second, in standing position, the dynamic behavior of CoP was assessed during two different tasks: bipedal quiet standing and LoS. For all measurements, the performance of the NMES-trained group was compared before and after the training period, with a reference nontrained group comprising non-frail older adults living at home.

Methods

Population

Sixteen older women took part in the study. Nine of them who resided in a long-term care facility (mean age 82.2 ± 4.4 years old, mean body size 1.56 ± 0.1 m, mean body weight 66.7 ± 12.5 kg) followed the NMES training (NMES group). The reference group (i.e., without NMES training) comprised seven older women (mean age 74 ± 4.6 years old, mean body size 1.6 ± 0.07 m, body

weight 67.7 ± 6.1 kg) who were living at home and performed only the pre- and post-session tests.

None of the participants had previous experience with the NMES training protocol, experienced a fall, or exhibited significant cardiac, neurological, cognitive or musculo-skeletal impairments. All of them were fully autonomous in their daily activities, as evidenced by the Katz score: 6/6 for all enrolled participants (Katz et al. 1970). All participants reported normal or corrected to normal vision (e.g., glasses, contact lenses).

In the framework of this study, participants in the NMES (institutionalized) group were considered as prefrail older adults based on their autonomy level, and they showed a strong reduction in the execution speed of functional tasks in comparison to the reference group (Timed Up and Go test performance = 5.3 ± 1.1 sec vs. 12.6 ± 6.7 sec for NMES group and control group, respectively, $u(14) = 3.33$, $P = 0.0009$). Since the reference group comprised younger individuals with a superior functional status (significantly higher score at the Timed Up and Go test) and a different lifestyle (living at home) compared to the NMES group, their reported performances were not considered as control values but as reference values in this study. Written informed consent was obtained for each participant, and the studies conformed to the standards set by the latest revision of the Declaration of Helsinki. The procedure was approved by the local geriatric ethics committee of the hospital of Beaune-21200, France.

Experimental design

On day 0, all participants completed the evaluation session (pre-session) (Fig. 1), which consisted of a full set of tests, including isometric maximal effort and the assessment of postural sways during LoS and quiet standing. Then, the NMES group underwent the NMES training program involving 12 sessions conducted three times per week for 4 weeks (Fig. 1). In the meantime, during this training period, the reference group continued with their habitual life without performing any specific physical training. Overall, 35 days after the pre-session, all participants completed the second, identical evaluation session (post-session).

Neuromuscular electrical stimulation training

No specific muscle training protocol was performed at least 3 months prior to the inclusion date. Training sessions were conducted in the sitting position to avoid pain or discomfort, and to prevent unexpected muscle fatigue that may result from the adoption of an unusual muscle position. Additionally, the sitting position facilitated interaction with the experimenters. Ankle, knee, and hip joints were fixed at 90° by an adjustable strap that maintains the position of the entire lower limb during the

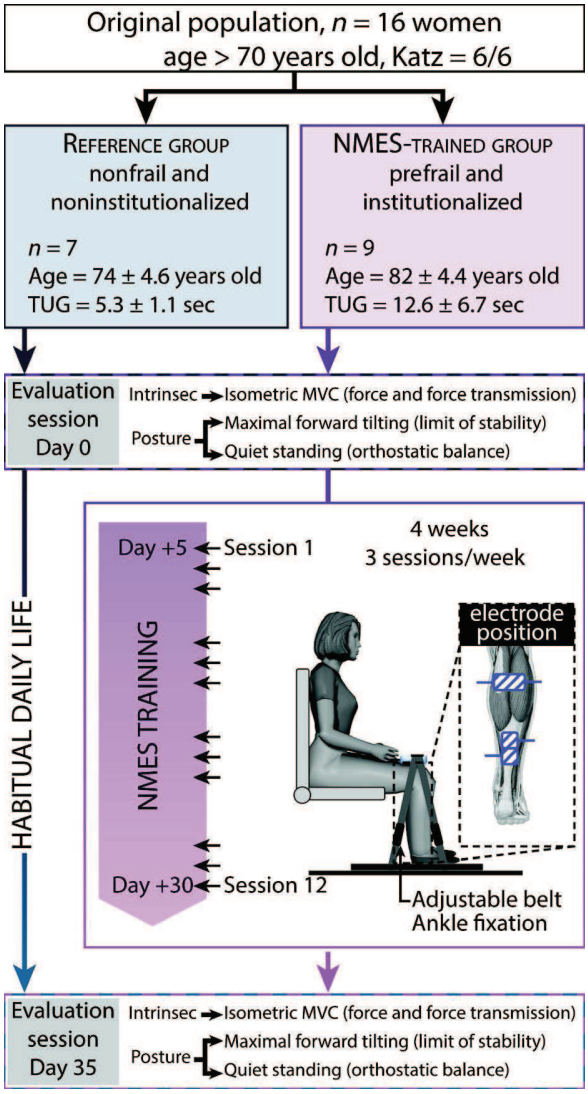

Figure 1. Experimental design. All of the enrolled participants were older than 70 years old and still fully autonomous (maximal score to Katz test), but NMES-trained participants had a lower performance on the functional "Timed-up and Go" test in comparison to their nontrained counterparts who constituted the reference group. Thirty-five days separated the two evaluation sessions. The main objectives of the evaluation sessions were the assessment of some intrinsic muscle and tendon properties during maximal voluntary contractions as well as the postural control characteristics during a challenging and quiet standing task. NMES training comprised two evaluation sessions conducted three times per week for 4 weeks. NMES-trained participants performed the training in sitting position, with the ankle, knee, and hip joints at 90°. The legs remained fixed by an adjustable belt that guaranteed isometric contraction of stimulated muscles.

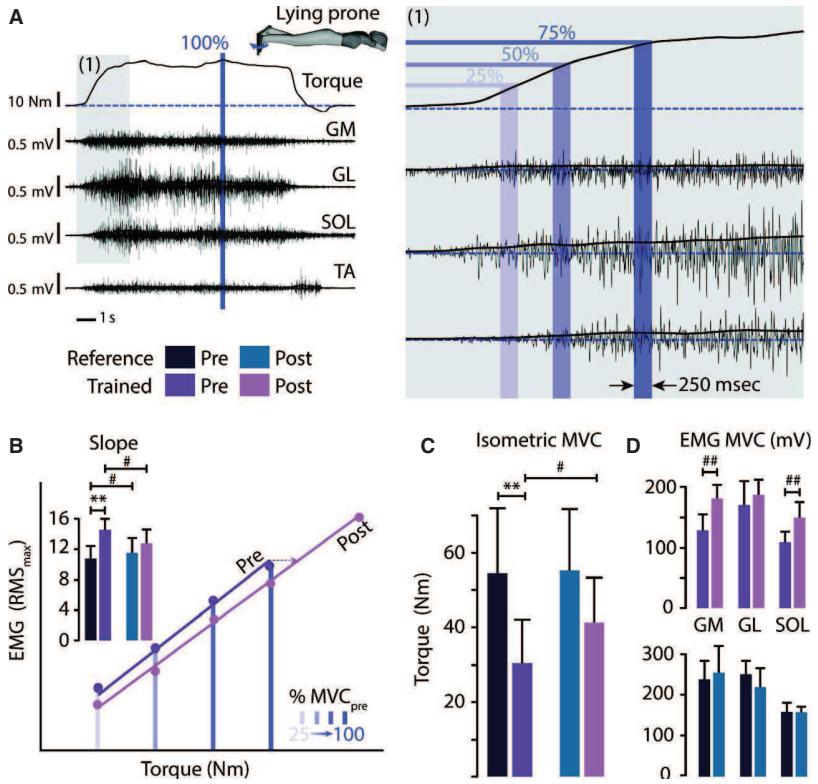

Figure 2. Method overview for the extraction of studied neuromuscular outcomes. Participants were lying prone and performed a progressive maximal voluntary contraction (MVC) in isometric plantarflexion (MVC marked by the blue "100%" line). (A) EMG activities of triceps surae (TS) muscles (GM, GL, and SOL) were recorded together with the main antagonist muscle (TA) and the net torque at ankle joint. (B) Relation between EMG activities of TS muscles and torque developed during plantar flexion. EMG activities were obtained from the sum of the RMS of each three TS muscles during 250 msec around the time points corresponding to 25%, 50%, 75%, and 100% of MVC_{pre} during the ascendant part of the contraction (1). The EMG / Torque relation is presented for a NMES participant at pre- (purple line) and post- (pink line) evaluation sessions. The plotted histogram shows the overall result in terms of the mean slope for both groups at both sessions. (C, D) Histograms of MVC in isometric plantarflexion (C) and root mean square (RMS) of EMG activities of the three TS muscles (D). #$P < 0.05$; ## and **$P < 0.01$.

activation of TS muscle (Fig. 1). Self-adhesive electrodes were placed on each leg with two cathodes (5 cm × 5 cm) with membrane-depolarizing properties positioned over the superficial aspect of soleus (SOL) muscle about 5 cm in distance from where the two heads of gastrocnemii join the Achilles tendon. The anode (10 cm × 5 cm) was placed along the middorsal line of shank, over both medial and lateral gastrocnemii. As used and described by Gondin et al. (2006), this configuration allowed coverage of the entire TS muscle (Fig. 1).

The NMES sessions were performed with the Energy Compex® device, and they consisted of 25 min of proper training with trains of stimulation (4 sec "ON" separated by 12 sec of rest, rectangular-wave pulsed currents lasting 350 μsec delivered at 100 Hz) that generated a hundred isometric contractions of the targeted muscle. For each training session and each participant, the starting stimulation intensity was set as the lowest intensity eliciting movement at the ankle joint, which was visually detected by a clear elevation of the knee when the participants were in the sitting position. Then the aforementioned adjustable strap was attached to the participant and the training started with a stimulation intensity which was reassessed every 2 min to reach the maximum tolerance threshold without causing any uncomfortable sensation, as described by the physical therapists (see Maffiuletti 2010). The 95% confidence intervals for the full-sample stimulation intensities were between 50 mA and 90 mA. This large range is explained by the interindividual variability in sensitivity thresholds. There was 100% compliance by each participant from the NMES group during the entire training session.

Torque, EMG assessments, and related data processing

Similar to Duclay et al. (2009), the participants laid prone on a test bench with their knee joints at full extension

and ankle joints at 90° (Fig. 2A). Measurements were made on the right foot, which was attached to the footplate of an ergometer (model OMF06M, OMICRO'N, Gambais, France). The rotation axis of the device was aligned with the anatomical ankle flexion–extension axis. After 2 min of muscular warm-up, the participants were instructed to gradually increasing their force from resting state to MVC within 4 sec to reach a plateau of maximal torque (Fig. 2A). A visual feedback of the developed torque was displayed in real time to help the participants appreciate their performance and to motivate them to deliver a true maximal effort (Fig. 2A). The task was repeated four times per participant, with 1 min rest between each attempt. The best attempt (i.e., the one showing the highest MVC) was selected for the subsequent data processing (Fig. 2B).

To assess the contribution of neural versus peripheral factors during potential muscle force gain (Moritani and de Vries 1979), EMG activity was also collected during the gradually increasing force task. EMG activities from the TS were recorded by means of 10-mm diameter silver-chloride surface electrode, with an interelectrode distance of 25 mm. The pair of electrodes for the SOL muscle was placed on the middorsal line of the leg, 5 cm below the MT junction of TS. For the gastrocnemius medialis (GM) and gastrocnemius lateralis (GL) muscles, the electrodes were fixed lengthwise over the middle of the muscle belly, following the European Recommendations for Surface Electromyography. The EMG activity of the main plantarflexor antagonist muscle, that is, the tibialis anterior (TA) muscle, was recorded during both PF efforts and dorsiflexion efforts (MVC tasks) in order to visualize and compute the coactivation level. The TA EMG electrodes were placed on the line at 1/3 distance between the tip of the fibula and the tip of the medial malleolus.

Torques and EMG signals were concurrently acquired at a sampling frequency of 5 kHz and processed with a multichannel analogue–digital converter (Biopac Systems Inc., Goleta, CA). TS EMG activities during PF were quantified using the root mean square (RMS) of the processed EMG signals of SOL, GM, and GL independently (Fig. 2D) and together (sum, Fig. 2B). The RMS values were calculated over a 250 msec period (i.e., 125 msec before and 125 msec after a defined time) at different time points during the gradually increasing force task, at pre-session maximal torque (100% MVC_{pre}): 25% $MVC_{pre,}$ 50% MVC_{pre}, 75% MVC_{pre}, and post-session maximal torque (100% MVC_{post}).

For each of these time points, the RMS was plotted for the entire TS as a function of the related torque, and a linear regression was computed (Fig. 2B). The change in the slope properties of the linear regression offered a way to discriminate between contributions from neural (upstream to neuromuscular junction) versus peripheral factors (downstream to neuromuscular junction) in order to reveal the potential mechanisms underlying the force gain change following the training period (Moritani and de Vries 1979).

Musculo-tendinous behavior and related data processing

During the aforementioned force task, the displacement of the MT junction was assessed with a 7.5 MHz linear-array B-mode probe (Esaote Biomedica®, AU5, Firenze, Italy). As described by Duclay et al. (2009), MT junction displacement was measured by tracking the displacement of GM during gradual isometric PF contraction (Fig. 3A and B). Tendon elongation was determined as the distance covered by the MT junction from rest to MVC relative to an external marker placed on skin (Fig. 3A and B). Tendon elongation was assessed for different torques, ranging from 10% to 100% MVC during the pre-session (MVC_{pre}) with an increment of 10%, and one supplementary measure was included during the post-session (100% MVC_{post}).

Tendon force was calculated by dividing the externally measured moment by the moment arm of tendon (set at 0.05 m, which corresponds to the mean value of Achilles tendon moment arm for an ankle joint fixed at 90°). MT stiffness was calculated at high contraction (at 100% MVC_{pre}) by dividing tendon force by tendon elongation. The average relationships between tendon elongation and tendon force are presented in Figure 3C and D.

LoS assessment and related data processing

As defined by Melzer et al. (2009), LoS can be described as the maximal A-P distance a person can intentionally displace the projection of his CoM within the BoS by leaning his body in a given direction without losing balance, stepping, or grasping. The participants were asked to lean as much as possible toward the anterior BoS boundary by tilting their entire body in the forward direction while keeping their arms along the trunk and their hip joints open without moving their feet. Two experimenters validated the participants' behavior during the habituation trials. The capacity of the participants to correctly perform the task was tested through kinematic, kinetic, and EMG evidence obtained from representative participants from both studied group (Fig. 4). Inappropriate movement (no forward movement of CoM, strong hip flexion, and no activation of ankle extensor muscles, or when making a step forward) performed by a young

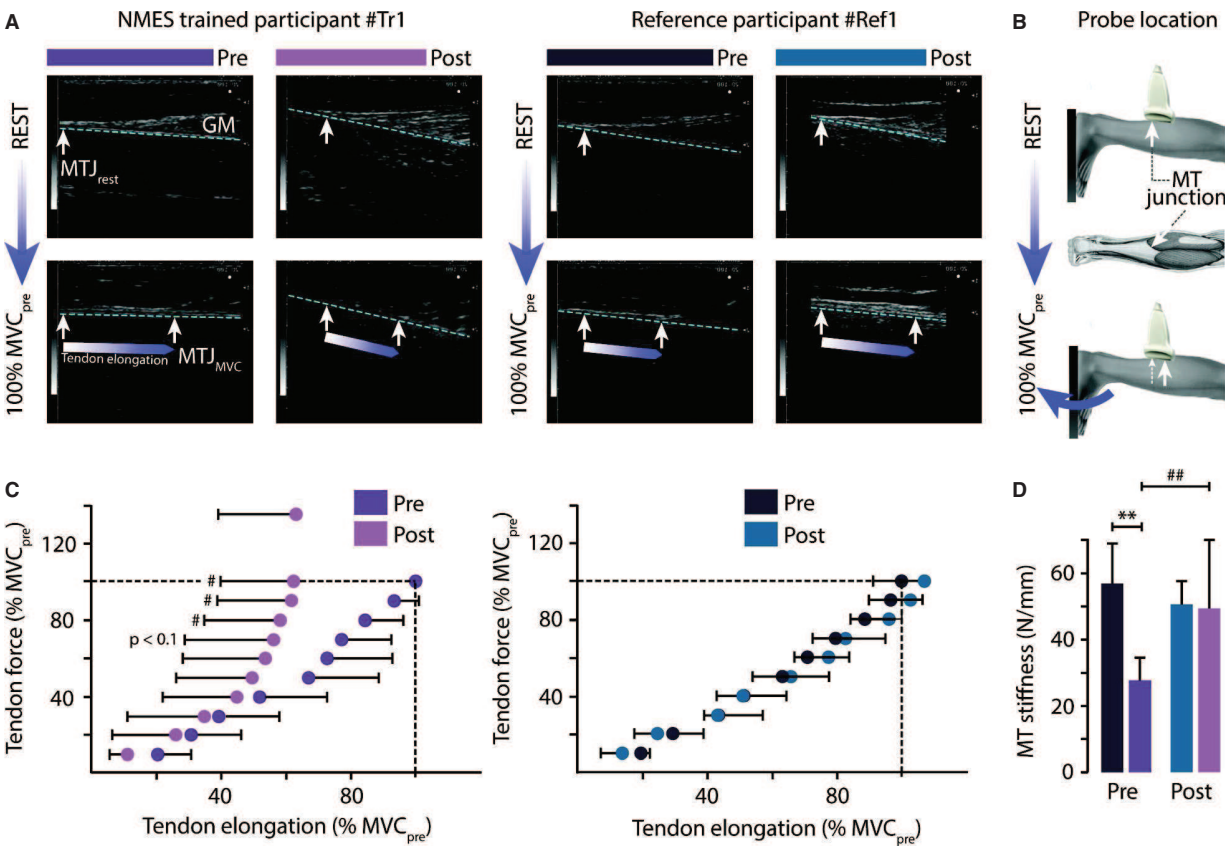

Figure 3. Evolution of musculotendinous junction properties. (A) Ultrasound images of musculotendinous (MT) junction elongation of the TS muscle during maximal voluntary contraction (MVC) in isometric plantarflexion for one participant of each group at both evaluation sessions. During MVC, the displacement of MT junction (white arrow) moves proximally, following the separation line between GM and SOL muscles (blue dashed line) (A, B). For the reference participant, the MT junction elongation for the same effort was not reduced at the post-session (white-blue arrow), and it clearly declined for the NMES-trained participant (A). (C) The mean relationship of tendon force/tendon elongation for each group at both evaluation sessions. The two relations are overlapping for the reference group. A reduction in elongation appears for high force values in the NMES-trained group. (D) Histogram of MT stiffness showing a strong increase for the trained group following NMES training, reducing the initial difference. #$P < 0.05$; ** and ##$P < 0.01$.

non-frail individual during the first spontaneous trial was corrected through demonstration in Figure 4. This latter illustrates that older adults from both studied groups were fully capable of properly performing the LoS task.

Each trial started with 5 ± 2 sec of quiet standing, followed by 25 ± 5 sec with two to four maximal LoS attempts. No strict rhythmic tilting was imposed on the participants in order to record their spontaneous dynamic postural behavior. Three valid trials (correct kinematic behavior and without moving feet) per participant were selected for the data analysis.

The CoP trajectories were recorded using a force platform. The maximal forward position of CoP (CoP_{max}) for each trial was used to calculate the forward LoS, that is, the A-P distance from ankle axis to CoP_{max} (Fig. 5A–C). To compare individuals with different height and feet sizes, LoS has been expressed as the percentage of BoS length, that is, the distance between anterior- and posterior boundaries (King et al. 1994; Schieppati et al. 1994).

To quantify the behavior of postural sways closed to CoP_{max}, the A-P speed of CoP has been calculated by deriving the A-P CoP position 2 sec prior and 2 sec after CoP_{max}. Representation of CoP speed through a color code enables easy visualization of the sway behavior (Fig. 5E and F). Mean frequency, mean amplitude, and amplitude variability were calculated from two time windows over the 2 sec prior to the CoP_{max} and the 2 sec after CoP_{max}. Moreover, this 2 + 2 sec corresponded to the observed minimal time to complete the full backward and forward movement of the tilting task among all recorded attempts.

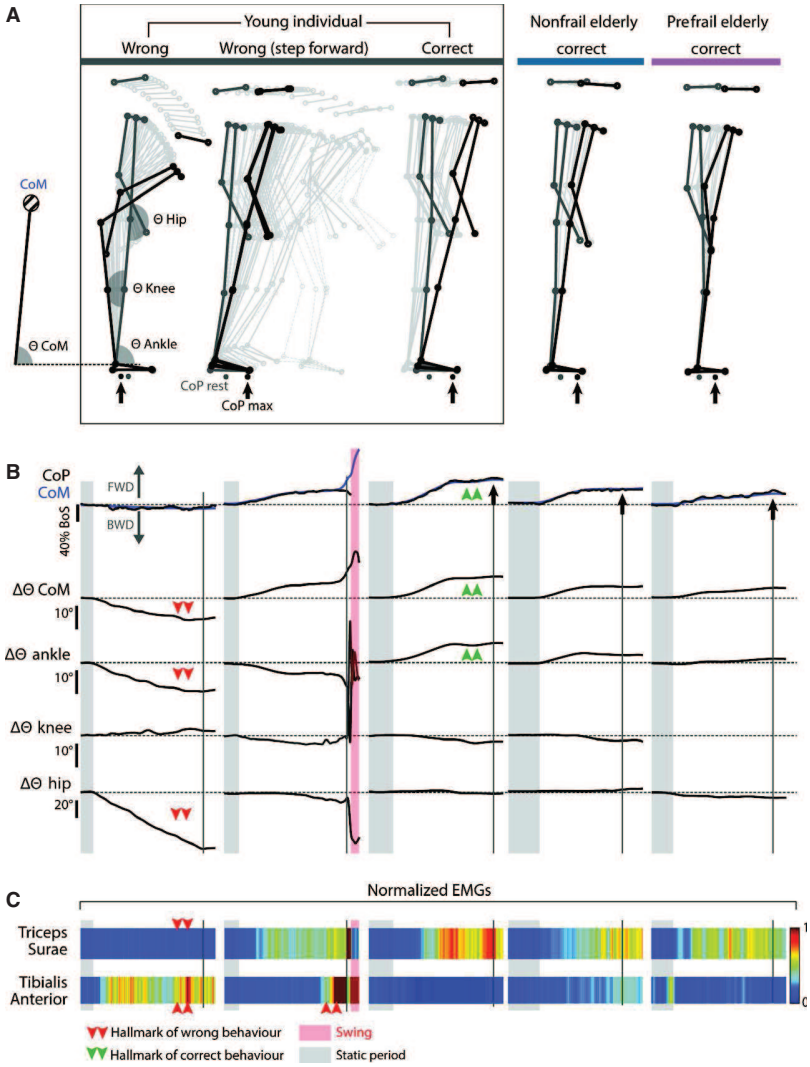

Figure 4. Kinematic (A, B), kinetic (B), and electromyographic (C) illustration of maximal limit of stability (LoS) task performed by a young individual and two elderly participants (non-frail and pre-frail). Three trials are presented for the young individual (grey panel) to better identify the hallmarks of a wrong versus a correct behavior. The trial on the left shows a hip flexion leading to a backward displacement of the center of mass (CoM) (i.e., opposite to expected direction) and absence of activation of targeted muscles (TS muscles). In the second trial, the subject did a step at the end of the attempt because CoM position has exceeded the LoS. The last trial of the young individual displays the correct behavior: CoM and center of pressure (CoP) are moving forward, with an isolated motion of ankle angle (hip and knee joint angle remain fixed) and an activation of the targeted muscles without significant co-contraction (silent TA). The two trials on the right show that both non-frail and pre-frail elderly participants were able to perform the task by respecting the afore-described kinematic, kinetic, and EMG hallmarks of the correct behavior.

The torque generated at the right ankle when reaching CoP_{max} was computed by integrating the vertical offset from the forceplate level and the ankle joint level. Then, the index of used force (IUF), that is, the index of force developed during standing compared to the intrinsic performance, was calculated as the ratio of torque at CoP_{max} and MVC during prone position for the corresponding evaluation session.

Quiet standing assessment and related data processing

Participants were asked to stand quietly and barefoot with eyes open. They were instructed to look straight ahead with the arms alongside their body and stare at a visual reference mark placed at a 2 m distance in front of them. Each foot was positioned on the force

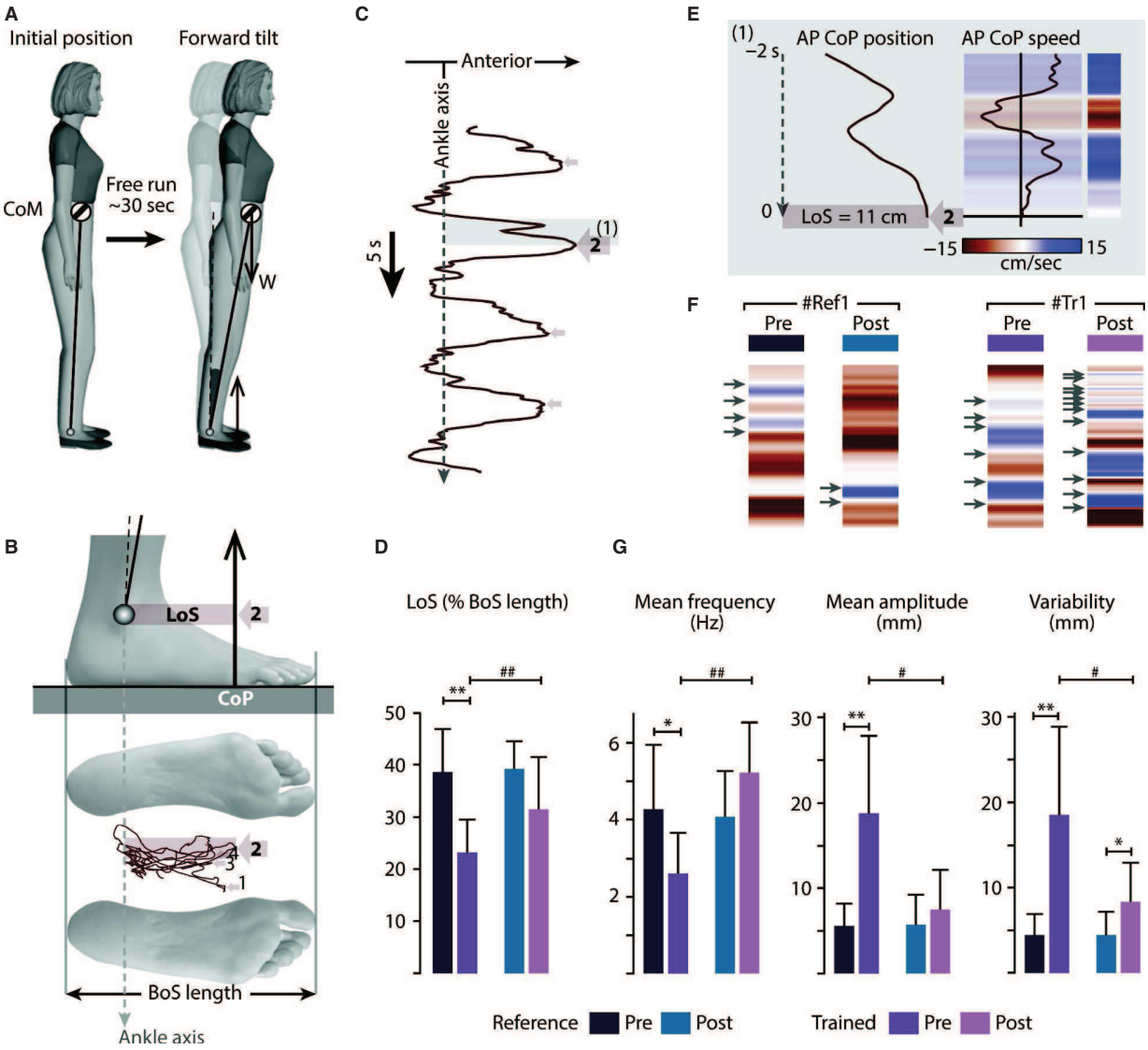

Figure 5. Limit of stability (LoS) task and data processing. (A) Illustration of the task from initial position to maximal forward tilt. From a bipedal standing position, participants were asked to reach and stay at the LoS in forward direction during approximately 30 sec. (B) Trajectory of the center of pressure (CoP) within the base of support during the task. For the presented trial, the maximal forward position of CoP was reached at the second sway (#2). (C) Anteroposterior (AP) position of CoP overtime. (D, G) Histogram representation of the extracted variables for each group and for both evaluation sessions: LoS (D) and the others computed CoP parameters 2 sec prior to reaching the LoS (G). (E) Analysis of AP CoP speed focused on 2 sec prior revealed the instantaneous speed and CoP sway frequency (color changes from blue to brown and inversely), with arrows indicating changes in the direction of postural sways. (F) Color code representation of the AP speed of CoP during the 2 sec time window prior to the LoS for one representative participant of each group. While the overall behavior seemed unchanged for the reference participant, a clear increase in maximal speed and frequency emerged for the NMES-trained participant. * and #$P < 0.05$; ** and ##$P < 0.01$.

plate (sampling frequency of 40 Hz), such that the distance between the medial side of the heels was 8.4 cm with an external rotation angle of 9°. The postural test consisted of three 30 sec trials with this quiet stance. For both A-P and M-L directions, three CoP variables were considered to describe the orthostatic postural control performance. The maximal range of CoP displacements indicated the maximal excursion of CoP in any direction. The speed of CoP displacements was calculated as the sum of the scalar displacements (i.e., cumulated

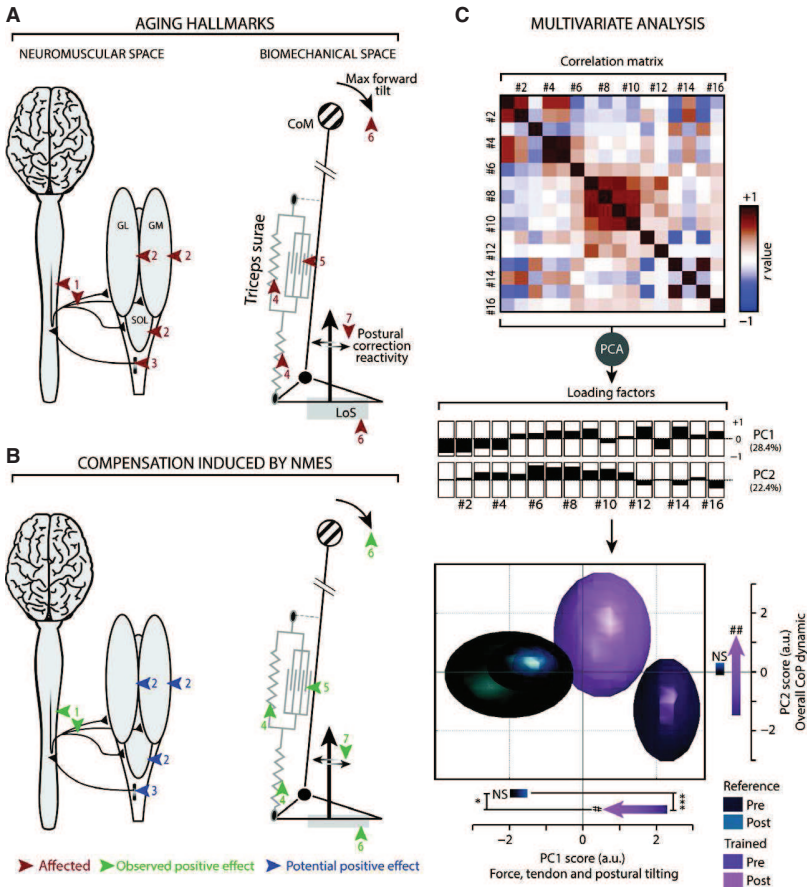

Figure 6. (A, B) Model highlighting the main neuromuscular and biomechanical elements involved in control of posture during forward body tilting, as discussed in the study. On the left side, the targeted muscles (GL, GM, and SOL) are represented with their tendon unit and their connections to the central nervous system through sensory and motor nervous fibers. On the right side, the overall body is sketched as an inverted pendulum with its center of mass (CoM) that oscillates around ankle joint. GL, GM, and SOL muscles are grouped together, forming the triceps surae (TS) complex, which is modeled by a contractile element and an elastic component in parallel while TS tendon is represented by a series of elastic components linked to the foot. Red arrows indicate the different sites affected by physiological aging: (1) neural descending pathway, including motoneurons, (2) muscle structures of TS muscle, (3) sensory pathway from Golgi Tendon Organ, (4) elastic components of muscle-tendon unit, (5) contractile component of the TS muscle, (6) maximal limit of stability of CoM and the related projected area within the base of support (LoS), and (7) dynamic reactivity to move center of pressure to correct postural tilting. Green arrows point to the elements that improved after the NMES training from the analyzed statistical results. Blue arrows show the potentially improved elements, which have to be corroborated with the quantified results. (C) Multivariate analysis was performed on the collected variables, including all of the studied components, to provide an overall vision of the evolution of each studied group. The correlation matrix of the 16 raw variables to be used in principal component analysis is presented. The histogram of loading factors represents the correlation of each variable with the corresponding principal component (PC). The two first PCs together explain 50.8% of the total variance. On the bottom part of panel C, the overall results of PCA in the 2-D space are defined by the two first PCs. Performances of all participants are clustered in ellipsoid surfaces according to their group and evaluation session. While for reference group, pre and post surfaces are overlapping, the surface of the NMES group significantly moved toward the area of the reference group, which provides visual and quantified evidence that NMES training reduces the difference between the pre-frail group and the reference group. * and #$P < 0.05$; ##$P < 0.01$; ***$P < 0.001$.

distance over the period of interest) divided by the sampling time. This measure has been shown to represent a key variable in the maintenance of postural stability, thereby providing essential functional information about the true nature of postural control in older adults (Maki et al. 1990; Deschamps et al. 2013).

Statistics

Nonparametric tests have been used to compare all the samples for each variable. Mann–Whitney tests were applied for the intergroup comparison (*$P < 0.05$, **$P < 0.01$, ***$P > 0.001$) and Wilcoxon signed-rank

tests were applied for the paired samples comparison ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P > 0.001$).

Principal component analysis

To offer an overall vision of the evolution of pre-frail group in response to the NMES training and in comparison to reference group, we implemented a multistep statistical procedure based on principal component analysis (PCA). We applied the methodology described in several studies, both in animal and human beings, which used PCA on a database comprising various biomechanical and neurophysiological variables (van den Brand et al. 2012; Mignardot et al. 2014). Briefly, PCA allowed the extraction of the most relevant information from the initial data by generating new, independent variables called principal components (PC). Each PC is a linear combination of the original variables that maximizes the amount of explained variance for each successive PC. The loading factors refer to the computed correlations between each selected PC and each variable. The performances (PC score, Fig. 6C) of each participant were clustered according to her group and to the evaluation session at the ellipsoid surface in a 2-D space constructed of the first two PCs. Thus, the above-described statistical analyses were applied to both selected PCs.

The performance of all participants at both time points and for each of the 16 variables used for the PCA has been plotted in scatter plots in Figure S1.

Results

Torque and EMG performances in prone position

The analysis of MVC revealed a difference between groups at pre-session ($P = 0.005$), which was mitigated at post-session ($P = 0.21$). In comparison to the reference group that showed no change in performance ($P = 0.47$), the pre-frail group demonstrated an improvement in MVC after NMES training (30.5 ± 12.5 vs. 41.3 ± 12.8 Nm, i.e. +26.2%, $P = 0.039$, Fig. 2C, Tables 1, 2). This result can be linked to their stronger EMG activity of their GM and SOL muscles (Fig. 2D, Tables 1, 2) and the reduction in the slope of the linear regression between EMG activity and torque (14.6 ± 1.4 vs. 12.8 ± 1.8, $P = 0.027$, Fig. 2B, Tables 1, 2).

Table 1. Mean value with standard deviation of all the variables used for the Principal Component Analysis and their outcomes in terms of loading factors on PC1 and PC2 for both groups and both time points.

		NMES trained		Reference		Loading factors (PCA)	
Variables	Number	Pre	Post	Pre	Post	PC1	PC2
Neuromuscular performance (lying)							
Isometric MVC (Nm)	1	30.5 ± 12.4	41.3 ± 12.8	54.6 ± 18.9	55.2 ± 17.8	−0.80	0.18
Regression slope – Torque versus EMG	2	14.6 ± 1.4	12.8 ± 1.8	10.8 ± 1.7	11.5 ± 1.9	−0.01	−0.44
MT stiffness index (N mm^{-1})	3	27.8 ± 7.3	49.5 ± 21.9	56.9 ± 21.7	50.9 ± 20.2	−0.75	0.25
Limit of stability task (standing)							
Limit of stability, LoS (% BoS length)	4	23.1 ± 6.5	31.5 ± 10.0	38.6 ± 8.3	39.1 ± 5.4	−0.57	0.51
Torque at LoS (Nm)	5	19.0 ± 8.2	24.3 ± 11.3	32.7 ± 10.0	32.7 ± 6.4	−0.49	0.51
Index of used force	6	0.7 ± 0.3	0.6 ± 0.2	0.6 ± 0.3	0.6 ± 0.2	0.35	0.28
CoP characteristics (2 sec prior LoS)							
Frequency (Hz)	7	2.6 ± 1.1	5.2 ± 1.3	4.3 ± 1.7	4.1 ± 1.2	−0.16	0.67
Amplitude (mm)	8	18.8 ± 9.1	7.5 ± 4.7	5.6 ± 2.4	5.7 ± 3.5	0.63	−0.42
Variability (mm)	9	18.9 ± 10.3	8.6 ± 4.6	4.8 ± 2.5	4.7 ± 2.7	0.65	−0.43
CoP characteristics (2 sec after LoS)							
Frequency (Hz)	10	3.7 ± 1.0	5.4 ± 2.2	3.7 ± 1.5	4.1 ± 1.1	0.20	0.39
Amplitude (mm)	11	18.2 ± 5.7	15.5 ± 8.0	37.1 ± 23.2	28.8 ± 14.0	−0.58	0.13
Variability (mm)	12	14.3 ± 4.5	16.5 ± 9.1	12.6 ± 10.2	12.8 ± 15.8	0.26	0.13
Quiet standing balance (CoP sway)							
Mean speed M-L (mm s^{-1})	13	5.8 ± 2.8	9.0 ± 3.5	5.4 ± 2.7	6.8 ± 1.7	0.44	0.74
Mean speed A-P (mm s^{-1})	14	13.2 ± 5.7	16.5 ± 6.9	10.4 ± 3.6	9.8 ± 2.5	0.57	0.65
Max range M-L (mm)	15	16.8 ± 7.6	22.0 ± 10.0	11.6 ± 3.1	16.3 ± 5.5	0.55	0.67
Max range A-P (mm)	16	28.0 ± 9.0	25.2 ± 8.7	18.7 ± 5.9	18.4 ± 4.7	0.65	0.47
Principal component analysis							
Score on PC1 (a.u.)		2.3 ± 0.9	0.5 ± 1.35	−2.0 ± 1.8	−1.5 ± 1.1		
Score on PC2 (a.u.)		−1.3 ± 1.8	1.3 ± 2.15	−0.1 ± 1.5	0.2 ± 0.9		

Table 2. Inter-group (Mann-Whitney, U-Test) and intra-group (Wilcoxon signed rank, WSR-Test) statistical outcomes.

		INTER-group				INTRA-group			
		Pre		Post		Reference		NMES	
Variables	Number	*U*	*P*	*U*	*P*	WSR	*P*	WSR	*P*
Neuromuscular performance (lying)									
Isometric MVC (Nm)	1	6.0	**0.005**	19.0	0.21	9.0	0.469	3.0	**0.039**
Regression slope – Torque versus EMG	2	61.0	**0.001**	44.0	0.199	0.0	**0.016**	41.0	**0.027**
MT stiffness index (N mm^{-1})	3	5.0	**0.003**	32.0	0.978	19.0	0.469	1.0	**0.008**
Limit of stability task (standing)									
Limit of stability (% BoS length)	4	3.0	**0.001**	13.0	0.051	10.0	1.000	1.0	**0.008**
Torque at CoPmax (Nm)	5	9.0	**0.016**	17.0	0.142	11.0	1.000	4.0	**0.027**
Index used force	6	35.5	0.722	30.5	0.997	16.0	0.813	32.0	0.301
CoP characteristics (2 sec prior LoS)									
Frequency (Hz)	7	13.0	**0.050**	49.0	0.066	16.5	0.730	0.0	**0.009**
Amplitude (mm)	8	60.0	**0.001**	41.5	0.315	14.0	0.938	42.0	**0.020**
Variability (mm)	9	61.0	**0.001**	51.0	**0.039**	14.0	0.938	41.0	**0.027**
CoP characteristics (2 sec after LoS)									
Frequency (Hz)	10	34.5	0.775	44.5	0.18	5.5	0.684	8.0	0.095
Amplitude (mm)	11	16.0	0.108	14.0	0.071	24.0	0.108	29.0	0.496
Variability (mm)	12	33.0	0.892	44.0	0.21	16.0	0.800	21.0	0.910
Quiet standing balance (CoP sway)									
Mean speed M-L (mm s^{-1})	13	39.5	0.426	44.5	0.181	6.0	0.205	1.0	**0.008**
Mean speed A-P (mm s^{-1})	14	39.5	0.425	53.0	**0.021**	15.0	0.933	6.0	0.055
Max range M-L (mm)	15	48.0	0.091	42.5	0.264	0.0	**0.022**	7.0	0.074
Max range A-P (mm)	16	50.0	0.055	43.5	0.221	14.0	1.000	31.0	0.359
Principal component analysis									
Score on PC1 (a.u.)		63.0	**0.0002**	56.0	**0.011**	6.0	0.205	42.0	**0.024**
Score on PC2 (a.u.)		19.0	0.204	40.0	0.397	10.0	0.554	0.0	**0.009**

Bold values are statistical significance threshold crossed.

Musculo-tendinous behavior

While no significant change in tendon elongation was observed for low and intermediate force values (up to 60% of MVC_{pre}), the NMES group revealed a reduction in distance traveled by the MT junction for high force value ($P < 0.1$ for 70% MVC_{pre}, $P < 0.05$ for 80% MVC_{pre}; Fig. 3C). No change was reported for the reference group, regardless of the developed force. The pre-frail group showed the lowest MT stiffness compared to the reference group at pre-session ($P = 0.003$) but they demonstrated significant improvement for this variable/parameter after training (27.8 ± 7.3 vs. 49.5 ± 21.9 N mm^{-1}, i.e., +44%, $P = 0.008$, Fig. 3D, Tables 1, 2), such that no more difference existed between groups at post-session ($P = 0.978$). MT stiffness was computed at 100% MVC_{pre}.

LoS and torque performance during tilting in standing position

While participants from the reference group were able to amply move their CoP when performing the LoS task (38.6 ± 8.3% of BoS length at pre-session), the performance was significantly lower for NMES participants at the pre-session (23.1 ± 6.5%, $P = 0.001$, Fig. 5D, Tables 1, 2). The statistical analysis revealed a significant improvement in NMES group performance after training (31.5% of BoS length at post-session, $P = 0.008$), with a value that did not differ significantly from that of post-session reference group ($P = 0.051$, Fig. 5D, Tables 1, 2).

Concerning the torque generated when reaching the LoS, the profile of the results can be regarded as close to those described for the LoS performance (Tables 1, 2). The IUF remained unchanged across the groups and the evaluation sessions, with stable values were around 0.65 (Tables 1, 2).

Postural sway during the tilting task

Although no significant change in CoP sway characteristics was observed for the 2 sec after CoP_{max}, all calculated characteristics were modified for the NMES group during the 2-sec period prior to CoP_{max} (Fig. 5G, Tables 1, 2). While the sway frequency for the reference group remained unchanged between sessions (4.3 ± 1.7

Hz at pre-session; 4.1 ± 1.2 Hz at post-session), this variable strongly increased for the NMES group (2.6 ± 1.1 Hz at pre-session; 5.2 ± 1.3 Hz at post-session; $P = 0.009$, Fig. 5G, Tables 1, 2). The statistical analysis also revealed a decrease in the amplitude ($P = 0.02$) and the variability ($P = 0.027$) of the sway after NMES training, while these characteristics remained stable for the reference group (Fig. 5G, Tables 1, 2). These outcomes were also transcribed through a color-coded visualization of CoP speed as represented in Figure 5F that displays the attempts of two representative participants from both groups.

Postural sway during quiet standing

No significant change in CoP sway characteristics was observed after the training period regarding the anteroposterior component. Nevertheless, we can note an effect of the session on the mediolateral component of the mean speed for the NMES group ($P = 0.008$, Tables 1, 2).

Principal component analysis

The first two PCs explained the 28.4% and 22.4% of total variance, respectively, and comprised mainly variables related to force, tendon, and postural tilting (PC1) as well as the overall dynamic properties of CoP (PC2). The statistical analysis performed on the score of both plotted PC showed for PC1, while the location of the reference group remained unchanged from pre- to post-sessions ($P = 0.205$), the NMES group differed significantly from the reference group at pre-session ($P = 0.0002$) and became significantly closer to it after the training ($P = 0.024$; horizontal axis on the 2D plot on Fig. 6C). Regarding PC2 (vertical axis on the 2D plot on Fig. 6C), the statistical analysis also indicated a modification of the location of the NMES group after the training period ($P = 0.009$), while the location of the reference group within the PC-space remained unchanged ($P = 0.554$, Tables 1, 2).

Discussion

The primary aim of this study was to characterize the effects of 4 weeks of TS NMES training on postural control in pre-frail older people. The second aim was to investigate how potential NMES-induced changes in force and force transmission at the level of ankle joint could be associated with changes in postural control, both in challenging LoS and quiet standing tasks. Our results showed that NMES training significantly reduced the differences between pre-frail participants' and reference participants' performance on challenging postural control. These results should be seen in relation to intrinsic neuromuscular and musculotendinous gains, which were currently observed in a functional balance context.

NMES improves voluntary muscle performance through both neural and peripheral adaptations

In agreement with previous results, the maximal voluntary force developed during PF effort was low among older people (Morse et al. 2004; Narici et al., 2004). Although some of the effects of aging in sedentary people on muscle force and its mechanical properties have already been reported (e.g., Ochala et al. 2004), the maximal voluntary force generated at the ankle joint has not been yet documented for older adults based on their residence type and frailty status. First, our results demonstrated that before NMES training, MVC performance while lying was significantly lower for pre-frail institutionalized participants in comparison to healthy noninstitutionalized participants (−44.2%). However, 4 weeks of NMES training significantly improved the performance of trained participants to 26.2% (Fig. 2C). Gondin et al. (2005, 2006) identified the mechanisms underlying NMES-related torque increase after 8 weeks training in young adults. Analysis of mid-quadriceps anatomical cross-sectional area demonstrated that an increase in both neuromuscular activation and peripheral adaptation explained the improvement in MVC (Gondin et al. 2005).

The current NMES training was performed over 4 weeks. Regarding this quite short period, we expected that mechanisms underlying the observed gain in torque production would be related mainly to neural adaptation. Accordingly, EMG maximal activity increased for both GM and SOL muscles following NMES training (Fig. 2D), reflecting stronger motoneuron activity (Fig. 6B).

The relationship between EMG and force on ongoing effort of PF (Fig. 2B) confirmed those results. Neural adaptations based on greater EMG activity of the TS muscle and peripheral adaptations, as suggested by reductions in slope (see Fig. 2B), explained the force gains. A direct measure of muscle changes through imagery is needed to confirm this hypothesis but NMES seems to have a positive effect against sarcopenia by increasing both the neural descending drive and muscle properties.

NMES modifies MT properties

Tendon is involved mainly in force transmission from muscles to bones and in fine to external environment, and vice versa. Its mechanical properties determine the speed of force transmission that must be considered when studying postural control. It is already known that the

muscle-tendon complex is more compliant with aging (Lexell et al. 1983; Narici and Maganaris 2006; Onambele et al. 2006; Narici et al. 2008), which could be a drawback when posture is suddenly disturbed and the reaction force has to be quickly transmitted to allow rapid postural corrections.

Our results demonstrate that the lower MT stiffness observed in the pre-frail group at the initial stage is reduced after NMES training (+43.9%, Fig. 3D) and moved closer to the reference group's value. As evidenced by echography pictures in Figure 3A, the MT junction displacement between rest and MVC_{pre} clearly decreased after NMES training for NMES group, while it remained unchanged for the reference participants. This improvement suggests that short-term NMES training induces a useful decrease in the time required for the force transmission. This point is of special interest when the older individuals need to respond as fast as possible to an unexpected postural perturbation. A stiff tendon of the plantarflexor muscle can quickly transmit the generated force to the BoS in order to adjust the position of CoP below the projection of CoM when the balance needs to be recovered (Morasso et al. 1999; Loram et al. 2005). In addition, the enhanced muscle-tendon force transmission might improve the ability of the central nervous system to finely tune the muscle activation pattern needed to meet the task constraints. This feed-forward control process could be recalibrated based on the sensory information provided by peripheral commands (e.g., Seidler et al. 2004). Thanks to the NMES training, the central nervous system could have become more efficient in predicting the optimal motor response because of optimized feed-forward control and postural control, thus preventing the risk of fall in older adults (Horak 2006; Doumas and Krampe 2010).

To summarize, the improvement in force capacity and force transmission properties through a higher MT stiffness revealed some intrinsic MT and neuromuscular activation changes, as observed with NMES performed in the lying position (without any postural constraints). However, the ability to translate these gains in a functional context where balance is precarious remained to be determined, in particular when performing a task demanding a high force. In this way, we used the LoS task that challenged balance performance.

The NMES-induced changes in muscle-tendon complex: toward evidence of a positive transfer in postural control

The anatomical joint configuration for this challenging LoS task was close to the studied lying prone position: the knee and hip joints were maintained extended and the ankle joint remained between 85° and 90° (Fig. 4B). We evidenced similar kinematic (Fig. 4A and B), kinetic (Fig. 4B), and electromyographic (Fig. 4C) characteristics for one young and two older participants representatives from both studied groups. All participants were fully able to correctly perform the expected behavior (see details in Fig. 4). In this respect, a reduced ability in older adults to widely move their CoP toward the BoS boundary (i.e. the LoS) has been reported in many studies (e.g., Cavanaugh et al. 1999; Kozak et al. 2003; Melzer et al. 2009). This deficit was consistently more pronounced for the pre-frail group than the nontrained group (−40.2%, Fig. 5D). But the striking result is that the NMES training significantly reduced this difference with an improvement of 26.8% between pre-training versus post-training performance (Fig. 5D). The IUF notably allowed to compare the torque generated in standing versus lying prone (intrinsic capacity). For all participants, the IUF remained unchanged around 60–70% of their MVC in the prone position (Tables 1, 2, Fig. S1). This finding highlighted the fact that the LoS task was consistent with the reduced level of force for tendon elongation after NMES training (Fig. 3C).

Regarding the analysis of CoP sway during the 2-sec time windows prior to CoP_{max} (Fig. 5), an interesting evolution in kinematic behavior between pre- and post-session is likely be related to the change in MT stiffness of TS. Indeed, CoP oscillated more frequently and less widely at post-NMES training session. This can be linked to an increased MT stiffness because a stiffer MT complex is de facto more able to faster transmit muscle force variations to the external environment. Inertia can thus be considered as reduced, enhancing both the perception of postural disturbances (sensory pathway) through a higher sensibility of muscle spindles, and the transmission of force to the external environment in order to adjust the posture depending on the perturbation (motor drive). Note that a possible learning effect of the LoS task between the sessions was rejected, since the values from untrained group did not vary.

Control assessment through quiet standing task

It seemed interesting to test the postural control during a simple task where the developed force is much less important. During quiet standing, the generated force was actually estimated at about 10% MVC in an older population (Billot et al. 2010). In this context, Amiridis et al. (2005) studied the effect of a 4-week NMES training (70 Hz) on TA muscle in older participants. They showed that while the maximal voluntary force during dorsiflexion effort improved, the postural control assessed during bipedal quiet standing task through A-P and M-L CoP range and variability remained unchanged. This is in line

with the present study, since the amount (CoP speed) and amplitude (CoP range) of anteroposterior postural sway (directly linked to the torque applied at the ankle joint) remained unchanged after the NMES training (Fig. S1, Tables 1, 2). These findings suggest that the current gains are likely to be transposed mainly in postural situations where a significant force is required.

A PCA supports the positive effect of NMES on the initial deficits

To summarize all of the collected data, we performed a PCA, which simplifies the overall evolution of each group after the 4-week period while maintaining highly precise quantification. The ellipsoid surface, which clustered each individual performance (PCs score) as a function of the group and the session, demonstrated that NMES group significantly moved toward the reference group ellipses after the 4-week period (Fig. 6C). The initial variables that contribute to PC1 correlate strongly with each other; they gather components related to force, tendon properties, and performance during the LoS task. Moreover, the NMES group statistically reduced their distance from reference group along the PC1 axis but without totally covering the gap that still separated them (Fig. 6C). Concerning PC2, which is mainly related to dynamic behavior of CoP during both standing tasks, the NMES group moved beyond the reference group. This evolution demonstrated that the NMES training effectively influenced the postural control. However, after training, the NMES group exhibited biomechanical behavior that still differed from the reference group. Overall, this original data analysis provides quantified evidence to support the alleviating effect of NMES on broad biomechanical and balance deficits related to physiological aging.

Methodological considerations

We acknowledge that there are some methodological limitations in our protocol. For example, the knee angle was different during the NMES training and the evaluation protocol. Although the contributions of SOL (monoarticular muscle) and gastrocnemii (biarticular muscles) of TS are knee- or ankle-angle dependent (Cresswell et al. 1995), it is somewhat difficult to precisely determine their contribution in terms of force production during voluntary or electrically induced contraction (Sale et al. 1982; Fouré et al. 2013). Thus, the lying prone position was chosen as the best compromise to avoid some difficulties encountered by the older adults in performing maximal PF without muscular effort for knee extension, as in sitting position. In this way, further investigations are necessary to characterize the force and MT stiffness during the NMES session but also while performing the LoS task. We also concede that MT stiffness assessed through longitudinal ultrasonography imagery does not represent the overall structural muscle and tendon unit. A more complete analysis, including cross-sectional area and muscle architecture, would be useful to better understand the full effect of NMES conditioning on peripheral changes.

Conclusion

This study provides encouraging evidence that high-frequency NMES training is a useful training paradigm to achieve a positive short-term effect on the muscle-tendon unit impaired by physiological aging. Four weeks of TS NMES training increased both force production and force transmission through changes in MT stiffness. These improvements promoted the postural control under a challenging situation through enhanced capacity to explore the BoS by widely and quickly controlling the center of pressure displacement. Future studies would strengthen these current results by considering various patient populations with a larger sample size to confirm that NMES actively contributes to the fight against neuromuscular impairments and its adverse functional consequences such as falls.

Acknowledgments

Odile Hyot, Bruno Vinceneux (PT) & Mickaël Crevecoeur, for their technical support.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Amiridis, I., F. Arabatzi, P. Violaris, E. Stavropoulos, and V. Hatzitaki. 2005. Static balance improvement in elderly after dorsiflexors electrostimulation training. Eur. J. Appl. Physiol. 94:424–433.

Bax, L., F. Staes, and A. Verhagen. 2005. Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomised controlled trials. Sports Med. 35:191–212.

Billot, M., E. M. Simoneau, J. Van Hoecke, and A. Martin. 2010. Age-related relative increases in electromyography activity and torque according to the maximal capacity during upright standing. Eur. J. Appl. Physiol. 109:669–680.

van den Brand, R., J. Heutschi, Q. Barraud, J. DiGiovanna, K. Bartholdi, M. Huerlimann, et al. 2012. Restoring voluntary

control of locomotion after paralyzing spinal cord injury. Science 336:1182–1185.

Caggiano, E., T. Emrey, S. Shirley, and R. L. Craik. 1994. Effects of electrical stimulation or voluntary contraction for strengthening the quadriceps femoris muscles in an aged male population. J. Orthop. Sports Phys. Ther. 20:22–28.

Cavanaugh, J. T., M. Shinberg, L. Ray, K. M. Shipp, M. Kuchibhatla, and M. Schenkman. 1999. Kinematic characterization of standing reach: comparison of younger vs. older subjects. Clin. Biomech. (Bristol, Avon) 14:271–279.

Cresswell, A. G., W. N. Löscher, and A. Thorstensson. 1995. Influence of gastrocnemius muscle length on triceps surae torque development and electromyographic activity in man. Exp. Brain Res. 105:183–209.

Darling, W. G., J. D. Cooke, and S. H. Brown. 1989. Control of simple arm movements in elderly humans. Neurobiol. Aging 10:149–157.

Deschamps, T., O. Beauchet, C. Annweiler, C. Cornu, and J. B. Mignardot. 2013. Postural control and cognitive decline in older adults: position versus velocity implicit motor strategy. Gait Posture. 39:628–630.

Doherty, T. J. 2003. Aging and sarcopenia. J. Appl. Physiol. 95:1717–1727.

Doumas, M., and R. T. Krampe. 2010. Adaptation and reintegration of proprioceptive information in young and older adults' postural control. J. Neurophysiol. 104:1969–1977.

Duclay, J., A. Martin, A. Duclay, G. Cometti, and M. Pousson. 2009. Behavior of fascicles and the myotendinous junction of human medial gastrocnemius following eccentric strength training. Muscle Nerve 39:819–827.

Ferri, A., G. Scaglioni, M. Pousson, P. Capodaglio, J. VanHoecke, and M. V. Narici. 2003. Strength and power changes of the human plantar flexors and knee extensors in response to resistance training in old age. Acta Physiol. Scand. 177:69–78.

Fouré, A., A. Nordez, and C. Cornu. 2013. Effects of eccentric training on mechanical properties of the plantar flexor muscle-tendon complex. J. Appl. Physiol. (1985), 114:523–537.

Glinsky, J., L. Harvey, and P. Van Es. 2007. Efficacy of electrical stimulation to increase muscle strength in people with neurological conditions: a systematic review. Physiother. Res. Int. 12:175–194.

Gondin, J., M. Guette, Y. Ballay, and A. Martin. 2005. Electromyostimulation training effects on neural drive and muscle architecture. Med. Sci. Sports Exerc. 37:1291–1299.

Gondin, J., J. Duclay, and A. Martin. 2006. Soleus- and gastrocnemii-evoked V-wave responses increase after neuromuscular electrical stimulation training. J. Neurophysiol. 95:3328–3335.

Gondin, J., L. Brocca, E. Bellinzona, G. D'Antona, N. A. Maffiuletti, D. Miotti, et al. 2011. Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis. J. Appl. Physiol. (1985), 110:433–450.

Gorgey, A. S., and R. E. Khalil. 2015. Neuromuscular electrical stimulation training increases intermuscular fascial length but not tendon cross-sectional area after spinal cord injury. Top. Spinal. Cord Inj. Rehabil. 21:87–92.

Grosset, J. F., F. Canon, C. Pérot, and D. Lambertz. 2014. Changes in contractile and elastic properties of the triceps surae muscle induced by neuromuscular electrical stimulation training. Eur. J. Appl. Physiol. 114:1403–1411.

Hill, C. 2001. Caring for the aging athlete. Geriatr. Nurs. 22:43–45.

Horak, F. B. 2006. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing 35:ii7–ii11.

Katz, S., T. D. Down, H. R. Cash, and R. C. Grotz. 1970. Progress in the development of the index of ADL. Gerontologist 10:20–30.

Kern, H., L. Barberi, S. Löfler, S. Sbardella, S. Burggraf, H. Fruhmann, et al. 2014. Electrical stimulation counteracts muscle decline in seniors. Front. Aging Neurosci. 6:189.

King, M. B., J. O. Judge, and L. Wolfson. 1994. Functional base of support decreases with age. J. Gerontol. 49:258–263.

Kozak, K., J. A. Ashton-Miller, and N. B. Alexander. 2003. The effect of age and movement speed on maximum forward reach from an elevated surface: a study in healthy women. Clin. Biomech. 18:190–196.

Lexell, J., K. Henriksson-Larsén, B. Winblad, and M. Sjöström. 1983. Distribution of different fiber types in human skeletal muscles: effects of aging studied in whole muscle cross sections. Muscle Nerve 6:588–595.

Lichtwark, G. A., and A. M. Wilson. 2008. Optimal muscle fascicle length and tendon stiffness for maximising gastrocnemius efficiency during human walking and running. J. Theor. Biol. 252:662–673.

Loram, I. D., C. N. Maganaris, and M. Lakie. 2004. Paradoxical muscle movement in human standing. J. Physiol. 556:683–689.

Loram, I. D., C. N. Maganaris, and M. Lakie. 2005. Human postural sway results from frequent, ballistic bias impulses by soleus and gastrocnemius. J. Physiol. 564:295–311.

Maffiuletti, N. A. 2010. Physiological and methodological considerations for the use of neuromuscular electrical stimulation. Eur. J. Appl. Physiol. 110:223–234.

Maffiuletti, N. A., R. Zory, D. Miotti, M. A. Pellegrino, M. Jubeau, and R. Bottinelli. 2006. Neuromuscular adaptations to electrostimulation resistance training. Am. J. Phys. Med. Rehabil. 85:167–175.

Maki, B. E., P. J. Holliday, and G. R. Fernie. 1990. Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. J. Am. Geriatr. Soc. 38:1–9.

Maki, B. E., P. J. Holliday, and A. K. Topper. 1994. A prospective study of postural balance and risk of falling in

an ambulatory and independent elderly population. J. Gerontol. 49:72–84.

Melzer, I., N. Benjuya, J. Kaplanski, and N. Alexander. 2009. Association between ankle muscle strength and limit of stability in older adults. Age Ageing 38:119–123.

Mignardot, J. B., T. Deschamps, E. Barrey, B. Auvinet, G. Berrut, C. Cornu, et al. 2014. Gait disturbances as specific predictive markers of the first fall onset in elderly people: a two-year prospective observational study. Front. Aging Neurosci. 25:6–22.

Morasso, P. G., G. Spada, and R. Capra. 1999. Computing the COM from the COP in postural sway movements. Hum. Mov. Sci. 18:759–767.

Moritani, T., and H. A. de Vries. 1979. Neural factors versus hypertrophy in the time course of muscle strength gain. Am. J. Phys. Med. 58:115–130.

Morse, C. I., J. M. Thom, M. G. Davis, K. R. Fox, K. M. Birch, and M. V. Narici. 2004. Reduced plantar flexor specific torque in the elderly is associated with a lower activation capacity. Eur. J. Appl. Physiol. 92:219–226.

Nachreiner, N. M., M. J. Findorff, J. F. Wyman, and T. C. McCarthy. 2007. Circumstances and consequences of falls in community-dwelling older women. J. Womens Health 16:1437–1446.

Narici, M. V., N. D. Reeves, C. I. Morse, and C. N. Maganaris. 2004. Muscular adaptations to resistance exercise in the elderly. J Musculoskelet Neuronal Interact. 4:161–164.

Narici, M. V., and N. Maffulli. 2010. Sarcopenia: characteristics, mechanisms and functional significance. Br. Med. Bull. 95:139–159.

Narici, M. V., and C. N. Maganaris. 2006. Adaptability of elderly human muscles and tendons to increased loading. J. Anat. 208:433–443.

Narici, M. V., N. Maffulli, and C. N. Maganaris. 2008. Ageing of human muscles and tendons. Disabil. Rehabil. 30:1548–1554.

Ochala, J., D. Lambertz, M. Pousson, F. Goubel, and J. V. Hoecke. 2004. Changes in mechanical properties of human plantar flexor muscles in ageing. Exp. Gerontol. 39:349–358.

de Oliveira Melo, M., F. A. Aragão, and M. A. Vaz. 2013. Neuromuscular electrical stimulation for muscle strengthening in elderly with knee osteoarthritis – a systematic review. Complement. Ther. Clin. Pract. 19:27–31.

Onambele, G. L., M. V. Narici, and C. N. Maganaris. 2006. Calf muscle-tendon properties and postural balance in old age. J. Appl. Physiol. 100:2048–2056.

Paillard, T., C. Lafont, C. Pérès, M. C. Costes-Salon, J. M. Soulat, R. Montoya, et al. 2005. Is electrical stimulation with voluntary muscle contraction of physiologic interest in aging women? Ann. Readapt. Med. Phys. 48:20–28.

Paizis, C., C. Papaxanthis, B. Berret, and T. Pozzo. 2008. Reaching beyond arm length in normal aging: adaptation of hand trajectory and dynamic equilibrium. Behav. Neurosci. 122:1361–1370.

Papadopoulos, M., I. Patsaki, A. Christakou, V. Gerovasili, and S. Nanas. 2013. Therapeutic applications of neuromuscular electrical stimulation in critical care patients. Hosp. Chron. 8:112–119.

Perez, M., A. Lucia, J. L. Rivero, A. L. Serrano, J. A. Calbet, M. A. Delgado, et al. 2002. Effects of transcutaneous short-term electrical stimulation on *M. vastus* lateralis characteristics of healthy young men. Pflügers Arch. 443:866–874.

Polcyn, A. F., L. A. Lipsitz, D. C. Kerrigan, and J. J. Collins. 1998. Age-related changes in the initiation of gait: degradation of central mechanisms for momentum generation. Arch. Phys. Med. Rehabil. 79:1582–1589.

Quittan, M., G. F. Wiesinger, B. Sturm, S. Puig, W. Mayr, A. Sochor, et al. 2001. Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure: a single-blinded, randomized, controlled trial. Am. J. Phys. Med. Rehabil. 80:206–214.

Report of the European Working Group on Sarcopenia in Older People; Cruz-Jentoft, A. J., J. P. Baeyens, J. M. Bauer, Y. Boirie, T. Cederholm, F. Landi, F. C. Martin, J. P. Michel, Y. Rolland, S. M. Schneider, E. Topinková, M. Vandewoude, and M. Zamboni. 2010. Sarcopenia: European consensus on definition and diagnosis. Age Ageing 39:412–423.

Robinovitch, S. N., F. Feldman, Y. Yang, R. Schonnop, P. M. Leung, T. Sarraf, et al. 2013. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. Lancet 381:47–54.

Rom, O., S. Kaisari, D. Aizenbud, and A. Z. Reznick. 2012. Lifestyle and sarcopenia-etiology, prevention, and treatment. Rambam Maimonides Med. J. 3:e0024.

Rosenberg, I. H. 1997. Sarcopenia: origins and clinical relevance. J. Nutr. 127:990–991.

Sale, D., J. Quinlan, E. Marsh, A. J. McComas, and A. Y. Belanger. 1982. Influence of joint position on ankle plantarflexion in humans. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 52:1636–1642.

Sarabon, N., L. Stefan, C. Jan, S. Milan, and K. Helmut. 2013. Strength training in elderly people improves static balance: a randomized controlled trial. Eur. J. Transl. Myol. Basic Appl. Myol. 23:85–89.

Schieppati, M., M. Hugon, M. Grasso, A. Nardone, and M. Galante. 1994. The limits of equilibrium in young and elderly normal participants and in Parkinsonians. Electroencephalogr. Clin. Neurophysiol. 93:286–298.

Seidler, R. D., D. C. Noll, and G. Thiers. 2004. Feedforward and feedback processes in motor control. NeuroImage 22:1175–1183.

Simoneau, E., A. Martin, and J. Van Hoecke. 2005. Muscular performances at the ankle joint in young and elderly men. J. Gerontol. A Biol. Sci. Med. Sci. 60:439–447.

Simoneau, E., A. Martin, and J. VanHoecke. 2007. Adaptations to long-term strength training of ankle joint muscles in old age. Eur. J. Appl. Physiol. 100:507–514.

Stapley, P., T. Pozzo, A. Grishin, and C. Papaxanthis. 2000. Investigating centre of mass stabilisation as the goal of posture and movement coordination during human whole body reaching. Biol. Cybern. 82:161–172.

Sutherland, D. H., L. Cooper, and D. Daniel. 1980. The role of ankle flexors in normal walking. J. Bone Joint Surg. Am. 62:354–363.

Vivodtzev, I., J. L. Pepin, G. Vottero, V. Mayer, B. Porsin, P. Levy, et al. 2006. Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. Chest 129:1540–1548.

Winter, D. A. 1995. Human balance and posture control during standing and walking. Gait Posture. 3:193–214.

Winter, D. A., A. E. Palta, F. Prince, and M. Ishac. 1998. Stiffness control of balance in quiet standing. J. Neurophysiol. 80:1211–1221.

Woollacott, M. H., A. Shumway-Cook, and L. M. Nashner. 1986. Aging and posture control: changes in sensory organization and muscular coordination. Int. J. Aging Hum. Dev. 23:97–114.

Wroblewski, A. P., F. Amati, M. A. Smiley, B. Goodpaster, and V. Wright. 2011. Chronic exercise preserves lean muscle mass in masters athletes. Phys. Sportsmed. 39:172–178.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Scatter plots of each variable used for the principal component analysis for both groups and both time points. All individuals' data are plotted together with their mean value (diamond) ± the 95% confidence interval.

Hemodialysis International 2015; **19**:553–561

The effect of hemodialysis session on postural strategies in older end-stage renal disease patients

Justine MAGNARD,[1] Julien LARDY,[1] Angelo TESTA,[2] Dan HRISTEA,[2] Thibault DESCHAMPS[1]

[1]*Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), University of Nantes, Nantes, France;* [2]*Dialysis Unit, ECHO Nantes Dialysis Association, Nantes, France*

Abstract

Patients suffering from end-stage renal disease experience multiple disabilities, such as muscle wasting, weakness, higher postural sway, and fall rates compared with healthy population, which has a negative effect on physical functioning and autonomy. The vital treatment of hemodialysis is recognized to induce important post-hemodialysis fatigue, hypotension, cramps, and headache due to the rapid fluid redistribution, among others. Nevertheless, even the well-known negative effect of aforementioned consequences of hemodialysis treatment, its effect on physical function, especially postural balance, is unclear. Thus, this study hypothesized the adverse effect of hemodialysis treatment on postural sway in 12 end-stage renal disease patients (mean age 63.3 ± 11 years) through the analysis of center-of-pressure (COP) trajectories recorded before and immediately after hemodialysis session. Evident postural alterations were observed at post-hemodialysis balance assessment for COP position-based ($Fs < 7.7$, $P < 0.02$) and COP velocity-based variables ($Fs > 2.33$, $P < 0.05$), without changes in complexity of COP time series in anteroposterior and mediolateral directions. These results suggest that period after hemodialysis treatment is particularly unsafe, as evidenced by important disability in postural control, and highlight the importance of the medical support and falls-related prevention strategies of these older frail patients after hemodialysis treatment.

Key words: Hemodialysis, posture, complexity, therapy

INTRODUCTION

The control of the human upright posture is a key component in performing daily life activities. In this context, the evaluation of balance disorders plays an increasingly important role in clinical practice and research on prevention of falls in the elderly and/or rehabilitation of specific populations.[1,2] Recently, interest in hemodialysis (HD)-related changes in postural sway in patients with end-stage renal diseases (ESRD) has emerged.[3,4] In this respect, the present study investigated the specific effect of HD treatment on balance deficits in patients with ESRD symptoms (i.e., uremic syndrome) by comparing center-of-pressure (COP) trajectories recorded before and after HD session.

The ESRD, which is a consequence of a progressive and irreversible loss of kidney functions, is substantially characterized by the uremic syndrome, the main features of

Correspondence to: T. Deschamps, PhD, Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), University of Nantes, 25 Bis Boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. E-mail: thibault.deschamps@univ-nantes.fr

DOI:10.1111/hdi.12307

which are overall hydration, arterial tension problems, anemia, metabolic acidosis, retention of nitrogenous substances (such as urea and creatinine), and abnormal electrolyte balance.[5] In spite of continuous therapeutic advances in the treatment of ESRD and associated comorbidities, these patients have poor physical functioning, low activity levels,[6] low muscle mass and strength,[5] and higher postural sway,[3] which are all directly linked to cardiovascular disease, bone mineral abnormalities, and muscle catabolism associated with ESRD. All these comorbidities are well known to be associated with high morbidity and mortality.[7] In addition, it is well recognized that ESRD patients have a dramatically higher fall rates compared with the general population (fall rate of 1.60 falls per HD patient year vs. 0.6–0.84 falls per people year in older, frail populations) and a high falls-related morbidity.[8]

Patients suffering from ESRD require a permanent renal replacement therapy to survive, such as HD treatment. This HD therapy typically consist of three HD sessions per week in order to remove waste, salt, and extra water to prevent them from building up in the body, keeping a safe level of certain chemicals in blood (such as potassium, bicarbonate, and sodium) to help control blood pressure. Moreover, a 4-hour conventional HD session immobilizes the patient, contributing directly to sedentary behavior that can further worsen their functional motor abilities. Considering additional factors specifically associated with HD treatment (e.g., post-dialysis fatigue,[9] change in calcium concentration[10]) and the known influence of time-of-day and daily fatiguing activities on balance,[11,34] which by extension increase the risk of fall,[2] the present analysis explored the effect of HD treatment on postural control in ESRD patients.

To our knowledge, only a very few studies have addressed this issue. For example, Cook et al.[8] revealed that HD treatment altered the motor function in older ESRD patients (≥65 years), weakening their strength and decreasing their mobility after the HD session, thus increasing the probability of fall when returning home. Likewise, Soangra et al.[12] examined the pre- and post-HD session performance of ESRD patients (mean age 54 ± 4 years) on the sit-to-walk (STW) test, namely a movement performance quite often involved in activities of daily living. Their findings demonstrated an overall degradation in performance on STW parameters (e.g., STW completion time, delay to reach peak flexion velocity), with some potential influence on higher risk of falls after the HD session.

Concerning specifically the balance assessment in ESRD patients, the postural instability and the implicit motor strategies of balance control are currently poorly understood. As far as we know, only two studies investigated this dimension directly through the analysis of COP trajectories recorded using force platforms (Figure 1). First, Shin et al.[4] showed that HD patients have poorer postural control compared with age-matched healthy people (mean age 48.7 ± 9.5 years), especially when the quiet standing is associated with a cognitive task. Second, a recent study conducted by Magnard et al.[3] examined the HD-related changes in postural sway in different age groups, individuals with different body mass index, and gender-matched healthy people (mean age 72 ± 10.8 years). It showed a significant alteration in postural stability among elderly ESRD patients, evidenced by a poorer active control of COP velocity dynamics as compared with the healthy participants. Up to now, however, no study compared postural sway in pre- and post-HD session, despite the relevance of aforementioned clinical arguments.

Due to the lack of studies, we examined the direct effect of HD treatment on postural sway of ESRD patients through the comparison of COP trajectories measured before and just after the HD session. Because the specific medical and physiological characteristics of ESRD patients induce higher body sways in daily life as compared with healthy people, our hypothesis was that HD therapy and the associated prolonged immobilization induces further alterations in postural control of these patients.

METHODS

Participants

Twelve ESRD patients (mean age 63.3 ± 11 years) undergoing HD therapy (4.5 hours ± 35 minutes per session, three sessions per week) consented to participate in this study (see Table 1 for participant's characteristics). All participants gave informed signed consent before enrollment. They were recruited in the outpatient HD confluent dialysis unit of the ECHO Dialysis Association in Nantes (France).

Experimental conditions and procedures

For all participants, data collection of postural sway was carried out during a single bout of about 3 minutes, after a rest period, before the HD session (pre-HD) at about 7.30 AM ± 30 minutes, and immediately after the HD session (post-HD) at about 12.30 PM ± 30 minutes. In all cases, from the moment they were standing, postural balance was immediately assessed. However, note that at

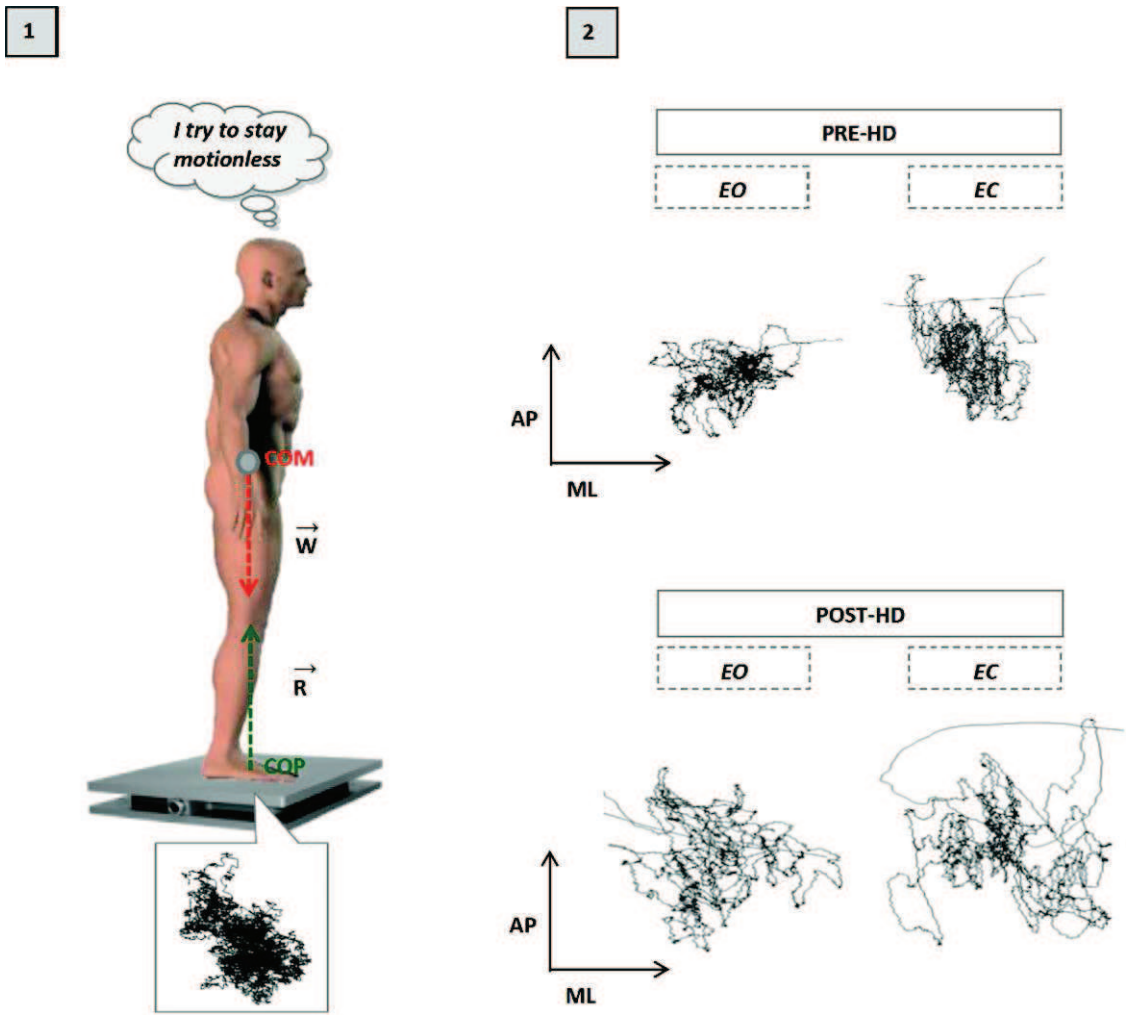

Figure 1 Representative examples of center-of-pressure trajectories recorded using a force platform [1], as a function of the time-of-hemodialysis (HD) session (pre-HD vs. post-HD) and vision condition (eyes open [EO] vs. eyes closed [EC]) [2]. AP = anteroposterior axis; ML = mediolateral axis.

the end of the HD session, the patients needed time (about 10 minutes) for stabilizing their arteriovenous fistula before balance assessment. The standing postural sway was measured using a Kistler force platform (model 9286BA) comprising two trials with stance with eyes open (EO) and stance with eyes closed (EC) measured in random order across participants in order to record the spontaneous postural behavior of these patients in both conditions. The ESRD patients were instructed to stand quietly while barefoot with the head in a straight ahead position, their arms along the body focusing on a black spot (2 cm in diameter) placed on a white wall in front of them at a 200-cm distance. For a trial of 51.2-s duration (sampling frequency of 100 Hz), the system was linked to

Table 1 Characteristics of the older hemodialysis patients

Total (N = 12)	
Age (years)	63.3 ± 11
Min–max	51–83
Gender (n men/women)	7/5
Height (cm)	164.43 ± 10.95
Min–max	149–183
Dry weight (kg)	63.0 ± 16.9
Min–max	45–101.4
Body mass index (kg/m^2)	23.34 ± 5.81
Min–max	15.9–36.8
Duration of HD (months)	95.83 ± 81
Min–max	15–300

HD = hemodialysis.

BioWare® 5.2.2 software (Kistler Group, Winterthur, Switzerland), thus providing COP series on the anteroposterior (AP) and mediolateral (ML) axes.

Note also that the weight of patients, well-known criteria of medical and physiological state of ESRD patients, was assessed during pre- and post-HD session.

Data analyses

Traditional measures

The dependent variables computed from the analysis of COP trajectories included mean range (in millimeters) and 95% confidence intervals (CI) of COP excursion in the AP and ML directions, standard deviation (SD) of position, area (95% confidence ellipse), and mean and SD of COP velocity in AP and ML directions. The average absolute maximal velocity (AAMV in mm/s) was also computed from the COP velocity series by extracting the maximum and minimum values of series within non-overlapping 2-second windows. Then the absolute values of these extremes were averaged (see Delignières et al.[13] for details). In fact, recent studies showed that the highest AAMVs that bound the COP velocity dynamics of postural sway were associated with cognitive impairment and fall risk.[2,14] We specifically identified that this AAMV was the most sensitive dependent variable to characterization of implicit postural control strategies[2,14] and an objective hallmark feature of HD-related changes in postural sway (see Magnard et al.[3]).

Structure of COP variability

COP regularity was also assessed using sample entropy (SampEn) analysis according to studies, which suggested that a decrease in complexity (i.e., irregularity) of COP time series indicates an adaptability loss, namely the (healthy) capacity to respond to changes in internal and external stimuli.[15,16] As such, SampEn is consistently used to characterize the temporal aspects of the postural sway variability (e.g., Cook et al. and Rigoldi et al.[8,17]), with the idea that SampEn close to 0 indicates greater regularity (i.e., less effective postural control) while a result near 2 represents higher complexity.[18] The quantification of regularity of COP trajectories by the SampEn (m, r, N) is the negative natural logarithm of the conditional probability, stating that a vector of length N, having repeated itself within a tolerance r for m point, will also repeat itself for m +1 points without allowing self-matches (see Lake et al.[19] for details). In line with the previous studies (e.g., Vaillancourt et al.[20]), the input variables for SampEn calculation were $m = 2$ and a tolerance range r was normalized to 0.2× the SD of COP time series. The presence of pathology or adverse effects of therapeutic interventions should be associated with more regular (less complex) postural behavior.

Statistical analysis

All data were normally distributed; thus, values are reported as mean ± SD (or standard error) throughout the text and the figures. To test the effects of time-of-HD session (pre vs. post) on the postural control, a paired t test was first carried out of all aforementioned variables. Between-session comparisons were then performed using a 2 (time-of-HD session) × 2 (vision) analyses of variance (ANOVAs) to test the effects of visual information processing on the postural control. Partial eta square ($_p\eta^2$) values are reported as measures of effect size, with $_p\eta^2 > 0.14$ considered a very large effect.[21] Finally, the weight of patients was compared between pre- and post-HD session using a paired t test with Cronbach's alpha set at 0.05.

RESULTS

For all participants, the HD session was without adverse events.

First, the paired t test for the patients' weight indicated a significant weight reduction after HD session ($t[1,11] = 8.241$, $P < 0.0001$, $_p\eta^2 = 0.86$), with a mean weight reduction of 2.27 ± 0.91 kg.

Concerning the traditional COP parameters, all means and 95% CIs pre- and post-HD test are presented in Table 2. The t tests revealed a significant effect of time-of-HD session, indicating postural alterations in post-HD evaluation as compared with balance assessment in pre-HD session, for many COP position-based variables (SD position AP, SD position ML and area) (all $Fs < 7.7$, $P < 0.02$) and COP velocity-based variables (mean velocity and AAMV AP) (all $Fs > 2.33$, $P < 0.05$) (see Table 3 and Figure 2 for all statistical results). Second, the two-way ANOVAs confirmed these findings, with significant

Table 2 Weight evolution (expressed in kg) of older ESRD patients between pre-HD and post-HD session

Pre-HD	Mean weight	64.51
	SD weight	16.49
	Min–max weight	47.52–103.50
Post-HD	Mean weight	62.24
	SD weight	15.97
	Min–max weight	45.80–99.50

ESRD = end-stage renal disease; HD = hemodialysis; SD = standard deviation.

Table 3 Comparisons of COP variables between pre- and post-HD session

COP position-based variables						
		Range position_AP (mm)	SD position_AP (mm)	Range position_ML (mm)	SD position_ML (mm)	Area (mm^2)
Pre-HD	Mean	27.81	4.79	20.81	3.27	332.49
	(95% CI)	(23.62–32.30)	(3.78–5.81)	(15.59–26.02)	(2.62–3.91)	(220.65–444.32)
Post-HD	Mean	32.95	5.89	22.47	4.08	517.51
	(95% CI)	(26.04–39.87)	(4.71–7.08)	(19.03–25.92)	(3.32–4.85)	(345.34–689.67)
COP velocity-based variables						
		Mean velocity (mm/s)	SD velocity_AP (mm/s)	SD velocity_ML (mm/s)	AAMV_AP (mm/s)	AAMV_ML (mm/s)
Pre-HD	Mean	14.21	21.16	16.53	40.47	26.29
	(95% CI)	(12.39–16.04)	(18.04–21.29)	(14.53–18.54)	(33.52–47.42)	(20.12–34.46)
Post-HD	Mean	15.94	23.57	18.51	47.23	30.98
	(95% CI)	(12.86–19.03)	(18.34–28.79)	(15.35–21.66)	(37.25–57.21)	(23.54–38.43)

AAMV = average absolute maximal velocity; AP = anteroposterior; CI = confidence intervals; COP = center of pressure; HD = hemodialysis; ML = mediolateral; SD = standard deviation.

adverse effect of time-of-HD session on postural control (Table 4). A significant effect of vision revealed changes in postural control in EC vs. EO conditions, but only for SD position ML (3.12 vs. 3.82 mm; −18.47%, P = 0.049, $_p\eta^2 = 0.31$). However, high tendencies to be impacted by the visual information were also observed for the SD velocities in AP and ML directions (18.17 vs. 15.18 mm/s; +19,64%; P = 0.09, $_p\eta^2 = 0.23$; 8.87 vs. 9.58 mm/s;

Table 4 Analysis of variance results for all the COP parameters for the different factors

COP position-based variables						
		Range position_AP	SD position_AP	Range position_ML	SD position_ML	Area
Time	F	4.370	**7.704**	0.549	**12.720**	**8.454**
	P	0.061	**0.018**	0.474	**0.004**	**0.014**
	$_p\eta^2$	0.284	**0.412**	0.047	**0.536**	**0.435**
Vision	F	0.341	0.044	3.958	**4.910**	3.224
	P	0.571	0.837	0.072	**0.049**	0.101
	$_p\eta^2$	0.031	0.004	0.264	**0.309**	0.227
Time*Vision	F	0.087	0.782	0.264	1.809	0.533
	P	0.774	0.395	0.617	0.206	0.481
	$_p\eta^2$	0.008	0.066	0.023	0.141	0.046
COP velocity-based variables						
		Mean velocity	SD velocity_AP	SD velocity_ML	AAMV_AP	AAMV_ML
Time	F	**6.356**	2.714	3.581	**6.903**	1.737
	P	**0.028**	0.127	0.085	**0.024**	0.214
	$_p\eta^2$	**0.366**	0.198	0.246	**0.386**	0.136
Vision	F	1.405	3.434	3.697	4.338	1.453
	P	0.261	0.090	0.081	0.061	0.253
	$_p\eta^2$	0.113	0.238	0.252	0.283	0.117
Time*Vision	F	2.116	1.200	0.645	0.844	0.563
	P	0.174	0.296	0.438	0.378	0.469
	$_p\eta^2$	0.161	0.098	0.055	0.071	0.049

Statistically significant results (P < 0.05) are indicated in bold.
AAMV = average absolute maximal velocity; AP = anteroposterior; COP = center of pressure; ML = mediolateral; SD = standard deviation.

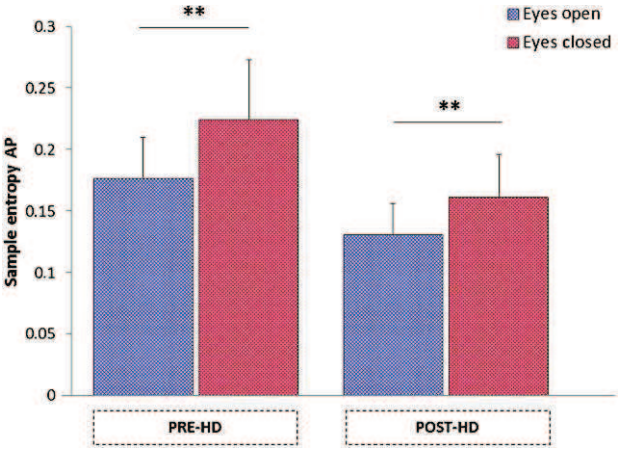

Figure 2 Illustration of the main effect of vision for the sample entropy values (with standard error bars) in antero-posterior (AP) center-of-pressure motions. No significant time-of-hemodialysis (HD) session × vision interaction was observed. **P < 0.01.

–7,45%, P = 0.08, $_p\eta^2$ = 0.25, respectively] and for the AAMV in the AP direction (47.25 vs. 39.90 mm/s; +18,43%; P = 0.06, $_p\eta^2$ = 0.28). Note that no significant time-of-HD session × vision interaction was found (all Fs < 0.39, P > 0.07).

Sample entropy results

The t tests revealed no main effect of time-of-HD session as an indicator of no change in regularity of postural sway before and after the HD session on both the AP (mean 0.201 ± 0.140 vs. 0.146 ± 0.101; t[1,11] = 1.691; P = 0.11, $_p\eta^2$ = 0.26) and ML directions (mean 0.242 ± 0.233 vs. 0.181 ± 0.122; t[1,11] = 1.19; P = 0.27, $_p\eta^2$ = 0.11). Second, the ANOVA revealed a main effect of vision in AP direction only ($F_{[1,11]}$ = 9.08, P = 0.01, $_p\eta^2$ = 0.45). No significant main effect of time-of-HD session ($F_{[1,11]}$ = 2.86, P = 0.118, $_p\eta^2$ = 0.21) or interaction emerged ($F_{[1,11]}$ = 0.26, P = 0.62, $_p\eta^2$ = 0.02) (Figure 3).

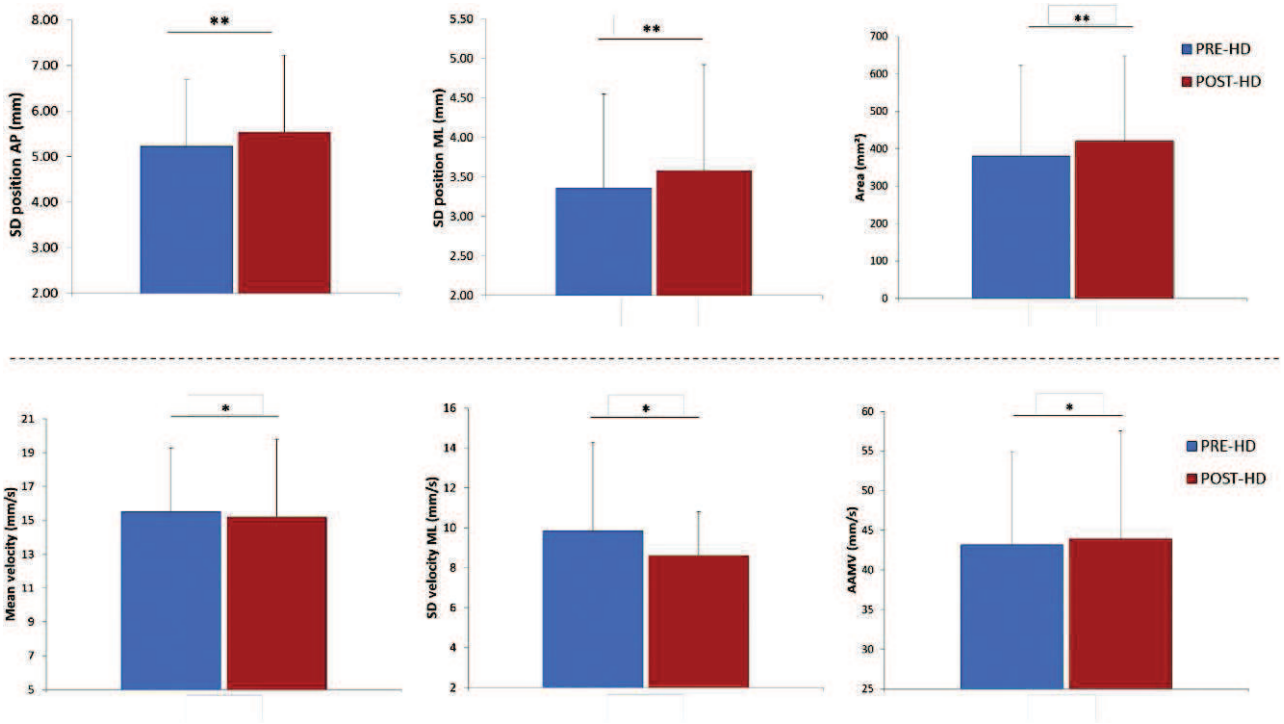

Figure 3 Significant effects of time-of-hemodialysis (HD) session on three center-of-pressure (COP) position-based variables (top) and three COP velocity-based variables (down). The vertical bars indicate the standard deviation. AAMV = average absolute maximal velocity; AP = anteroposterior; ML = mediolateral; SD = standard deviation. *P < 0.05, **P < 0.01.

DISCUSSION

The current study aimed to investigate the effects of a single HD session on the postural sway of older patients with ESRD by comparing COP trajectories measured before and immediately after the HD session. Consistent with the recent preliminary study of Soangra et al.,[12] the findings supported our main assumption that HD session therapy affected postural balance of ESRD patients negatively. Precisely, we reported higher postural sway in post-HD session compared with pre-HD session, for most COP position and velocity variables (Table 3). These changes in variability of postural control were not associated with a higher complexity of COP time series: the regularity of COP trajectories was similar before and after the HD session. No evidence of different ineffective postural control strategies has emerged as a function of time-of-HD session.

First, the HD treatment, aimed to keep the organism in as safe condition as possible in terms of waste, liquids, blood pressure, and chemical substances that causes intradialytic fluids redistribution, can provoke weakness in lower limbs. Indeed, Shulman et al.[22] showed that plasma water is being removed more from the peripheral compartments of body than from the trunk. This finding suggests that plasma refill during the HD session is used to preserve primarily central blood volume rather than peripheral compartments, such as postural (calf) muscles and lower extremities, which can explain the increase of postural sway variability immediately after the HD session. Second, the significant weight reduction due to the elimination of accumulated fluids and the fatigue associated with the HD treatment[9] could also be considered as primary factors responsible for significant alterations of postural stability. Even if no physiological and/or psychological measure has been to record how exhausted the ESRD patients were, it is well documented that the ESRD patients who received a HD treatment for longer than 2 years experienced increased fatigue compared with the other patients,[23] and the fatigue increased with an advanced age.[24] It is important to underline that patients in this study were relatively old (mean age 63.3 ± 11 years) and only two of them were treated by HD therapy for less than 2 years (15 and 20 months, respectively). Third, electrolyte disturbances incurred by HD treatment can adversely affect the neuromuscular performance of ESRD patients. Indeed, on the one hand, the rapid changes in calcium concentration during HD session could impair the muscle function, as shown in Berchtold et al.,[25] through a decline in both force production and resistance to fatigue. On the other hand, acidosis could unfavorably affect neuromuscular function of patients, deteriorating actomyosin interaction and the steps in cross bridge cycle.[26] Thereby, less force production at the same level of activation could be observed. In sum, these biochemical disturbances could be responsible for muscular strength degradation in this specific population suffering from sarcopenia, especially in older patients.[27]

Even if the results of traditional COP parameters confirm a greater difficulty in controlling posture in EC compared with in EO condition,[3] the lack of time-of-HD session × vision interaction might indicate that the visual information processing influences postural control to the same extent, regardless of the pre- or post-HD postural evaluation. Because of the aforementioned specific consequences of HD treatment (e.g., immobilization, fluids redistribution), it is most likely that the impaired balance in ESRD patients after HD session is less associated with the visual input rather than with the deficits in integration of proprioceptive and/or vestibular information.

Nevertheless, this point needs to be clarified with respect to the results of structure of COP trajectories. For older ESRD patients, the effect of HD session on postural sway variability (e.g., increase of COP mean velocity) is not associated with change in the structure of COP variability (see sample entropy results). The necessary physiopathological benefits of HD therapy for ESRD patients do not positively influence the system complexity, originally regarded as the capability of adaptability and flexibility useful for an individual to respond to external perturbations.[28] These somewhat counter-intuitive results are in line with previous studies highlighting the bidirectional influence of task constraints in postural control in different (pathologic) adults.[29,30] In this respect, the entropy information was higher in the EC condition than in EO on the AP COP motion. This finding is consistent with Hong et al.'s study[31] that found contrasting effects on the COP regularity (i.e., complexity) when young healthy subjects were asked to maintain two (normal vs. tandem) stance conditions with EO and EC. Specifically, the tandem stance associated with visual feedback withdrawal increased the irregularity of COP signals as evidenced by a highest value of entropy. The current changes in COP regularity and variability observed among ESRD patients as a function of visual information challenge the hypothesis of age-/disease-related unidirectional changes in "loss of complexity."[16,20,30,32] Our current findings showed that the visual constraints, unlike the HD therapy itself, influence changes in complexity of postural control in ESRD patients.[31] Thus, the postural responses observed in EC condition likely rely on proprioceptive and vestibular information to meet the task-specific demands. In this

context, the ESRD patients would have mobilized other implicit postural control strategies indicative of a necessary reweighting of sensory information from proprioceptive system at relatively fast time scale. Because of their specific physiopathology and potential comorbidities (e.g., more than one in two HD patients have one or more neuropathies[33]), the impaired balance in ESRD probably reflects deficits in integration of proprioceptive inputs rather than the visual inputs. The increase in COP irregularity in EC condition might be an index of a *positive but extremely difficult* adaptation required to meet the immediate postural task constraints. Future research on HD-related adverse changes in postural sway by manipulating information from visual/proprioceptive systems should provide further support for precise characterization of sensory reweighting dynamics and bidirectional change in physiological complexity in ESRD patients.

To conclude, this study found a negative effect of a HD session on the postural balance of older ESRD patients. Indeed, even when we included a low sample size of patients, which was difficult to obtain partly due to the difficulty to recruit volunteers from this specific frail population, in the analysis, our results showed the first indication of direct effect of HD treatment on COP trajectories and variability. Nevertheless, although the reported effects were very large (see the measures of effect size), which suggests an acceptable consistency to the current findings, these latter do need to be confirmed in a larger population. From a new perspective, it could be interesting to determine in further studies the duration of these alterations of postural sway in order to adapt the care system to the fall-related potential danger.[8] Hence, in support of our purpose, the present findings are of special clinical interest to improve the management and the efficacy of ESRD patients' support when they leave the medical center after HD treatment.

ACKNOWLEDGMENTS

The research was supported by grants from the Region of Pays de la Loire, France, for the project "RP3AP." This study also received support from Research Mission of Directorate for Research Studies, Evaluation and Statistics (Direction de la recherche, des études, de l'évaluation et des statistiques—MiRe-DRESS) and IRePS (French public health research institute).

DISCLOSURES

The sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The authors report no conflicts of interest. For funding information, see "The Global Forum on Home Hemodialysis: Sponsorship and Disclosure Statements."

Manuscript received January 2015; revised February 2015.

REFERENCES

1 Jacobs JV. Why we need to better understand the cortical neurophysiology of impaired postural responses with age, disease, or injury. *Front Integr Neurosci*. 2014; **29**:8–69.
2 Mignardot J-B, Beauchet O, Annweiler C, Cornu C, Deschamps T. Postural sway, falls and cognitive status: A cross-sectional study among older adults. *J Alzheimers Dis*. 2014; **41**:431–439.
3 Magnard J, Hristea D, Lefrançois G, Testa A, Paris A, Deschamps T. Implicit postural control strategies in older hemodialysis patients: An objective hallmark feature for clinical balance assessment. *Gait Posture*. 2014; **40**:723–726.
4 Shin S, Chung HR, Fitschen PJ, et al. Postural control in hemodialysis patients. *Gait Posture*. 2014; **39**:723–727.
5 Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: Effects on muscle strength, muscle quality, and physical function. *Kidney Int*. 2003; **63**:291–297.
6 Headley S, Germain M, Mailloux P, et al. Resistance training improves strength and functional measures in patients with end-stage renal disease. *Am J Kidney Dis*. 2002; **40**:355–364.
7 Johansen KL, Chertow GM, Ng AV, et al. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int*. 2000; **57**:2564–2570.
8 Cook WL, Tomlinson G, Donaldson M, et al. Falls and fall-related injuries in older dialysis patients. *Clin J Am Soc Nephrol*. 2006; **1**:1197–1204.
9 Sklar A, Newman N, Scott R, Semenyuk L, Schultz J, Fiacco V. Identification of factors responsible for postdialysis fatigue. *Am J Kidney Dis*. 1999; **34**:464–470.
10 Saiki JK, Vaziri ND, Naeim F, Meshkinpour H. Dialysis-induced changes in muscle strength. *J Dial*. 1980; **4**:191–201.
11 Deschamps T, Magnard J, Cornu C. Postural control as a function of time-of-day: Influence of a prior strenuous running exercise or demanding sustained-attention task. *J Neuroeng Rehabil*. 2013; **10**:26.
12 Soangra R, Lockhart TE, Lach J, Abdel-Rahman EM. Effects of hemodialysis therapy on sit-to-walk characteristics in end stage renal disease patients. *Ann Biomed Eng*. 2013; **41**:795–805.

13 Delignières D, Torre K, Bernard PL. Transition from persistent to anti-persistent correlations in postural sway indicates velocity-based control. *PLoS Comput Biol*. 2011; **7**:e1001089.
14 Deschamps T, Beauchet O, Annweiler C, Cornu C, Mignardot J-B. Postural control and cognitive decline in older adults: Position versus velocity implicit motor strategy. *Gait Posture*. 2014; **39**:628–630.
15 Pincus SM, Goldberger AL. Physiological time-series analysis: What does regularity quantify? *Am J Physiol*. 1994; **266**:H1643–H1656.
16 Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging*. 2002; **23**:23–26.
17 Rigoldi C, Cimolin V, Camerota F, et al. Measuring regularity of human postural sway using approximate entropy and sample entropy in patients with Ehlers-Danlos syndrome hypermobility type. *Res Dev Disabil*. 2013; **34**:840–846.
18 Donker SF, Roerdink M, Greven AJ, Beek PJ. Regularity of center-of-pressure trajectories depends on the amount of attention invested in postural control. *Exp Brain Res*. 2007; **181**:1–11.
19 Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. *Am J Physiol Regul Integr Comp Physiol*. 2002; **283**:R789–R797.
20 Vaillancourt DE, Sosnoff JJ, Newell KM. Age-related changes in complexity depend on task dynamics. *J Appl Physiol*. 2004; **97**:454–455.
21 Cohen J. *Statistical Power Analysis for the Behavioural Sciences*. New York, Academic Press. 1988.
22 Shulman T, Heidenheim AP, Kianfar C, Shulman SM, Lindsay RM. Preserving central blood volume: Changes in body fluid compartments during hemodialysis. *ASAIO J*. 2001; **47**:615–618.
23 Letchmi S, Das S, Halim H, et al. Fatigue experienced by patients receiving maintenance dialysis in hemodialysis units. *Nurs Health Sci*. 2011; **13**:60–64.
24 Liu H. Fatigue and associated factors in hemodialysis patients in Taiwan. *Res Nurs Health*. 2006; **29**:40–50.
25 Berchtold MW, Brinkmeier H, Muntener M. Calcium ion in skeletal muscle: Its crucial role for muscle function, plasticity, and disease. *Physiol Rev*. 2000; **80**:1215–1265.
26 Debold EP. Recent insights into muscle fatigue at the cross-bridge level. *Front Physiol*. 2012; **3**:151.
27 Domanski M, Ciechanowski K. Sarcopenia: A major challenge in elderly patients with end-stage renal disease. *J Aging Res*. 2012; 754739.
28 Delignières D, Marmelat V. Fractal fluctuations and complexity: Current debates and future challenges. *Crit Rev Biomed Eng*. 2012; **40**:485–500.
29 Morrison S, Colberg SR, Parson HK, Vinik AI. Relation between risk of falling and postural sway complexity in diabetes. *Gait Posture*. 2012; **35**:662–668.
30 Vaillancourt DE, Newell KM. Changing complexity in human behavior and physiology through aging and disease. *Neurobiol Aging*. 2002; **23**:1–11.
31 Hong SL, Manor B, Li L. Stance and sensory feedback influence on postural dynamics. *Neurosci Lett*. 2007; **423**:104–108.
32 Lipsitz LA, Goldberger AL. Loss of "complexity" and aging. Potential applications of fractals and chaos theory to senescence. *JAMA*. 1992; **267**:1806–1809.
33 O'Regan J, Walsh R, Kelly D, Plant L, Eustace J, McNamara B. Neuropathy in the hemodialysis population: A review of neurophysiology referrals in a tertiary center. *Ren Fail*. 2012; **34**:538–541.
34 Jorgensen MG, Rathleff MS, Laessoe U, Caserotti P, Nielsen OBF, Aagaard P. Time-of-day influences postural balance in older adults. *Gait Posture*. 2012; **35**:653–657.

Gait & Posture 40 (2014) 723–726

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Short Communication

Implicit postural control strategies in older hemodialysis patients: An objective hallmark feature for clinical balance assessment

Justine Magnard [a], Dan Hristea [b], Gaëlle Lefrancois [b], Angelo Testa [b], Anne Paris [b], Thibault Deschamps [a,*]

[a] University of Nantes, Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), F-44000 Nantes, France
[b] Dialysis Unit, ECHO Nantes Dialysis Association, France

ARTICLE INFO

Article history:
Received 2 April 2014
Received in revised form 8 July 2014
Accepted 11 July 2014

Keywords:
Posture
Velocity control hypothesis
Hemodialysis patients

ABSTRACT

Elderly patients with end stage renal diseases (ESRD) undergoing hemodialyis (HD) present poorer physical function and higher accident falls than healthy elderly population. Therefore, the aim of this study was to examine the HD-related changes in postural sway in ESRD patients, as an objective hallmark of their functional abilities. We hypothesized that the ESRD symptoms (*i.e.* uremic syndrome) and the HD therapy affected the postural control, evidenced by higher bounding limits of center-of-pressure (COP) velocity dynamics. Fifty-five participants, including 28 HD patients and 27 age, body mass index and gender-matched healthy participants H_S (70.42 ± 13.69 years; 23.46 ± 4.67 kg/m^2; 35.7% women *vs.* 73.62 ± 6.59 years; 25.09 ± 3.54 kg/m^2; 37% women), were asked to maintain quiet stance on force platform, with eyes open and eyes closed. COP parameters were mean and standard deviation (SD) of position, velocity and average absolute maximal velocity (AAMV) in antero-posterior and medio-lateral directions. The results revealed a significant main effect of group on velocity-based variables, highlighting that mean velocity, SD velocity and AAMV ($p < 0.01$) were higher for HD as compared to H_S. These findings identified the bounding limits of COP velocity as an objective hallmark feature of HD-related changes in postural sway. The clinical assessment of this active control of COP velocity dynamics could be useful to examine the effects of targeted intradialytic exercise programs on functional performances and for early detection of increased fall risk in HD patients.

1. Introduction

More than two million people with end stage renal diseases (ESRD) are currently treated worldwide by dialysis. The ESRD are substantially characterized by the uremic syndrome, whose main features are an arterial hypertension, an overall hydration, a metabolic acidosis and retention of nitrogenous substances – urea and creatinine, and an abnormal electrolyte balance [1]. Despite significant progress in dialysis techniques and in the treatment of associated comorbidities, patients with ESRD undergoing hemodialysis (HD) have decreased physical functioning, diminished muscle mass and altered muscle quality, and all of these features are associated with an increased morbidity and mortality risk [2].

The relationship between older patients with ESRD and impairments in motor function and balance has been established in several surveys, revealing a greater frequency of falls and fractures in HD patients than in controls [3,4]. For example, the fall risk in HD population is higher than in the general community (a fall rate of 1.60 falls/patient-year *vs.* 0.6–0.84 falls/people-year in older, frail populations), and fall-related morbidity is high [5]. Because poorer balance stability is identified as a powerful predictor of falls in older adults with and without cognitive impairment [6,7], balance assessment and in particular the analysis of center-of-pressure (COP) trajectories recorded using force platforms could be helpful to understand ESRD-related changes in postural sway that expose to greater fall risk [8]. In this vein, Shin et al. [9] showed that HD patients have poorer postural control than age-matched healthy subjects (mean age 48.7 ± 9.5 years), in particular while quiet standing with a cognitive task. Unfortunately not investigated in [9], this finding is likely to be related to deficits in integration of visual, proprioceptive and vestibular inputs necessary for efficient postural control [10].

* Corresponding author at: University of Nantes, Laboratory "*Motricité, Interactions, Performance*" (EA 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. Tel.: +33 02 51 83 72 14; fax: +33 02 51 83 72 10.
E-mail address: thibault.deschamps@univ-nantes.fr (T. Deschamps).

http://dx.doi.org/10.1016/j.gaitpost.2014.07.009
0966-6362/

In this context, we have recently demonstrated a key role for COP velocity-based variables in postural sway in older healthy individuals, with cognitive impairment and/or history of falls [11,12]. By assessing the most sensitive velocity-based variables, namely the average absolute maximal velocity (AAMV in mm/s), we specifically showed that the highest AAMVs that bound the COP velocity dynamics of postural sway were associated with cognitive impairment and fall risk. Our findings highlighted the COP velocity-based corrective control process as a hallmark feature of cognitive impairment-related changes in postural sway. This point might be of special interest for clinical balance assessment and falls prevention in older HD patients [12].

Thus we aimed to characterize the implicit postural control strategies in 28 *older* HD patients in comparison with 27 age-matched controls (mean age 72 ± 10.8 years). Because the physiological functions induce continuous body sways [13], our hypothesis was that the ESRD symptoms (*e.g.* uremic syndrome-related liquid movements) and the HD therapy affected the postural control leading to higher bounding limits of COP velocity dynamics, apart from the fact that HD patients have low levels of daily physical activity [2].

2. Methods

2.1. Participants

55 individuals volunteered to take part in this investigation, including 28 HD patients (10 women) and 27 age, body mass index and gender-matched healthy participants H_S (10 women. Control subjects were admitted to the study if they had no history of renal impairment, no past history or current symptoms of neuromuscular dysfunction. All participants gave informed signed consent before enrollment. Independent sample *t*-tests were performed for HD *vs.* H_S age, and body mass index [$t(19) = 0.39$, $p = 0.69$, $t(19) = 1.53$, $p = 0.14$, respectively]. A Chi square test was conducted for the gender variable [$\chi^2 = 0.03$, $p = 85$] (see Table 1 for participants' baseline characteristics). All HD patients are on thrice-weekly HD therapy for longer than 3 months and were recruited in the outpatient HD Laennec Dialysis unit and Confluent Dialysis unit of the ECHO Dialysis Association in Nantes (France).

2.2. Procedure

For all data collection of postural sway, the participants were asked to maintain standing position on a Kistler force platform (model 9286BA) according to two trials of quiet stance: stance with eyes open (EO) and stance with eyes closed (EC) (random order across participants). Participants were instructed to stand quietly while barefoot, with the head in a straight-ahead position, their arms along the body, and each foot positioned on the platform plate that maintained the distance between the medial sides of the heel at 8.4 cm with an external rotation angle of 9° [11,12]. During EO conditions, they were instructed to look at a black spot (with a diameter 2 cm diameter) placed on a white wall in the front of them at a 2 m distance. For a trial of 51.2 s duration (sampling frequency of 5 Hz), the system was linked to BioWare® 5.2.2 software, providing COP series on the antero-posterior (AP) and medio-lateral (ML) axes.

Table 1
Clinical characteristics of the participants ($n = 55$).

	HD group ($n = 28$)	H_S group ($n = 27$)	Total ($n = 55$)
Age (years)	70 ± 13.64	73.62 ± 6.59	72 ± 10.8
[95% CI]	[64.81; 75.18]	[64.81; 75.18]	[64.07; 74.92]
Male gender, *n* (%)	18 (64.3)	17 (63)	35 (63.6)
BMI (kg/m^2)	23.41 ± 4.59	25.09 ± 3.54	24.26 ± 4.2
[95% CI]	[21.41; 25.16]	[23.69; 26.49]	[23.13; 25.4]
Duration of HD (months)	87.10 ± 80.56	NA	
min–max	11–308		

2.3. Statistics

The COP parameters were mean and standard deviation (SD) of position and velocity in AP and ML directions. We also computed the AAMV from the COP velocity series by extracting the maximum and minimum values of series within non-overlapping windows (of a length of 2 s). Then the absolute values of these extremes were averaged (see [11,12] for details). For testing the effects of Group (HD *vs.* H_S) on the postural control, a one-way ANOVA was first carried out for each aforesaid dependent variable. Then between-group comparisons were performed using 2 (Group) × 2 (Vision) ANOVAs to test the effects of visual information processing on the postural control. Partial eta square ($_p\eta^2$) values are reported as measures of effect size, with very large effects considered for $_p\eta^2 \geq 0.14$ [14].

3. Results

We first focused on the postural performance considering only the effects of Group factor (all statistical results are summarized in Table 2). The analysis found a main effect of Group on velocity-based variables, revealing that mean, SD velocity and AAMV were significantly higher in HD patients compared with H_S. Besides the analyses for many COP position variables showed that postural sway is not significantly different according to groups.

Secondly, the two-way ANOVAs confirmed these findings, with significant effects of Group for all velocity-based variables ($Fs > 7.32$; $p < 0.01$). Moreover a significant effect of Vision revealed alterations in postural control in EC *vs* EO conditions, as found for the mean velocity [13.86 ± 7.31 *vs.* 12.22 ± 6.02 mm/s; +13.42%; $p = 0.02$; $_p\eta^2 = 0.096$], the SD velocity [19.1 ± 10.89 *vs.* 16.09 ± 8.39 mm/s; +18.7%; $p = 0.008$; $_p\eta^2 = 0.124$] and the AAMV [22.75 ± 13.43 *vs.* 18.91 ± 10.12 mm/s; +20.3%; $p = 0.004$; $_p\eta^2 = 0.147$] in the AP direction (Fig. 1). Note that no significant Group × Vision interaction was found [all $Fs < 4.34$, $p > 0.07$].

4. Discussion

The results confirmed the bounding limits of COP velocity as an objective hallmark feature of HD-related changes in postural sway. Contrary to most of position variables, mean velocity, SD velocity and AAMV are actually higher for HD, as compared to healthy participants (Table 2). Even if these results corroborate changes in

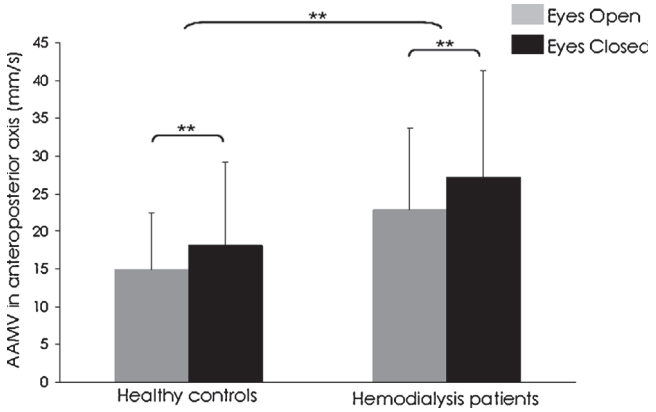

Fig. 1. Effects of vision (open eyes – *in gray vs.* closed eyes – *in black*) on the average absolute maximal velocity (AAMV) (mm/s) in antero-posterior axis, as a function of Group (healthy controls *vs.* hemodialys patients). Error bars correspond to the standard deviation. Significant differences at $^{**}p < 0.01$.

Table 2
Comparisons between HD patients and age- and BMI-matched H_S group (one-way analysis of variance results). Statistically significant results ($p < 0.05$) are indicated in bold.

Outcomes (Significant values)	H_S group, mean [95% CI]	HD group, mean [95% CI]	F	p	$_p\eta^2$
1. COP position-based variables					
1.1 Eyes Open					
Mean position_AP (mm)	−19.28 [−26.35; −12.19]	−28.28 [−39.74; −16.82]	1.85	0.179	0.034
SD position_AP (mm)	4.81 [4.22; 5.41]	5.69 [5.81; 6.58]	2.82	0.09	0.051
Mean position_ML (mm)	−1.09 [−5.49; 3.3]	1.95 [−3.62; 7.53]	0.771	0.384	0.014
SD position_ML (mm)	3.13 [2.59; 3.68]	4.62 [3.64; 5.61]	**7.234**	**0.01**	**0.12**[a]
1.2 Eyes Closed					
Mean position_AP (mm)	−14.6 [−21.73; −7.46]	−25.91 [−35.04; −16.78]	3.982	0.051	0.07
SD position_AP (mm)	5.113 [4.39; 5.83]	5.66 [4.69; 6.63]	0.875	0.354	0.016
Mean position_ML (mm)	−1.82 [−6.65; 3.01]	1.6 [−4.16; 7.37]	0.865	0.356	0.016
SD position_ML (mm)	2.64 [2.15; 3.14]	3.73 [2.99; 4.47]	**6.177**	**0.016**	**0.104**[a]
2. COP velocity-based variables					
2.1 Eyes Open					
Mean velocity (mm/s)	9.74 [7.93; 11.54]	14.61 [12.15; 17.07]	**10.59**	**0.002**	**0.167**[a]
Mean velocity_AP (mm/s)	4.48 [3.57; 5.4]	6.67 [5.35; 7.98]	**10.41**	**0.002**	**0.164**[a]
SD velocity_AP (mm/s)	12.65 [10.31; 14.99]	19.41 [15.86; 22.96]	**10.47**	**0.002**	**0.165**[a]
Mean velocity_ML (mm/s)	7.68 [6.27; 9.1]	11.36 [9.51; 13.2]	**7.71**	**0.008**	**0.127**[a]
SD velocity_ML (mm/s)	7.37 [5.89–8.86]	13.81 [9.28; 18.34]	**7.45**	**0.009**	**0.123**[a]
AAMV_AP (mm/s)	14.84 [11.85–17.82]	22.84 [18.63; 27.05]	**10.02**	**0.003**	**0.159**[a]
AAMV_ML (mm/s)	8.46 [6.73–10.18]	13.81 [9.28; 18.34]	**9.09**	**0.004**	**0.146**[a]
2.2 Eyes Closed					
Mean velocity (mm/s)	11.43 [8.88; 13.98]	16.21 [13.32; 19.09]	**6.45**	**0.014**	**0.109**[a]
Mean velocity_AP (mm/s)	4.84 [3.86; 5.83]	6.26 [5.25; 7.27]	**6.3**	**0.015**	**0.106**[a]
SD velocity_AP (mm/s)	15.42 [11.82; 19.03]	22.65 [18.21; 27.09]	**6.68**	**0.013**	**0.112**[a]
Mean velocity_ML (mm/s)	9.32 [7.09; 11.55]	13.55 [10.92; 16.18]	**4.28**	**0.043**	**0.075**[a]
SD velocity_ML (mm/s)	7.91 [6.31–9.51]	10.98 [8.89; 13.08]	**5.68**	**0.021**	**0.097**[a]
AAMV_AP (mm/s)	18.1 [13.69–22.51]	27.23 [21.77; 32.7]	**7.07**	**0.01**	**0.118**[a]
AAMV_ML (mm/s)	9.36 [7.44–11.28]	12.38 [10.28; 14.48]	**4.74**	**0.023**	**0.082**[a]

COP: center of pressure; AP: anteroposterior; ML: mediolateral. SD: standard deviation; AAMV: average absolute maximal velocity. H_S: healthy controls; HD: hemodialysis patients.
[a] Significant difference between H_S and HD groups.

poor postural stability in HD patients [3,9], these findings demonstrate that the velocity information is the most sensitive form of sensory information to (de)stabilize posture in HD as compared to age-matched healthy participants.

In accordance with [11,12], we argue an adverse impact of ESRD on the active corrective control process of COP velocity dynamics, especially in anteroposterior direction. Even if quiet standing under eyes closed condition induces adverse changes in intermittent velocity-based control of posture (*i.e.* highest velocity thresholds), no Group × Vision interaction was found. This lack of interaction indicates that visual information processing causes alterations in postural control to the same extent whatever the status of older participants. Thus we suggest that the impaired balance in ESRD might be more related to deficits in integration of proprioceptive and/or vestibular inputs rather than the visual input [10], probably because of their specific physiopathology (*e.g.*, atrophy in the lower extremity muscles, low muscle strength, acidosis, abnormalities in vitamin D metabolism or in serum calcium concentration, prolonged inactivity, malnutrition, inadequate dialysis or hyperparathyroidism [1]). To this aim, further research is required to test the specific HD-related adverse changes in postural sway by removing/attenuating the sensory information from the visual, somatosensory and vestibular systems.

In support of our purpose, the present finding is of special interest for clinical balance assessment in order to examine the effects of long-term targeted intradialytic exercise programs on functional performances [15]. Moreover, the assessment of this active control of COP velocity dynamics might be also useful for early detection of increased fall risk in HD patients [11,12].

Author contributions

All authors meet all of the following criteria: (1) contributing to the conception and design, or analyzing and interpreting data; (2) drafting the article or revising it critically for important intellectual content; and (3) approving the final version to be published.

Acknowledgements

The study was sponsored by the University Hospital of Nantes. The research is also sponsored in part by the ACTICLAN prize provided by Fresenius Kabi, France.

The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Conflict of interest statement

The authors report no conflicts of interest.

References

[1] Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. Kidney Int 2003;63:291–7.
[2] Johansen KL, Chertow GM, Ng AV, Mulligan K, Carey S, Schoenfeld PY, et al. Physical activity levels in patients on hemodialysis and healthy sedentary controls. Kidney Int 2000;57:2564–70.
[3] Blake C, O'Meara YM. Subjective and objective physical limitations in high-functioning renal dialysis patients. Nephrol Dial Transplant 2004;19(12):3124–9.
[4] Desmet C, Beguin C, Swine C, Jadoul M, Université Catholique de Louvain Collaborative Group. Falls in hemodialysis patients: prospective study of incidence, risk factors, and complications. Am J Kidney Dis 2005;45:148–53.
[5] Cook WL, Tomlinson G, Donaldson M, Markowitz SN, Naglie G, Sobolev B, et al. Falls and fall-related injuries in older dialysis patients. Clin J Am Soc Nephrol 2006;1:1197–204.
[6] King MB, Tinetti ME. Falls in community-dwelling older persons. J Am Geriatr Soc 1995;43:1146–54.
[7] Horikawa E, Matsui T, Arai H, Seki T, Iwasaki K, Sasaki H. Risk of falls in Alzheimer's disease: a prospective study. Intern Med 2005;44:717–21.
[8] Brauer SG, Burns YR, Galley P. A prospective study of laboratory and clinical measures of postural stability to predict community-dwelling fallers. J Gerontol A Biol Sci Med Sci 2000;55:M469–76.

[9] Shin S, Chung HR, Fitschen PJ, Kistler BM, Park HW, Wilund KR, et al. Postural control in hemodialysis patients. Gait Posture 2014;39:723–7.
[10] Doumas M, Krampe RT. Adaptation and reintegration of proprioceptive information in young and older adults' postural control. J Neurophysiol 2010;104:1969–77.
[11] Deschamps T, Beauchet O, Annweiler C, Cornu C, Mignardot JB. Postural control and cognitive decline in older adults: position versus velocity implicit motor strategy. Gait Posture 2014;39:628–30.
[12] Mignardot J-B, Beauchet O, Annweiler C, Cornu C, Deschamps T. Postural sway, falls and cognitive status: a cross-sectional study among older adults. J Alzheimers Dis 2014;41:431–9.
[13] Conforto S, Schmid M, Camomilla V, D'Alessio T, Cappozzo A. Hemodynamics as a possible internal mechanical disturbance to balance. Gait Posture 2011;14:28–35.
[14] Cohen J. Statistical power analysis for the behavioural sciences. 3rd ed. New York: Academic Press; 1988.
[15] Magnard J, Deschamps T, Cornu C, Paris A, Hristea D. Effects of a six-month intradialytic physical ACTIvity program and adequate NUTritional support on protein-energy wasting, physical functioning and quality of life in chronic hemodialysis patients: ACTINUT study protocol for a randomised controlled trial. BMC Nephrol 2013;14:259.

Journal of Alzheimer's Disease 41 (2014) 431–439
DOI 10.3233/JAD-132657
IOS Press

Postural Sway, Falls, and Cognitive Status: A Cross-Sectional Study among Older Adults

Jean-Baptiste Mignardot[a], Olivier Beauchet[b], Cédric Annweiler[b,c], Christophe Cornu[a] and Thibault Deschamps[a,*]
[a]*Laboratory "Motricité, Interactions, Performance", University of Nantes, Nantes, France*
[b]*Department of Neuroscience, Division of Geriatric Medicine, UNAM, Angers University Hospital, Angers, France*
[c]*Robarts Research Institute, The University of Western Ontario, London, ON, Canada*

Handling Associate Editor: Eija Lönnroos

Accepted 30 January 2014

Abstract.
Background: Cognitive impairment-related changes in postural sway increase fall risk among older adults. Better understanding this association could be helpful for fall prevention.
Objective: To examine the center-of-pressure (COP) velocity association with cognitive status and history of falls, in cognitively healthy individuals (CHI), patients with mild cognitive impairment (MCI), and with mild-to-moderate Alzheimer's disease (MMAD).
Methods: Six hundred and eleven older community-dwellers (77.2 ± 7.9 years; 51.8% men) were separated into CHI, MCI, and MMAD participants. By computing the average absolute maximal velocity (AAMV), the bounding limits of COP velocity dynamics were determined while participants were asked to maintain quiet stance on a force platform with eyes open or with eyes closed. Age, gender, history of falls, body mass index, medications, handgrip strength, Timed Up & Go score were used as covariates.
Results: The multivariate ANCOVA, with AAMV in eyes open and eyes closed conditions as dependent variables, showed that the highest AAMVs that bound the COP velocity dynamics of postural sway were associated with cognitive impairment ($p = 0.048$) (i.e., lowest limits in CHI and MCI as compared with MMAD) and falls ($p = 0.033$) (i.e., highest limits in fallers).
Conclusions: These findings identified the bounding limits of COP velocity as a hallmark feature of cognitive impairment-related changes in postural sway, in particular for MMAD. This point is of special interest for clinical balance assessment and fall prevention in MMAD patients in order to plan long-term targeted fall-prevention programs.

Keywords: Accidental falls, Alzheimer's disease, mild cognitive impairment, postural balance

INTRODUCTION

Falls are common in older population and often lead to fractures and psychological trauma, self-imposed restriction in daily activities, and consequently, loss of independence [1–3]. Older adults with cognitive impairment from mild cognitive impairment (MCI) to dementia, have higher prevalence of falls [4–7]. Recently, some studies have characterized some cognitive impairment-related changes in gait performance, suggesting the existence of a motor phenotype of unsafe gait in MCI and mild dementia [8–11]. For example, an increase in the variability of stride-to-stride time (i.e., worst gait performance and control) has been identified as a specific biomarker of MCI patients [12]. In addition, evidence of balance impairment has been widely reported in MCI or Mild-to-Moderate Alzheimer's disease (MMAD) [13–17]. All these data suggest that the implicit postural control strategies in older adults with cognitive impairment may be a clinical hallmark of early cognitive

*Correspondence to: Thibault Deschamps, PhD, Laboratory « Motricité, Interactions, Performance » (EA 4334), University of Nantes, 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. Tel.: +33 02 51 83 72 14; Fax: +33 02 51 83 72 10; E-mail: thibault.deschamps@univ-nantes.fr.

ISSN 1387-2877/14/$27.50

dysfunction and may help to diagnose individuals with increased fall risk [18].

Because poorer balance stability is identified as a powerful predictor of falls in older adults with cognitive disorders [19–25], balance assessment and, in particular, the analysis of center-of-pressure (COP) trajectories recorded using force platforms could be helpful to understand cognitive impairment-related changes in postural sway that expose to greater fall risk [18, 26, 27] (Fig. 1). For example, it has been reported that MMAD individuals had increased postural sways, indicative of reduced postural control [28, 29]. Within this framework of postural control, it has been shown that postural sway is left unchecked until a threshold in COP velocity is reached. Velocity series appear to be bounded between upper and lower limits, evidencing a velocity-based corrective control process instead of position-based control of posture [30]. According to this COP velocity-based hypothesis, an active control of velocity dynamics for *non-faller* older cognitively healthy individuals (CHI), unlike age-matched MCI or MMAD subjects, has been shown recently [18]. By assessing the most sensitive velocity-based variables, namely the average absolute maximal velocity (AAMV in mm/s) in the antero-posterior direction, we found a significant effect of cognitive status, with higher limits of COP velocity for MCI and MMAD than CHI. More details about the relevance and the determination of AAMV variables can be read in [18, 27].

We had the opportunity to examine the effects of cognitive decline on COP velocity in the GAIT (Gait and Alzheimer Interactions Tracking) study, which is a cross-sectional study designed to compare gait characteristics of CHI and patients with MCI and MMAD [18]. The objectives of the present study were 1) to compare the limits of COP velocity in CHI, MCI, and MMAD participants, and 2) to examine the association between COP velocity and the cognitive status and history of falls of subjects. We hypothesized that the limits of COP velocity dynamics, as essential sensory information to stabilize posture [30], should allow a fine clinical discrimination between older adults with and without cognitive impairment, and their related fall risk.

METHODS

Participants

From November 2009 to December 2012, a total of 611 older community-dwellers (mean age $\pm$ standard deviation, 77.21 ± 7.89 years; 48.23% female) were recruited in the GAIT cohort, which is an observational cross-sectional study designed to examine gait and balance characteristics of CHI and patients with MCI and MMAD. The baseline characteristics of the participants were summarized in Table 1 using means and standard deviations, or frequencies and percentages, as appropriate. This study was approved by the Local Ethical Committee of Angers (reference: n° 2009-A00533-54) and was conducted in accordance with the Declaration of Helsinki (1986). The sampling and data collection procedures have been described elsewhere [31]. In summary, all participants were referred for a memory complaint by their primary care physician to the memory clinic of Angers University Hospital. Eligibility criteria were age 60 years and over and no acute medical illness in the three past months. For the present analysis, exclusion criteria were severe AD (i.e., Mini-Mental State Examination score (MMSE) $\leq$10), neurological and psychiatric diseases with the exception of cognitive impairment, and the inability to stand on one leg for at least five seconds. Participants in the study were included after having given their written consent for research.

Neuropsychological and physical assessment

Neuropsychological assessment was performed during a face-to-face examination carried out by a neuropsychologist. The following standardized tests were used to probe several aspects of cognitive function: MMSE [32] and Frontal Assessment Battery [33], Alzheimer's Disease Assessment Scale-cognitive subscale [34], the Trail Making Test parts A and B [35], the French version of the Free and Cued Selective Reminding Test [36, 37], and the Instrumental Activities of Daily Living scale [37, 38].

The diagnoses of MCI and AD were made during multidisciplinary meetings involving geriatricians, neurologists, and neuropsychologists of Angers University Memory Clinic, and were based on the above-mentioned neuropsychological tests, physical examination findings, blood tests and magnetic resonance imaging (MRI) of the brain. MCI was diagnosed according to the consensus criteria of Winblad et al. [39]. Participants with all categories of MCI were included in this study, i.e., amnestic and non-amnestic, as well as single and multiple affected domains. The diagnosis of AD followed the Diagnostic and Statistical Manual of Mental Disorders, 4th edition and National Institute of Neurological and Communicative

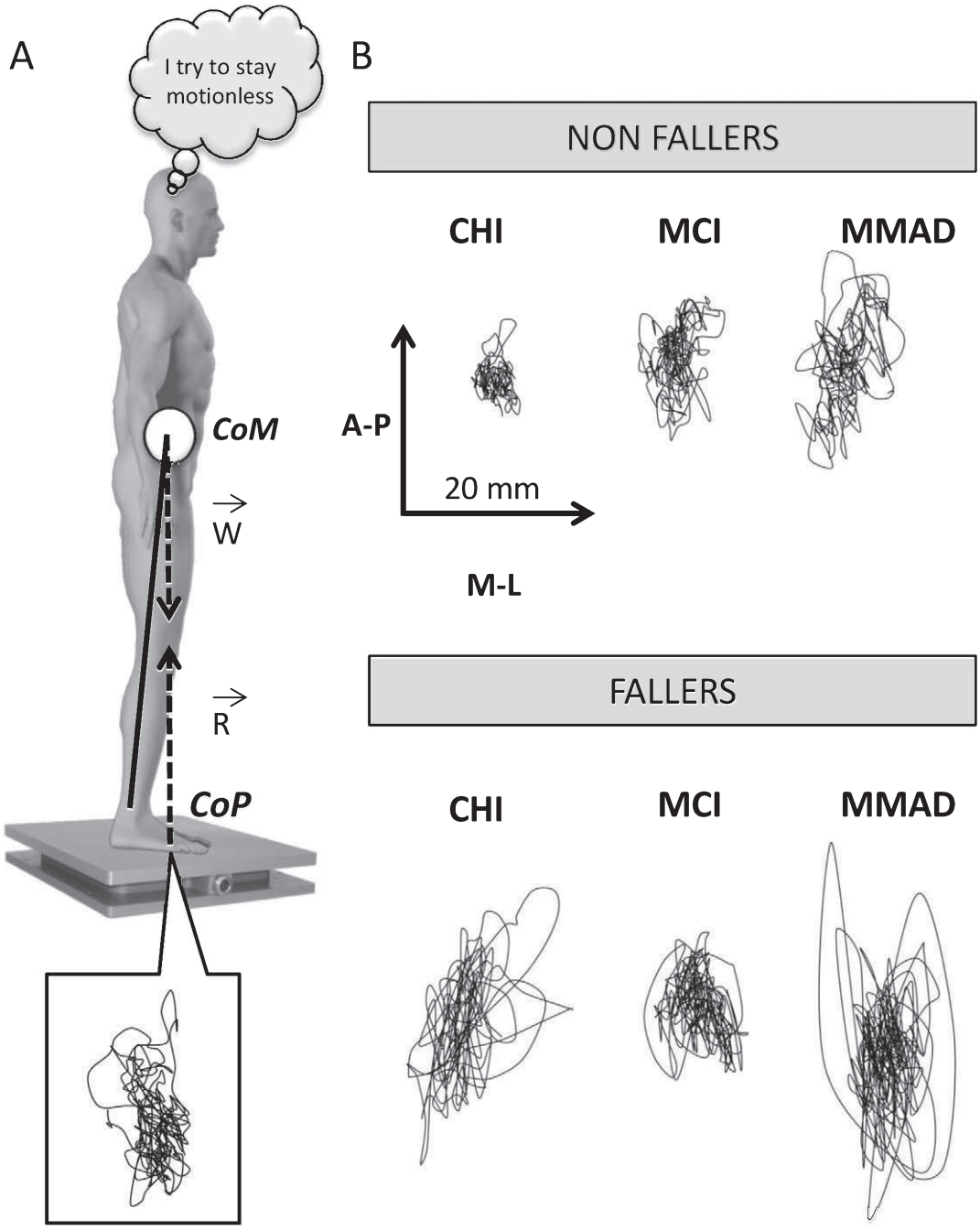

Fig. 1. Representative examples of center-of-pressure (COP) trajectories recorded using a force platform (A), as a function of the cognitive status (CHI, MCI, and MMAD) and fall risk (non-fallers versus fallers) (B). CHI, cognitive healthy individual; MCI, mild cognitive impairment; MMAD, mild-to-moderate dementia; AP, anteroposterior axis; ML, medio-lateral axis.

Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [40]. A mild stage of MMAD was defined for a MMSE score ≥ 20, and moderate stage for a MMSE score between 19 and 11. Participants who were neither MCI nor AD and who had normal neuropsychological and functional performance were considered as cognitively healthy [9, 18].

Height (cm), weight (kg), and body mass index (BMI) (kg/m2) were assessed for each participant. The

Table 1
Baseline characteristics of participants according to their cognitive status ($n = 611$)

	Total	CHI ($n = 228$)	MCI ($n = 140$)	MMAD ($n = 243$)
Age (years), mean ± SD[a (1, 2, 3)]	77.2 ± 7.9	72.5 ± 6.1	74.7 ± 7.3	83 ± 5.8
Female gender, n (%)[a (2, 3)]	290 (47.5)	92 (40.3)	48 (34.3)	150 (61.7)
BMI (kg/m^2), mean ± SD	26.3 ± 4.1	26 ± 3.4	26.4 ± 4.7	30.7 ± 9.9
Education level* (/4), n (%)[a (1, 2, 3)]	1 = 33 (5.4);	1 = 1 (2.3);	1 = 4 (2.8);	1 = 28 (11.5);
	2 = 307 (50.2);	2 = 77 (33.8);	2 = 75 (53.6);	2 = 155 (63.8);
	3 = 172 (28.1);	3 = 86 (37.7);	3 = 42 (30);	3 = 44 (18.1);
	4 = 64 (16.2)	4 = 64 (28.1)	4 = 19 (13.6)	4 = 16 (6.6)
Use of psychoactive drugs (yes), n (%)[a (2, 3)]	82 (13.4)	12 (5.3)	12 (8.6)	58 (23.9)
Medications (total number/day), mean ± SD[a (2, 3)]	4.2 (3.2)	3.1 (2.7)	3.6 (3.1)	5.6 (3.1)
Maximal Handgrip Strength (kg), mean ± SD[a (2, 3)]	26.1 ± 10.3	30.7 ± 9.9	29.5 ± 9.9	19.7 ± 7.6
Timed Up and Go (s), mean ± SD[a (2, 3)]	13.9 ± 6.7	10.8 ± 3.8	11.9 ± 4.3	17.9 ± 7.8
MMSE, mean ± SD[a (1, 2, 3)]	24.1 ± 5.2	28 ± 2.3	26.1 ± 2.4	19.3 ± 4.4
FAB, mean ± SD[a (1, 2, 3)]	14 ± 3.6	16.5 ± 1.7	14.9 ± 2.1	11.1 ± 3.5
Eyes open AAMV AP (mm.s^{-1}), mean ± SD[a (2, 3)]	18.8 ± 9.3	15.9 ± 7.5	17.8 ± 9.3	22.2 ± 9.6
Eyes closed AAMV AP (mm.s^{-1}), mean ± SD[a (2, 3)]	22.7 ± 12.6	19.7 ± 10.3	22.1 ± 14.8	26 ± 12
Falls in previous year, n (%)[a (2, 3)]	230 (37.6)	74 (32.4)	38 (27.1)	118 (48.6)

χ^2 or univariate one-way analyses of variance with HSD-Tukey *post-hoc* test were used to compare CHI, MCI, and MMAD groups. CHI, cognitive healthy individual; MCI, mild cognitive impairment; MMAD, mild-to-moderate dementia; BMI, body mass index; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; AP, anteroposterior direction; AAMV, absolute average maximal velocity. *Categorical variable in four points: 1/no school; 2/secondary school certificate 3/graduate degree; 4/university degree. [a]Main effect of cognitive status. [1]Significant difference between CHI and MCI groups. [2]Significant difference between CHI and MMAD groups. [3]Significant difference between MCI and MMAD groups.

use of psychoactive drugs including benzodiazepines, antidepressants, or antipsychotics, and the number of drugs taken per day were also recorded. Education level was evaluated as a categorical variable by the number of years spent in education, as following: 1/no school; 2/secondary school; 3/high school; 4/graduate studies.

Basic mobility was assessed with the Timed Up & Go test (TUG) [41]. The maximal isometric voluntary contraction strength of the hand was measured with a hand-held dynamometer; the handgrip measurement was repeated three times on the preferred hand, with a few seconds of recovery between each effort. All readings were recorded in kilograms (kg) with one highest reading chosen for the analysis [42]. Finally, the participants were interviewed using a standardized questionnaire, gathering information on the history of falls over the past year. A fall was defined as an event resulting in a person coming to rest unintentionally on the ground or at other lower level, not as the result of a major intrinsic event or an overwhelming hazard. In case of mild-to-moderate cognitive impairment, information on falls was obtained from a guardian, a nurse, or a person who lived with the participants. All detailed characteristics of the sample are shown in Table 1.

Postural assessment

The standing postural sway on a firm surface was measured using a force platform (101 × 101 cm; BioRescue, Dune®, France), equipped with three pressure gauges. The participants were asked to maintain a barefoot standing position with eyes opened and each foot positioned on a platform plate that maintained the distance between the medial sides of the heel at 8.4 cm with an external rotation angle of 9°. Participants were instructed to look straight ahead, with arms kept by the side of the body, and focused on a visual reference mark placed in front of them at a 100 cm distance. The postural test consisted of two trials of quiet stance: stance with eyes open (EO) and stance with eyes closed (EC). For each trial of 51.2 s duration (sampling frequency of 5 Hz), the system was linked to PosturalRescue® 2.0 software, providing COP series on the antero-posterior (AP) and medio-lateral (ML) directions of sway. None of the collected data relative to the COP parameters were filtered (see Fig. 1). For each visual condition, we deliberately chose to compute only one variable based on COP velocity: the average absolute maximal velocity (AAMV) in AP direction. Indeed, as stated in the introduction, we recently reported that this dependent variable was the most sensitive for characterization of postural control, as a function of visual condition, age, and cognitive impairment [18]. The AAMV was computed from the COP velocity series by extracting the maximum and minimum values of the series within non-overlapping windows (of a length of 2 s). Then the absolute values of these extremes were averaged [18, 27].

Statistics

Participants were separated into three groups based their cognitive status. Firstly, between-group comparisons (i.e., CHI, MCI, and MMAD) were performed using a one way analysis of variance (ANOVA) with Bonferroni corrections, HSD-Tukey *post-hoc*, or Chi-square test, as appropriate.

Secondly, a single multivariate analysis of covariance (MANCOVA) for the two variables of interest (i.e., AAMV direction in EO and EC conditions in the AP direction), with the cognitive status (×3) (i.e., CHI, MCI, and MMAD) and the fall risk (×2) (fallers versus non-fallers) as between-participants factors, and age, gender, BMI, education, use of psychoactive drugs, number of drugs taken per day, handgrip strength, and TUG as potential confounding factors (covariates) [21, 43] was performed. The multivariate Wilks' lambda F was used for this analysis. *p*-values <0.05 were considered as statistically significant. Partial eta square (${}_p\eta 2$) values are reported as measures of effect size. All statistics were performed using SPSS software (version 20.0; SPSS, Inc., Chicago, IL).

RESULTS

General characteristics

The mean and standard deviations of the baseline characteristics of the three groups (CHI, MCI, and MMAD) are presented in Table 1. Overall, a significant difference between the groups was revealed for all confounding factors: age [$F(2, 608) = 177.52$, $p < 0.0001$], gender [$\chi^2 = 34.2$, $p < 0.0001$], education level [$F(2, 608) = 55.19$, $p < 0.0001$], use of psychoactive drugs [$\chi^2 = 462.5$, $p < 0.0001$], medications (total number per day) [$F(2, 608) = 47.27$, $p < 0.0001$], handgrip strength [$F(2, 608) = 102.63$, $p < 0.0001$], and TUG [$F(2, 608) = 97.52$, $p < 0.0001$]. No main effect of cognitive status was shown for the BMI [$F(2, 608) = 1.654$, $p = 0.192$]. *Post-hoc* analyses systematically showed significant differences between the CHI and MMAD groups, and between the MCI and MMAD groups ($p < 0.05$, Table 1). Taken together, these results revealed that the MMAD patients were significantly older and had a higher prevalence of falls compared to CHI ($p = 0.0003$) and MCI ($p = 0.0001$). They also had a lower handgrip strength compared to CHI ($p < 0.0001$) and MCI ($p < 0.0001$).

Posture, cognitive impairment, and falls

Using the multivariate analysis of covariance, controlling for gender, age, BMI, education level, use of psychoactive drugs, number of drugs taken per day, handgrip strength, and TUG, significant main effects of cognitive status ($p = 0.048$) and fall risk in the past year ($p = 0.033$) were shown (Table 2). *Post hoc* analysis using Bonferroni adjustment revealed that the bounding limits of COP velocity dynamics were significantly lower in CHI and MCI compared with MMAD ($p < 0.001$), but no difference between CHI and MCI was found ($p = 0.102$). In addition, the maximal absolute values of COP velocity in the AP direction were different as a function of fall risk, with higher limits in fallers on average (+0.73 mm·s^{-1}, i.e., 3.5%; $p < 0.05$). Note that no cognitive status × fall risk interaction was found ($p = 0.666$). Overall, the increase in AAMVs due to fall risk was statistically identical for each of three listed groups (CHI, MCI, and MMAD).

DISCUSSION

The present cross-sectional study with a prospective collection of data owes its originality to comparison of implicit postural control strategies in older adults with and without cognitive impairment from MCI to MMAD, according to their history of falls (i.e., fallers versus non-fallers). The aim of this study was to test the sensitivity of velocity-based posturographic variables, and to explore the associated postural control strategies in CHI and in MCI-MMAD older patients for discriminating early cognitive dysfunction and potentially diagnosing individuals with fall risk. In line with recent prospective examination of fall risk factors in MCI or Alzheimer's disease [21, 22], our study confirms the importance of velocity information to optimize postural sway [30], and as a variable of specific interest for fall prevention in populations with cognitive impairment [43, 44]. Here, we provide two major findings. First, in support of our hypothesis, the bounding limits of COP velocity dynamics (i.e., the average absolute maximal velocity in the antero-posterior direction) increased with the highest levels of cognitive impairment, as an index of adverse changes in intermittent velocity-based control of posture [27]. Second, the subjects who had fallen showed the highest absolute values of velocity, suggesting that the control of postural sway is implicitly corrected and reversed at high velocity thresholds. Since no cognitive status × fall risk interaction was found, identical effects of falls in

Table 2
Mean values (standard deviations) for center-of-pressure velocity-based variables (average absolute maximal velocity –AAMV- in eyes open and eyes closed conditions in anteroposterior direction) according to cognitive status (i.e., CHI, MCI, and MMAD) and history of falls in the past year (i.e., fallers versus non-fallers) adjusted on baseline characteristics. F and p values are from multivariate analysis of covariance. Significant results are indicated in bold type (i.e., $p < 0.05$). CHI, cognitive healthy individual; MCI, mild cognitive impairment; MMAD, mild-to-moderate dementia

Between-participant variables	F values	*p*-value	eta^2	Eyes open AAMV ($mm \cdot s^{-1}$)	Eyes closed AAMV ($mm \cdot s^{-1}$)
Cognitive status	**2.391**	**0.048**	$_p\eta 2 = 0.009$		
CHI				15.9 (7.5)	19.7 (10.3)
MCI				17.8 (9.3)	22.1 (14.8)
MMAD				22.2 (9.6)	26 (12)
Fall history (yes versus no)	**3.437**	**0.033**	$_p\eta 2 = 0.011$		
Non-fallers				17.9 (8.7)	22.4 (12.6)
Fallers				20.3 (10)	23.3 (12.2)
Cognitive status × fall history	0.595	0.666	$_p\eta 2 = 0.002$		
CHI – Non-fallers				15.5 (6.7)	19.2 (10.3)
Fallers				17.6 (8.8)	20.7 (10.4)
MCI – Non-fallers				17.5 (9.5)	22 (14.5)
Fallers				18.3 (8.9)	22.2 (15.8)
MMAD – Non-fallers				21.8 (8.7)	26.6 (12.3)
Fallers				22.5 (10.6)	25.2 (11.7)
COVARIATES*					
Female gender	**8.817**	**0.000**	$_p\eta 2 = 0.029$		
Age	**5.452**	**0.005**	$_p\eta 2 = 0.018$		
Education level	0.34	0.712	$_p\eta 2 = 0.001$		
Body mass index	**5.47**	**0.004**	$_p\eta 2 = 0.018$		
Use of psychoactive drugs	**0.056**	**0.000**	$_p\eta 2 = 0.001$		
Medications (total number/day)	**1.03**	**0.003**	$_p\eta 2 = 0.008$		
Maximal handgrip strength	0.941	0.391	$_p\eta 2 = 0.003$		
Timed Up & Go	1.684	0.186	$_p\eta 2 = 0.006$		

*Overall to be a female, advanced in age, with increased body mass index, taking a greater number of medications per day tend to enhance the bounding limits of COP velocity dynamics, indicative of reduced postural control.

past year on the postural performance were observed, whatever the cognitive status. This lack of interaction indicates that fall causes alterations in postural control to the same extent whatever the cognitive status of older adult. This might strengthen the emerging view that the bounding limits of COP velocity dynamics are primarily relevant for capturing the progression of cognitive impairment [18]. But when falls and cognitive impairment are analyzed together, the velocity-based variables, despite the good sensitivity for revealing the effects of group or fall risk factors on postural control, may be not sufficient, in particular for MMAD. In fact, there may be real difficulties to take account for multicollinearity among potential confounding variables and the inclusion of multiple parameters in the same model [45]. A data reduction of high-dimensional balance data to a low-dimensional set of essential features may be also helpful to refine the categorization of patients (MCI or MMAD) with or without risk of falls, while scanning a large number of potential confounding variables that may highly constrain the relationship between the cognitive impairment-related changes in postural control and risk of falls. In summary, the original comparison of older adults with different levels of cognitive impairment (CHI, MCI, and MMAD) and the present findings highlighted a promising hallmark of early cognitive dysfunction, even when explored on range of main confounding factors related to postural instability and falls [18, 21, 43].

Like prior studies and the difficulty of accounting for variables associated with force platform data in predicting falls (even in prospective follow-up studies) [46–48], our results support the idea that the dynamic dimension of balance assessment is of primary interest for discriminating elderly populations with and without cognitive impairment and high fall risk [18, 27]. This statement is in line with recent studies showing that changes in postural sway (assessed by path length of COP, a velocity-based variable) are associated with an increased fall risk in MCI [21, 23]. In summary, we argue that the relevant postural variables for identifying early cognitive impairment and the associated fall risk should address more than just the static nature of COP variables but also the analysis of velocity-based postural control strategies as a crucial component of falls prediction (and *de facto* primary prevention pro-

grams). In view of the current retrospective recording of falls, further research is required to test and validate this assumption in a prospective independent cohort.

These results may nevertheless have implications for improved clinical utilization of posturography [49], by collecting first and foremost new COP velocity-based variables, namely the AAMV in the AP direction. On that basis, a decline in reweighting of velocity information revealed by high AAMV values both in EO and EC conditions can be an effective index of changes in the sensory integration process, which is essential for maintaining balance in older adults [50]. In neurophysiological studies, velocity information in implicit control strategy during quite stance has been found to be of great importance in CHI, by the modulation of ankle extensor muscle activity [30, 51]. Because of well-documented progressive changes to critical regions of the brain that underlie executive decline and motor dysfunction in MCI and MMAD (e.g., the prefrontal cortex) [52–54], the association between changes in reweighting velocity information, the cognitive status and the fall risk might reflect a deficit in active COP velocity control or correction processes [27, 30]. This assumption is in line with the contribution of the prefrontal cortex to the maintenance of postural balance and the underlying pathophysiology of falls [55, 56].

Some limitations of this study need to be considered. First, it should be noted that the number of persons with MCI identified as fallers in this study was relatively low ($n = 38$), compared with CHI ($n = 74$) and MMAD ($n = 118$), and the size of MCI sample should be increased to reinforce the statistical power. Second, the findings of a powerful postural hallmark of cognitive impairment and associated fall risk reported here are not applicable to patients with severe dementia, although it is likely that these patients will also display an altered intermittent control of velocity (i.e., highest absolute values of the threshold that bound the dynamics of velocity). Finally, the cross-sectional design and the recruitment performed in a single memory clinic may be limitations to exploring the association between the implicit postural control strategies, the cognitive status or the fall risk compared to a prospective cohort design.

CONCLUSIONS

This study identified the bounding limits of COP velocity dynamics through the easy computation of AAMV in EO and EC conditions as a promising postural hallmark of cognitive impairment with a strong association between poorer cognitive ability and poorer balance performance. Moreover identifying people with and without cognitive impairment who are at risk of falls risk via the evaluation of the postural control strategies might be a valuable window of opportunity for fall-prevention interventions. For example, we suggest that the postural control strategies in MMAD might be positively modified by considering a walking exercise program as a safe means for the optimization of this sensory input recalibration process [57, 58]. Precisely, the effects of specific exercise might improve the ability of the central nervous system to predict the muscle activation locomotor pattern needed to perform the movement. This feedforward control process could be recalibrated based on sensory information provided by peripheral commands [59]. With exercise, the central nervous system would become more efficient in predicting the optimal motor response, because of an optimized feedforward control, and possibly in preventing the postural (velocity-based) control alterations and fall risk in the elderly [60, 61]. In any case, further studies focusing upon these specific assumptions are needed to determine whether this potential postural hallmark is also validated and applicable within an independent cohort of cognitively impaired older people for fundamental and clinical purposes of prediction of cognitive decline and associated fall risk.

ACKNOWLEDGMENTS

The research was supported by grants from the Region of Pays de la Loire, France, for the project "RP3AP" and by the French Ministry of Health (Projet Hospitalier de Recherche Clinique national n° 2009-A00533-54). This study received also support from Research Mission of Directorate for Research Studies, Evaluation and Statistics (Direction de la recherche, des études, de l'évaluation et des statistiques – MiRe-DRESS) and IRePS (French public health research Institute).

The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2132).

REFERENCES

[1] Arfken CL, Lach HW, Birge SJ, Miller JP (1994) The prevalence and correlates of fear of falling in elderly persons living in the community. *Am J Public Health* **84**, 565-570.

[2] Tinetti ME, Mendes de Leon CF, Doucette JT, Baker DI (1994) Fear of falling and fall related efficacy in relationship to functioning among community-living elders. *J Gerontol* **49**, 140-147.
[3] Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE (2008) Fear of falling: Measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing* **37**, 19-24.
[4] Morris JC, Rubin EH, Morris EJ, Mandel SA (1987) Senile dementia of the Alzheimer's type: An important risk factor for serious falls. *J Gerontol* **42**, 412-417.
[5] Myers AH, Baker S, Van Natta M, Abbey H, Robinson EG (1991) Risk factors associated with falls and injuries among elderly institutionalized person. *Am J Epidemiol* **133**, 1179-1190.
[6] Lord SR, Sherrington C, Menz HB, Close JCT (2007) *Falls in Older People: Risk Factors and Strategies for Prevention*, 2nd ed., Cambridge University Press, Cambridge.
[7] Tinetti ME, Speechley M, Ginter SF (1988) Risk factors for falls among elderly persons living in the community. *N Engl J Med* **319**, 1701-1707.
[8] Beauchet O, Allali G, Berrut G, Hommet C, Dubost V, Assal F (2008) Gait analysis in demented subjects: Interests and perspectives. *Neuropsychiatr Dis Treat* **4**, 155-160.
[9] Beauchet O, Allali G, Thiery S, Gautier J, Fantino B, Annweiler C (2011) Association between high variability of gait speed and mild cognitive impairment: A cross-sectional pilot study. *J Am Geriatr Soc* **59**, 1973-1974.
[10] Dodge HH, Mattek NC, Austin D, Hayes TL, Kaye JA (2012) In-home walking speeds and variability trajectories associated with mild cognitive impairment. *Neurology* **78**, 1946-1952.
[11] Verghese J, Wang C, Lipton RB, Holtzer R (2013) Motoric cognitive risk syndrome and the risk of dementia. *J Gerontol A Biol Sci Med Sci* **68**, 412-418.
[12] Beauchet O, Allali G, Launay C, Herrmann FR, Annweiler C (2013) Gait variability at fast-pace walking speed: A biomarker of mild cognitive impairment? *J Nutr Health Aging* **17**, 235-239.
[13] Leandri M, Cammisuli S, Cammarata S, Baratto L, Campbell J, Simonini M, Tabaton M (2009) Balance features in Alzheimer's disease and amnestic mild cognitive impairment. *J Alzheimers Dis* **16**, 113-120.
[14] Merlo A, Zemp D, Zanda E, Rocchi S, Meroni F, Tettamanti M, Recchia A, Lucca U, Quadri P (2012) Postural stability and history of falls in cognitively able older adults: The Canton Ticino study. *Gait Posture* **36**, 662-666.
[15] Rolland Y, Abellan van Kan G, Nourhashemi F, Andrieu S, Cantet C, Guyonnet-Gillette S, Vellas B (2009) An abnormal "one-leg balance" test predicts cognitive decline during Alzheimer's disease. *J Alzheimers Dis* **16**, 525-531.
[16] Taylor ME, Delbaere K, Lord SR, Mikolaizak AS, Close JC (2013) Physical impairments in cognitively impaired older people: Implications for risk of falls. *Int Psychogeriatr* **25**, 148-156.
[17] Verghese J, Wang C, Lipton RB, Holtzer R (2013) Motoric cognitive risk syndrome and the risk of dementia. *J Gerontol A Biol Sci Med Sci* **68**, 412-418.
[18] Deschamps T, Beauchet O, Annweiler C, Cornu C, Mignardot JB (2014) Postural control and cognitive decline in older adults: Position versus velocity implicit motor strategy. *Gait Posture* **39**, 628-630.
[19] Eriksson S, Gustafson Y, Lundin-Olsson L (2008) Risk factors for falls in people with and without a diagnose of dementia living in residential care facilities: A prospective study. *Arch Gerontol Geriatr* **46**, 293-306.
[20] Muir SW, Gopaul K, Montero Odasso MM (2012) The role of cognitive impairment in fall risk among older adults: A systematic review and meta-analysis. *Age Ageing* **41**, 299-308.
[21] Delbaere K, Kochan NA, Close JCT, Menant JC, Sturnieks DL, Brodaty H, et al. (2012) Mild cognitive impairment as a predictor of falls in community-dwelling older people. *Am J Geriatr Psychiatry* **10**, 845-853.
[22] Horikawa E, Matsui T, Arai H, Seki T, Iwasaki K, Sasaki H (2005) Risk of falls in Alzheimer's disease: A prospective study. *Intern Med* **44**, 717-721.
[23] Liu-Ambrose TY, Ashe MC, Graf P, Beattie BL, Khan KM (2008) Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Phys Ther* **88**, 1482-1491.
[24] Lorbach ER, Webster KE, Menz HB, Wittwer JE, Merory JR (2007) Physiological falls risk assessment in older people with Alzheimer's disease. *Dement Geriatr Cogn Disord* **24**, 260-265.
[25] Whitney J, Close JCT, Jackson SHD, Lord SR (2012) Understanding risk of falls in people with cognitive impairment living residential care. *J Am Med Dir Assoc* **13**, 535-540.
[26] Brauer SG, Burns YR, Galley P (2000) A prospective study of laboratory and clinical measures of postural stability to predict community-dwelling fallers. *J Gerontol A Biol Sci Med Sci* **55**, M469-M476.
[27] Delignières D, Torre K, Bernard P-L (2011) Transition from persistent to anti-persistent correlations in postural sway indicates velocity-based control. *PLoS Comput Biol* **7**, 2.
[28] Suttanon P, Hill KD, Said CM, Logiudice D, Lautenschlager NT, Dodd KJ (2012) Balance and mobility dysfunction and falls risk in older people with mild to moderate Alzheimer disease. *Am J Phys Med Rehabil* **91**, 12-23.
[29] Kato-Narita EM, Nitrini R, Radanovic M (2011) Assessment of balance in mild and moderate stages of Alzheimer's disease: Implications on falls and functional capacity. *Arq Neuropsiquiatr* **69**, 202-207.
[30] Jeka J, Kiemel T, Creath R, Horak F, Peterka R (2004) Controlling human upright posture: Velocity information is more accurate than position or acceleration. *J Neurophysiol* **92**, 2368-2379.
[31] Annweiler C, Fantino B, Schott AM, Krolak-Salmon P, Allali G, Beauchet O (2012) Vitamin D insufficiency and mild cognitive impairment: Cross-sectional association. *Eur J Neurol* **19**, 1023-1029.
[32] Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
[33] Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: A Frontal Assessment Battery at bedside. *Neurology* **55**, 1621-1626.
[34] Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**, 1356-1364.
[35] Brown EC, Casey A, Fisch RI, Neuringer C (1958) Trail making test as a screening device for the detection of brain damage. *J Consult Psychol* **22**, 469-474.
[36] Grober E, Buschke H, Crystal H, Bang S, Dresner R (1988) Screening for dementia by memory testing. *Neurology* **38**, 900-903.
[37] Van der Linden M, Coyette F, Poitrenaud F, Kalafat M, Calicis F, Adam F (2006) L'épreuve de rappel libre/rappel indicé à 16 items (RL/RI-16). In *L'évaluation des troubles de la mémoire*, (ed. Solal), Marseille.

[38] Pérès K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P (2006) Restriction in complex activities of daily living in MCI: Impact on outcome. *Neurology* **67**, 461-466.
[39] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. (2004) Mild cognitive impairment–beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* **256**, 240-246.
[40] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* **34**, 939-944.
[41] Podsiadlo D, Richardson S (1991) The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* **39**, 142-148.
[42] Sayer AA, Syddall HE, Martin HJ, Dennison EM, Anderson FH, Cooper C (2006) Falls, sarcopenia, and growth in early life: Findings from the Hertfordshire cohort study. *Am J Epidemiol* **164**, 665-671.
[43] Shin BM, Han SJ, Jung JH, Kim JE, Fregni F (2011) Effect of mild cognitive impairment on balance. *J Neurol Sci* **305**, 121-125.
[44] Franssen EH, Souren LE, Torossian CL, Reisberg B (1999) Equilibrium and limb coordination in mild impairment and mild Alzheimer's disease. *J Am Geriatr Soc* **47**, 463-469.
[45] Muir SW, Berg K, Chesworth B, Klar N, Speechley M (2010) Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: A systematic review and meta-analysis. *J Clin Epidemiol* **63**, 389-406.
[46] Baloh RW, Corona S, Jacobson KM, Enrietto JA, Bell T (1998) A prospective study of posturography in normal older people. *J Am Geriatr Soc* **46**, 438-443.
[47] Pajala S, Era P, Koskenvuo M, Kaprio J, Törmäkangas T, Rantanen T (2008) Force platform balance measures as predictors of indoor and outdoor falls in community-dwelling women aged 63-76 years. *J Gerontol* **63A**, 171-178.
[48] Piirtola M, Era P (2006) Force platform measurements as predictors of falls among older people- a review. *Geront* **52**, 1-16.
[49] Visser JE, Carpenter GG, van der Kooij H, Bloem BR (2008) The clinical utility of posturography. *Clin Neurophysiol* **119**, 2424-2436.
[50] Redfern MS, Jennings JR, Mendelson D, Nebes RB (2009) Perceptual inhibition is associated with sensory integration in standing postural control among older adults. *J Gerontol B Psychol Sci Soc Sci* **64**, 569-576.
[51] Masani K, Popovic MR, Nakazawa K, Kouzaki M, Nozaki D (2003) Importance of body sway velocity information in controlling ankle extensor activities during quiet stance. *J Neurophysiol* **90**, 3774-3782.
[52] Dolcos F, Rice HJ, Cabeza R (2002) Hemispheric asymmetry and aging: Right hemisphere decline or asymmetry reduction. *Neurosci Biobehav Rev* **26**, 819-825.
[53] Olazarán J, Hernández-Tamames JA, Molina E, García-Polo P, Dobato JL, Álvarez-Linera J, et al. (2013) Clinical and anatomical correlates of gait dysfunction in Alzheimer's disease. *J Alzheimers Dis* **33**, 495-505.
[54] Clément F, Gauthier S, Belleville S (2013) Executive functions in mild cognitive impairment: Emergence and breakdown of neural plasticity. *Cortex* **49**, 1268-1279.
[55] Campbell AD, Dakin CJ, Carpenter MG (2009) Postural responses explored through classical conditioning. *Neuroscience* **164**, 986-997.
[56] Mihara M, Miyai I, Hatakenaka M, Kubota K, Sakoda S (2008) Role of the prefrontal cortex in human balance control. *Neuroimage* **43**, 329-336.
[57] Blanchette A, Moffet H, Roy J, Bouyer LJ (2012) Effects of repeated walking in a perturbing environment: A 4-day locomotor learning study. *J Neurophysiol* **108**, 275-284.
[58] Lackner JR, DiZio PA (2000) Aspects of body self-calibration. *Trends Cogn Sci* **4**, 279-288.
[59] Seidler RD, Noll DC, Thiers G (2004) Feedforward and feedback processes in motor control. *Neuroimage* **22**, 1175-1183.
[60] Doumas M, Krampe RT (2010) Adaptation and reintegration of proprioceptive information in young and older adults' postural control. *J Neurophysiol* **104**, 1969-1977.
[61] Horak FB (2006) Postural orientation and equilibrium: What do we need to know about neural control of balance to prevent falls? *Age Ageing* **35**, ii7-ii11.

Exp Brain Res (2014) 232:2243–2253
DOI 10.1007/s00221-014-3915-z

RESEARCH ARTICLE

Effects of total sleep deprivation on the perception of action capabilities

Yannick Daviaux · Jean-Baptiste Mignardot · Christophe Cornu · Thibault Deschamps

Received: 10 December 2013 / Accepted: 11 March 2014 / Published online: 2 April 2014

Abstract Changes in a subject's state have been shown to modulate the perceptual update of his or her action capabilities. In parallel, sleep deprivation impairs in cognitive functions. It involves common neural structures that support the perception of successfully achieving a motor task. Thus, the study investigated the effect of 24 h of sleep deprivation on the perception of action capabilities. Twenty-four healthy participants were randomly separated into two groups (*control* group vs. 24 h *sleep deprivation* group). Participants in the *control* group slept at home according to their habitual sleep–wake schedule. The 24-h *sleep deprivation* group stayed awake in the laboratory. Participants estimated the limit of their maximal height of stepping-over a bar before and after the sleep intervention. These estimations were compared to each participant's actual maximal stepping-over height. Physical performance (measured by maximal voluntary quadriceps contraction and repetitive vertical jumping tests) and perceptual inhibition tests (measured by choice reaction time tasks) were also performed for three sessions at three time points t_0, t_{+12h}, and t_{+24h} with $t_0 = 8{:}00$ a.m. for all participants. Participants in the 24-h *sleep deprivation* group showed impairments in perceived over-stepping performance and impaired cognitive functioning (higher reaction time), while no changes were observed in actual performance in the over-stepping, voluntary quadriceps contraction, or jumping tasks. The cognitive processing of inputs that specify the estimated consequences of motor action is discussed as the main explanation for the inability to successfully update the perception of action capabilities after sleep deprivation.

Keywords Sleep deprivation · Perception · Action capabilities · Cognition

Y. Daviaux · J.-B. Mignardot · C. Cornu · T. Deschamps (✉)
Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), University of Nantes, 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France
e-mail: thibault.deschamps@univ-nantes.fr

J.-B. Mignardot
Up-COURTINE Lab, Centre for Neuroprosthetics and Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Introduction

Human beings are flexible actors, quite capable of changing their intended action to produce alternative behaviors. However, performing a given behavior successfully requires one to perceive a specific action as possible to perform, and subsequently to understand the ways in which body movements must be controlled to actually perform that action. Such possibilities for behavior known as action "affordances" (Gibson 1979; Warren 1984) reflect the task-specific fit between the properties of the environment and the individual's capabilities for movement. Ellis and Tucker (2000) suggested that the brain representation of a whole action potentiated by the environment can be sub-divided into sensorimotor components. One main component specifically involving the dorsal neural pathway relates to perception of action capabilities (Binkofski and Buxbaum 2013; Borghi and Riggio 2009; Thill et al. 2013). Thus, the present study examined the effects of sleep deprivation on the perception of action capabilities in a judgment task of (successfully) stepping-over a bar (Burton 1992; Fajen and Matthis 2011; Jiang and Mark 1994).

Changes in one's perception of action capabilities

A plethora of studies suggest that people are adept at relating (updating) visual information to their action capabilities to

promote the effective selection and execution of actions (Fajen et al. 2009; Higuchi et al. 2011; Malek and Wagman 2008; Ramenzoni et al. 2008; Regia-Corte and Wagman 2008; Stoffregen et al. 1999; Weast et al. 2011; Yu et al. 2011). However, numerous studies showed that changes in the perceiver-actor's state (e.g., fitness level, fatigue, pain, age, anxiety) influence the perception of action capabilities (Bhalla and Proffitt 1999; Deschamps et al. 2014; Graydon et al. 2012; Hackney and Cinelli 2013; Pijpers et al. 2006, 2007; Sakurai et al. 2013).

In spite of substantial evidence highlighting the relative difficulty to accurately update the perception of action capabilities during periods when perceivers experience altered adaptive/homeostatic needs, to the best of our knowledge, no study has directly investigated whether 24 h of total sleep deprivation (TSD) could have an effect on an individual's perception of his or her own action capabilities. Given the evidence that TSD attenuates a person's ability to perform a variety of psychomotor tasks (Frey et al. 2004; Patel et al. 2008; Scott et al. 2006), it could be suggested that the failure to update one's perception of his or her action capabilities could increase the risk of accidents in night shift work, decrease performance in military personnel or athletes, or decrease performance on a variety of everyday tasks (Graydon et al. 2012; Hackney and Cinelli 2013; Sakurai et al. 2013). Thus, this study aimed to investigate the effects of TSD on the perception of action capabilities, with assessments of performance across cognitive and physical domains as parallel outcome measures. Even if TSD did not establish adverse effects on participants' "meta-cognitive" ability to accurately assess their own cognitive performance (e.g., Baranski and Pigeau 1997; Baranski et al. 1994; Dorrian et al. 2000), this study addressed the role that the cognitive and/or sensory-motor functions may play in the expected adverse effects of TSD on the perception of action capabilities.

Consequences of total sleep deprivation on cognition

Consequences of TSD (defined as a case of sleep reduction in which the organism is awake for an unusually prolonged period of time) on cognitive abilities, executive performance, mood, behavior, and/or an organism's state are well established (see Killgore 2010; Orzel-Gryglewska 2010; Poudel et al. 2013, for recent reviews). Specifically, numerous studies have shown clear detrimental effects of TSD on cognitive functions, including decision-making, planning skills, and vigilant attention (Zhang and Liu 2008). For example, inhibition efficiency in a classic Go-No Go task is impaired following TSD (Drummond et al. 2006). Broadly speaking, such research has revealed that cognitive control, and specifically our executive mental function responsible for updating appropriate actions and for inhibiting inappropriate responses, declines as a function of time spent awake (Ratcliff and Dongen 2009). Beyond these consistent findings, it remains unclear whether the relationship between cognitive functioning and TSD affects the perception of action capabilities.

Even if not directly investigated, knowledge about the neurophysiological mechanisms involved in the perception of action capabilities and TSD-related cognitive impairment might guide our hypotheses. Indeed, Thill et al. (2013) presented a recent review of neurophysiological models of neuronal systems involved in the selection and specification of the perceived appropriate action. This selection is accomplished based on top-down processes that mainly occur within the prefrontal cortex (PFC) and act on various stages of the dorsal neural pathways, including the premotor cortex, which is involved in the preparation/execution of actions (Cisek 2007). Along with these recent studies, the effect of TSD on cerebral responses to cognitive performance (e.g., response inhibition) has been found to be associated with activation in the PFC and premotor areas, among others (Chuah et al. 2006; Smith et al. 2013). Considering all these arguments, we predict that the adverse effects of TSD on cognitive control would also influence the perception of action capabilities because of the significant role of PFC.

Consequences of total sleep deprivation on physical performance

Total sleep deprivation (TSD) of up to 24 h has not been shown to influence physical performance capabilities or cardiovascular responses to exercise (Oztürk et al. 2007; Souissi et al. 2003; Vardar et al. 2007). Nevertheless, the effect of TSD on muscular capabilities remains unclear. Meney et al. (1998) reported that one night of TSD did not decrease the strength in the muscles of the hand, leg, or back on the day right after TSD; on day 2, only a significant decrease in back strength was observed. On the other hand, some studies have found that maximal voluntary contraction of quadriceps decreased more in a TSD condition than in a control condition (without sleep deprivation) when subjects performed previously intermittent sprints (Skein et al. 2011). Because the integration of sensory-motor inputs might guide the perception of action capabilities, the effects of TSD on performance were assessed in a force production task (quadriceps maximal voluntary contraction) and an inter-limbs coordination task (repetitive vertical jumping). As the extensors of lower limbs are the main muscles activated when actually performing our experimental task of stepping-over a bar, these two aforementioned performances are functionally relevant to participants' stepping-over capabilities. Thus, we predicted that physical performance would be not altered by sleep deprivation because the

selected tasks did not require a long exhausting engagement of participants, unlike Skein et al. (2011), but rather an assessment of muscular qualities of force, velocity, and coordination at a given time.

Aims of the study and hypotheses

In short, prior research has shown that sleep deprivation has various effects on human performance at different levels of functioning (see Boonstra et al. 2007 for an integrated review) and has main effects on executive function. However, the effects of exercise on cognitive functioning and motor performance after TSD still need to be clarified. Therefore, in the current experiment, we aimed to characterize the effects of TSD on the perception of action capabilities in a task of stepping-over a bar. We hypothesized that a TSD of 24 h would be associated with a decrease in the perceived ability to perform the task (but not a decrease in actual performance) because of the adverse effects of TSD on the efficiency of cognitive functioning. Inhibitory function, assessed by two-choice reaction time tasks, was also expected to be vulnerable to 24-h TSD (i.e., highest reaction times at t_{+24h}).

Methods

Participants

Twenty-four students (50 % females) at the University of Nantes (France) aged 21.4 ± 5.3 years (mean ± SD) (height = 171.5 ± 0.09 cm, weight = 67 ± 12.78 kg) volunteered to participate in the present experiment. Participation included a 2-day protocol and three sessions (at t_0, t_{+12h}, and t_{+24h}). Participants were equally and randomly divided into two experimental groups: a "control" group (mean age 20.08 ± 2.23 years; six women; body mass index 21.41 ± 5.39 kg m^{-2}) and a 24-h *sleep deprivation* group ($G_{24\text{-SD}}$) (mean age 22.66 ± 7.15 years; six women; body mass index 23.05 ± 1.82 kg m^{-2}). Independent sample *t* tests revealed no difference in age or body mass index between groups [$t(22) = 1.19$, $p = 0.24$, $t(22) = 0.99$, $p = 0.32$, respectively]. No participants exhibited any visual (or corrected vision) or physical impairment, any psychiatric or neurological disorders, or took long-term medications. Participants were asked to avoid the intake of caffeine, nicotine and alcohol the day before and during the experiment. Students were not paid for their participation in the experiment, and they had no previous experience with the experimental tasks. They were clearly informed of the experimental tasks before providing written consent. This study was conducted according to the Helsinki Statement (1964).

Tasks and apparatus

Self-estimated or actual stepping-over capabilities

The apparatus consisted of two separate poles (120 cm in height) and a bar (120 cm long, 1.6 cm diameter) laid across them. The experimenter manually laid the bar on wedges. The wedges were hidden from subjects and could be adjusted at intervals of 2.5 cm (Fig. 1).

For each of three experimental sessions, a series of performance estimates and actual performance was recorded. Participants were first asked to estimate the maximum height of the bar that they could step over (perceived H_{max} in cm). The criteria for the stepping-over action were that participants had to step over the bar without holding onto anything else and without jumping (i.e., they always had to keep at least one foot on the ground). As the experimenter moved the bar in randomized discrete steps (excluding hysteresis effect), the participants were asked to say "yes" or "no" as they judged whether or not they would be able to cross the bar according to the aforementioned criteria. Two blocks of estimates were performed, with a random presentation of eleven bar positions ranging from 70 to 95 cm. Then, the actual maximum height of stepping-over the bar (actual H_{max} in cm) was measured. The bar's height was successively increased until the participant could not step over the bar without holding on to something or jumping for two consecutive trials, or when the bar dropped or the participant refused to step over. As soon as the experimenter judged that the maximal height was reached, the same bar height was tested a second time to assess the consistency of actual performance.

Quadriceps maximal voluntary contraction

During each experimental session, the participants performed maximal voluntary isometric contractions (MVCs) of the *quadriceps femoris* muscles to quantify the maximal force production for their dominant leg. Force production was performed on a Biodex® System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY), with the angle of the knee joint set at 70° (Blazevich et al. 2007). After a warm-up of 5 min, participants received encouragement while performing two MVC trials (about 5 s each), separated by 2 min of rest. The best performance was considered.

Vertical jumping test

An infrared timing system (Optojump, Microgate SRL, Rome, Italy) was used to conduct a functional vertical jumping test. In each session, participants were required to perform five consecutive countermovement vertical jumps,

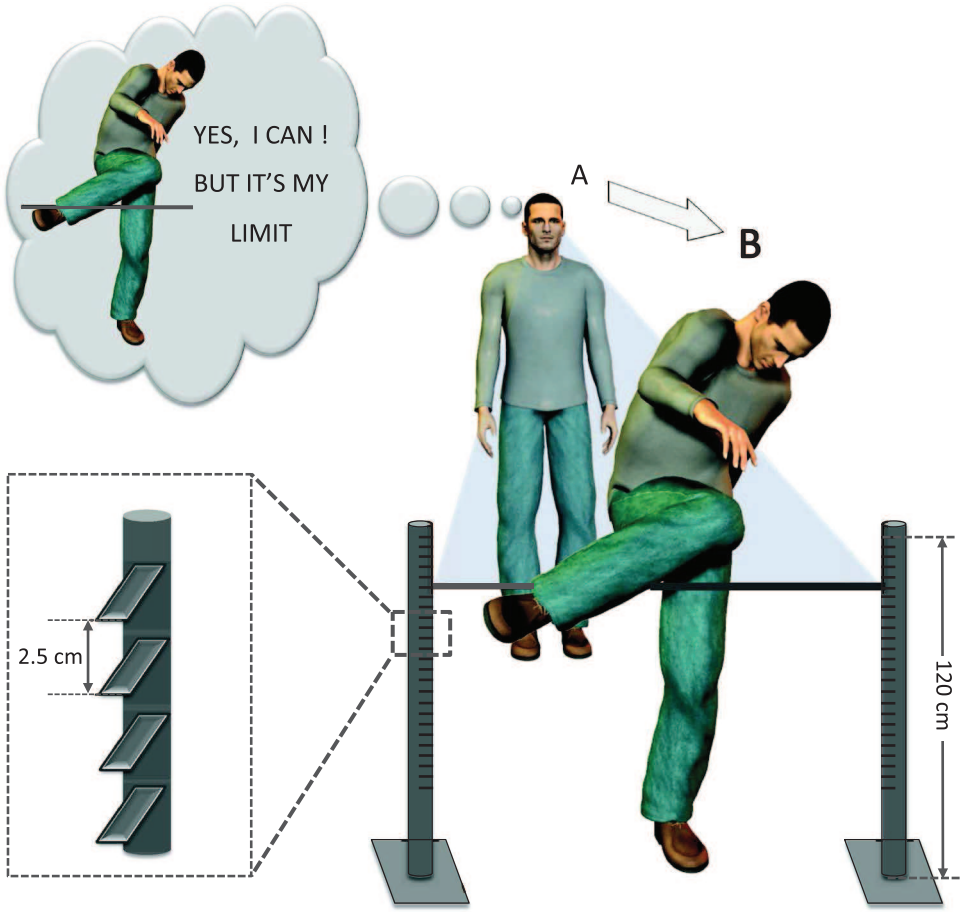

Fig. 1 Experimental set-up

with instructions to reach and maintain a maximal height with each jump. No time constraint was imposed.

Cognitive tasks

Based on reaction times to specific stimuli on a computer screen, a test of perceptual inhibition was performed by exactly replicating the MAPIT protocol (see Redfern et al. 2009 for details). For this perceptual task, participants saw a black arrow pointing either to the left or to the right and were instructed to press a corresponding key assigned either to left- or right-pointing arrows. Participants viewed two types of trials: congruous and incongruous. In congruous trials, the spatial location of the 2-cm-long arrow (which appeared 15 cm to the right or left of the central fixation point on the screen) corresponded with the direction the arrow pointed (e.g., a left-pointing arrow appeared to the left of fixation). In incongruous trials, participants were instructed to inhibit processing the arrow's spatial location and to focus only on the direction it pointed. Thus, the arrow pointed to the direction that did not correspond with its location (e.g., a right-pointing arrow appeared to the left side of central fixation point). Two blocks each included 20 congruous and 20 incongruous randomly intermixed trials, for a total of 80 trials. The participants' reaction time (RT) was measured as the time elapsed between the presentation of the arrow and the onset of the key press. A trial started with the presentation of a black central fixation cross for 300 ms followed by the arrow's display, which was presented for 300 ms. The interval between the warning signal (the cross) and the response signal (the arrow) was preset and varied randomly between 1 and 2 s so that the participant could not anticipate stimulus onset (Mendelson et al. 2010). Participants were allotted a maximum of 2 s to respond and were given no feedback about their reaction time, even in the case of a response error. The inter-trial interval was fixed at 2 s after the participant's response.

As in previous studies (Nassauer and Halperin 2003; Redfern et al. 2009), the spatial response tendency was reinforced just prior to congruous/incongruous blocks by presenting 40 visuo-spatial two-choice RT trials in which participants responded to a black rectangle presented in either the right or the left of the computer screen with the congruous key (i.e., *a two-choice RT with spatial uncertainty*). In addition, two separate blocks of 40 two-equiprobable choice RT baseline trials were presented just prior to and after these blocks. In these baseline trials,

arrows were presented in the center of the screen, randomly pointing either to the left or to the right, and participants responded with the key corresponding to the direction of the arrow (i.e., *a two-choice RT with directional uncertainty*). The inter-trial interval was fixed at 2 s.

In sum, participants completed 200 two-choice reaction time trials in about 25 min.

Subjective self-assessments

Before and after each session, participants were asked to answer three questions (via a 100 mm visual analogue scale calibrated from 0, "not at all," to 100, "absolutely") about their physical fitness ("I am feeling physically in great shape"), attentional fatigue ("I am feeling mentally and attentionally fit"), and sleepiness ("I am feeling sleepy"). The three items were presented successively in random order, and participants had to draw a vertical mark on the 100 mm line. The distance of the vertical mark from the left extremity ("not at all") was measured manually in centimetres and considered for analysis.

Experimental protocol

For all participants, the 2-day protocol included three sessions, at about 8:00 a.m. and 8:00 p.m. ± 15 min on the first day (day 1) and at 8:00 a.m. ± 15 min the next morning (day 2). Note that the 8:00 a.m. assessments did not require participants to awaken earlier than they would normally to arrive for testing because their courses started at 8:00 a.m. every day. For the *control* group, participants slept at home in their bed according to their habitual sleep–wake schedule (mean sleep duration of 6.8 ± 0.6). The 24-h *sleep deprivation* group was sleep deprived for about 25.9 h ± 0.4, while three experimenters took turns observing participants in order to ensure that they did not fall asleep. Participants were allowed to engage in non-strenuous activities, such as reading, listening to music, watching videos, and conversing. Participants performed all aforementioned tasks in a random order within each session with the exception that the cognitive tasks were always completed last.

Data analysis and statistics

All data were normally distributed; thus, values are reported as mean ± SD (or SE) throughout the text and the figures. Note that all estimates made at t_0 were considered as the baseline performance of participants. Specifically, we assumed that the baseline over- or under-estimation (i.e., differences between perceived and actual H_{max}) can be derived from individuals' inability to consider experimental restrictions when making judgments regarding actions (Fischer 2000; Graydon et al. 2012) and/or from individual characteristics (such as expertise or fitness level), which have also been shown to influence perception of action capabilities (Bhalla and Proffitt 1999; Higuchi et al. 2011; Weast et al. 2011). Focusing on the dynamics of the perception of action capabilities as a function of sleep deprivation conditions, the baseline difference between perceived H_{max} and actual H_{max} at t_0 was thus removed from the perceived H_{max} collected at t_0, t_{+12h}, and t_{+24h}.

Stepping-over capabilities

To test the effects of time-of-day and sleep deprivation on the perception of action capabilities, we compared maximum estimate and actual performance during the three sessions as a function of Group. Thus, an analysis of variance (ANOVA) with 3 within-participants factors (Session—t_0, t_{+12h}, and t_{+24h}) and 2 (Group) between-participants factors was performed for each dependent variable. To provide additional insight into the effect of sleep deprivation on the relationship between the perception of action capabilities and actual performance, the ratio of perceptual estimation divided by the actual performance was calculated. A ratio of one indicates a perfect match, whereas a ratio greater or less than one indicates an over- or under-estimation, respectively. As the data were normalized as a function of the baseline difference between perceived H_{max} and actual H_{max} at t_0, only the ratios were compared at t_{+12h}, and t_{+24h}, using Mann–Whitney U tests.

Physical measures

For the mean vertical jumping performance (mean height in cm of five consecutive jumps) or the maximal voluntary quadriceps contractions, similar 3 (Session) × 2 (Group) two-way ANOVAs were carried out to verify that participants' physical abilities were similar across groups, even though one group of participants was sleep deprived.

Reaction time measures

Mean RTs for each task (i.e., the two-choice RT with spatial uncertainty, the two-choice RT with directional uncertainty, and the perceptual congruous or incongruous RT) were computed for each participant. For all these four tasks, a 3 (Session) × 2 (Group) ANOVA was carried out with each mean RT as dependent variable.

Self-assessments

For each item ("sleepy," "physically fit" and "attentionally fit"), a 3 (Session) × 2 (Group) ANOVA was conducted using the mean scores (in cm) as the dependent variable.

For each analysis, the level of significance was $p < 0.05$. Following significant effects, the least significant difference comparisons were used as post hoc tests. Whenever the sphericity assumption in a repeated-measures ANOVA was violated (Mauchly's test), the corrected tests of significance were used. In that case, paired t tests were used as post hoc comparisons (with alpha levels corrected for multiple comparisons). Partial eta squared ($_p\eta^2$) values are reported as measures of effect size, with moderate and large effects considered for $_p\eta^2 = 0.07$ and $_p\eta^2 \geq 0.14$, respectively (Cohen 1988).

Results

Stepping-over capabilities

Perceptual boundaries

The mean maximal perceived H_{max} was used as the perceptual boundary in that condition. Overall, the perceptual boundary was equivalent across groups (main effect of Group: $F(1, 22) = 2.025$, $p = 0.169$, $_p\eta^2 = 0.084$), with a perceived H_{max} at 79.09 ± 6.59 versus 83.06 ± 7.81 cm for $G_{24\text{-SD}}$ and G_{CONT}, respectively. Moreover, the H_{max} was identical across sessions (main effect of session at t_0, t_{+12h}, and t_{+24h}: $F(2, 44) = 0.446$, $p = 0.598$, $_p\eta^2 = 0.02$), indicating that participants estimated their maximal height consistently over time. Finally, a decrease in perceptual boundary was apparent at t_{+24h} as compared to t_0, but only for the $G_{24\text{-SD}}$ [Group × Session interaction: ($F(2, 44) = 3.895$, $p = 0.027$, $_p\eta^2 = 0.15$)]. Precisely, participants in the $G_{24\text{-SD}}$ estimated a shorter height at t_{+24h} compared to t_0 (−3.58 cm, i.e., 4.42 %; $p = 0.01$). For the G_{CONT}, equivalent values at t_0 and t_{+24h} were found (+1.77 cm, i.e., 2.15 %; $p = 0.201$) (Fig. 2).

Actual behavioral boundaries

Behavioral boundaries were equivalent across sessions (main effect of Session: $F(2, 44) = 2.543$, $p = 0.09$, $_p\eta^2 = 0.104$), with similar actual H_{max} performances at t_0 (81.56 ± 5.35 cm), t_{+12h} (81.66 ± 5.29 cm), and t_{+24h} (82.91 ± 4.87 cm). The analysis indicated identical perceived performance between groups [$F(1, 22) = 0.26$, $p = 0.608$, $_p\eta^2 = 0.012$; 81.52 ± 5.86 cm for $G_{24\text{-SD}}$ versus 82.56 ± 4.32 for G_{CONT}]. In addition, no significant Group × Session interaction was found [$F(2, 44) = 0.34$, $p = 0.713$, $_p\eta^2 = 0.015$], evidencing no change in actual stepping-over performance as a function of sessions.

Ratio

The ratio of perceptual boundary divided by the actual boundary was statistically equivalent between the G_{CONT} (1.01 ± 0.09) and the $G_{24\text{-SD}}$ (0.97 ± 0.05) at t_{+12h} ($Z = 1.38$; $p = 0.16$). But the $G_{24\text{-SD}}$ underestimated their action capabilities at t_{+24h}, with a lower ratio (0.93 ± 0.05) than participants in the G_{CONT} (1.00 ± 0.08) ($Z = 2.10$; $p = 0.03$).

Functional measurements

Vertical jumping performance

The ANOVA for jumping mean height revealed a main effect of Session [$F(2, 44) = 7.83$, $p < .001$, $_p\eta^2 = 0.272$], with a significant improvement at t_{+12h} (26.73 ± 5.17 cm) as compared to t_0 (25.48 ± 5.3 cm) and t_{+24h} (25.44 ± 5.2 cm). The performances were statistically equivalent between groups (no main effect of

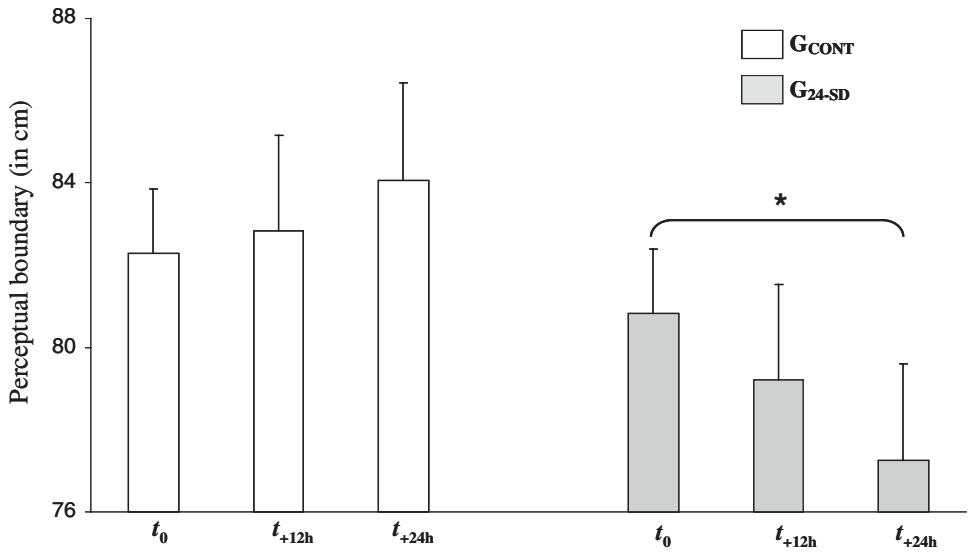

Fig. 2 Group × Session interaction for perceptual boundaries (in cm), namely the perceived maximal height of stepping-over the bar. *Error bars* correspond to the SE. Significant differences at *$p < .05$

Group: $G_{24\text{-SD}}$ versus G_{CONT}: $F(1, 22) = 0.025$, $p = 0.87$, ${}_p\eta^2 = 0.001$), and no significant Session × Group interaction ($F(2, 44) = 0.028$, $p = 0.97$, ${}_p\eta^2 = 0.001$), indicating that participants maintained their jumping performance regardless of the sleep deprivation condition.

Maximal voluntary quadriceps contraction

The analysis of variance revealed similar MVC scores at t_0 (185.21 ± 53.22 N m^{-1}), t_{+12h} (192.43 ± 56.69 N m^{-1}), and t_{+24h} (189.73 ± 52.84 N m^{-1}): $F(2, 44) = 0.894$, $p = 0.416$, ${}_p\eta^2 = 0.047$. Overall, both groups performed similarly [$F(1, 22) = 0.64$, $p = 0.431$, ${}_p\eta^2 = 0.044$], with 198.27 ± 44.8 N m^{-1} and 180.75 ± 59.88 N m^{-1} for $G_{24\text{-SD}}$ and G_{CONT}, respectively.

Reaction time measures (RT)

All mean RTs collected during the perceptual inhibitory test protocol are summarized in Table 1. Considering all participants and all cognitive tasks, relatively few errors were made: 5.75 % of the RTs (i.e., 276 of 4,800 RTs). Note also that the $G_{24\text{-SD}}$ made more errors than the participants in G_{CONT}, especially in the congruous/incongruous RT conditions at t_{+24h} (6.35 vs. 2.08 %, respectively).

All ANOVAs revealed similar RT scores between groups. However, these analyses also revealed a main effect of Session (except for the choice reaction time task with directional uncertainty) and a systematic Session × Group interaction for all RT tasks (see Table 2 for all statistical results). Overall, these findings indicate that mean RTs

Table 1 Mean reaction time performances (RTs) for the four probe reaction time tasks as a function of group (the "24-h sleep deprivation" group—$G_{24\text{-SD}}$—and the "Control" group—G_{CONT}), and Session (at t_0, t_{+12h} and t_{+24h})

Mean RTs (95 % confidence limits)	t_0		$t_{+12\,h}$		t_{+24h}	
	$G_{24\text{-SD}}$	G_{CONT}	$G_{24\text{-SD}}$	G_{CONT}	$G_{24\text{-SD}}$	G_{CONT}
Two-choice RT with spatial uncertainty (ms)	347.83 (327.98; 367.68)	352.16 (327.98; 367.68)	346.25 (319.22; 373.27)	333.91 (316.06; 351.76)	395.34 (327.57; 463.12)	334.67 (312.34; 356.98)
Two-choice RT with directional uncertainty (ms)	414.51 (389.46; 439.56)	404.75 (383.7; 425.79)	404.5 (379.8; 429.21)	387.9 (362.01; 413.78)	440.08 (397.3; 482.86)	387.14 (354.78; 419.49)
Perceptual congruous RT (ms)	470.38 (435.18; 505.59)	474.38 (433.97; 514.8)	443.24 (410.47; 476.01)	449.46 (411.46; 487.47)	489.94 (434.47; 545.41)	439.82 (402.66; 476.97)
Perceptual incongruous RT (ms)	531.26 (492.69; 569.83)	523.9 (478.86; 568.94)	499.06 (456.93; 541.19)	491 (452.18; 529.81)	576.42 (500.38; 652.47)	490.73 (450.41; 531.04)

Table 2 Analysis of variance results (F values) for all the choice RT measures for the different factors

Mean RTs	Group (1, 22)	Session (2, 44)	Session × Group (2, 44)
Two-choice RT with spatial uncertainty (ms)	1.509 (${}_p\eta^2 = 0.07$)	**3.887*$^{(3)}$** (${}_p\eta^2 = 0.163$)	**5.99**$^{**(a, b)}$ (${}_p\eta^2 = 0.231$)
Two-choice RT with directional uncertainty (ms)	2.66 (${}_p\eta^2 = 0.108$)	2.28 (${}_p\eta^2 = 0.094$)	**3.70***$^{(a, b)}$ (${}_p\eta^2 = 0.144$)
Perceptual congruous RT (ms)	0.314 (${}_p\eta^2 = 0.014$)	**4.205***$^{(1, 3)}$ (${}_p\eta^2 = 0.16$)	**5.961**$^{**(b)}$ (${}_p\eta^2 = 0.231$)
Perceptual incongruous RT (ms)	1.516 (${}_p\eta^2 = 0.064$)	**5.033***$^{(1, 3)}$ (${}_p\eta^2 = 0.186$)	**5.929**$^{**(a, b)}$ (${}_p\eta^2 = 0.212$)

Factors were Group and Session. Degrees of freedom are shown in parentheses

RT reaction time

* $p < .05$, ** $p < .01$

[1] Significant difference between t_0 and t_{+12h}

[2] Significant difference between t_0 and t_{+24h}

[3] Significant difference between t_{+12h} and t_{+24h}

[a] Significant difference between t_0 and t_{+24h} for the $G_{24\text{-SD}}$

[b] Significant difference between the $G_{24\text{-SD}}$ and the G_{CONT} at t_{+24h}

Bold values are statistically significant at $p < 0.05$

increased from the first session (t_0) to the third (t_{+24h}) for participants in the G_{CONT}, but not for participants in the $G_{24\text{-}SD}$. Moreover, RTs were significantly higher for the $G_{24\text{-}SD}$ than the G_{CONT} at t_{+24h} (Table 1). For example, when considering the perceptual inhibition tests, participants from $G_{24\text{-}SD}$ obtained higher RTs at t_{+24h} compared to the G_{CONT} for perceptual congruous trials (+50.12 ms, i.e., 11.13 %; $p < .01$) and perceptual incongruous trials (+85.69 ms, i.e., 17.46 %; $p < .04$) (Fig. 3). When combined with the error data, these results were not due to a speed–accuracy trade off.

Self-assessments

For each question ("physical fit," "attentionally fit," and "sleepiness"), the analyses revealed a main effect of Group (all Fs > 6.85; $p < 0.02$), a main effect of Session (all Fs > 9.45; p < 0.001), and a systematic Session × Group interaction (all Fs > 9.97; $p < 0.001$). Overall, the participants in the $G_{24\text{-}SD}$ felt more physically and attentionally tired and perceived a higher level of sleepiness compared to the participants in the G_{CONT}, especially at t_{+24h} (Fig. 4).

Discussion

Our aim in the current study was to investigate the effects of 24 h of acute TSD on the perception of action capabilities by examining the perceptual and behavioral boundaries (perceived or actual H_{max}) in a task of stepping-over a bar. The current study also tests for parallel changes in cognitive functioning (assessed through choice reaction time)

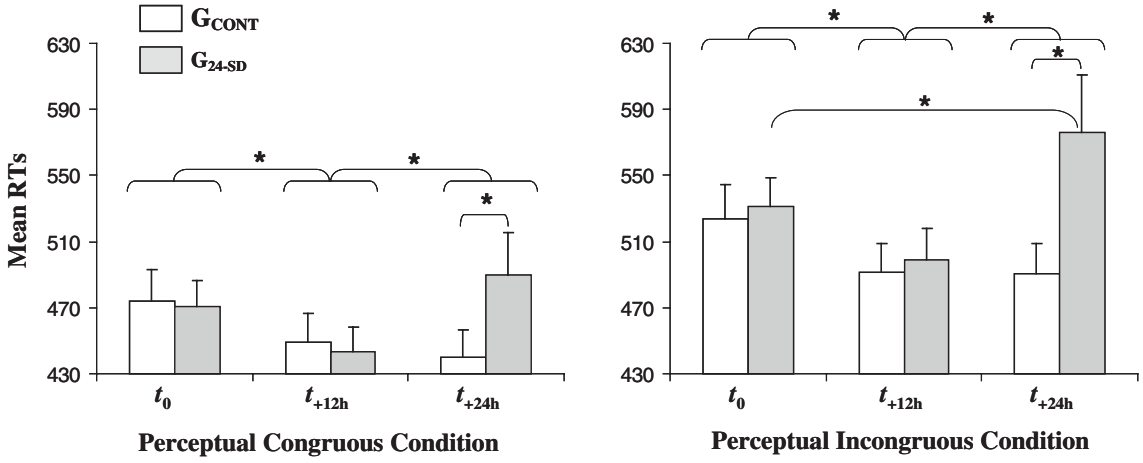

Fig. 3 Group × Session interaction for the reaction time performance (RTs) for both perceptual congruous and incongruous inhibition tests. *Error bars* correspond to the SE. Significant differences at *$p < .05$

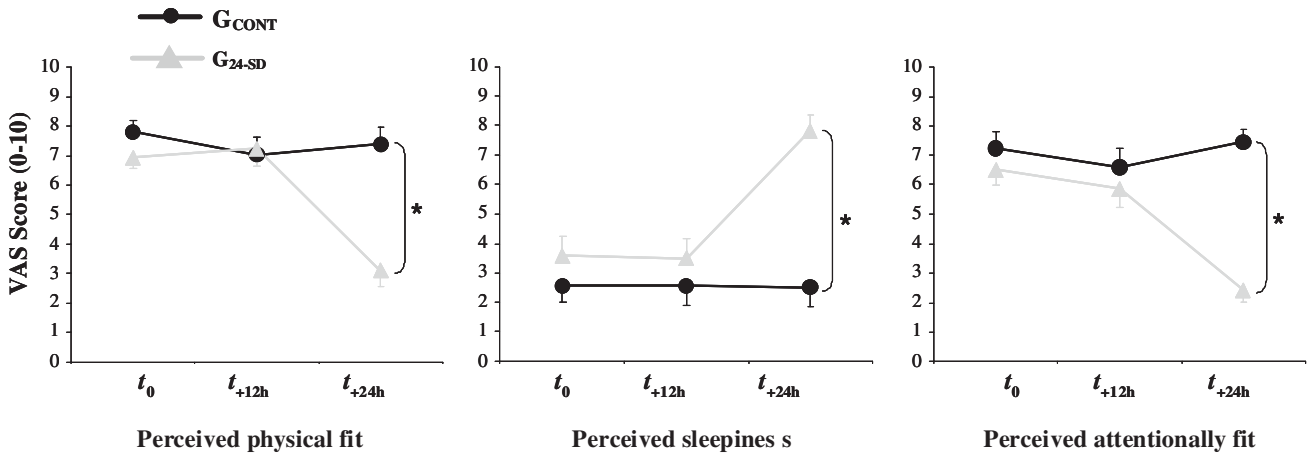

Fig. 4 Group × Session interaction for the mean self-reported scores (in cm) (via a 10-cm visual analogue scale—VAS—calibrated from 0 score "not at all" to 10 score "absolutely") for the three items ("physically fit", "sleepiness", and "attentionally fit"). *Error bars* correspond to the SE. Significant differences at *$p < .05$

and/or in physical performance and motor skills (assessed with force production and vertical jumping tests).

As expected, participants exhibited lower perceived H_{max} after one night of sleep deprivation (at t_{+24h}) but no concomitant change in actual performance over time was observed. This means either that individuals had rather conservative estimates of their action capabilities at t_{+24h} (Dorrian et al. 2000; Graydon et al. 2012) or they showed a misperception of their stepping-over action capabilities, evidencing their *cognitive* vulnerability to extended wakefulness periods when relating visual information to their action capabilities. Indeed, no change in physical performance (i.e., vertical jumps and maximal voluntary contractions of the *quadriceps femoris* muscles) was found in either the 24-h sleep deprivation group or the control group, while an impairment in inhibitory process was only observed only in the *deprivation* group. Contrary to the findings of Baranski et al. (1994), evidencing that cognitive performance self-assessments are unaffected by TSD, this is the first study to demonstrate that the "sensory-motor" ability to estimate one's own motor ability is vulnerable to extended wakefulness.

This study cannot distinguish with certainty which of these alternatives (i.e., intentionally conservative estimates or altered cognitive functioning) explains the results. The potential for participants in the TSD condition to modify their performance to increase a "safety margin" is particularly relevant when motor tasks may induce risky behaviors (i.e., falling) and a high risk of accident (Comalli et al. 2013; Jones et al. 2006). Thus, it could be assumed that participants in the TSD group moderate their performance estimates to expose the system to less risk as a protective mechanism (Deschamps et al. 2014) and their ability to accurately assess the cognitive performance impairment (Dorrian et al. 2000; Baranski and Pigeau 1997). But we assume that the present experimental stepping-over task did not induce a highly risky context. As outlined in the introduction, it can be reasonably hypothesized that sleep deprivation led to a misperception of action capabilities because of impaired cognitive functioning.

Are the changes in perceptual performance independent (or not) from changes in actual performance?

Above all, the findings on perceptual boundaries have to be discussed regarding the dynamics of actual boundaries (Comalli et al. 2013). Previous research has shown that the perception of action capabilities can vary (or not) in a concomitant way with changes in actual performances (Deschamps et al. 2014; Hackney and Cinelli 2013; Malek and Wagman 2008; Regia-Corte and Wagman 2008). For example, Noël et al. (2011) investigated the perceptions of their ability to cross over a bar among both young and elderly adults. The updating of perceptual boundaries was consistent with changes in actual action capabilities, although they were inaccurate. Indeed, whereas the older adults perceived that their actual performance was lower compared to young adults, they overestimated their action capabilities (i.e., 12.5 cm difference between estimated performance and real performance). These findings support two possible mechanisms to specify changes in perceptual boundaries: (1) the accurate update of new action capabilities (dynamically modified by the experimental context and/or environmental properties) (e.g., Comalli et al. 2013) and/or (2) a perceptual impairment (i.e., inaccurate perception of the extent of changes in action capabilities as the actual performance effectively changed, or only a perceptual impairment without change in actual performance). In our study, actual H_{max} performances did not vary over time, arguing that perceptual alterations might be closely attributable to changes in the perceptive updating process over time for the $G_{24\text{-SD}}$.

Thus, it is important to determine the impairment sources that are responsible for inefficient cognitive updating of perception of action capabilities. We argue that the perception of motor action features, anticipation of the consequences of actions (i.e., the way individuals perceive the environment in terms of the costs of acting within it; Deschamps et al. 2014; Witt et al. 2004, 2009), and perceptive cognitive process are all involved in the perception of action capabilities.

Perception of motor action features as a source of perceptual alterations in action capabilities

Clearly, after 24 h of wakefulness, individuals are much less likely to perform actions that they believe will be uncomfortable, painful, and/or unachievable. As supported by the self-assessment results, participants' evaluation of their own physical fitness was significantly lower at t_{+24h} of sleep deprivation, which is consistent with their conservative behaviors, as revealed by lower H_{max} estimates. Again, related to a protective mechanism assumption, it may be suggested that individuals in the $G_{24\text{-SD}}$ have self-assessed a decrease (not found in the present case) in physical capacities from kinesthetic inputs or from incorrect self-expectations of sleep deprivation's effects. Whatever the explanation, subjects deprived of sleep for 26.5 h underestimated their maximum over-stepping height without changes in their actual performance.

These findings reinforce the relevance for characterizing the effects of TSD on both force production by using an MVC test and lower limb synergy abilities through the functional CMJ test. As reported, the effect of TSD on both tests was not significant, which is in accordance with previous studies (Meney et al. 1998; Souissi et al. 2003;

Vardar et al. 2007). This first key result suggests that the dynamic properties of the body and individuals' motor potential necessary for action performance may not be at the origin of the decrease in the assessment of physical fitness and consequently in perceptual boundaries. As a plausible alternative, although indirectly supported by the current findings, we suggest that conservative perceptual behavior is a direct consequence of sleep-deprivation-induced impairments in cognitive processing of kinesthetic inputs. Further investigation should specify which cortical structures, and neurophysiological processes could support this assumption (Babkoff et al. 2005; Thill et al. 2013).

Is the alteration in cognitive processes a source of changes in the perception of action capabilities?

Similar to previous studies, sleep deprivation was associated with a decrease in attention, as shown by an increase in reaction time performance and lower scores on attention self-assessment. With respect to attentional processing requirements, consistent findings underlined the importance of considering the interplay of cognitive load (or attentional cost), fatigue, and motor performance (Deschamps et al. 2011; Murian et al. 2008). Accordingly, our present results strongly suggest that perceptual output for action capabilities is altered during prolonged wakefulness because TSD impairs the central executive processes, with adverse effects on attention and response inhibition. Further research is required to test the specific relationship between changes in the perception of action capabilities and TSD-related cognitive impairment.

Conclusion

This study demonstrated deleterious effects of acute sleep deprivation on the sensory-motor ability necessary to consider one's action capabilities to insure safe and efficient motor control. We argue that the cognitive processing of external (i.e., environmental cues) and internal (i.e., the subject's physical state) inputs that specify the estimated consequences of motor action could be the explanation for the inability to successfully update the perception of action capabilities after sleep deprivation. Future research on these specific assumptions should provide further neurophysiological support for the failure of updating the perception of action capabilities with TSD.

Acknowledgments The research was supported by grants from the Region of Pays de la Loire (France). This was not an industry supported study. The research was supported by grants from the Region of Pays de la Loire (France). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest The authors declare that they have no competing interests.

References

Babkoff H, Zukerman G, Fostick L, Ben-Artzi E (2005) Effect of the diurnal rhythm and 24 h of sleep deprivation on dichotic temporal order judgment. J Sleep Res 14:7–15. doi:101111/j1365-2869200400423x

Baranski JV, Pigeau RA (1997) Self-monitoring cognitive performance during sleep deprivation: effects of modafinil d-amphetamine and placebo. J Sleep Res 6:84–91

Baranski J, Pigeau R, Angus R (1994) On the ability to self-monitor cognitive performance during sleep deprivation: a calibration study. J Sleep Res 3:36–44

Bhalla M, Proffitt DR (1999) Visual-motor recalibration in geographical slant perception. J Exp Psychol Hum 25:1076–1096

Binkofski F, Buxbaum LJ (2013) Two action systems in the human brain. Brain Lang 127:222–229. doi:101016/jbandl201207007

Blazevich AJ, Cannavan D, Coleman DR, Horne S (2007) Influence of concentric and eccentric resistance training on architectural adaptation in human quadriceps muscles. J Appl Physiol 103:1565–1575. doi:101152/japplphysiol005782007

Boonstra TW, Stins JF, Daffertshofer A, Beek PJ (2007) Effects of sleep deprivation on neural functioning: an integrative review. Cell Mol Life Sci 64:934–946. doi:101007/s00018-007-6457-8

Borghi AM, Riggio L (2009) Sentence comprehension and simulation of object temporary canonical and stable affordances. Brain Res 1253:117–128. doi:101016/jbrainres200811064

Burton G (1992) Nonvisual judgement of the crossability of path gaps. J Exp Psychol Hum 18:698–713

Chuah YML, Venkatraman V, Dinges DF, Chee MWL (2006) The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. J Neurosci 26:7156–7162. doi:101523/JNEUROSCI0906-062006

Cisek P (2007) Cortical mechanisms of action selection: the affordance competition hypothesis. Proc R Soc B-Biol Sci 362:1585–1599. doi:101098/rstb20072054

Cohen J (1988) Statistical power analysis for the behavioural sciences. Academic Press, New-York

Comalli D, Franchak J, Char A, Adolph K (2013) Ledge and wedge: younger and older adults' perception of action possibilities. Exp Brain Res 228:183–192. doi:101007/s00221-013-3550-0

Deschamps T, Murian A, Hug F (2011) Reciprocal aiming precision and central adaptations as a function of mechanical constraints. J Electromyogr Kines 21:968–973. doi:101016/jjelekin201108009

Deschamps T, Hug F, Hodges P, Tucker K (2014) Influence of experimental pain on the perception of action capabilities and performance of a maximal single leg hop. J Pain 15:271.e1–271.e7. doi:10.1016/j.jpain.2013.10.016

Dorrian J, Lamond N, Dawson D (2000) The ability to self-monitor performance when fatigued. J Sleep Res 9:137–144

Drummond SPA, Paulus MP, Tapert SF (2006) Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. J Sleep Res 15:261–265. doi:101111/j1365-2869200600535x

Ellis R, Tucker M (2000) Micro-affordance: the potentiation of components of action by seen objects. Br J Psychol 91:451–471

Fajen BR, Matthis JS (2011) Direct perception of action-scaled affordances: the shrinking gap problem. J Exp Psychol Hum 37:1442–1457. doi:101037/a0023510

Fajen BR, Riley MA, Turvey MT (2009) Information, affordances, and control of action in sport International. Int J Sport Psychol 40:79–107

Fischer MH (2000) Estimating reachability: whole body engagement or postural stability? Hum Mov Sci 19:297–318
Frey DJ, Badia P, Wright KP (2004) Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. J Sleep Res 13:305–315. doi:101111/j1365-2869200400429x
Gibson JJ (1979) The ecological approach to visual perception. Erlbaum, London
Graydon MM, Linkenauger SA, Teachman BA, Proffitt DR (2012) Scared stiff: the influence of anxiety on the perception of action capabilities. Cogn Emot 26:1301–1315. doi:101080/026999312012667391
Hackney AL, Cinelli ME (2013) Older adults are guided by their dynamic perceptions during aperture crossing. Gait Posture 37:93–97. doi:101016/jgaitpost201206020
Higuchi T, Murai G, Kijima A, Seya Y, Wagman JB, Imanaka K (2011) Athletic experience influences shoulder rotations when running through apertures. Hum Mov Sci 30:534–549. doi:101016/jhumov201008003
Jiang Y, Mark LS (1994) The effect of gap depth on the perception of whether a gap is crossable. Percept Psychophys 56:691–700
Jones CB, Dorrian J, Jay SM, Lamond N, Ferguson S, Dawson D (2006) Self-awareness of impairment and the decision to drive after an extended period of wakefulness. Chronobiol Int 23:1253–1263. doi:101080/07420520601083391
Killgore WD (2010) Effects of sleep deprivation on cognition. Prog Brain Res 185:105–129. doi:101016/B978-0-444-53702-700007-5
Malek EA, Wagman JB (2008) Kinetic potential influences visual and remote haptic perception of affordances for standing on an inclined surface. Q J Exp Psychol 61:1813–1826. doi:101080/17470210701712978
Mendelson DN, Redfern MS, Nebes RD, Richard Jennings J (2010) Inhibitory processes relate differently to balance/reaction time dual tasks in young and older adults. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 17:1–18. doi:101080/13825580902914040
Meney I, Waterhouse J, Atkinson G, Reilly T, Davenne D (1998) The effect of one night's sleep deprivation on temperature mood and physical performance in subjects with different amounts of habitual physical activity. Chronobiol Int 15:349–363. doi:103109/07420529808998695
Murian A, Deschamps T, Temprado JJ (2008) Effects of force production and trial duration on bimanual performance and attentional demands in a rhythmic coordination task. Mot Control 12:21–37
Nassauer KW, Halperin JM (2003) Dissociation of perceptual and motor inhibition processes through the use of novel computerized conflict tasks. J Int Neuropsych Soc 9:25–30
Noël M, Bernard A, Luyat M (2011) The overestimation of performance: a specific bias of aging? Ger Psychol Neuropsychiatr Vieil 9:287–294. doi:101684/pnv20110290
Orzel-Gryglewska J (2010) Consequences of sleep deprivation. Int J Occup Med Environ 23:95–114. doi:102478/v10001-010-0004-9
Oztürk L, Bulut E, Vardar SA, Uzun C (2007) Effects of sleep deprivation on anaerobic exercise-induced changes in auditory brainstem evoked potentials. Clin Physiol Funct I 27:263–267. doi:101111/j1475-097X200700746x
Patel M, Gomez S, Berg S, Almbladh P, Lindblad J, Petersen H et al (2008) Effects of 24-h and 36-h sleep deprivation on human postural control and adaptation. Exp Brain Res 185:165–173. doi:101007/s00221-007-1143-5
Pijpers JRR, Oudejans RRD, Bakker FC, Beek PJ (2006) The role of anxiety in perceiving and realizing affordances. Ecol Psychol 18:131–161. doi:101207/s15326969eco1803_1
Pijpers JR, Oudejans R, Bakker FC (2007) Changes in the perception of action possibilities while climbing to fatigue on a climbing wall. J Sport Sci 25:97–110. doi:101080/02640410600630894
Poudel GR, Innes CRH, Jones RD (2013) Distinct neural correlates of time-on-task and transient errors during a visuomotor tracking task after sleep restriction. Neuroimage 77:105–113. doi:101016/jneuroimage201303054
Ramenzoni V, Riley MA, Davis T, Shockley K, Armstrong R (2008) Tuning into another person's action capabilities: perceiving maximal jumping-reach height from walking kinematics. J Exp Psychol Hum 34:919–928. doi:101037/0096-1523344919
Ratcliff R, Dongen HPA (2009) Sleep deprivation affects multiple distinct cognitive processes. Psychon Bull Rev 16:742–751. doi:103758/PBR164742
Redfern MS, Jennings JR, Mendelson D, Nebes RD (2009) Perceptual inhibition is associated with sensory integration in standing postural control among older adults. J Gerontol B Psychol 64:569–576. doi:101093/geronb/gbp060
Regia-Corte T, Wagman JB (2008) Perception of affordances for standing on an inclined surface depends on height of center of mass. Exp Brain Res 191:25–35. doi:101007/s00221-008-1492-8
Sakurai R, Fujiwara Y, Ishihara M, Higuchi T, Uchida H, Imanaka K (2013) Age-related self-overestimation of step-over ability in healthy older adults and its relationship to fall risk. BMC Geriatr 13–44:1011. doi:86/1471-2318-13-44
Scott JPR, McNaughton LR, Polman RCJ (2006) Effects of sleep deprivation and exercise on cognitive motor performance and mood. Physiol Behav 87:396–408. doi:101016/jphysbeh200511009
Skein M, Duffield R, Edge J, Short MJ, Mündel T (2011) Intermittent-sprint performance and muscle glycogen after 30 h of sleep deprivation. Med Sci Sport Exer 43:1301–1311. doi:101249/MSS0b013e31820abc5a
Smith JL, Jamadar S, Provost AL, Michie PT (2013) Motor and non-motor inhibition in the Go/NoGo task: an ERP and fMRI study. Int J Psychophysiol 87:244–253. doi:101016/jijpsycho201207185
Souissi N, Sesboüé B, Gauthier A, Larue J, Davenne D (2003) Effects of one night's sleep deprivation on anaerobic performance the following day. Eur J Appl Physiol 89:359–366. doi:101007/s00421-003-0793-7
Stoffregen TA, Gorday KM, Sheng YY (1999) Perceiving affordances for another person's actions. J Exp Psychol Hum 25:120–136. doi:101037/0096-1523251120
Thill S, Caligiore D, Borghi AM, Ziemke T, Baldassarre G (2013) Theories and computational models of affordance and mirror systems: an integrative review. Neurosci Biobehav R 37:491–521. doi:101016/jneubiorev201301012
Vardar SA, Öztürk L, Kurt C, Bulut E, Sut N, Vardar E (2007) Sleep deprivation induced anxiety and anaerobic performance. J Sport Sci Med 6:532–537
Vickers JN (2007) Perception cognition decision training: the quiet eye in action. Human Kinetics, Champaign, IL
Warren WH (1984) Perceiving affordances: visual guidance of stair climbing. J Exp Psychol Hum 10:683–703
Weast JA, Shockley K, Riley MA (2011) The influence of athletic experience and kinematic information on skill-relevant affordance perception. Q J Exp 64:689–706. doi:101080/174702182010523474
Witt JK, Proffitt DR, Epstein W (2004) Perceiving distance: a role of effort and intent. Perception 33:577–590. doi:101068/p5090
Witt JK, Linkenauger SA, Bakdash JZ, Augustyn JS, Cook A, Proffitt DR (2009) The long road of pain: chronic pain increases perceived distance. Exp Brain Res 192:145–148. doi:101007/s00221-008-1594-3
Yu Y, Bardy BG, Stoffregen TA (2011) Influences of head and torso movement before and during affordance perception. J Motor Behav 43:45–54. doi:101080/002228952010533213
Zhang N, Liu HT (2008) Effects of sleep deprivation on cognitive functions. Neurosci Bull 24:45–48. doi:101007/s12264-008-0910

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 3 (March), 2014: pp 271.e1-271.e7
Available online at www.jpain.org and www.sciencedirect.com

Online Exclusive

Influence of Experimental Pain on the Perception of Action Capabilities and Performance of a Maximal Single-Leg Hop

Thibault Deschamps,* François Hug,*,† Paul W. Hodges,† and Kylie Tucker†

**University of Nantes, Laboratory "Motricité, Interactions, Performance" (EA 4334), Nantes, France.*
†The University of Queensland, Centre for Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, St. Lucia, Queensland, Australia.

Abstract: Changes in an individual's state—for example, anxiety/chronic pain—can modify the perception of action capabilities and physical task requirements. In parallel, considerable literature supports altered motor performance during both acute and chronic pain. This study aimed to determine the effect of experimental pain on perception of action capabilities and performance of a dynamic motor task. Performance estimates and actual performance of maximal single-leg hops were recorded for both legs in 13 healthy participants before, during, and after an episode of acute pain induced by a single bolus injection of hypertonic saline into vastus lateralis of 1 leg, with the side counterbalanced among participants. Both estimation of performance and actual performance were smaller ($P < .01$) during pain than before and after pain. This decrease in estimation and performance during pain was apparent for hops using either leg, but it was greater ($P < .01$) for the painful leg (−10.8 ± 12.1 cm) than for the control leg (−5.5 ± 7.9 cm). Participants accurately estimated their performance in all conditions for both legs. The results provide evidence that healthy participants have the ability to update the action-scaled relationship between perception and ability during acute pain.

***Perspective:** This study demonstrates that the relationship between perceived physical ability and actual performance is effectively updated during acute muscle pain. This match between perceived ability and performance could be relevant during clinical pain assessment, with the potential to be a biomarker of transition from acute to chronic pain state.*

***Key words:** Performance, hypertonic saline, action capabilities, hop.*

The adaptation required to achieve a given behavior within constantly changing environmental constraints is an integral part of human daily life. The task-specific fit between the properties of the environment and the individual's action capabilities is known as an "affordance." Therefore, individuals perceive the properties of the world in terms of what they can do with them.[7] For instance, the affordance "stair-climbability" is related to both the characteristics of the stair (eg, riser height) and the physical capability of the individual.[38] Numerous studies demonstrate that healthy humans accurately perceive their physical capabilities for tasks such as reaching,[24] grasping,[25] jumping,[32] and walking through apertures.[10] However, the perception of action capabilities is compromised during periods of altered psychological state. For example, Graydon et al[10] reported that anxious participants underestimate their reaching, grasping, and passing ability compared to nonanxious participants, and argued that these behaviors reflect a protective mechanism. This suggests that individuals in the stressful conditions update their "safety margin" for a task, which would potentially expose them to less risk.

Considerable literature supports altered motor performance during acute experimental pain—for example,

Received July 16, 2013; Revised October 8, 2013; Accepted October 29, 2013.
The NHMRC provided research fellowships for P.H. (ID401599) and K.T. (ID1009410). This work was completed at Nantes University, France. Financial support for K.T. was also provided by a Queensland Government Research Travel Fellowship, 2012. Project support was provided by an NHMRC program grant (to P.H.: ID631717).
The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
The authors report no conflicts of interest.
Address reprint requests to Thibault Deschamps, PhD, University of Nantes, Laboratory "Motricité, Interactions, Performance" (EA 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. E-mail: thibault.deschamps@univ-nantes.fr
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.10.016

reduced force-generating capacity (in most[8,9,16,34] but not all studies[35]), and altered kinetics around the joint related to the painful muscle.[1,14-17,27] This alteration of performance is also observed in people with chronic musculoskeletal pain—for example, reduced force-generating capacity,[9,22,23] altered kinetics,[4] and reduced time to task failure during submaximal tasks.[28] Altered motor performance during pain may serve to reduce stress on painful tissue and/or avoid further pain.[24,37] It is unclear if the individual in pain accurately perceives this change in performance ability. If not, the individual with pain could overestimate his or her physical capabilities (ie, the function is reduced but perception in performance ability is not altered) and thus be more likely to overuse the painful part with potential for both short-term (acute injury) and long-term consequences. Alternatively, they may underestimate their physical abilities, or overestimate the physical cost of performing a movement task (eg, walking distance is overestimated in people with chronic pain[40]) and thus reduce movement/physical activity (as observed in older adults with chronic pain[11]), which may be harmful to general health in the long term.

This study used an acute pain model to investigate the effect of pain on the perception of action capabilities in healthy participants to provide a first and critical step toward understanding the unique potential for pain to modify the relationship between motor performance and perceived abilities. We hypothesized that consistent with other observations, maximal performance of the motor task would be reduced during acute pain, and that this reduction in maximal performance would be associated with reduction of the estimated ability to perform the task. Finally, as theories of the adaptation to acute pain predict changes in motor performance in and around the painful region, with little evidence (or consideration) of more generalized effects on motor performance including movement of body regions other than the painful part, we hypothesized that changes in motor performance, if present, would be confined to the painful leg. To test these hypotheses, we investigated the effect of acute experimental leg pain in healthy participants on both perception of action capabilities and performance of single-leg hops.

Method

Participants

Thirteen healthy males volunteered to participate in the study (age 28.7 ± 5.5 years; height 179.2 ± 5.3 cm; weight 73.5 ± 7.7 kg [mean ± standard deviation]). All participants indicated a preference to lead with the left leg when high-jumping. Exclusion criteria included visual or physical impairments, psychiatric or neurologic disorders, or any long-term medication use. Participants were informed of the experimental tasks before providing written consent. The experimental design of the study was approved by the Ethical Committee of Nantes Ouest IV (reference: no. CPP-MIP-002) and was conducted in accordance with the Declaration of Helsinki.

Materials and Apparatus

A rigid blue carpet (2 cm thick, 7 m long, 1 m wide) was laid on floor, with white masking tape placed across the width of the carpet to indicate the start position. A line of masking tape placed midline (perpendicular to the start line, in the middle of the carpet) extended 5 m from the start position. Participants were asked to focus on and aim for the midline when estimating their hop performance and when performing the single-leg hop task. No other visual marks were available.

To measure the participants' judgment of their perceived ability, they were asked to estimate the distance they predicted they would be able to hop by indicating "stop" as the experimenter (T.D.) moved a stick (placed transversely across the width of the carpet and with a 120-cm handle) gradually (~20 cm/sec) away from the starting line. At this point, the participants gave instructions ("farther" or "closer") to the experimenter to make minor adjustments to the stick's position in order to estimate the maximal distance they predicted they could achieve with a maximal single-leg hop, as accurately as possible. A wooden graduated ruler (3 m long, not visible to the participant) that lay on the edge of the carpet was used by a second investigator (K.T.) to measure the indicated distance.

For the single-leg hop performance, hop distance was determined using a digital camera (Casio Exilim EX-ZR100; Casio, Tokyo, Japan; sampling frequency of 120 Hz) that was aligned with the estimated hop performance but was not in the visual range of the participant. To overcome image parallax, a calibration of the camera image was performed before and after the experiment.

Procedure

Participants first performed 5 minutes of warm-up cycling on a cycle ergometer (power output = 100 W). The perception and performance tasks were then explained to the participants and they performed 3 practice hops on each leg.

A series of performance estimates and actual performance was recorded before pain, during pain (approximately 5 minutes after completion of the prepain trials, allowing time for the induction of experimental pain), and after pain had ceased (approximately 5 minutes after completion of the "pain" trial). Participants performed 6 performance estimates (3 per leg, in counterbalanced order between participants) of their own maximal single-leg hop performance during the prepain and postpain conditions, and 4 performance estimates (2 per leg) during pain. The reduced number during pain is based on time restrictions of this pain model. Maximal leg performance was defined as the maximal distance at which one could hop from 1 leg (without using the opposite leg for stability before the jump) and land on that same leg, without losing balance.[2,29,33] Participants were instructed to stand on the required leg, with the lead toe behind the starting line, and to make their judgment by considering their action capabilities at the present instant. To limit the potential for

memory or visual cues to influence estimation of performance (or actual task performance), participants closed their eyes and turned away from the carpet between each performance estimate, whereas the experimenter (T.D.) returned to the starting position. After providing the series of performance estimates for both legs, participants were instructed to perform a series of 6 single-leg hop tests (3 trials per leg, in counterbalanced order between participants) during the prepain and postpain conditions and 2 single-leg hop tests (1 per leg) during pain. Participants stood in the same starting position before each hop, and at least 40 seconds of recovery was provided between 2 consecutive trials of the same leg to minimize fatigue (typically, less than 30 seconds is sufficient[33]).

Experimental Pain

Acute experimental muscle pain was induced by a single bolus injection of hypertonic saline (1 mL, 5% NaCl, 25 mm × 25 gauge needle) into the distal portion of the vastus lateralis (of the dominant or nondominant leg, with pain side counterbalanced between participants). Pain level was reported on an 11-point numerical rating scale, where 0 = no pain and 10 = most extreme pain imaginable. Once pain level was reported as at least 2/10, participants were instructed to move to the "start line" for the performance estimates to begin. Pain level was reported immediately before and following each performance estimate and hop, during the pain condition. The average of these 2 pain estimates were used for analysis. After completion of the pain trial, participants drew the region of pain experienced on their own leg, and a photograph was taken (Fig 1).

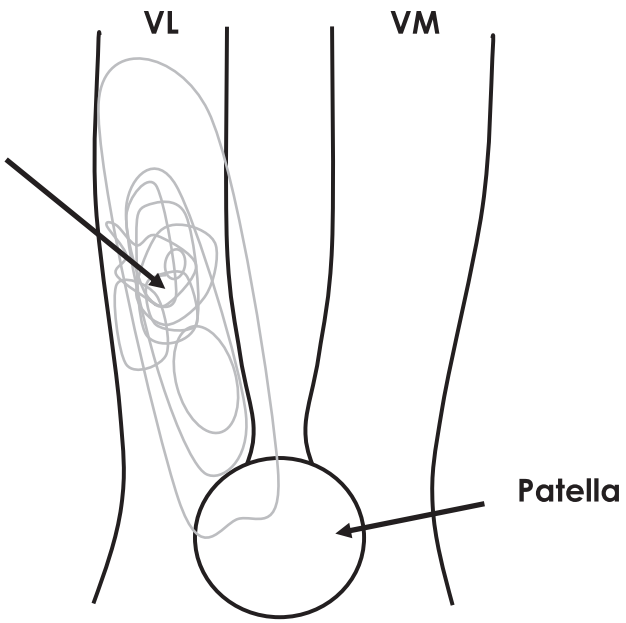

Figure 1. The location of painful injection (arrow) and area of pain (open gray circles) reported by participants on completion of pain trials are shown overlaid on a representative image of the distal thigh and knee cap (patella). VL, vastus lateralis; VM, vastus medialis.

Data Analysis

All data were normally distributed and thus values are reported as mean ± standard deviation. Statistical analyses were performed on the *average* and the *maximum* performance estimates and actual performance for each condition. The results were the same, irrespective of which measure we used, and therefore only maximum data (ie, 1 value per condition) are discussed.

Reported pain intensity was compared, using a 2-way analysis of variance with repeated measures, that is, 2 (Measure—estimates and performance) × 2 (Leg—control and painful leg). The effect of pain on both maximum estimate and actual performance was determined using a 3-way analysis of variance with repeated measures, that is, 3 (Condition—prepain, pain, and postpain) × 2 (Measure—estimates and performance) × 2 (Leg—control and painful leg). To provide additional insight into the effect of pain on the relationship between perception of action capabilities and actual performance, the ratio of perceptual estimation divided by the actual performance was calculated. A ratio of 1 indicates a perfect match, whereas a ratio greater or less than 1 indicates an over- or underestimation, respectively. These ratios were compared using a 2-way analysis of variance with repeated measures, that is, 3 (Condition—prepain, pain, and postpain) × 2 (Leg—control and painful leg).

Tukey honestly significant difference comparisons were used for post hoc tests following significant main effects. Significance was set at $P < .05$. Partial eta square ($_p\eta^2$) values are reported as measures of effect size, with moderate and large effects considered for $_p\eta^2 = .07$ and $_p\eta^2 \geq .14$, respectively.[5]

Results

Pain Intensity

The reported pain intensity during the performance estimates (5.3 ± .5/10) was slightly higher than that reported immediately following the actual hop performance (4.7 ± .4/10), main effect measure: $F(1, 12) = 8.34$, $P < .02$, $_p\eta^2 = .410$. However, there was no difference in the intensity of pain reported "between legs"—that is, reported pain intensity was similar when participants stood on their test (painful) or control (nonpainful) leg and estimated their maximal hop, and when they performed the hop on the painful and nonpainful leg, main effect of leg: $F(1, 12) = .187$, $P = .67$, $_p\eta^2 = .015$. Note that no significant measure × leg interaction was found: $F(1, 12) = .48$, $P = .50$, $_p\eta^2 = .038$.

Performance Estimates and Actual Performance

Before pain was induced, participants estimated that they could perform a single-leg hop of 194.1 ± 28.6 cm, and their maximum hop performance was 201.6 ± 24.2 cm. There was no significant main effect of measure; performance estimate vs actual performance: $F(1, 12) = .912$, $P = .36$, $_p\eta^2 = .071$, or significant interaction considering this factor (all Fs < 1.63, Ps > .22).

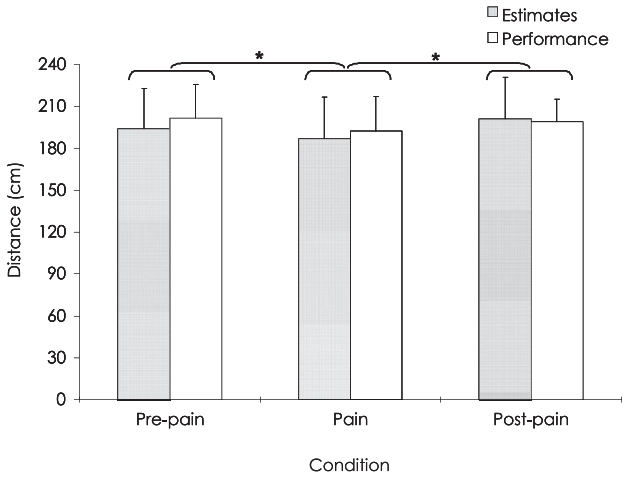

Figure 2. Both the estimation of performance ability and actual performance were reduced during acute pain compared to the prepain and postpain conditions. Error bars correspond to the standard deviation. Significant differences at $*P < .05$.

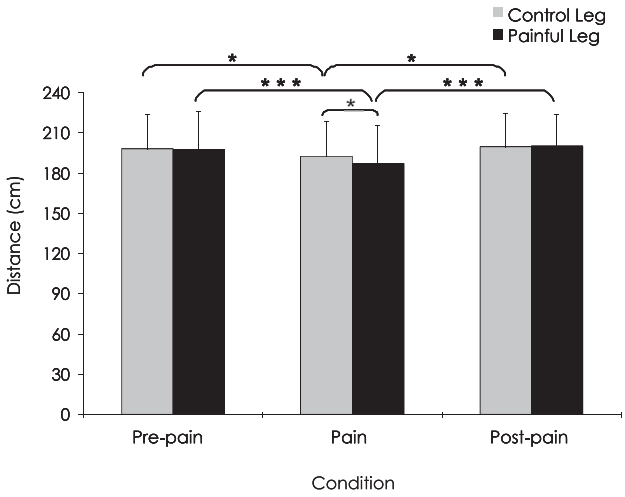

Figure 3. Performance estimates and actual performance were similar and are therefore averaged to demonstrate the reduction in these measures during the painful condition. This reduction was observed for both the legs but was greater in the painful (black) than the nonpainful (gray) leg. Error bars correspond to the standard deviation. Significant differences at $*P < .05$; $***P < .001$.

Both estimation of performance and actual performance were reduced during acute pain; main effect condition: $F(2, 24) = 8.61$, $P < .01$, ${}_p\eta^2 = .418$; post hoc pain versus prepain -8.1 ± 14.2 cm, that is, -4.1%, $P < .02$; pain versus postpain -10.2 ± 15.2 cm, that is, -5.1%, $P < .01$; prepain versus postpain, $P = .71$ (Fig 2). The decrease in both estimation and performance during pain was apparent for hops using either leg, but it was greater for the painful leg than for the control leg; -10.8 ± 12.1 cm vs -5.5 ± 7.9 cm for painful and control leg, interaction condition $\times$ leg: $F(2, 24) = 3.76$, $P < .01$, ${}_p\eta^2 = .239$; post hoc: $P < .01$ (Fig 3).

The ratio of perceptual estimation divided by the actual performance was $.96 \pm .11$, $.96 \pm .09$, and $1.00 \pm .12$, for prepain, pain, and postpain, respectively. The ratio was not affected by condition: $F(2, 24) = 1.365$, $P = .275$, ${}_p\eta^2 = .102$; or leg: $F(1, 12) = .475$, $P = .504$, ${}_p\eta^2 = .083$. In addition, no significant interaction condition $\times$ leg: $F(1, 12) = .715$, $P = .478$, ${}_p\eta^2 = .056$, was observed.

Discussion

The aim of the present study was to determine if acute pain alters the relationship between perceived ability and actual performance in healthy participants. In support of our first hypothesis, the performance of the single-leg hop was reduced during acute pain. In support of our second hypothesis, there was no change in the relationship between perceived ability and actual performance such that participants' perception of their ability to hop was adjusted in a manner that was concordant with their change in performance. As both the actual performance and estimation of performance were reduced in a similar manner, this indicates that the task-specific perception of action capabilities was unchanged during acute pain. This means either that the healthy individuals accurately estimated the reduction in their ability to perform the task during acute pain or that they adjusted their actual performance on the basis of an estimated/expected reduction in ability. This study cannot distinguish which of these alternatives explains the results. In contrast to our third hypothesis, there was also a reduction in both the task performance and estimation of performance when the task was performed with the nonpainful leg. However, this reduction was smaller than that observed for the painful side. This provides evidence of a more subtle generalized change in motor performance and perception of motor performance that does not necessarily relate to the immediate location of pain, but with lesser magnitude.

Various studies have shown that task performance is altered during experimental pain (eg, reduced torque during maximal voluntary contractions[8,9,16,35] and altered kinetics during movement tasks[1,13-15,17,27]). This reduction in maximal performance is thought to relate to either a reduction in total motor drive (eg, generalized inhibition of the muscles in or near the painful site; see review[26]), which is not supported by all studies,[22] or a change in the manner in which the force is generated. With respect to the latter, reorganization of the control of movement such as a redistribution of muscle activity within and between the muscles used to perform the task has been hypothesized (see review[18]). This is the first study to test and demonstrate reduced maximal performance in a dynamic, multijoint task (ie, distance of a single-leg hop) during acute pain.

Although the reduction in performance might be explained by an actual reduction in maximal ability to perform the task (eg, inability to exert maximal effort), the maximal performance might also be reduced as a protective mechanism, whereby individuals in pain moderate their performance (and estimation of performance ability) to increase the "safety margin" for the task to expose their system to less risk. This is supported in part

by the smaller, but significant, reduction in performance and performance estimation in the nonpainful leg. In that case, the individual may still reduce the maximal performance to increase the safety margin, as a contribution from the painful leg is required to stabilize the individual if he or she were to lose balance with hopping. Reduction of the actual performance (use of a more conservative strategy that is less than the true maximum potential) would lessen the chance of loss of balance, and thus reduce the possibility to need to use the painful region (for balance).

The second key finding is that participants accurately predicted their decrease in performance ability during acute pain (or they performed in a way that they had predicted). This provides evidence that the presence of experimental pain did not alter the critical cognitive updating process, and that an adequate protective mechanism was maintained to meet the painful context. This is in line with our understanding that the (re)calibration of perceived action capabilities is dynamic and can evolve both rapidly (reviewed in[6]) and over longer time scales—for example, in people with chronic pain[40] and in older adults.[12,30] For instance, people with chronic low back pain estimated a larger distance to walk to a target than pain-free controls,[40] which is argued to be associated with the perception of greater effort required to achieve this distance. This supports the idea that individuals perceive the environment in terms of the costs of acting within it. Overall, these results highlight a (re)calibration of action capabilities during painful episodes.[20] This process may be interpreted as a change in pain function that relates performance estimation to the requirements that the environment imposes on the patients who are living with chronic pain. Further work is necessary to determine the effectiveness of this process in different clinical populations.

Finally, contrary to our expectations, the present study results highlight an influence of pain on both perceived action capabilities and performance that is not specific to the action being performed local to the site of pain. We observed a decrease in estimation and performance of the maximal hop, for both the painful and the nonpainful leg (albeit greater reductions on the painful side), during pain (Fig 2). It is possible that the presence of pain in an unrelated region diverts attention from the experimental task, and that this reduction in attention to the task may compromise performance.[19] This has been shown for other distractors, not related to pain. For example, distraction by points of light while climbing on a high traverse reduces both perceived and actual performance.[31] It is also possible that the reduced performance in the nonpainful leg is related to a protective mechanism (as discussed above). Finally, consistent with the muscle-based perception and the tensegrity hypothesis,[3] generalized effects of altered motor ability in one region may affect performance ability in an unrelated muscle. For example, a handgrip fatiguing task has been shown to alter the maximal force-generating capacity of plantar flexor muscles.[21] Again, we can argue from these unexpected findings that an acute muscle pain (induced in healthy young participants) does not alter the necessary updating process of their motor capabilities, as both performance ability and perceived ability changed in parallel. Further research is required to test this assumption of shared processes for top-down control of (selecting and recalibrating) the perception of performance ability and motor adaptation to pain.[36]

The within-subject study design allowed us to explore the potential for acute experimental pain to alter maximal performance ability, perception of maximal performance ability, and the relationship between these measures with a modest (n = 13) sample size. Effect sizes were moderate to large for the primary outcome measures used in this study, which is likely to be enhanced by the homogeneity (young, fit males) of the participants. Larger sample size may be required in future studies if a more heterogeneous participant group is included (ie, in relation to pain beliefs, duration, and effect of clinical pain conditions).

Conclusion

This experiment was conducted to determine whether acute muscle pain influences the relationship between perceived ability and actual performance in healthy participants. We provide evidence that healthy individuals effectively update the perception of their action capabilities during acute pain; that is, the short-term reduction in motor performance during acute experimental pain is associated with a recalibration of perception of movement capabilities. Evidence that the reduced performance (and perception of performance ability) occurs both local and contralateral to the painful site provides some evidence that the reduction in performance is not necessarily related to reduced motor potential, but rather increasing the "safety margin" of the task. The potential for an individual in pain to modify his or her performance ability to increase a "safety margin" is particularly relevant when measures such as the single-leg hop test are used in clinical pain studies to determine progression and/or recovery from lower limb pain conditions.[39] This is because, independent of any functional alteration present in clinical populations, the acute nociceptive stimulation (in combination with the individuals' cognitive processes associated with this experience) is sufficient to induce a reduction in task performance; that is, reduced single-leg hop may be associated with current pain (and potentially pain-related cognitions) rather than actual functional capability.

This study provides a first step toward understanding the potential for pain to modify the relationship between motor performance and perceived abilities. It is now critical to determine if the perception process of action capabilities is updated in a similar way in more diverse samples of people with differing pain cognitions, and in people living with clinical pain. We argue that it is possible that an alteration in perception of action capabilities could be relevant during clinical pain assessment,

with the potential for this measure to be an early biomarker of the transition from an acute to chronic pain state.

References

1. Bonifazi M, Ciccarone G, Della Volpe R, Spidalieri R, Rossi A: Influences of chemically-induced muscle pain on power output of ballistic upper limb movements. Clin Neurophysiol 115:1779-1785, 2004

2. Booher LD, Hench KM, Worrell TW, Stikeleather J: Reliability of three single-leg hop tests. J Sports Rehabil 2: 165-170, 1993

3. Carello C, Silva PL, Kinsella-Shaw JM, Turvey MT: Muscle based perception: Theory, research and implications for rehabilitation. Rev Bras Fisioter 12:339-350, 2008

4. Claudon B, Poussel M, Billon-Grumillier C, Beyaert C, Paysant J: Knee kinetic pattern during gait and anterior knee pain before and after rehabilitation in patients with patellofemoral pain syndrome. Gait Posture 36:139-143, 2012

5. Cohen J: Statistical Power Analysis for the Behavioural Sciences. New York, Academic Press, 1988

6. Fajen BR, Riley MA, Turvey MT: Information, affordances, and the control of action in sport. Int J Sport Psychol 40: 79-107, 2008

7. Gibson JJ: The Ecological Approach to Visual Perception. Boston, Houghton Mifflin, 1979

8. Graven-Nielsen T, Lund H, Arendt-Nielsen L, Danneskiold-Samsøe B, Bliddal H: Inhibition of maximal voluntary contraction force by experimental muscle pain: A centrally mediated mechanism. Muscle Nerve 26:708-712, 2002

9. Graven-Nielsen T, Svensson P, Arendt-Nielsen L: Effects of experimental muscle pain on muscle activity and coordination during static and dynamic motor function. Electroencephalogr Clin Neurophysiol 105:156-164, 1997

10. Graydon MM, Linkenauger SA, Teachman BA, Proffitt DR: The influence of anxiety on the perception of action capabilities. Cogn Emot 26:1301-1315, 2012

11. Griffin DW, Harmon DC, Kennedy NM: Do patients with chronic low back pain have an altered level and/or pattern of physical activity compared to healthy individuals? A systematic review of the literature. Physiotherapy 98:13-23, 2012

12. Hackney AL, Cinelli ME: Older adults are guided by their dynamic perceptions during aperture crossing. Gait Posture 37:93-97, 2013

13. Henriksen M, Aaboe J, Simonsen EB, Alkjaer T, Bliddal H: Experimentally reduced hip abductor function during walking: Implications for knee joint loads. J Biomech 42: 1236-1240, 2009

14. Henriksen M, Alkjaer T, Lund H, Simonsen EB, Graven-Nielsen T, Danneskiold-Samsøe B, Bliddal H: Experimental quadriceps muscle pain impairs knee joint control during walking. J Appl Physiol 103:132-139, 2007

15. Henriksen M, Alkjaer T, Simonsen EB, Bliddal H: Experimental muscle pain during a forward lunge—the effects on knee joint dynamics and electromyographic activity. Br J Sports Med 43:503-507, 2009

Acknowledgments

The authors thank Dr Raphaël Gross for performing the medical examination.

16. Henriksen M, Graven-Nielsen T, Aaboe J, Andriacchi TP, Bliddal H: Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. Arthritis Care Res 62:501-509, 2010

17. Henriksen M, Rosager S, Aaboe J, Graven-Nielsen T, Bliddal H: Experimental knee pain reduces muscle strength. J Pain 12:460-467, 2011

18. Hodges PW, Tucker K: Moving differently in pain: A new theory to explain the adaptation to pain. Pain 152:S90-S98, 2011

19. Ingham D, Tucker KJ, Tsao H, Hodges PW: The effect of pain on training-induced plasticity of the corticomotor system. Eur J Pain 10:1028-1034, 2011

20. Jacobs DM, Michaels CF: Lateral interception I: Operative optical variables, attunement, and calibration. J Exp Psychol Hum Percept Perform 32:443-458, 2006

21. Kennedy A, Hug F, Sveistrup H, Guével A: Fatiguing handgrip exercise alters maximal force-generating capacity of plantar-flexors. Eur J Appl Physiol 113:559-566, 2013

22. Khan SI, McNeil CJ, Gandevia SC, Taylor JL: Effect of experimental muscle pain on maximal voluntary activation of human biceps brachii muscle. J Appl Physiol 111: 743-750, 2011

23. Lindstroem R, Graven-Nielsen T, Falla D: Current pain and fear of pain contribute to reduced maximum voluntary contraction of neck muscles in patients with chronic neck pain. Arch Phys Med Rehabil 93: 2042-2048, 2012

24. Linkenauger SA, Witt JK, Proffitt DR: Taking a hands-on approach: Apparent grasping ability scales the perception of perceived object size. J Exp Psychol Hum Percept Perform 37:1432-1441, 2011

25. Linkenauger SA, Witt JK, Stefanucci JK, Bakdash JZ, Proffitt DR: The effects of handedness and reachability on perceived distance. J Exp Psychol Hum Percept Perform 35: 1649-1660, 2009

26. Lund JP, Donga R, Widmer CG, Stohler CS: The pain-adaptation model: A discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol 69:683-694, 1991

27. Madeleine P, Voigt M, Arendt-Nielsen L: Reorganisation of human step initiation during acute experimental muscle pain. Gait Posture 10:240-247, 1999

28. Mannion AF, O'Riordan D, Dvorak J, Masharawi Y: The relationship between psychological factors and performance on the Biering-Sørensen back muscle endurance test. Spine J 11:849-857, 2011

29. Munro AG, Herrington LC: Between-session reliability of four hop tests and the agility t-test. J Strength Cond Res 25: 1470-1477, 2011

30. Noel M, Bernard A, Luyat M: The overestimation of performance: A specific bias of aging? Geriatr Psychol Neuropsychiatr Vieil 9:287-294, 2011

31. Pijpers J, Oudejans RRD, Bakker FC, Beek PJ: The role of anxiety in perceiving and realizing affordances. Ecol Psychol 18:131-161, 2006

32. Ramenzoni VC, Riley MA, Davis T, Shockley K, Armstrong R: Tuning in to another person's action capabilities: Perceiving maximal jumping-reach height from walking kinematics. J Exp Psychol Hum Percept Perform 34: 919-928, 2008

33. Reid A, Birmingham TB, Stratford PW, Alcock G, Giffin JR: Hop testing provides a reliable and valid outcome measure during rehabilitation after anterior cruciate ligament reconstruction. Phys Ther 87:337-349, 2007

34. Slater H, Arendt-Nielsen L, Wright A, Graven-Nielsen T: Experimental deep tissue: Pain in wrist extensors: A model of lateral epicondylalgia. Eur J Pain 7:277-288, 2003

35. Slater H, Arendt-Nielsen L, Wright A, Graven-Nielsen T: Sensory and motor effects of experimental muscle pain in patients with lateral epicondylalgia and controls with delayed onset muscle soreness. Pain 114:118-130, 2005

36. Thill S, Caligiore D, Borghi AM, Ziemke T, Baldassarre G: Theories and computational models of affordance and mirror systems: An integrative review. Neurosci Biobehav Rev 37:491-521, 2013

37. Tucker K, Larsson A-K, Oknelid S, Hodges PW: Similar alteration of motor unit recruitment strategies during the anticipation and experience of pain. Pain 153:636-643, 2012

38. Warren WH: Perceiving affordances: Visual guidance of stair climbing. J Exp Psychol Hum Percept Perform 10: 683-703, 1984

39. Wipfler B, Donner S, Zechmann CM, Springer J, Siebold R, Paessler HH: Anterior cruciate ligament reconstruction using patellar tendon versus hamstring tendon: A prospective comparative study with 9-year follow-up. Arthroscopy 27:653-665, 2011

40. Witt JK, Linkenauger SA, Bakdash JZ, Augustyn JS, Cook A, Proffitt DR: The long road of pain: Chronic pain increases perceived distance. Exp Brain Res 192:145-148, 2009

Gait & Posture 39 (2014) 628–630

Contents lists available at SciVerse ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Short communication

Postural control and cognitive decline in older adults: Position versus velocity implicit motor strategy

Thibault Deschamps [a,*], Olivier Beauchet [b], Cédric Annweiler [b], Christophe Cornu [a], Jean-Baptiste Mignardot [a]

[a] University of Nantes, Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), F-44000 Nantes, France
[b] Department of Neuroscience, Division of Geriatric Medicine, UPRES EA 4638, UNAM, Angers University Hospital, Angers, France

ARTICLE INFO

Article history:
Received 9 March 2013
Received in revised form 2 May 2013
Accepted 1 July 2013

Keywords:
Posture
Cognitive decline
Velocity control hypothesis

ABSTRACT

The present study explored the impact of cognitive decline on postural control strategies in older adults with and without cognitive decline from mild cognitive impairment (MCI) to mild-to-moderate Alzheimer disease (MMAD). We hypothesized that the cognitive decline affected the postural control leading to higher bounding limits of COP velocity dynamics. Based on a cross-sectional design, 175 *non-faller* older adults were recruited in Angers University Hospital, France, including 50 cognitively healthy individuals [CHI] (mean age 76.42 ± 4.84 years; 30% women), 64 age- and body mass index-matched participants with MCI (mean age 77.51 ± 6.32 years; 39% women), and 61 age- and body mass index-matched participants with MMAD (mean age 78.44 ± 3.97 years; 62% women). For all data collection of postural sway, the participants were asked to maintain quiet stance on force platform. The postural test consisted of two trials of quiet stance, with eyes open and with eyes closed. The COP parameters were mean and standard deviation (SD) of position, velocity and average absolute maximal velocity (AAMV) in antero-posterior and medio-lateral directions. Overall, the analysis concerning all COP parameters revealed a significant main effect of cognitive status on velocity-based variables, with post hoc comparisons evidencing that SD velocity and AAMV increased with cognitive impairment. The current findings suggest an active control (or corrective process) of COP velocity dynamics for CHI, whereas MCI and MMAD are affected by COP movements.

1. Introduction

Based on Collins and De Luca's assumption [1] supporting the idea of a position-based control of posture, Delignières et al. [2] have recently shown the key role of center-of-pressure (COP) velocity-based variables for quiet standing stability in young and older cognitively healthy individuals [CHI]. Precisely, they have found that postural sway is not fixed until a threshold in velocity is reached. Velocity series appear bounded between an upper and a lower limits, underlining the possibility of an implicit motor strategy supported by velocity-based control instead of a position-based control of posture. These findings highlighted new variables of interest, in particular those that bound the dynamics of velocity in COP time series such as the average absolute maximal velocity (AAMV) when assessing postural balance in CHI. It has been previously reported difference in implicit motor strategy of balance control between CHI and those with cognitive decline [3]. Few studies have directly investigated the cognitive status' impact on postural control in older people compared to age-related effect [3–11]. Moreover, balance was usually assessed with parametric measurements such as single leg stance or tandem walking [3,5,7–9], which prevents inferring conclusions on the implicit motor strategy of balance control. Recently, Suttanon et al. [9] showed that static balance assessed by the sway velocity was more altered with higher limits of velocity range in mild-to-moderate Alzheimer disease (MMAD) compared to cognitively healthy controls [9]. The present analysis explored the impact of cognitive decline on postural control strategies in older adults with and without cognitive decline from mild cognitive impairment (MCI) to MMAD. To our knowledge, no study has yet investigated the assumption of a velocity-based processs. Our hypothesis was that the cognitive decline affected the postural control leading to higher bounding limits of COP velocity dynamics.

2. Methods

2.1. Participants

A total of 175 *non-faller* older adults were recruited in Angers University Hospital, France, including 50 CHI (mean age

* Corresponding author at: University of Nantes, Laboratory «Motricité, Interactions, Performance» (EA 4334), 25 bis boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France. Tel.: +33 02 51 83 72 14; fax: +33 02 51 83 72 10.
E-mail address: thibault.deschamps@univ-nantes.fr (T. Deschamps).

0966-6362/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gaitpost.2013.07.001

76.42 ± 4.84 years; 30% women), who were compared with 64 age- and BMI-matched participants with MCI (mean age 77.51 ± 6.32 years; 39% women), and 61 age- and BMI-matched participants with MMAD (mean age 78.44 ± 3.97 years; 62% women). All participants were recruited from the Gait and Alzheimer Interactions Tracking (GAIT) cohort, which is an observational cross-sectional study designed to examine gait and balance in older community-dwellers reporting subjective memory complaint. The sampling and data collection procedures have been described elsewhere in detail [4]. For the present analysis, exclusion criteria were severe Alzheimer's disease (i.e., Mini-Mental State Examination score (MMSE) ≤ 10), acute medical illness in the three past months, neurological and psychiatric diseases with the exception of cognitive impairment, and inability to stand on one leg for at least five seconds. The experimental design of the study was approved by the Local Ethical Committee of Angers (Reference No. 2009-A00533-54).

2.2. Neuropsychological assessment

Neuropsychological assessment was performed during a face-to-face examination carried out by a neuropsychologist. The following standardized tests were used to probe several aspects of cognitive function: MMSE, Frontal Assessment Battery (FAB), ADAS-cog, TMT parts A and B, French version of the Free and Cued Selective Reminding Test and Instrumental Activities of Daily Living scale (IADL). The diagnoses of MCI and MMAD were based on the above-mentioned neuropsychological tests, physical examination findings, blood tests and Magnetic Resonance Imaging (MRI) of the brain. Participants with all categories of MCI were included in this study. The diagnosis of MMAD followed the DSM-IV and NINCDS/ADRDA criteria. Mild stage of MMAD was defined for a MMSE score ≥ 20, and moderate stage for a MMSE score between 10 and 19. Participants who were neither MCI nor MMAD and who had normal neuropsychological and functional performance were considered as CHI ([4] for details).

2.3. Postural assessment

The standing postural sway was measured using a force platform (101 cm × 101 cm; BioRescue, Dune®, France). The participant was instructed to maintain barefoot standing position, and to look straight ahead, with arms kept by the side of the body, and focused on a visual reference mark placed in front of them at a 100 cm distance. The postural test consisted of two trials of quiet stance: stance with eyes open (EO) and with eyes closed (EC). For a trial of 51.2 s duration (sampling frequency of 5 Hz), the system was linked to PosturalRescue® 2.0 software, providing COP series on the antero-posterior (AP) and medio-lateral (ML) axes.

2.4. Statistics

For the baseline characteristics (age and BMI), a one-way analysis of variance (ANOVA) with 3 (Group) between-subjects factor was performed. Similar to [10], the COP parameters were mean and standard deviation (SD) of position and velocity in AP and ML directions. We also computed the AAMV [2]. For testing the effects of cognitive status on the postural control, a one-way ANOVA was carried out for each aforesaid dependent variable.

Table 1
Comparisons between MCI, MMAD and age- and BMI-matched CHI group (one-way analysis of variance results). Statistically significant results ($p < 0.05$) are indicated in bold.

Outcomes (significant values)	CHI, mean [95% CI]	MCI group, mean [95% CI]	MMAD group, mean [95% CI]	*F*	*p*
Baseline characteristics					
Age (years)	76.42 [75.04–77.79]	77.51 [75.93–79.09]	78.4 [77.39–79.42]	2.031	0.134
Body mass index (kg/m^2)	26.05 [25.18–26.91]	26.28 [25.43–27.13]	26.62 [25.39–27.85]	0.311	0.733
COP position-based variables					
Eyes open					
Mean position_AP (mm)	−18.15 [−23.43; −12.86]	−15.68 [−20.46; −10.91]	−18.86 [−24.18; −13.55]	0.451	0.637
SD position_AP (mm)	5.23 [4.8; 5.66]	5.62 [5.22; 6.02]	6.06 [5.36; 6.76]	2.286	0.105
Mean position_ML (mm)	−0.006 [−3.46; 3.47]	−1.24 [−3.7; 1.21]	−0.07 [−3.12; 3.27]	0.254	0.776
SD position_ML (mm)	3.3 [2.9; 3.69]	3.19 [2.85; 3.53]	3.76 [3.34; 4.19]	2.553	0.081
Eyes closed					
Mean position_AP (mm)	−12.36 [−17.67; −7.05]	−12.15 [−16.99; −7.3]	−15.19 [−20.65; −9.73]	0.438	0.646
SD position_AP (mm)	5.53 [4.94; 6.11]	5.5 [5.04; 5.96]	6.42 [5.76; 7.08]	**3.431**	**0.035**[b]
Mean position_ML (mm)	−0.406 [−4.28; 3.46]	−1.64 [−4.79; 1.49]	0.78 [−2.9; 4.46]	0.503	0.605
SD position_ML (mm)	3.04 [2.69; 3.38]	3.02 [2.62; 3.43]	3.93 [3.4; 4.46]	**5.576**	**0.005**[b,c]
COP velocity-based variables					
Eyes open					
Mean velocity (mm/s)	10.33 [9.21; 11.46]	12.34 [11; 13.68]	14.64 [12.97; 16.31]	**8.576**	**0.000**[a,b,c]
SD velocity (mm/s)	6.8 [6.04; 7.57]	8.06 [7.14; 8.99]	6.8 [8.5; 8.99]	**8.025**	**0.000**[a,b,c]
Mean velocity_AP (mm/s)	8.11 [7.22; 9.01]	9.63 [8.57; 10.69]	11.52 [10.22; 12.82]	**8.782**	**0.000**[b,c]
Mean velocity_ML (mm/s)	4.8 [4.19; 5.41]	5.81 [5.1; 6.52]	6.75 [5.89; 7.61]	**6.376**	**0.002**[a,b]
AAMV_AP (mm/s)	15.65 [13.62–17.68]	19.29 [16.49–22.09]	23.07 [20.47–25.67]	**7.861**	**0.001**[a,b,c]
AAMV_ML (mm/s)	9.64 [8.1–11.19]	11.58 [9.94–13.22]	12.86 [11.38–14.34]	**3.966**	**0.021**[b]
Eyes closed					
Mean velocity (mm/s)	12.34 [10.8; 13.87]	14.78 [12.69; 16.87]	18.05 [15.69; 20.41]	**7.217**	**0.001**[a,b,c]
SD velocity (mm/s)	8.52 [7.42; 9.62]	9.89 [8.38; 11.4]	11.88 [10.26; 13.51]	**5.05**	**0.007**[b,c]
Mean velocity_AP (mm/s)	10.08 [8.77; 11.39]	11.85 [10.21; 13.5]	14.66 [12.79; 16.52]	**7.392**	**0.001**[b,c]
Mean velocity_ML (mm/s)	5.23 [4.58; 5.89]	6.53 [5.42; 7.64]	7.81 [6.61; 9.02]	**5.555**	**0.005**[b]
AAMV_AP (mm/s)	19.83 [17.05–22.62]	24.62 [20.42–28.81]	29.44 [25.71–33.17]	**6.223**	**0.002**[a,b,c]
AAMV_ML (mm/s)	10.96 [9.17–12.76]	13.13 [10.68–15.57]	15.13 [13–17.25]	**3.382**	**0.036**[b]

COP: center of pressure; AP: anteroposterior; ML: mediolateral; SD: standard deviation; AAMV: average absolute maximal velocity; CHI: cognitive healthy individual; MCI: mild cognitive decline; MMAD: mild and moderate dementia.
[a] Significant difference between CHI and MCI groups.
[b] Significant difference between CHI and MMAD groups.
[c] Significant difference between MCI and MMAD groups.

3. Results

All statistical results are summarized in Table 1. Firstly, there were no significant differences between the groups for age and BMI. Secondly, the analysis concerning all COP parameters revealed a main effect of the cognitive status on velocity-based variables, with post hoc comparisons evidencing that SD velocity and AAMV increased with cognitive impairment. Besides the analyses for many COP position variables showed that postural sway is not significantly different according to cognitive decline.

4. Discussion

The present study confirms new velocity-based variables of interest when assessing postural balance, for both fundamental and clinical purposes [2]. In support of our hypothesis, the thresholds' values that bound the dynamics of COP movement speed (as estimated by computing the AAMV) significantly depend on the progression of cognitive impairment. Contrary to position variables, SD velocity and AAMV are actually higher for MCI and MMAD, as compared to CHI, especially in the AP direction (Table 1).

Even if these results corroborate changes in poor postural stability in patients with MCI or MMAD [9,11], it is the first time to the best of our knowledge that different postural control strategies are clearly demonstrated in CHI and in age-matched MCI–MMAD participants. Precisely, we suggest an active control (or corrective process) of COP velocity dynamics for CHI [2], whereas MCI and MMAD are affected by COP movements, especially in anteroposterior direction. Actually, our current support is in line with the aging effects and declines in executive function in standing postural control or in physical performance [12]. For example, recent studies showed that changes in usual walking speed were associated with alterations of execution functions (such as information updating and monitoring) [13], specifically in older adults with MCI [14]. This hypothesis of a possible velocity-based process degradation as a function of cognitive impairment is supported by recent studies investigating how balance control evolves when confronted with specific dual-task training strategies in elderly individuals with balance impairment [15]. Moreover, age-related neural changes experienced by individuals with MCI or MMAD in specific inhibitory function may result in alterations in the sensory integration process – essential for maintaining balance in older adults [12] – because of the degradation of velocity information. The assumption of a velocity-based process for postural control may be a key to identify a new interesting biomarker of early cognitive dysfunction [4], especially to potentially diagnose individuals with increased fall risk.

Author contributions

Deschamps has full access to all of the data in the study, takes responsibility for the data, the analyses and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsor.

All authors meet all of the following criteria: (1) contributing to the conception and design, or analyzing and interpreting data; (2) drafting the article or revising it critically for important intellectual content; and (3) approving the final version to be published.

Acknowledgements

The research was supported by grants from the Region of Pays de la Loire, France, for the project "RP3AP" and by the French Ministry of Health (Projet Hospitalier de Recherche Clinique National No. 2009-A00533-54). The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

References

[1] Collins JJ, De Luca CJ. Open-loop and closed-loop control of posture: a random-walk analysis of center-of-pressure trajectories. Exp Brain Res 1993;95:308–18.
[2] Delignières D, Torre K, Bernard P-L. Transition from persistent to anti-persistent correlations in postural sway indicates velocity-based control. PLoS Comput Biol 2011;7(2).
[3] Franssen EH, Souren LE, Torossian CL, Reisberg B. Equilibrium and limb coordination in mild impairment and mild Alzheimer's disease. J Am Geriatr Soc 1999;47(4):463–9.
[4] Beauchet O, Allali G, Launay C, Herrmann FR, Annweiler C. Gait variability at fast-pace walking speed: a biomarker of mild cognitive impairment? J Nutr Health Aging 2012.
[5] Eggermont LH, Gavett BE, Volkers KM, Blankevoort CG, Scherder EJ, Jefferson AL, et al. Lower-extremity function in cognitively healthy aging, mild cognitive impairment, and Alzheimer's disease. Arch Phys Med Rehabil 2010;91(4):584–8.
[6] Maquet D, Lekeu F, Warzee E, Gillain S, Wojtasik V, Salmon E, et al. Gait analysis in elderly adult patients with mild cognitive impairment and patients with mild Alzheimer's disease: simple versus dual task: a preliminary report. Clin Physiol Funct Imaging 2010;30:51–6.
[7] Kato-Narita EM, Nitrini R, Radanovic M. Assessment of balance in mild and moderate stages of Alzheimer's disease: implications on falls and functional capacity. Arq Neuropsiquiatr 2011;69(2A):202–7.
[8] Bramell-Risberg E, Jarnlo G-B, Elmstahl S. Separate physical tests of lower extremities and postural control are associated with cognitive impairment. Results from the general population study Good Aging in Skåne (GÅS-SNAC). Clin Interv Aging 2012;7:195–205.
[9] Suttanon P, Hill KD, Said CM, Logiudice D, Lautenschlager NT, Dodd KJ. Balance and mobility dysfunction and falls risk in older people with mild to moderate Alzheimer disease. Am J Phys Med Rehabil 2012;91:12–23.
[10] Deschamps T, Magnard J, Cornu C. Postural control as a function of time-of-day: influence of a prior strenuous running exercise or demanding sustained-attention task. J NeuroEng Rehabil 2013;10:26.
[11] Rapp MA, Krampe RT, Baltes PB. Adaptive task prioritization in aging: selective resource allocation to postural control is preserved in Alzheimer disease. Am J Geriatr Psychiatry 2006;14(1):52–61.
[12] Redfern MS, Jennings JR, Mendelson D, Nebes RD. Perceptual inhibition is associated with sensory integration in standing postural control among older adults. J Gerontol Psychol Sci 2009;64B(5):569–76.
[13] Beauchet O, Annweiler C, Montero-Odasso M, Fantino B, Herrmann FR, Allali G. Gait control: a specific subdomain of executive function? J NeuroEng Rehabil 2012;9:12.
[14] McGough EL, Kelly VE, Logsdon RG, McCurry SM, Cochrane BB, Engel JM, et al. Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "Up & Go" test. Phys Ther 2011;91:1198–207.
[15] Silsupadol P, Lugade V, Shumway-Cook A, van Donkelaar P, Chou L-S, Mayr U, et al. Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. Gait Posture 2009;29:634–9.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 25 February 2014
doi: 10.3389/fnagi.2014.00022

Gait disturbances as specific predictive markers of the first fall onset in elderly people: a two-year prospective observational study

Jean-Baptiste Mignardot[1,2], Thibault Deschamps[1]*, Eric Barrey[3,4], Bernard Auvinet[5], Gilles Berrut[1,6], Christophe Cornu[1], Thierry Constans[7] and Laure de Decker[6]

[1] *Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), University of Nantes, Nantes, France*
[2] *Up-COURTINE Lab, Centre for Neuroprosthetics and Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland*
[3] *Unité de Biologie Intégrative des Adaptations à l'Exercice (Inserm U902) Genople, Université d'Evry Val d'Essonne, Évry, France*
[4] *GABI, UMR-1313, INRA, Jouy-en-Josas, France*
[5] *Service de Rhumatologie, Centre Hospitalier de Laval, Laval, France*
[6] *Gérontopôle des Pays de la Loire, CHU de Nantes, Nantes, France*
[7] *Geriatrics Department, Centre Hospitalier Universitaire de Tours, Tours, France*

Edited by:
Hari S. Sharma, Uppsala University, Sweden

Reviewed by:
Marcia Chaves, Federal University of Rio Grande do Sul, Brazil
Shin Murakami, Touro University-California, USA

****Correspondence:***
Thibault Deschamps, Laboratory "Motricité, Interactions, Performance" (E.A. 4334), University of Nantes, 25 Bis Boulevard Guy Mollet, BP 72206, 44322 Nantes Cedex 3, France
e-mail: thibault.deschamps@univ-nantes.fr

Falls are common in the elderly, and potentially result in injury and disability. Thus, preventing falls as soon as possible in older adults is a public health priority, yet there is no specific marker that is predictive of the *first* fall onset. We hypothesized that gait features should be the most relevant variables for predicting the first fall. Clinical baseline characteristics (e.g., gender, cognitive function) were assessed in 259 home-dwelling people aged 66 to 75 that had never fallen. Likewise, global kinetic behavior of gait was recorded from 22 variables in 1036 walking tests with an accelerometric gait analysis system. Afterward, monthly telephone monitoring reported the date of the first fall over 24 months. A principal components analysis was used to assess the relationship between gait variables and fall status in four groups: non-fallers, fallers from 0 to 6 months, fallers from 6 to 12 months and fallers from 12 to 24 months. The association of significant principal components (PC) with an increased risk of first fall was then evaluated using the area under the Receiver Operator Characteristic Curve (ROC). No effect of clinical confounding variables was shown as a function of groups. An eigenvalue decomposition of the correlation matrix identified a large statistical PC1 (termed "*Global kinetics of gait pattern*"), which accounted for 36.7% of total variance. Principal component loadings also revealed a PC2 (12.6% of total variance), related to the "*Global gait regularity.*" Subsequent ANOVAs showed that only PC1 discriminated the fall status during the first 6 months, while PC2 discriminated the first fall onset between 6 and 12 months. After one year, any PC was associated with falls. These results were bolstered by the ROC analyses, showing good predictive models of the first fall during the first six months or from 6 to 12 months. Overall, these findings suggest that the performance of a standardized walking test at least once a year is essential for fall prevention.

Keywords: risk of fall, gait analysis, gait variability, gait speed, accelerometric device, fall-related injuries, home-dwelling people, principal components analysis

INTRODUCTION

In view of the high prevalence of individuals in elderly populations with a risk of falling and the potentially dramatic consequences of fall-related injuries (e.g., fractures and psychological trauma) leading to self-imposed restriction in daily activities and, consequently, loss of independence (Arfken et al., 1994; Tinetti et al., 1994a; Tinetti and Williams, 1997; Scheffer et al., 2008), avoidance or delay of the first fall onset is a major public health concern. As reported by the WHO (2007), falls are the second leading cause of accidental or unintentional-injury deaths worldwide with more than 420,000 individuals dying from falls globally, of which over 80% are in low- and middle-income countries. In addition, 37.3 million falls each year require medical attention, with about 40% of all serious fall-related injuries among the elderly resulting in hospital admission. After hospitalization, 30–40% of these patients are transferred to a nursing home. Altogether, 30% of people *over the age of 65 years* that live in the community fall at least once per year and this proportion increases greatly with age. To tackle the major public health challenges of preventing falls in older adults as soon as possible, we argue that it is crucial to identify specific markers that are significantly associated with an increased risk of the first fall onset. Identifying these markers would help the medical professional to prescribe an intervention early enough to effectively prevent a fall.

Up to now, considerable literature on the identification of risk factors for falls in the elderly and on the prediction of recurrent falls has been published (Tinetti et al., 1988; Nevitt et al., 1989; Wickham et al., 1989; O'Loughlin et al., 1993;

Mahoney et al., 1994; Luukinen et al., 1995; Thapa et al., 1995; Tinetti and Williams, 1997; Lord et al., 2000; Rubenstein and Josephson, 2002; Stel et al., 2003). According to significant meta-analyses (Gillespie et al., 2012; Bloch et al., 2013), among the most important intrinsic predictors of falls are taking medications [Odds Ratio = 4.24 (3.06–5.88) 95% Confidence interval), abnormal balance test [$OR = 2.26$ (1.79–2.85)], low body mass index [$OR = 2.05$ (1.70–2.48)], fracture history [$OR = 1.89$ (1.53–2.34)], vision impairment [$OR = 1.49$ (1.39–1.59)], cardiac rhythm disorder [$OR = 1.42$ (1.14–1.75)], impaired cognition [$OR = 1.96$ (1.80–2.14)], or limited activity [$OR = 1.32$ (1.01–1.72)].

More specifically, it is well documented that a large proportion of falls in the elderly occur during walking (Wild et al., 1981; Campbell et al., 1989; Robinovitch et al., 2013). Thus, gait disturbances (e.g., decreased speed, changes in stride time variability, or medio-lateral symmetry) have been associated with falls (Rubenstein et al., 1988; Tinetti et al., 1988; Maki, 1997; Hausdorff et al., 2001; Auvinet et al., 2003; Vassallo et al., 2003; Brach et al., 2005; Verghese et al., 2009; Toebes et al., 2012; Weiss et al., 2013). For example, Mirelman et al. (2012) conducted a five-year prospective study that showed that gait disturbances, and especially dual-task gait variability, were associated with future falls, while controlling for age, gender and history of falls the year prior to the participants' initial screening. However, as far as we know, no prospective cohort study has replicated or confirmed these findings in home-dwelling people aged 65–75 *that had never fallen*. Thus our approach owes its originality both to this particular cohort (i.e., primary prevention policy) and to the compression of dimension of collected gait variables as essential information to be related to risk of the first fall in older population; In this particular context (i.e., the "unknown" cohort), we hypothesized that the average walking speed and stride regularity should be the most relevant variables to discriminate non-fallers from fallers. With an economic, easy to use, and non-invasive accelerometric device, this 2-year prospective study aimed to examine the correlations between specific gait patterns and falls. In addition, we also sought to characterize the duration between the fall-risk screening test and a potential fall using an original multi-step statistical analysis.

MATERIALS AND METHODS

PARTICIPANTS

A total of 259 older adults (mean age 69.6 ± 2.7 years; 61.5% women) who never had fall experience, were recruited for the present cohort, which is a prospective observational multicenter study designed to identify the risk factors for the first fall in elderly community-dwellers. This study was approved by the Local Ethical Committee of the Region of Pays de la Loire (France) (reference: n° 2004/05, "*Facteurs prédictifs du risque de première chute chez les personnes âgées* (predictive factors of risk of the first fall in elderly people); CCPPRP n°1, favorable opinion the 20th July 2004) and was conducted in accordance with the Declaration of Helsinki (last modified in 2004).

Each participant was screened by medical staff for their medical history, personal information (age, gender), physical and clinical baseline characteristics according to the aforementioned predictors of falls: taking medications, abnormal balance test (one leg standing test), body mass index, fracture history (lower limb surgery during the five past years), vision impairment (global visual acuity score), cardiac rhythm disorder (normality of electrocardiogram), impaired cognition (Mini-Mental State Examination "MMSE" and Frontal Assessment Battery "FAB" tests) and limited activity (Daily physical activity).

Eligibility criteria were age between 66 and 75 years, living at home, never fallen, and an ability to walk without assistance (for at least 30 s). Previous falls (or not) were evaluated during the first meeting with the patient, by asking them if they have already fallen. To clarify the definition of fall, the geriatric medicine doctors explained the WHO definition, with case examples. The question of fall event was discussed again with the participant during the presentation of the study and during the first baseline visit (inclusion visit). For the present analysis, exclusion criteria were refusal to give consent or lack capacity to give consent or if the participant was hospitalized at the time of screening. Participants were included after having given their written informed consent for research.

Basic gait mobility was assessed using an accelerometric device (see the *Gait assessment* section below) in order to characterize the overall locomotor behavior of each participant. After this baseline assessment, all the participants received standardized phone calls from the research medical staff each month during the first year, and every three months during the second year in order to obtain information regarding any falls or related incidents. The telephone calls were performed by trained interviewers, and were similar to the procedure used in the literature (e.g., Stalenhoef et al., 2002). By using open-ended questions, the date, circumstances, causes and consequences of falls, and changes in living conditions and life events were collected. If necessary, the interviewers reminded the WHO definition to the participants, with case examples. A fall was defined as "unintentionally on the ground or lower level, not as a result of a major intrinsic event (such as a stroke) or overwhelming hazard" (Tinetti et al., 1988; WHO, 2007).

CATEGORIZATION OF FALLERS GROUPS ACCORDING TO THE DATE OF THE FIRST FALL ONSET

At the end of the follow-up period, a committee of geriatric medicine doctors analyzed the circumstances of each fall recorded during the prospective follow-up in order to verify and, if appropriate, validate that the fall occurred during usual living conditions and was factually consistent with the definition-related criteria of a fall (WHO, 2007). For example, a fall occurring while practicing a high-risk sport or because of ice on the sidewalk was not considered as a falling event. About 5% of collected falls were rejected by this committee of experts. Three participants were then excluded from this study before the analysis. During the 24-month follow-up period, 72 subjects (27.40%) reported falling one or more times. Among the reported first falls, 20 participants (7.72%) fell during the first six months, 26 (10.04%) between the sixth and twelfth months and 26 (10.04%) during the second year. 69 of the 72 subjects that fell reported falling only once and 3 fell multiple times during the follow-up period. Note also that the committee kept blind for the gait assessment results as the

geriatric M.D. met. In addition, none of them has been involved in the statistical process.

GENERAL BASELINE CHARACTERISTICS

According to the main factors identified involved in the risk of falling in older people (Gillespie et al., 2012; Bloch et al., 2013), the relationship between falls and these potential confounding factors was examined by means of multinomial logistic regression analysis. By performing this statistical analysis for each variable separately, we specified the association between (the risk of) the first fall and these clinical factors, with the non-fallers group used as the reference level. The baseline clinical characteristics were gender, taking medications, daily physical activity (above 30 min per day), one leg standing test (above 5 s), lower limb surgery during the five previous years, and abnormal electrocardiogram *as binary variables*, and age, body mass index, global visual acuity score, and MMSE and FAB tests as parametric variables.

ACCELEROMETRIC GAIT ANALYSIS DEVICE

The gait analysis system used in this study included a 3-D-acceleration sensor, a data logger and a computer program for processing the acceleration signals and calculating the gait parameters (Locometrix®, **Figure 1**). The sensor weighs 20 g and is composed of three accelerometers placed perpendicularly to each other and housed in a moulded box ($40 \times 18 \times 18$ mm). The sensor is incorporated into an elastic belt, which was fastened around the subject's waist, so that the sensor was placed over the L3–L4 inter-vertebral space (**Figure 1**). The first accelerometer was aligned with the cranio-caudal axis of the body, the second one with the antero-posterior axis and the third one with the medio-lateral axis. Signals were recorded by a data logger at a sampling frequency of 100 Hz and an anti-aliasing filter with a cut-off frequency of 50 Hz was applied. This data logger weighed 140 g and was housed in a box ($65 \times 22 \times 12$ mm) (see Auvinet et al., 1999, 2002, for further details).

GAIT ASSESSMENT

Four tests were carried out on each subject walking at his/her own comfortable speed down and back along a 30 m straight hospital corridor. No prompting signals were used. The 30 m distance was long enough to ensure a constant speed over 25 s in order to select a steady state walking pattern of 20 s for analysis. All subjects wore their usual walking shoes avoiding high heels or hard-soled shoes. The walking speed was measured with an electronic stopwatch synchronized with the gait data logger. Although subjects were asked to walk in a straight line with their arms free, the trajectory was not imposed and the corridor width was limited so the conditions of walking allowed a large degree of freedom for walk disorder expression with the environmental conditions carefully standardized. Overall, considering the 259 subjects, 1036 tests of 30 m distance have been recorded or approximately 30 kilometers and 60000 strides.

GAIT VARIABLES

The software program Locometrix® automatically calculated kinematic and kinetic gait variables after selecting a steady state walk sample of 20.48 s. This sample included exactly 1024 points of acceleration measurements on each axis, which provided an optimal calculation for Fast Fourier Transformation (FFT) and other algorithms. This period corresponded to 19–21 walk cycles-about 28 m for healthy adult subjects. All the biomechanical variables were calculated from the walk sample 3D-accelerations signals for each person. These variables were derived from calculating of several algorithms as indicated in **Table 1**: time measure, vectorial calculations, FFT, autocorrelation, wavelet analysis and statistical regressions. Further explanations on the calculation of the variables can be obtained in previous validation papers of the accelerometric gait analysis device (Auvinet et al., 1999, 2002). This gait analysis system has been extensively used for clinical trials both in humans and animals (Paquet et al., 2003; Auvinet et al., 2011; Barthélémy et al., 2011). The 22 collected variables are presented in detail in **Table 1**.

DATA AND STATISTICAL ANALYSIS OF GAIT

We tried to characterize the overall gait behavior for the different (non) fallers groups by performing a statistical analysis consisting of a seven-step procedure. Specifically, we replicated the statistical process mainly based on a principal components analysis (PCA) as described in recent studies (Courtine et al., 2009; Musienko et al., 2011; van den Brand et al., 2012).

Step 1

A total of 22 gait variables providing detailed quantification of the overall locomotor behavior from the 3-axis accelerometric device that were collected (**Figure 1**).

Step 2

A PCA was applied on all computed variables. This PCA allowed the extraction of the most relevant information from the initial data by generating new independent variables called Principal Components (PC). Each PC linearly combines the original variables to maximize the amount of explained variance for each successive PC (**Figure 1**).

Step 3

We then computed correlations (PC loadings) between each measured parameter and each selected PC. In order to understand what each PC reflected, we focused on the variables that showed the highest PC loading ($r > 0.5, p < 0.05$). PC1 accounted for the largest part of the variance (36.7%), PC2 for 12.6% of the total variance and PC3 for 7.9% of the total variance) (**Figure 1**). Note that these three PCs are sufficient to summarize the entire collected data because there is a very strong correlation ($r = 0.92$, $p < 0.001$) between the eigenvector constructed with these first three PCs and the eigenvector constructed from all the PCs (i.e., 100% of the variance).

Step 4

The overall locomotor behavior of each group was then displayed in a 3-D space defined by the newly constructed variables, PC1–3 (57.2% of explained variance) (**Figure 2**). Note that clear differences emerged visually across the groups. The displayed ellipsoid volumes for each group were located from the mean value of the three PC eigenvectors for each group, and their diameters corresponded to the 95% confidence interval (95% CI).

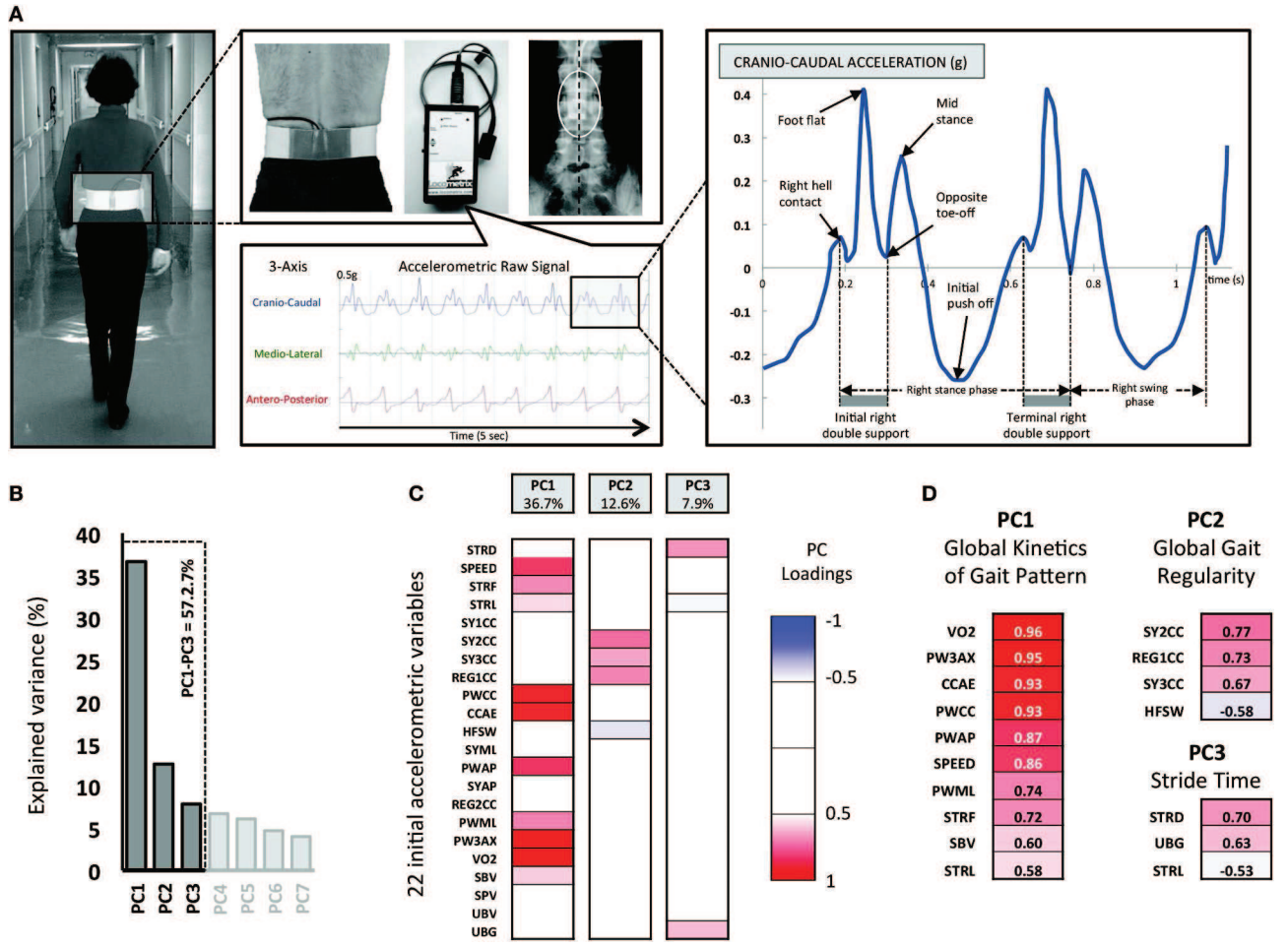

FIGURE 1 | The experimental Locometrix® gait analysis system for the walking test and first methodological steps of the Principal Components Analysis (PCA). (A) The accelerometric sensor is applied in the middle of the lower back using an elastic beltfastened around the subject's waist. The sensors are connected to a data logger, which is attached onto the front part of the belt. The participants were requested to walk at their own comfortable speed along a 30 m straight corridor. The sensor provides the cranio-caudal, medio-lateral and antero-posterior raw acceleration signals. Then the software allowed to select walk sample of 20 s to calculated 22 variables related to kinetics, regularity, power and expended energy of locomotor behavior. **(B)** 22792 pieces of data corresponding to 22 variables, extracted from 1036 walking trials, were used for the PCA. The three retained principal components (PC) are shown with their associated eigenvalues, for 57.2% of the total variance. **(C)** Each initial variable, as correlated with a PC with $|r| > 0.5$ ($p < 0.05$), was considered "significant" and used for interpretation. The color code corresponds to these component loadings. **(D)** The resulting analysis identified three groups of variables that can be related to (i) the *Global kinetics of gait pattern* (PC1), (ii) *Global gait regularity* (PC2) and (iii) the *Stride time* (PC3).

Step 5

The expected differences between groups were represented by histograms (**Figure 2**), which correspond to the mean position ±95% CI, according to the three PC eigenvectors. One-Way analysis of variance (ANOVA) was used to examine the between-groups effects with each eigenvector as dependent variable. This fifth step allowed for the identification of the delay-related predictive marker of the first fall onset.

Step 6

In order to specify the relationships between the occurrence of the first fall event during the follow-up and extracted PCs (step 5), we assessed the Area Under the Curve (AUC) of the Receiving Operating Characteristics (ROC), plotted from the sensitivity and sensibility of the PCs eigenvectors, for the three fallers groups in comparison *to the non-fallers group*: fallers (+0 to +6 months) vs. non-fallers, fallers (+6 to +12 months) vs. non-fallers, fallers (+12 to +24 months) vs. non-fallers (**Figure 3**).

Step 7

Lastly, Odds ratios (OR) were quantified by performing multiple univariate logistic regressions after a dichotomization process, necessary to transform the continuous eigenvectors, by the computation of the *Youden Index* (Youden, 1950; Shapiro, 1999; Greiner et al., 2000). The latter consisted of the determination of the cut-off value (J), from a maximization process of (Sensibility + Specificity) − 1; $\{J = \text{maxc}\ [\text{Se(c)} + \text{Sp(c)} - 1]\}$. On this basis, survival curves analyses using Kaplan-Meier testing were

Table 1 | Details of 22 gait variables collected from the accelerometric gait analysis device.

Short title	Full title	Units	Methods	Brief definition
SPEED	Speed	m/s	Regression model	Average linear speed of forward displacement
STRF	Stride frequency	Hz	Fast Fourier Transform	Number of walk cycles per unit of time
STRD	Stride duration	s	Time measure	Average duration between two successive ground contact of the same foot
STRL	Stride length	m	Speed/SF	Average length between two successive ground contact of the same foot
PWCC	Power in CC axis	W/kg	Fast Fourier Transform	Power extracted from the FFT spectrum in CC axis
PWAP	Power in AP axis	W/kg	Fast Fourier Transform	Power extracted from the FFT spectrum in AP axis
PWML	Power in ML axis	W/kg	Fast Fourier Transform	Power extracted from the FFT spectrum in ML axis
PW3AX	Total mechanical power on the 3 axes	W/kg	Combination	Sum of the 3 powers extracted from the FFT spectrum in CC, AP, LM axes
VO2	Oxygen consumption estimate	ml/min/kg	Regression model	Estimation of oxygen consumption based on high correlations between VO2 and power and SF variables
SBV	Support and breaking vector	g	Vector calculation	Averaged vector of the first part of support phase (deceleration or breaking phase)
SPV	Support and propulsion vector	g	Vector calculation	Averaged vector of the second part of the support phase (propulsion)
UBG	Unloading and breaking vector	g	Vector calculation	Averaged vector during unloading and breaking phase
UBV	Unloading and propulsion vector	g	Vector calculation	Averaged vector during unloading and propulsion phase
SY1CC	Symmetry index 1 CC axis	Without	Autocorrelation	Comparison of the left and right acceleration patterns on CC axis (both acceleration amplitude and time on all the strides)
SY2CC	Symmetry index 2 CC axis	Without	Wavelet analysis+autocorrelation	Comparison of the left and right acceleration patterns on CC axis (both signal energy and time over all the sample)
SY3CC	Symmetry index 3 CC axis	Without	Wavelet analysis+autocorrelation	Comparison of the left and right acceleration patterns on CC axis (both signal energy and time on all the strides)
SYML	Symmetry index 4 ML axis	Without	Wavelet analysis+autocorrelation	Comparison of the left and right acceleration patterns on ML axis (both signal energy and time on all the strides)
SYAP	Symmetry index 2 AP axis	Without	Wavelet analysis+autocorrelation	Comparison of the left and right acceleration patterns on AP axis (both signal energy and time on all the strides)
REG1CC	Regularity index 1 CC axis	Without	Autocorrelation	Variability analysis of the pattern in successive strides of the sample by analysis of the acceleration patterns in CC axis
REG2CC	Regularity index 2 CC axis	Without	Wavelet analysis+autocorrelation	Variability analysis of the pattern in successive strides of the sample by analysis of the signal energy patterns in AP axis
CCAE	CC acceleration energy	J/	Wavelet analysis	Total Energy of the wavelet spectrum on CC acceleration signal
HFSW	High frequency shock wave	%	Wavelet analysis	Percentage of the total energy due to high frequency >4Hz due to foot impacts and transient

performed to assess if the identified markers were significantly associated to fall as a function of its occurrence delay.

RESULTS

BASELINE CLINICAL CHARACTERISTICS

The mean and standard deviations, or frequencies and percentages, as appropriate, of the baseline characteristics of the entire sample and the four groups [non-fallers, fallers (+0 to +6 months), fallers (+6 to +12 months) and fallers (+12 to +24 months)] are presented in **Table 2**. To identify potential differences between non-fallers and fallers, One-Way ANOVAs (or equivalent non-parametric Kruskal-Wallis test as appropriate) were performed for all clinical variables. Note that no main effect of group was found, whatever the tested clinical variable.

Table 2 | Baseline clinical characteristics (mean ± standard deviation *SD*, or percentages) of the entire sample and the four groups: non-fallers, fallers from 0 to 6 months, fallers from 6 to 12 months and fallers from 12 to 24 months.

	Full sample ($n = 259$)	Non fallers ($n = 187$)	Fallers (+0 to +6 months) ($n = 20$)	Fallers (+6 to +12 months) ($n = 26$)	Fallers (+12 to +24 months) ($n = 26$)
Gender (woman, %)	152(58.7)	115(61.5)	10(50)	12(46.2)	15(57.7)
Age (years ± *SD*)	69.5 ± 2.6	69.4 ± 2.5	71.1 ± 2.7	69.3 ± 2.8	69.2 ± 2.5
Body mass index (kg.m^{-2} ± *SD*)	26.1 ± 3.6	26 ± 3.6	26.6 ± 3.8	26.2 ± 3.8	26.5 ± 3.2
Taking medications (%)	209(81)	145(78)	17(85)	24(92.3)	24(92.3)
Daily physical activity > 30 min (%)	201(77.6)	148(79)	15(75)	20(76.9)	18(69.2)
Global visual acuity score (a.u. ± *SD*)	1.7 ± 5.9	1.7 ± 6.0	0.6 ± 0.2	2.9 ± 9.5	0.9 ± 0.8
MMSE (score/30 ± SD)	27.2 ± 2.5	27.1 ± 2.4	27.1 ± 3.0	27.4 ± 2.5	27.1 ± 2.4
FAB (Score/18 ± *SD*)	13.9 ± 2.7	13.8 ± 2.6	13.4 ± 2.6	14.2 ± 3.3	13.9 ± 3.1
One leg standing > 5 s (%)	225(87.2)	164(87.5)	16(80)	22(84.6)	23(88.4)
No lower limb surgery (%)	220(85.3)	160(85.4)	15(75)	22(84.6)	23(88.4)
Not abnormal electrocardiogram (%)	202(78.3)	151(80.6)	13(65)	18(69.2)	20(76.9)

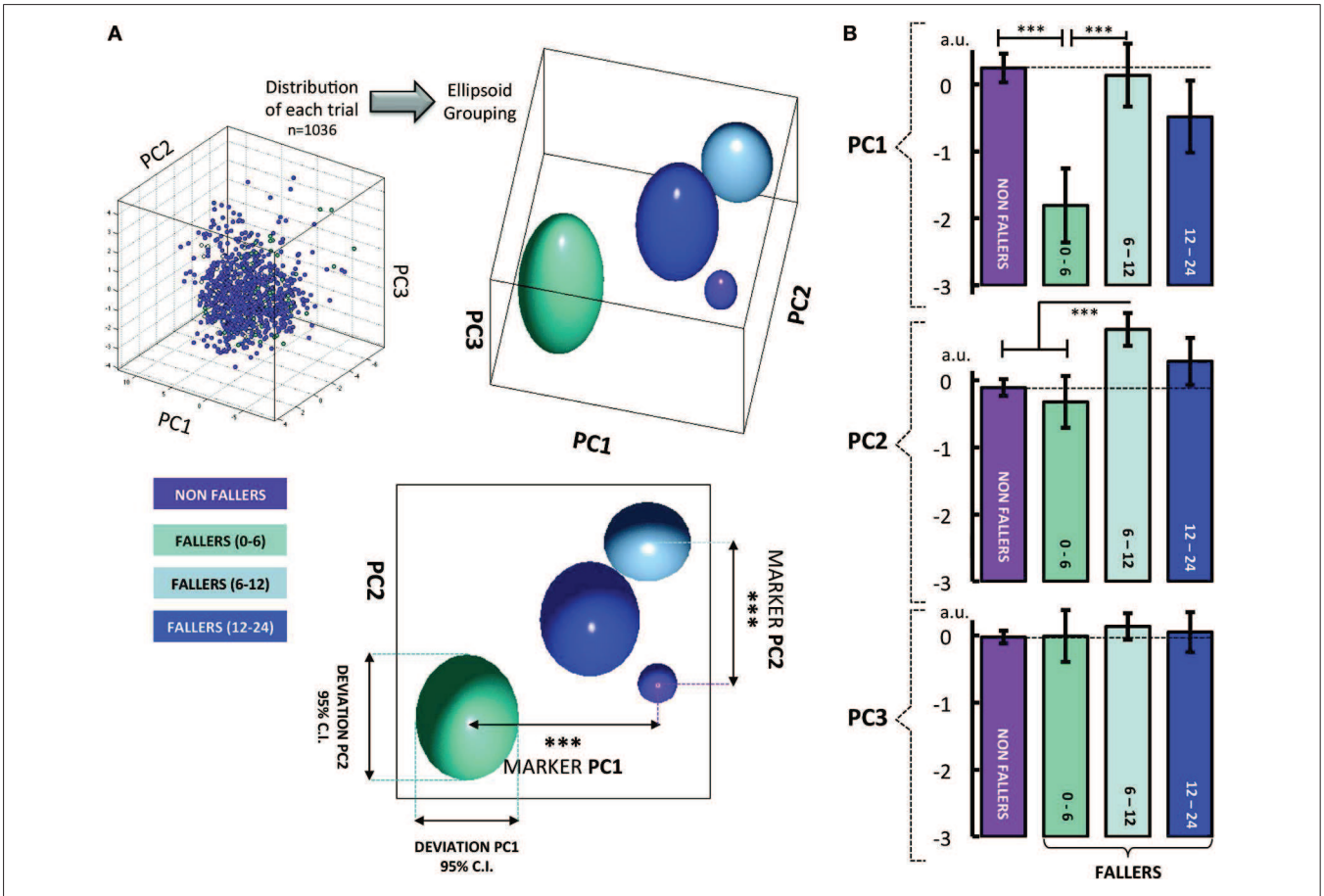

FIGURE 2 | (A) When results from all walking tests are visualized in a 3-D space defined by the newly constructed variables PC1–3 (57.2% of explained variance), clear differences can be seen between the four groups: non-fallers, fallers from 0 to 6 months, fallers from 6 to 12 months and fallers from 12 to 24 months. For the PC1, the participants who fell from 0 to 6 months show a clear difference in behavior compared to the three other groups. Similarly, when considering the PC2, the fallers from 6 to 12 months can be significantly differentiated from all the other groups. With PC3, no differentiation between groups was found. Note that the group of fallers from 12 to 24 months displays a behavior very similar to the non-fallers group. **(B)** These visual findings are confirmed by one-way analysis of variance, with the 4 groups used as a differential factor between subjects. The HSD Tukey tests were used as *post-hoc* tests following significant effects. The histograms represent the mean score of eigenvector for each group with ±95% confidence intervals. *Note.* $^{*}p < 0.05$, $^{**}p < 0.01$ $^{***}p < 0.001$.

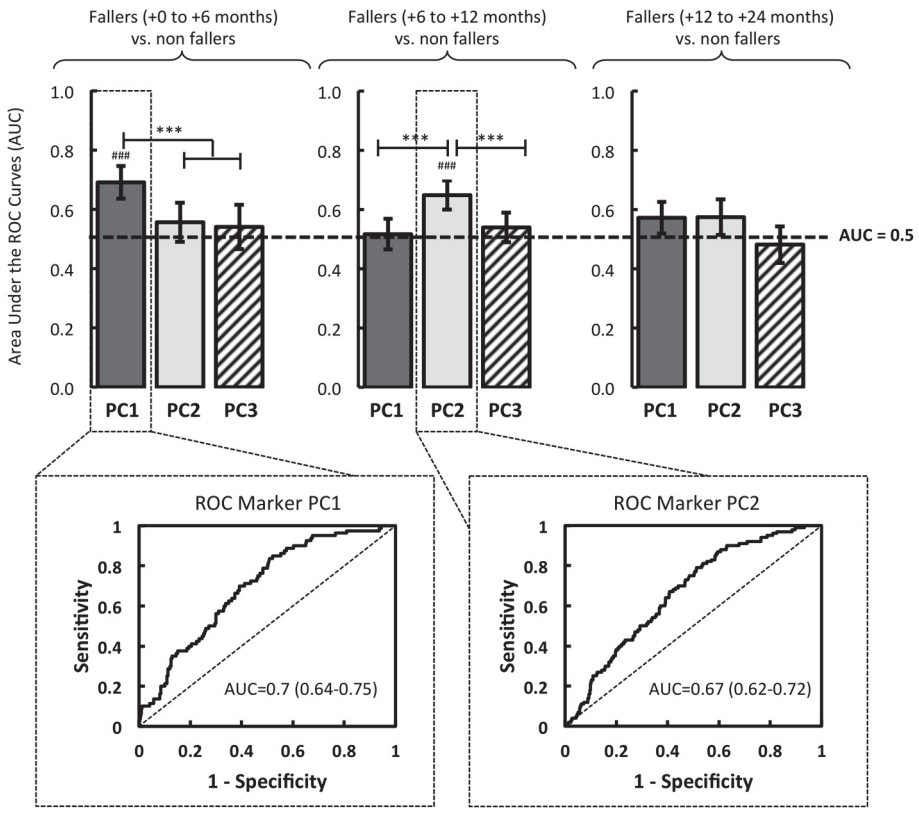

FIGURE 3 | Based on logistic regressions performed with the eigenvectors of PC1, PC2 and PC3, the quality of the models was evaluated by the area under the Receiver Operator Characteristic (ROC) Curve (AUC). The resulting models were compared in relation to three groups of fallers: fallers from 0 to 6 months, fallers from 6 to 12 months, and fallers from 12 to 24 months. The significant AUC (i.e., different from a random law) are displayed in the figure where $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, or $^{\#\#\#}p < 0001$. *Note.* Significant difference between models is reported: $^{*}p < 0.05$, $^{**}p < 0.01$ $^{***}p < 0.001$.

In addition, the overall statistical results are presented for each of these confounding variables in **Table 3**, with the regression coefficient $\beta \pm$ the standard deviation and p-value. It is worthy to note that only a significant association between falls and age was found for the fallers group (+0 to +6 months), with the non-fallers used as the reference level ($\beta = 0.23 \pm 0.09$; $p = 0.01$). There were no other significant relations, no matter what the confounding factor included in the multinomial logistic regression analysis.

Steps 1–4

PC1 is composed of the following variables ($r > 0.5$, $p < 0.05$), which represent 80.6% of the PC1-variance and 36.7% of the total variance: *VO2, PW3AX, CCAE, PWCC, PWAP, SPEED, PWML, STRF, SBV, STRL* (see **Figure 1** and **Table 1** for the details). We denominated this PC1 the "*Global kinetics of gait pattern,*" including the mechanical power and temporo-spatial variables of walking gait. Principal component loadings also revealed a PC2 called "*Global gait regularity*," which is composed of following variables ($r > 0.5$, $p < 0.05$), representing 54.3% of the PC2-variance and 12.6% of the total variance: *SY2CC, REG1CC, SY3CC, HFSW* (see **Figure 1** and **Table 1** for details). This component included three variables related to gait symmetry and regularity of walking strides (low variability). Finally, PC3 is constituted of variables ($r > 0.5$, $p < 0.05$) which represent 49.7% of the PC3-variance and 7.9 % of the total variance: *STRD, UBG, STRL* (see **Figure 1** and **Table 1** for details). We labeled PC3 "*Stride time*," including both stride duration and sum of acceleration vectors averaged by a part of stride time duration.

Step 5

The decomposition of the PC eigenvectors according to the non-faller groups showed a significant effect of group for PC1 [$F_{(3,\ 1032)} = 13.58$, $p < 0.001$] and PC2 [$F_{(3,\ 1032)} = 10.06$, $p < 0.001$]. No main effect of the group was shown with PC3 [$F_{(3,\ 1035)} = 0.48$, $p = 0.7$]. The following HSD-Tukey *post-hoc* tests showed that the fallers (+0 to +6 months) are greatly different from the non-fallers ($p < 0.001$) and the fallers (+6 to +12 months) ($p < 0.001$) on PC1. When considering PC2 "*Global gait regularity*," the *post-hoc* comparisons revealed that the fallers (+6 to +12 months) differed from the non-fallers ($p < 0.001$) and the fallers (+0 to +6 months) ($p < 0.001$) (**Figure 2**).

Step 6

The ROC analysis revealed that PC1 had a significant predictive power of the first fall onset during the first six months after the initial screening: AUC = 0.7 (0.64–0.75, 95% CI) ($p < 0.001$). Over the course of these first six months, no association

Table 3 | Regression coefficient β ± standard deviation and *p*-value for all baseline characteristics, obtained by multinomial logistic regression analysis.

	Non fallers = *reference* (*n* = 187)					
	Fallers (+0 to +6 months) (*n* = 20)		Fallers (+6 to +12 months) (*n* = 26)		Fallers (+12 to +24 months) (*n* = 26)	
	β ± *SD*	*p*	β ± *SD*	*p*	β ± *SD*	*p*
Gender	0.47 ± 0.47	0.320	0.62 ± 0.42	0.139	0.16 ± 0.43	0.707
Age	0.23 ± 0.09	**0.010**	−0.02 ± 0.08	0.805	−0.03 ± 0.08	0.750
Body mass index	0.05 ± 0.06	0.472	0.02 ± 0.06	0.734	0.04 ± 0.06	0.495
Taking medications	0.44 ± 0.65	0.504	1.19 ± 0.76	0.118	0.74 ± 0.64	0.249
Daily physical activity (>30 min)	0.27 ± 0.55	0.626	0.16 ± 0.50	0.746	0.55 ± 0.46	0.231
Global visual acuity	−0.05 ± 0.09	0.558	−0.09 ± 0.08	0.275	0.03 ± 0.08	0.743
MMSE	0.01 ± 0.17	0.959	0.09 ± 0.18	0.625	0.07 ± 0.17	0.693
FAB	−0.055 ± 0.08	0.496	0.057 ± 0.083	0.490	0.006 ± 0.078	0.938
One leg standing (>5sec)	0.68 ± 0.68	0.322	0.71 ± 0.61	0.245	−0.07 ± 0.78	0.924
No lower limb surgery	0.89 ± 0.56	0.117	0.28 ± 0.59	0.635	−0.05 ± 0.65	0.936
Not abnormal electrocardiogram	0.78 ± 0.53	0.141	0.81 ± 0.47	0.084	0.42 ± 0.51	0.408

Note. Significant results are indicated in bold type (i.e., p < 0.05).

between the PC1 and falls was found (AUC < 0.5, $p > 0.05$) (**Figure 3**).

In the same vein, the logistic regression analysis revealed a relevant interest of PC2, significantly associated with an increased risk of first fall onset only when it occurred between the sixth and the twelfth months: AUC = 0.67 (0.62-0.72, 95% CI) ($p < 0.001$) (**Figure 3**). Note that no predictive power of PC3 was determined by the ROC analysis (AUC < 0.5, $p > 0.05$), whatever the date of the first fall onset.

Step 7

The logistic regression parameters showed ORs of 3.89 (2.2–6.7, 95% CI) ($p < 0.001$) and of 3.6 (2.16–5.89, 95% CI) ($p < 0.001$), for PC1 and PC2, respectively. Lastly, considering only the non-fallers and fallers (+0 to +6 months), Kaplan-Meier's distributions of falls differed significantly between those with values lower than cut-off value PC1 eigenvector and those with values higher than the cut-off value PC1 (log-rank test = 31.74, $p < 0.001$; **Figure 4**). For the non-fallers and fallers (+6 to +12 months), similar difference of Kaplan-Meier's distributions of falls was found between those with values lower than cut-off value PC2 eigenvector and those with values higher than the cut-off value PC2 (log-rank test = 27.15, $p < 0.001$; **Figure 4**).

DISCUSSION

Using a very simple and economical gait analysis system that allowed ecological measurements, we proposed a metrological and statistical analysis of gait patterns in home-dwelling people aged 66–75, with follow-up telephone calls each month during the first year, and every three months during the second year. The current findings provide for the first time the possibility of identifying relevant indicators of imminent fall occurrence, that is the "*Global kinetics of gait pattern*" (PC1) and the "*Global gait regularity*" (PC2). In addition to the fact that the identification of these markers is relatively easy to envisage in clinical settings (i.e., safe test, short duration, and low cost), and might of special interest to accurately estimate the available time before the occurrence of the first fall. Furthermore, this new key information might be useful for recommending a specific fall-prevention program. From a clinical viewpoint, to perform a walking test at least once a year might be essential for fall prevention.

It is important to bear in mind that the current cohort is very specific and original (i.e., home-dwelling people that had never fallen), and by definition has no previous evidence. In this respect, it is not necessarily surprising that no difference between the four groups was found when considering all the screened clinical variables (see **Table 3**). It might be suggested that the present population was "full-matched" at the time of inclusion, with the same well-documented multifactorial risks for falling (Gillespie et al., 2012; Bloch et al., 2013). Thus our current findings on the specific gait markers reinforce the main idea to accurately assess gait behavior for this healthy home-dwelling population. But this point needs to be confirmed and to be precisely tested in a prospective independent cohort. Nevertheless the current findings observed in an original cohort confirm that the gait analysis is probably one of best tools to predict the first fall onset, and most importantly, its occurrence time frame.

SPECIFIC GAIT MARKERS AND RISK OF FIRST FALL

Numerous studies have already demonstrated the relationship between gait disorders and risk of falling in the elderly, by supporting the idea that a decrease in walking speed in usual conditions and an increase of stride-time variability are strong predictors of falls (Dargent-Molina et al., 1996; Brach et al., 2005; Verghese et al., 2009; Studenski et al., 2011). However, as far as we know, all the conclusions drawn in the current retro- or prospective studies cannot be implemented in a population of healthy elderly people that have never fallen. Indeed, studies with prospective follow-up for falls do not warrant that the participants included in the cohorts had not already fallen before the year preceding the initial screening.

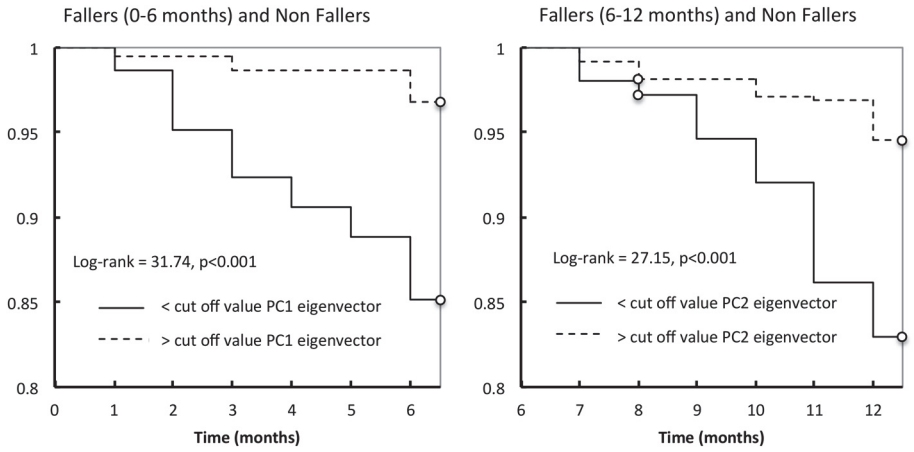

FIGURE 4 | Kaplan-Meier estimates of the probability of a first fall occurrence during the first year follow-up according to the cut-off value of PC1 eigenvector (left) or PC2 eigenvector (right).

In this original context, the alterations in *global kinetics of gait pattern* (i.e., the PC1) can be used as a new locomotor marker, which is significantly associated with an increased risk of imminent fall occurrence. Based on a data reduction of high-dimensional gait data to a low-dimensional set of essential features, our analysis actually showed that PC1 discriminated the fall status during the first 6 months (see **Figures 2**, **3**). Moreover, these results are bolstered by the ROC analyses: the logistic model showed that PC1 was significantly related to a higher risk of first fall during the first six months (AUC $= 0.7$, $p < 0.001$, OR $= 3.89$, $p < 0.001$). It is also worth noting that this first marker is modeled by a few variables (VO2: $r = 0.957$, $p < 0.001$, PW3AX: $r = 0.952$, $p < 0.001$ and CCAE: $r = 0.927$, $p < 0.001$), which are closely linked to symptoms of hypokinesia (see **Table 1**). Indeed, it is well established in the literature that aging can lead to impairments in the central and/or peripheral nervous system, which are consequently reflected in executive functions, or by a decrease in physical, functional and locomotor performance (e.g., Lundin-Olsson et al., 1997).

In this light, the slowing down of walking speed—a variable that composes the PC1—might be partially explained by a decrease in volume / thickness of white and gray matter at the cortical and subcortical levels (i.e., corticospinal tract, cortical atrophy in the frontal, parietal, hippocampal and motor-cortex), which are in charge of the programming and the execution of locomotor commands (Annweiler and Montero-Odasso, 2012; de Laat et al., 2012; Dumurgier et al., 2012; Rosano et al., 2012). Moreover, considering pathways downstream of the CNS, physiological aging also causes alterations in nerve conduction velocities (Borg, 1981; Wang et al., 1999; Scaglioni et al., 2002), muscle synergies/coordination (Woollacott et al., 1986; Olafsdottir et al., 2007), contractility of acto-myosin bridges (Frontera and Bigard, 2002; D'Antona et al., 2003), and transmission of force to the skeletal system (Narici and Maganaris, 2006; Onambele et al., 2006; Carroll et al., 2008). All these changes might cause impairment in motor skills, postural control and gait speed (Baloh et al., 1998; Brach and VanSwearingen, 2002; Amiridis et al., 2003; Capodaglio et al., 2005; Buatois et al., 2006; Jung et al., 2006; Paterson and Warburton, 2010). Taken together, these aforementioned studies might explain the observed hypokinetic behavior in participants that have fallen during the first 6 months, as an evidence of lack of flexibility (Hausdorff et al., 1996; Jordan et al., 2007).

The second major result highlighted in this study is the relevance of the "*Global gait regularity*" marker strongly related to the occurrence of a possible first fall 6–12 months after the initial screening test (AUC $= 0.67$, $p < 0.001$, $OR = 3.6$, $p < 0.001$). Given the three variables included in the PC2 (these variables are SY2CC: $r = 0.766$, $p < 0.001$, REG1CC: $r = 0.733$, $p < 0.001$ and SY3CC: $r = 0.675$, $p < 0001$), the locomotor behavior is characterized by changes in regularity and symmetry parameters.

There is clear evidence to suggest that the *global gait regularity* or gait variability (usually reported by using the coefficient of variation of stride time) is strongly associated with a risk of falling (Brach et al., 2005; Montero-Odasso et al., 2009; Lord et al., 2011; Beauchet et al., 2012; Toebes et al., 2012). From a neurophysiological point of view, some studies have clearly shown that changes in gait variability could be the result of atrophy and dysfunction in the parietal cortex (right angular gyrus) and hippocampus, which supports the idea of the decline of sensorimotor areas involved in executive functions (Camicioli et al., 1997; Marquis et al., 2002; Hausdorff, 2005; Zimmerman et al., 2009; Zwergal et al., 2012; Beauchet et al., 2013). More precisely, according to the results of Beauchet et al. (2013), the focal neurodegeneration (especially in the parietal cortex, which is strongly involved in executive functions) might have altered the spatial displacement in relation to the surrounding environment, with subsequent impairment in gait regularity. In the same vein, Zwergal et al. (2012) demonstrated a relationship between age and the cortical control of gait, evidenced by higher attentional cost for controlling locomotor activity with age (i.e., the component of voluntary and executive function processes during the control of gait). In particular, they showed that the supraspinal locomotor centers remained preserved during aging, but multisensory

cortical control of locomotion changed with age. If young people adopt an automated mode of locomotion, the multisensory cortical activation in elderly persons occurs as a result of reduced reciprocal inhibitory sensory interaction. This might serve as a compensatory mechanism for peripheral sensory decline with age and confirm the more costly and irregular mode of locomotion in the elderly (see Zwergal et al., 2012, for details).

WHAT COULD BE DONE WITH THESE SIGNIFICANT MARKERS?

The aforementioned morpho-functional alterations in muscular peripheral and central nervous systems as the source of gait disturbances are the result of natural physiological aging and apoptosis (Lexell, 1997; Tomlinson and Irving, 1977). Despite the inevitable component of aging, it is, however, possible to reduce or delay this age-related cognitivo-motor decline, through the preservative effects of adapted and regular physical activity. In fact, many studies have already demonstrated the positive impact of different exercise programs (e.g., voluntary muscular strength, neuromuscular electrostimulation, aerobic exercises, functional daily living exercises, combined training, dancing) on the daily activities and autonomy, quality of life, balance and/or walking (Fiatarone et al., 1994; Tinetti et al., 1994b; Dionne et al., 2003; Gauchard et al., 2003; Robinson et al., 2004; Toulotte et al., 2004; Capodaglio et al., 2005; Paillard et al., 2005; Sievänen and Kannus, 2007).

A subject exhibiting a generalized hypokinesia (i.e., indicative of imminent fall occurrence a maximum of 6 months prior to falling), could have an urgent need to be included in a prevention program. For example, the neuromuscular changes following a muscular training program are well-documented in the literature in order to improve locomotor skills (Scaglioni et al., 2002; Capodaglio et al., 2005; Paillard et al., 2005). In parallel, or perhaps a priority given this patient profile, the implementation of structured safety programs for the daily living environment is of special interest for reducing risk factors (Tinetti et al., 1994b; Cumming et al., 1999; Sievänen and Kannus, 2007).

A subject with alterations in gait regularity and symmetry (i.e., the "*gait variability*" marker linked to the occurrence of a potential first fall 6–12 months), would have enough time to benefit from specific therapeutic actions (multi-localized actions leading to a more efficient adaptation). This suggestion is in agreement with a recent study by Trombetti et al. (2011), which showed the benefits of a 6-month exercise multitasking program (performed at the tempo dictated by piano music), on the recovery of gait variability at normal levels, associated with a significant reduction of falling risk in the elderly.

LIMITS AND CONCLUDING REMARKS

Some limitations of the present study need to be considered. First, it should be noted that the number of fallers group was relatively low for each subgroup: $n = 20$ for fallers (+0 to +6 months), $n = 26$ for fallers (+6 to +12 months) and fallers (+12 to +24 months), and the size of fallers sample should be increased to reinforce the predictive power of our first risk profile model. The possibility of over-fitting results needs to be considered. It is worth reminding that each subject performed four gait tests. Thus each walking test was considered as "a subject" that can be implemented into the PCA and subsequent statistical analyses (Courtine et al., 2009; van den Brand et al., 2012). Accordingly, all the analyses have been performed by considering 748 nonfallers-related tests and 288 fallers-related tests (i.e., 1036 "walking tests"). When fallers have been splitted in subgroups, then the analyses have been performed with $n = 80$ fallers-related tests for 0–6 months, or $n = 104$ fallers-related tests for 6–12 months or >12 months. This validated methodological procedure provided the advantage to reinforce the internal validity of results. Secondly, the regular follow-up phone-calls did not allow for re-assessment of the participants, in particular with regard to the walking test, in order to check what parameters were altered after the fall. Lastly, this observational design did not allow for the control of the risk factors and events during the follow-up portion of the study. Even if there is a significant association between gait parameters and future falls (with potential clinical impact in terms of recommendations for specific fall-prevention programs), no causal link between the currently observed indicators and the first fall onset can clearly be drawn.

In any event, for the first time, the alterations in *global kinetics of gait pattern* and *gait regularity* have been identified as locomotor markers in older people that had never fallen. We suggest that these two specific gait markers might help the medical profession to prescribe an intervention early enough to effectively prevent a fall in *healthy* elderly people. Within this context of effective primary prevention, medical professionals could also recommend urgent changes in the patient's environment and recommend structured safety programs that will target suboptimal practices for environmental and personal safety.

ACKNOWLEDGMENTS

The research was supported by grants from the Region of Pays de la Loire, France, for the project "RP3AP." This study received also support from Research Mission of Directorate for Research Studies, Evaluation and Statistics (Direction de la recherche, des études, de l'évaluation et des statistiques—MiRe-DRESS) and IRePS (French public health research institute). The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. Special thanks to Olivier Lantéri and Claude Trichet, directors of the Institut inter Régional pour la Santé (IRSA), a French public health institute.

REFERENCES

Amiridis, I. G., Hatzitaki, V., and Arabatzi, F. (2003). Age-induced modifications of static postural control in humans. *Neurosci. Lett.* 350, 137–140. doi: 10.1016/S0304-3940(03)00878-4

Annweiler, C., and Montero-Odasso, M. (2012). Vascular burden as a substrate for higher-level gait disorders in older adults. A review of brain mapping literature. *Panminerva Med.* 54, 189–204.

Arfken, C. L., Lach, H. W., Birge, S. J., and Miller, J. P. (1994). The prevalence and correlates of fear of falling in elderly persons living in the community. *Am. J. Public Health* 84, 565–570. doi: 10.2105/AJPH.84.4.565

Auvinet, B., Berrut, G., Touzard, C., Moutel, L., Collet, N., Chaleil, D., et al. (2002). Reference data for normal subjects obtained with an accelerometric device. *Gait Posture* 16, 124–134. doi: 10.1016/S0966-6362(01)00203-X

Auvinet, B., Berrut, G., Touzard, C., Moutel, L., Collet, N., Chaleil, D., et al. (2003). Gait abnormalities in elderly fallers. *J. Aging Phys. Act.* 11, 40–52.

Auvinet, B., Chaleil, D., and Barrey, E. (1999). Accelerometric gait analysis for use in hospital outpatients. *Rev. Rhum. Engl. Ed.* 66, 389–397.

Auvinet, B., Chaleil, D., Cabane, J., Dumolard, A., Hatron, P., Juvin, R., et al. (2011). The interest of gait markers in the identification of subgroups among fibromyalgia patients. *BMC Musculoskelet. Disord.* 12:258. doi: 10.1186/1471-2474-12-258

Baloh, R. W., Corona, S., Jacobson, K. M., Enrietto, J. A., and Bell, T. (1998). A prospective study of posturography in normal older people. *J. Am. Geriatr. Soc.* 46, 438–443.

Barthélémy, I., Barrey, E., Aguilar, P., Uriarte, A., Le Chevoir, M., Thibaud, J. L., et al. (2011). Longitudinal ambulatory measurements of gait abnormality in dystrophin-deficient dogs. *BMC Musculoskelet. Disord.* 12:75. doi: 10.1186/1471-2474-12-75

Beauchet, O., Annweiler, C., Celle, S., Bartha, R., Barthélémy, J. C., and Roche, F. (2013). Higher gait variability is associated with decreased parietal gray matter volume among healthy older adults. *Brain Topogr.* 27, 293–295. doi: 10.1007/s10548-013-0293-y

Beauchet, O., Annweiler, C., Montero-Odasso, M., Fantino, B., Herrmann, F. R., and Allali, G. (2012). Gait control: a specific subdomain of executive function? *J. Neuroeng. Rehabil.* 9, 12. doi: 10.1186/1743-0003-9-12

Bloch, F., Thibaud, M., Tournoux-Facon, C., Brèque, C., Rigaud, A. S., Dugué, B., et al. (2013). Estimation of the risk factors for falls in the elderly: can meta-analysis provide a valid answer? *Geriatr. Gerontol. Int.* 13, 250–263. doi: 10.1111/j.1447-0594.2012.00965.x

Borg, J. (1981). Properties of single motor units of the extensor digitorum brevis in elderly humans. *Muscle Nerve* 4, 429–434. doi: 10.1002/mus.880040513

Brach, J. S., Berlin, J. E., Van Swearingen, J. M., Newman, A. B., and Studenski, S. A. (2005). Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. *J. Neuroeng. Rehabil.* 2, 21. doi: 10.1186/1743-0003-2-21

Brach, J. S., and VanSwearingen, J. M. (2002). Physical impairment and disability: relationship to performance of activities of daily living in community-dwelling older men. *Phys. Ther.* 82, 752–761.

Buatois, S., Gueguen, R., Gauchard, G. C., Benetos, A., and Perrin, P. P. (2006). Posturography and risk of recurrent falls in healthy non-institutionalized persons aged over 65. *Gerontology* 52, 345–352. doi: 10.1159/000094983

Camicioli, R., Howieson, D., Lehman, S., and Kaye, J. (1997). Talking while walking: the effect of a dual task in aging and Alzheimer's disease. *Neurology* 48, 955–958. doi: 10.1212/WNL.48.4.955

Campbell, A. J., Borrie, M. J., and Spears, G. F. (1989). Risk factors for falls in a community-based prospective study of people 70 years and older. *J. Gerontol.* 44, 112–117. doi: 10.1093/geronj/44.5.M112

Capodaglio, P., Capodaglio, E. M., Ferri, A., Scaglioni, G., Marchi, A., and Saibene, F. (2005). Muscle function and functional ability improves more in community-dwelling older women with a mixed-strength training programme. *Age Ageing* 34, 141–147. doi: 10.1093/ageing/afi050

Carroll, C. C., Dickinson, J. M., Haus, J. M., Lee, G. A., Hollon, C. J., Aagaard, P., et al. (2008). Influence of aging on the *in vivo* properties of human patellar tendon. *J. Appl. Physiol.* 105, 1907–1915. doi: 10.1152/japplphysiol.00059.2008

Courtine, G., Gerasimenko, Y., van den Brand, R., Yew, A., Musienko, P., Zhong, H., et al. (2009). Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat. Neurosci.* 12, 1333–1342. doi: 10.1038/nn.2401

Cumming, R. G., Thomas, M., Szonyi, G., Salkeld, G., O'Neill, E., Westbury, C., et al. (1999). Home visits by an occupational therapist for assessment and modification of environmental hazards: a randomized trial of falls prevention. *J. Am. Geriatr. Soc.* 47, 1397–1402.

D'Antona, G., Pellegrino, M. A., Adami, R., Rossi, R., Carlizzi, C. N., Canepari, M., et al. (2003). The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. *J. Physiol.* 552, 499–511. doi: 10.1113/jphysiol.2003.046276

Dargent-Molina, P., Favier, F., Grandjean, H., Baudoin, C., Schott, A. M., Hausherr, E., et al. (1996). Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 348, 145–149. doi: 10.1016/S0140-6736(96)01440-7

de Laat, K. F., Reid, A. T., Grim, D. C., Evans, A. C., Kötter, R., van Norden, A. G., et al. (2012). Cortical thickness is associated with gait disturbances in cerebral small vessel disease. *Neuroimage* 59, 1478–1484. doi: 10.1016/j.neuroimage.2011.08.005

Dionne, I. J., Ades, P. A., and Poehlman, E. T. (2003). Impact of cardiovascular fitness and physical activity level on health outcomes in older persons. *Mech. Ageing Dev.* 124, 259–267. doi: 10.1016/S0047-6374(02)00193-8

Dumurgier, J., Crivello, F., Mazoyer, B., Ahmed, I., Tavernier, B., Grabli, D., et al. (2012). MRI atrophy of the caudate nucleus and slower walking speed in the elderly. *Neuroimage* 60, 871–878. doi: 10.1016/j.neuroimage.2012.01.102

Fiatarone, M. A., O'Neill, E. F., Ryan, N. D., Clements, K. M., Solares, G. R., Nelson, M. E., et al. (1994). Exercise training and nutritional supplementation for physical frailty in very elderly people. *N. Engl. J. Med.* 330, 1769–1775. doi: 10.1056/NEJM199406233302501

Frontera, W. R., and Bigard, X. (2002). The benefits of strength training in the elderly. *Sci. Sports* 17, 109–116. doi: 10.1016/S0765-1597(02)00135-1

Gauchard, G. C., Gangloff, P., Jeandel, C., and Perrin, P. P. (2003). Physical activity improves gaze and posture control in the elderly. *Neurosci. Res.* 45, 409–417. doi: 10.1016/S0168-0102(03)00008-7

Gillespie, L. D., Robertson, M. C., Gillespie, W. J., Sherrington, C., Gates, S., Clemson, L. M., et al. (2012). Interventions for preventing falls in older people living in the community. *Cochrane Database Syst. Rev.* 9, CD007146. doi: 10.1002/14651858.CD007146.pub3

Greiner, M., Pfeiffer, D., and Smith, R. D. (2000). Principals and practical application of the receiver operating characteristic analysis for diagnostic tests. *Prev. Vet. Med.* 45, 23–41. doi: 10.1016/S0167-5877(00)00115-X

Hausdorff, J. M. (2005). Gait Variability, methods modelling and meaning. *J. Neuroeng. Rehabil.* 2, 19. doi: 10.1186/1743-0003-2-19

Hausdorff, J. M., Purdon, P. L., Peng, C. K., Ladin, Z., Wei, J. Y., and Goldberger, A. L. (1996). Fractal dynamics of human gait: stability of long-range correlations in stride interval fluctuations. *J. Appl. Physiol.* 80, 1448–1457.

Hausdorff, J. M., Rios, D. A., and Edelberg, H. K. (2001). Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch. Phys. Med. Rehabil.* 82, 1050–1056. doi: 10.1053/apmr.2001.24893

Jordan, K., Challis, J. H., and Newell, K. M. (2007). Speed influences on the scaling behavior of gait cycle fluctuations during treadmill running. *Hum. Mov. Sci.* 26, 87–102. doi: 10.1016/j.humov.2006.10.001

Jung, S. H., Ostbye, T., and Park, K. O. (2006). A longitudinal study of the relationship between health behavior risk factors and dependence in activities of daily living. *J. Prev. Med. Public Health* 39, 221–228.

Lexell, J. (1997). Evidence for nervous system degeneration with advancing age. *J. Nutr.* 127, 1011–1013.

Lord, S., Baker, K., Nieuwboer, A., Burn, D., and Rochester, L. (2011). Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? *J. Neurol.* 258, 566–572. doi: 10.1007/s00415-010-5789-8

Lord, S. R., Sherrington, C., and Menz, H. B. (2000). *Falls in Older People: Risk Factors and Strategies for Prevention*. New York, NY: Cambridge University Press.

Lundin-Olsson, L., Nyberg, L., and Gustafson, Y. (1997). "Stops walking when talking" as a predictor of falls in elderly people. *Lancet* 349, 617. doi: 10.1016/S0140-6736(97)24009-2

Luukinen, H., Koski, K., Laippala, P., and Kivelä, S. L. (1995). Predictors for recurrent falls among the home-dwelling elderly. *Scandinavian J. Prim. Health Care* 13, 294–299. doi: 10.3109/02813439508996778

Mahoney, J., Sager, M., Dunham, M. C., and Johnson, J. (1994). Risk of falls after hospital discharge. *J. Am. Geriatr. So.* 42, 269–274.

Maki, B. E. (1997). Gait changes in older adults: predictors of falls or indicator of fear ? *J. Am. Geriatr. Soc.* 45, 313–320.

Marquis, S., Moore, M. M., Howieson, D. B., Sexton, G., Payami, H., Kaye, J. A., et al. (2002). Independent predictors of cognitive decline in healthy elderly persons. *Arch. Neurol.* 59, 601–606. doi: 10.1001/archneur.59.4.601

Mirelman, A., Herman, T., Brozgol, M., Dorfman, M., Sprecher, E., Schweiger, A., et al. (2012). Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS ONE* 7:e40297. doi: 10.1371/journal.pone.0040297

Montero-Odasso, M., Casas, A., Hansen, K. T., Bilski, P., Gutmanis, I., Wells, J. L., et al. (2009). Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study. *J. Neuroeng. Rehabil.* 6:35. doi: 10.1186/1743-0003-6-35

Musienko, P., van den Brand, R., Märzendorfer, O., Roy, R. R., Gerasimenko, Y., Edgerton, V. R., et al. (2011). Controlling specific locomotor behaviors through multidimensional monoaminergic modulation of spinal circuitries. *J. Neurosci.* 31, 9264–9278. doi: 10.1523/JNEUROSCI.5796-10.2011

Narici, M. V., and Maganaris, C. N. (2006). Adaptability of elderly human muscles and tendons to increased loading. *J. Anat.* 208, 433–443. doi: 10.1111/j.1469-7580.2006.00548.x

Nevitt, M. C., Cummings, S. R., Kidd, S., and Black, D. (1989). Risk factors for recurrent non syncopal falls. *J. Am. Med. Assoc.* 261, 2663–2668. doi: 10.1001/jama.1989.03420180087036

O'Loughlin, J. L., Robitaille, Y., Boivin, J. F., and Suissa, S. (1993). Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. *Am. J. Epidemiol.* 137, 342–354.

Olafsdottir, H., Yoshida, N., Zatsiorsky, V. M., and Latash, M. L. (2007). Elderly show decreased adjustments of motor synergies in preparation to action. *Clin. Biomech.* 22, 44–51. doi: 10.1016/j.clinbiomech.2006.08.005

Onambele, G. L., Narici, M. V., and Maganaris, C. N. (2006). Calf muscle-tendon properties and postural balance in old age. *J. Appl. Physiol.* 100, 2048–2056. doi: 10.1152/japplphysiol.01442.2005

Paillard, T., Lafont, C. Pérès, C., Costes-Salon, M. C., and Soulat, J. M. (2005). Is electrical stimulation with voluntary muscle contraction of physiologic interest in aging women? *Ann. Readapt. Med. Phys.* 48, 20–28. doi: 10.1016/j.annrmp.2004.08.005

Paquet, J. M., Auvinet, B., Chaleil, D., and Barrey, E. (2003). Analysis of gait disorders in Parkinson's disease assessed with an accelerometer. *Rev. Neurol. (Paris).* 159, 786–789.

Paterson, D. H., and Warburton, D. E. (2010). Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. *Int. J. Behav. Nutr. Phys. Act.* 7, 38. doi: 10.1186/1479-5868-7-38

Robinovitch, S. N., Feldman, F., Yang, Y., Schonnop, R., Leung, P. M., Sarraf, T., et al. (2013). Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* 381, 47–54. doi: 10.1016/S0140-6736(12)61263-X

Robinson, B. S., Gordon, J. M., Wallentine, S. W., and Visio, M. (2004). Relationship between lower-extremity joint torque and the risk for falls in a group of community dwelling older adults. *Physiother. Theory Pract.* 20, 155–173. doi: 10.1080/09593980490487500

Rosano, C., Studenski, S. A., Aizenstein, H. J., Boudreau, R. M., Longstreth, W. T., and Newman, A. B. (2012). Slower gait, slower information processing and smaller prefrontal area in older adults. *Age Ageing* 41, 58–64. doi: 10.1093/ageing/afr113

Rubenstein, L. Z., and Josephson, K. R. (2002). The epidemiology of falls and syncope. *Clin. Geriatr. Med.* 18, 141–158. doi: 10.1016/S0749-0690(02)00002-2

Rubenstein, L. Z., Robbins, A. S., Schulman, B. L., Rosado, J., Osterweil, D., and Josephson, K. R. (1988). Falls and instability in the elderly. *J. Am. Geriatr. Soc.* 36, 266–278.

Scaglioni, G., Ferri, A., Minetti, A. E., Martin, A., Van Hoecke, J., Capodaglio, P., et al. (2002). Plantar flexor activation capacity and H reflex in older adults: adaptations to strength training. *J. Appl. Physiol.* 92, 2292–2302. doi: 10.1152/japplphysiol.00367.2001

Scheffer, A. C., Schuurmans, M. J., van Dijk, N., van der Hooft, T., and de Rooij, S. E. (2008). Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing* 37, 19–24. doi: 10.1093/ageing/afm169

Shapiro, D. E. (1999). The interpretation of diagnostic tests. *Stat. Methods Med. Res.* 8, 113–134. doi: 10.1191/096228099666928387

Sievänen, H., and Kannus, P. (2007). Physical activity reduces the risk of fragility fracture. *PLoS Med.* 4:e222. doi: 10.1371/journal.pmed.0040222

Stalenhoef, P. A., Diederiks, J. P., Knottnerus, J. A., Kester, A. D., and Crebolder, H. F. (2002). A risk model for the prediction of recurrent falls in community-dwelling elderly: a prospective cohort study. *J. Clin. Epidemiol.* 55, 1088–1094. doi: 10.1016/S0895-4356(02)00502-4

Stel, V. S., Pluijm, S. M., Deeg, D. J., Smit, J. H., Bouter, L. M., and Lips, P. (2003). A classification tree for predicting recurrent falling in community-dwelling older persons. *J. Am. Geriatr. Soc.* 51, 1356–1364. doi: 10.1046/j.1532-5415.2003.51452.x

Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., et al. (2011). Gait speed and survival in older adults. *JAMA* 305, 50–58. doi: 10.1001/jama.2010.1923

Thapa, P. B., Gideon, P., Fought, R. L., and Ray, W. A. (1995). Psychotropic drugs and risk of recurrent falls in ambulatory nursing home residents. *Am. J. Epidemiol.* 142, 202–211.

Tinetti, M. E., Baker, D. I., McAvay, G., Claus, E. B., Garrett, P., Gottschalk, M., et al. (1994b). A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N. Engl. J. Med.* 331, 821–827. doi: 10.1056/NEJM199409293311301

Tinetti, M. E., Mendes de Leon, C. F., Doucette, J. T., and Baker, D. I. (1994a). Fear of falling and fall related efficacy in relationship to functioning among community-living elders. *J. Gerontol.* 49, 140–147. doi: 10.1093/geronj/49.3.M140

Tinetti, M. E., and Williams, C. S. (1997). Falls, injuries due to falls, and the risk of admission to a nursing home. *N. Engl. J. Med.* 337, 1279–1284. doi: 10.1056/NEJM199710303371806

Tinetti, M., Speechley, M., and Ginter, S. F. (1988). Risk factors for falls among elderly persons living in the community. *N. Engl. J. Med.* 319, 1701–1707. doi: 10.1056/NEJM198812293192604

Toebes, M. J., Hoozemans, M. J., Furrer, R., Dekker, J., and van Dieën, J. H. (2012). Local dynamic stability and variability of gait are associated with fall history in elderly subjects. *Gait Posture* 36, 527–531. doi: 10.1016/j.gaitpost.2012.05.016

Tomlinson, B. E., and Irving, D. (1977). The numbers of limb motor neurons in the human lumbosacral cord throughout life. *J. Neurol. Sci.* 34, 213–219. doi: 10.1016/0022-510X(77)90069-7

Toulotte, C., Thévenon, A., and Fabre, C. (2004). Effects of training on static and dynamic balance in elderly subjects who have had a fall or not. *Ann. Readapt. Med. Phys.* 47, 604–610. doi: 10.1016/S0168-6054(04)00179-5

Trombetti, A., Hars, M., Herrmann, F. R., Kressig, R. W., Ferrari, S., and Rizzoli, R. (2011). Effect of music-based multitask training on gait, balance, and fall risk in elderly people: a randomized controlled trial. *Arch. Intern. Med.* 171, 525–533. doi: 10.1001/archinternmed.2010.446

van den Brand, R., Heutschi, J., Barraud, Q., DiGiovanna, J., Bartholdi, K., Huerlimann, M., et al. (2012). Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science* 336, 1182–1185. doi: 10.1126/science.1217416

Vassallo, M., Sharma, J. C., Briggs, R. S., and Allen, S. C. (2003). Characteristics of early fallers on elderly patient rehabilitation wards. *Age Ageing* 32, 338–342. doi: 10.1093/ageing/32.3.338

Verghese, J., Holtzer, R., Lipton, R. B., and Wang, C. (2009). Quantitative gait markers and incident fall risk in older adults. *J. Gerontol. A. Biol. Sci. Med. Sci.* 64, 896–901. doi: 10.1093/gerona/glp033

Wang, F. C., de Pasqua, V., and Delwaide, P. J. (1999). Age-related changes in fastest and slowest conducting axons of thenar motor units. *Muscle Nerve* 22, 1022–1029. doi: 10.1002/(SICI)1097-4598(199908)22:8%3C1022::AID-MUS3%3E3.3.CO;2-6

Weiss, A., Brozgol, M., Dorfman, M., Herman, T., Shema, S., Giladi, N., et al. (2013). Does the evaluation of gait quality during daily life provide insight into fall risk? A novel approach using 3-day accelerometer recordings. *Neurorehabil. Neural Repair 27*, 742–52. doi: 10.1177/1545968313491004

Wickham, C., Cooper, C., Margetts, B. M., and Barker, D. J. (1989). Muscle strength, activity, housing and the risk of falls in elderly people. *Age Ageing* 18, 47–51. doi: 10.1093/ageing/18.1.47

Wild, D., Nayak, U. S., and Isaacs, B. (1981). How dangerous are falls in old people at home? *Br. Med. J. (Clin. Res. Ed.)* 282, 266–268. doi: 10.1136/bmj.282.6260.266

Woollacott, M. H., Shumway-Cook, A., and Nashner, L. M. (1986). Aging and posture control: changes in sensory organization and muscular coordination. *Int. J. Aging Hum. Dev.* 23, 97–114. doi: 10.2190/VXN3-N3RT-54JB-X16X

WHO. (2007). *World Health Organization Report. Global Report on Falls Prevention in Older Age*, 47p. Available online at: http://www.who.int/ageing/publications/Falls_prevention7March.pdf

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer* 3, 32–35. doi: 10.1002/1097-0142(1950)3:1%3C32::AID-CNCR2820030106%3E3.0.CO;2-3

Zimmerman, M. E., Lipton, R. B., Pan, J. W., Hetherington, H. P., and Verghese, J. (2009). MRI- and MRS-derived hippocampal correlates of quantitative locomotor function in older adults. *Brain. Res.* 1291, 73–81. doi: 10.1016/j.brainres.2009.07.043

Zwergal, A., Linnb, J., Xiong, G., Brandt, T., Struppa, M., and Jahna, K. (2012). Aging of human supraspinal locomotor and postural control in fMRI. *Neurobiol. Aging* 33, 1073–1084. doi: 10.1016/j.neurobiolaging.2010.09.022

Conflict of Interest Statement: Prof. Eric Barrey and Dr. Bernard Auvinet developed and validated the gait analysis software Locometrix® for medical and sport applications. This device has been patented by INRA and is sold under exclusive license by the company Centaure Metrix. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 August 2013; paper pending published: 29 September 2013; accepted: 06 February 2014; published online: 25 February 2014.

*Citation: Mignardot J-B, Deschamps T, Barrey E, Auvinet B, Berrut G, Cornu C, Constans T and de Decker L (2014) Gait disturbances as specific predictive markers of the first fall onset in elderly people: a two-year prospective observational study. Front. Aging Neurosci. **6**:22. doi: 10.3389/fnagi.2014.00022*

This article was submitted to the journal Frontiers in Aging Neuroscience.

Magnard et al. BMC Nephrology 2013, 14:259
http://www.biomedcentral.com/1471-2369/14/259

BMC Nephrology

STUDY PROTOCOL Open Access

Effects of a six-month intradialytic physical ACTIvity program and adequate NUTritional support on protein-energy wasting, physical functioning and quality of life in chronic hemodialysis patients: ACTINUT study protocol for a randomised controlled trial

Justine Magnard[1], Thibault Deschamps[1], Christophe Cornu[1], Anne Paris[2] and Dan Hristea[2*]

Abstract

Background: Protein-energy wasting (PEW) is common in hemodialysis patients and is a powerful predictor of morbidity and mortality. Although much progress has been made in recent years in identifying the causes and pathogenesis of PEW in hemodialysis patients, actual management by nutritional interventions is not always able to correct PEW. Some investigators suggest that physical exercise may increase the anabolic effects of nutritional interventions, and therefore may have a potential to reverse PEW. The aim of this study is to investigate the effect of intra-dialytic progressive exercise training and adequate nutritional supplementation on markers of PEW, functional capacities and quality of life of adult hemodialysis patients.

Methods and design: Fifty end-stage renal disease patients undergoing hemodialysis, who meet the diagnostic criteria for PEW, will be randomly allocated into an *exercise* or *control* group for 6 months. The exercise consists of a progressive submaximal individualized cycling exertion using an adapted cycle ergometer, during the three weekly dialysis sessions. Biological markers of nutrition (albumin, prealbumin) will be followed monthly and all patients will be assessed for body composition, walk function, muscle strength, postural stability and quality of life at baseline and during the eighth week (t_{+2}), the sixteenth week (t_{+4}) and the twenty-fourth week (t_{+6}) of the 6-month adapted rehabilitation program.

Discussion: The successful completion of this current trial may give precious clues in understanding PEW and encourage nephrologists to extend prescription of exercise programs as well as therapeutic and as preventive interventions in this high-risk population.

Trial registration: The protocol for this study was registered with the France Clinical Trials Registry NCT01813851.

Keywords: Hemodialysis, Protein-energy wasting, Nutritional supplementation, Intradialytic physical activity, Quality of life

* Correspondence: dhristea@echo-sante.com
[2]ECHO Nantes, Centre de dialyse Laënnec, 23, rue des Piliers de la Chauvinière, 448000 Saint Herblain, France
Full list of author information is available at the end of the article

Background

Nowadays, more than two million people are treated worldwide by dialysis for end-stage renal failure [1]. Despite significant progress in dialysis techniques and in the treatment of associated comorbidities, hemodialysis (HD) patients experience an impairment of their quality of life and have a much higher risk of mortality compared to an age-matched population. A sedentary lifestyle and an altered nutritional status have been identified as major risk factors for adverse outcomes in dialysis patients [2,3].

Dialysis patients have decreased physical functioning (assessed by peak oxygen consumption ($\dot{V}O2$ max), physical performance tests, and self-reported functioning), diminished muscle mass and altered muscle quality, and all of these features are associated with an increased mortality risk [4-6]. These disturbances are directly related to renal failure and comorbidities, and also to adverse effects from medical treatments and from the dialysis itself. Dialysis induces notable metabolic changes: hypovolemia due to ultrafiltration, and rapid changes in electrolyte concentrations and systemic inflammation, which can all adversely affect physical function [7]. In addition, dialysis imposes immobilization over 12–18 hours a week, thereby directly contributing to sedentary behavior that can further worsen the medical condition of HD patients. This vicious circle can finally lead to the development of disability, loss of independence, and death [8]. For all these reasons dialysis patients have low levels of daily physical activity [9]. Therefore, it seems rational to promote programs for exercise training in this population.

In this vein, a large amount of literature published in the past 30 years has documented a myriad of potential benefits from exercise. Several include: increased maximal oxygen uptake capacity ($\dot{V}O2$ max), improved blood-pressure control [10], decreased arterial stiffness [11], decreased systemic inflammation [12], improved solute removal by dialysis [13,14], increased muscle mass, quality and force [15], and favorable psychological adaptations (e.g., higher perceived quality of life) [16]. Thus there is a large body of evidence that the impact of end-stage renal disease (ESRD) can be – for at least a significant part - counteracted by exercise training [7,17-20].

Along with this altered overall physical functioning, malnutrition is highly prevalent in the ESRD population, and is well-documented to be a strong predictor of mortality. Significant evidence comes from the data of large observational trials (USRDS, DOPPS [1-21]) showing that malnourished dialysis patients have an increased risk of mortality [22,23]. In this context, the International Society of Renal Nutrition and Metabolism (ISRNM) has recommended the term "protein–energy wasting" (PEW) to describe the loss of body protein mass and fuel reserves and have defined the diagnostic criteria for this state (see Table 1).

Table 1 ISRNM criteria for the clinical diagnosis of PEW in maintenance dialysis patients

Criteria*	
Serum chemistry:	
	Serum albumin < 3.8 g per 100 ml
	Serum prealbumin < 30 mg per 100 ml
	Serum cholesterol < 100 mg per 100 ml
Body mass:	
	BMI < 23
	Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
	Total body fat percentage < 10%
Muscle mass:	
	Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
	Reduced mid-arm muscle circumference area (reduction > 10% in relation to 50^{th} percentile of reference population)
	Creatinine appearance
Dietary intake:	
	Unintentional low dietary protein intake <0.80 $g.kg^{-1}.day-1$ for at least 2 months
	Unintentional low dietary energy intake <25 $kcal.kg^{-1}.day-1$ for at least 2 months

*At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease related PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2-4 weeks apart.
ISRNM, international society of renal nutrition and metabolism; PEW, protein-energy wasting; BMI, body mass index.

All these criteria are individually associated with an increased risk of adverse outcome so it can be assumed that the concomitant presence of at least three criteria is an even more powerful predictor of morbidity and mortality. However, to the best of our knowledge, until now no report exists about the prevalence and clinical outcomes of PEW (as defined by the ISRNM). It can be noted, however, that a large observational French study reported that 36% of HD patients had a prealbumine < 300 mg/dl, 20% had albumin < 35 g/l and 62% a diminished lean body mass (LBM) < 90% [24].

The mechanisms causing PEW are complex and multifactorial: low nutrient intake (sometimes due to dietary restriction), loss of nutrients into dialysate, abnormalities that stimulate protein degradation and/or decrease protein synthesis. On this last point, we can include the production of inflammatory cytokines, oxidative and carbonyl stress, endocrine disorders (hyperparathyroidism, hypogonadism, diabetes, decreased insuline/insuline like growth factor (IGF) signaling), acidosis, electrolyte

imbalance, and anemia [25]. Further, low daily physical activity causes the loss of muscle mass and force and thereby directly contributes to worsen PEW. Traditional management of PEW according to international guidelines (coming from the EBPG working group on nutrition [26]) consists of dietary counseling, oral nutritional supplements, enteral feeding, and in severe cases, the use of intradialytic or total parenteral nutrition. Several studies, however, have shown that these interventions are not always able to correct PEW [27].

Simultaneously, considerable literature has pointed out the anabolic effects of physical activity. For example, both strength and endurance exercise induce transcriptional changes in genes (IGF, myostatin) favoring anabolic muscle [28]. Morevover, histologic and computed tomography studies have clearly demonstrated a decrease in muscle atrophy and an improvement of the overall muscular structure and quality (increased proportion of type II, oxydative fibers) [29]. There is also some evidence that intradialytic exercise, combined with oral or parenteral nutrition, enhances amino acid uptake and protein accretion in the muscles of HD patients [30,31]. Strong arguments exist for programming the adapted exercise training during the dialysis session rather than on non dialysis days, as there is better adherence by patients who feel safer doing exercise under medical monitoring, as a the counteraction to the inactivity due to the dialysis session, and due to a greater removal of uremic toxins (as shown for urea (KT/V) and phosphorous) by improved tissue mobilization. In addition, according to the large amount of published clinical trials, the risks of prescribing exercise even in this frail population are limited and the benefits largely prevail. Musculoskeletal injuries and cardio-vascular events are the most common risks of physical exercise. Both types of adverse events occur more frequently with high-intensity exercise than with submaximal exercise [32]. In this present trial, patients will be advised to exercise at a moderate level of perceived exertion and will be under continuous supervision by medical personnel. It should also be mentioned that European guidelines on nutrition in HD patients explicitly recommends regular physical exercise [26].

In sum, there are strong arguments in the literature to prescribe exercise in HD combined with nutritional interventions in patients suffering from PEW in an attempt to enhance the anabolic effects of nutrition and hereby reverse this high-risk state.

Specific aims

The aim of this randomized controlled trial is to analyze the impact of a progressive intra-dialytic exercise program combined with nutritional support following current guidelines on nutritional parameters defined for PEW and its potential to reverse PEW. In addition, this trial will study the effect of intradialytic exercise on functional performance (walking, postural control, and muscular strength), body composition and health-related quality of life in HD patients.

Methods and design

Study design

This study is a multicenter, open-label randomized controlled trial. The study will be conducted at the outpatient HD Laennec Dialysis unit and Confluent Dialysis unit of the ECHO Dialysis Association. HD patients will be randomly distributed into a *control* or an *exercise* group. The randomization sequence of the participants will be generated by a computer program. A bio-statistician not involved in recruitment and assessment will perform the randomization.

The present study was approved by the Ethical Committee of Nantes Ouest IV (reference: ID RCB n°2012-A01662-41), and was conducted in accordance with the Declaration of Helsinki (last modified in 2004). All participants will receive written and verbal information about the aims and procedures of the study and will sign a consent form to participate in the study.

Participants' recruitment

All of the 210 patients treated by hemodialysis or online-hemodiafiltration in the participating centers will be screened for the presence of criteria for PEW. The principal investigators will review the existing patients' database for serum albumin, serum prealbumin, C-reactive protein (CRP) levels, body mass index (BMI) and the presence of weight loss according to the PEW criteria. Potential subjects will have additional tests (measure of lean body mass index by bio-impedance and a 3-day dietary record by a qualified dietician in order to evaluate their protein and energy intake). Patients fulfilling inclusion/exclusion criteria and having signed an informed consent for the study participation will undergo randomization generated by a computer program. We expect to recruit approximately fifty HD patients for this study.

Inclusion criteria

- Adult patients, male or female (Age > 18 years).
- Minimum hemodialysis vintage of 3 months.
- Stable on HD, in gender.
- No recent hospitalization.
- No acute or chronic medical conditions that would make exercise training potentially hazardous or primary outcomes impossible to assess.
- Patients who meet the following criteria for PEW (according to [25]), meeting at least three out of the four listed categories and at least one test in each of selected category:

- *Serum chemistry criteria*: Serum albumin level < 38 g/L (Bromcresol Green), or serum prealbumin < 300 mg/L,
- *Body mass criteria*: BMI < 23 kg/m^2, or unintentional weigh loss > 5% over 3 months or > 10% over 6 months,
- *Muscle mass criteria*: lean body mass (LBM) estimated by bioimpedance spectroscopy (Body Composition Monitor (BCM) Fresenius, Bad Homburg, Germany) lower than the 10th percentile of an aged-matched normal population. This method is validated in dialysis patients [33,34].
- Dietary intake criteria: Unintentional low dietary protein intake < 1 g/kg of ideal weight/day for at least 2 months, unintentional low dietary energy intake < 30 kcal/kg of ideal weight/day for at least 2 months.

- Informed consent of the patient.

Exclusion criteria

- Contraindication or inability to perform the physical exercise.
- Inadequate dialysis Kt/V < 1.2.
- Presence of a cardiac pacemaker (incompatible with the BCM measures).
- Systemic inflammation CRP > 20 mg/l.
- Pregnant woman.
- Patient under guardianship.
- Participation in another clinical interventional trial.
- Unstable on dialysis.

Intervention

All the patients will continue their usual dialysis procedure (HD or HDF). No modifications of dialysis modality or prescriptions are allowed except for adaptation of dry weight using clinical criteria.

Both patients in the control and exercise groups will receive dietary counseling by a trained dietician. The prescription of oral nutritional complements or intradialytic parenteral nutrition will be adapted to patient needs according to the dietary record in order to attain goals set by the EBP guidelines for gender energy intake 30–40 kcal/kg of ideal weight/day, and protein intake > 1.1 g/kg of ideal weight/day.

Exercise group

A 6-month adapted rehabilitation program will be conducted by means of progressive submaximal individualized cycling exercise, consisting of three sessions per week. The exercise will be prescribed during the first two hours of dialysis session using an adapted cycle ergometer (« Reck moto-med letto ») that allows cycling in a supine position at different resistance levels. The cycle ergometer displays the number of revolutions per minute, the power developed and the distance virtually traveled. For the patient, these types of visual feedback are motivational factors that are recognized in the literature [35]. Further, it should be noted that this cycle ergometer also allows for passive motorized pedaling (i.e., the patient can pedal without effort).

The aim of this 6-month individualized program is to reach a 30 min duration of continuous cycling at a moderate exercise intensity, which corresponds to the level "3 – moderate" on the Borg Rating Perceived Exertion (RPE) scale (graduated from 0 to 10, where 0 = no effort at all, and 10 = most extreme effort imaginable). According to recommendations issued from a large scale meta-analysis [36], the exercise will be initially performed at this intensity exercise perceived as moderate by the patient on the RPE scale (i.e., level 3). We deliberately chose this method based on the patient's rating perceptions rather than a method based on the heart rate assessment because many dialysis patients have automatic impairment or drug treatments that can interfere with the heart rate control. This method is readily accessible, reproducible and easy to use. Several exercise training intensity levels at 50% to 85% of the maximal oxygen consumption correspond consistently to ratings of 3–7 levels on the Borg RPE scale [37].

To estimate the targeted moderate exercise intensity, an exercise protocol with an increasing intensity on the cycle ergometer will be performed at the inclusion, before the rehabilitation program. During this first evaluation, after a warm-up of 5 minutes without resistance, the patient will pedal with a self-selected chosen cadence against an increasing resistance imposed by the cycle ergometer, until the patient reaches a level perceived as moderate, namely level 3 on the Borg RPE scale. A similar monthly assessment will be realized to update the intensity of cycling exercise. During these sessions, the patient will be regularly asked about level of shortness of breath, any feelings of fatigue and pain, with a visual analogue scale (0–10 cm), in order to reduce the exercise intensity if necessary.

During a dialysis session, the cycling exercise will be performed in the first half of the session. After a 5 min warm-up without resistance, the patient will gradually reach the intensity corresponding to level 3 on the Borg RPE scale. Then the patient will be instructed to maintain this cycling exercise intensity for at least 10 minutes during the first month, 15 minutes during the second one, 20 minutes for the two next months in order to achieve the targeted exercise duration of 30 minutes in the two last months. The first target is to observe an evolution of their functional capacity/performance over time. Finally, a period of active recovery (pedaling

without resistance) followed by a period of passive pedaling recovery will end the exercise session. Blood pressure and heart rate will be measured at the beginning and the end of the exercise session. Heart rate will be maintained below 70% of maximum heart rate during the cycling exercise. At the end of the dialysis session, the HD patient will be asked to estimate pain level, boredom level and mood as perceived during the session, with a visual analogue scale graduated from 0 to 10. Nephrologists, nurses, and a specialist in adapted physical activities will monitor the patient.

Control group

Similarly, at the end of each dialysis session, the "control" patient will be asked to estimate his pain level, boredom level and mood perceived during the session, with a visual analogue scale graduated from 0 to 10 [38].

Outcome measures

All the measures listed below will be assessed at the baseline t_0, and during the eighth week (t_{+2}), the sixteenth week (t_{+4}) and the twenty-fourth week (t_{+6}) of the 6-month adapted rehabilitation program.

Primary outcome measures

The primary outcome of this study is the number of patients who are no longer in a state of protein energy wasting after 6 months of exercise training compared to the control group. We define correction of PEW as the normalization of albumin and prealbumine, and of the lean tissue index, considering these items to be the clinically most relevant for the diagnostic criteria of PEW.

Biological sample

Patients in both groups will have routine serum chemistry measures according to follow-up guidelines for dialysis patients in terms of serum electrolytes, -bicarbonate, s-urea and creatinine, urea reduction rate, KT/V monthly, PTH and 25 OH vitamine D, which will be measured at the beginning and at the end of the study. Patients will receive oral native vitamin D supplementation in order to maintain serum 25 OH levels in the normal laboratory range.

Dietetics survey

Protein and energy intake will be assessed by a qualified dietitian by means of a 3 day food record at the beginning and at the end of the study.

Secondary outcome measures

Secondary outcome measures include: (i) changes in biological markers of nutrition (albumin and prealbumine), body composition (LTI, FTI), muscle strength, walk function, postural stability, quality of life, days of hospitalization, and survival.

Biological markers of nutrition (albumin and prealbumine)

Serum albumine and -prealbumine will be measured monthly. BMI will be calculated at month t_{+2}, t_{+4} and t_{+6}. Serum albumine is measured by the bromcresol green method (normal range (38–52 g/l), serum prealbumine is measured by the immune-turbidimetric method (normal range 300–400 mg/l).

Body composition

Body-composition (overhydration, lean tissue index (LTI, kg/m^2) and fat tissue index (FTI, kg/m^2) will be measured by bioimpedance spectroscopy using a Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) at month 2, 4 and 6 just before the midweek dialysis session.

Walk function

The walk function assessment will be performed using a 6 min-walk-test (6MWT). This test has been considered to be an appropriate test to assess a patient's functional and physiological response and cardiovascular fitness [39]. Patients will walk along a measured circuit (15 m), and are instructed to cover as much distance as possible in the six minutes. Blood pressure, heart rate and rating perceived exertion (RPE) will be assessed before and after the 6MWT.

Muscle strength

Maximal quadriceps strength during a knee extension will be tested using a manual dynamometer (Metil Industry©, Belgium). Patients will perform three maximal leg extensions in sitting position before a dialysis session. At least five minutes of recovery will be provided between 2 consecutive measurements.

Quality of life

The self-reported quality of life will be evaluated using the Medical Outcome Study Short Form 36 (SF-36) [40-42], which has been documented to be reliable and valid in dialysis patients [10,43]. This SF-36 is a generic multidimensional instrument consisting of eight multi-item scales representing: (1) physical functioning (extent to which health limits physical activities, such as self-care, walking, and climbing stairs), (2) social functioning (extent to which physical health or emotional problems interfere with normal social activities), (3) role-functioning physical (extent to which physical health interferes with work or other dally activities), (4) role-functioning emotional (extent to which emotional problems interfere with work or other daily activities), (5) mental health (general mental health, including depression, anxiety, behavioral and emotional control, and general positive effect), (6) vitality (feeling energetic and full of pep rather than tired and worn out), (7) bodily pain (intensity of pain and effect of pain

on normal work, both inside and outside the home), and (8) general health perceptions (personal evaluations of current health, health outlook, and resistance to illness).

Postural stability

Balance during a quiet stance will be tested after a rest period before the dialysis session. The postural test will consist of two conditions of quiet stance: stance on a firm surface with eyes open (EO) and stance on a firm surface with eyes closed (EC). Participants will stand quietly while barefoot, with the head in a straight-ahead position, their arms along the body. During conditions with eyes open, they will be instructed to look at a black spot (with a diameter 2 cm diameter) placed on a white wall in the front of them at a 2 m distance. For each condition, two trials will be performed. The duration of each trial will be 60 s followed by a rest period of 1 minute. During thee condition with EO, the subject's eyes will focus on a stationary eye-level visual target (a black spot with a 2 cm diameter) situated at a 2 m distance. For all data collection of postural sway, we will use a Kistler force plateform (model 9286BA) with subject weight normalization. Data will be sampled at 100 Hz and recorded online. The body sway will be quantified by displacement of the center of foot pressure (COP) in the anterior-posterior (AP) and in the medial-lateral direction (ML). For measuring all of the COP parameters, raw data will be filtered using a fourth-order Butterworth, zero-phase low-pass at 10 Hz. The COP parameters will then be the mean and standard deviation (SD) of COP position in AP and ML directions, SD of velocity in AP and ML directions, mean velocity and area (90% confidence ellipse) (see [44] for details of formulas).

Statistical analysis

The sample size was calculated considering the number of patients who are no longer in a state of protein energy wasting after 6 months of exercise training compared to the control group. For a significance level of 0.05 and 80% power, it was estimated that 22 participants would be required in each group.

Results will be expressed as minimum to maximum or percentage of change, as applicable, and mean ± standard deviation. To test the effects of Group (Exercise *versus* Control) on all outcome measures, univariate two-way analyses of variance (ANOVAs), with the Group (×2) as between-subjects factor and Time (t_0, t_{+2}, t_{+4} and t_{+6}) as the within subject factor, will be carried out for each aforesaid dependent variable. For each analysis, the level of significance was $p < 0.05$. Newman-Keuls comparisons will be used for post-hoc tests following significant effects. If the sphericity assumption in ANOVA is violated (Mauchly's test), corrected tests of significance will be used [45,46]. In that case, the paired t-tests with corrected alpha level will be used as post-hoc comparisons. All the statistical analyses will be conducted using a SPSS software package.

Discussion

To our knowledge, this is the first trial investigating the impact of intradialytic exercise combined with an individualized nutritional support on protein energy wasting. It is also the first trial to investigate the influence of exercise on postural balance, which is of special interest for fundamental and clinical purposes (i.e., the important issue of physical condition in dialysis patients). An improved postural balance signifies a decreased incidence of falls and fractures in this high-risk population [47]. The main forces of this trial will be the randomized design and the individualized management of "real life" patients suffering from PEW. It can be argued that the nutritional support will not be the same in all patients as some will have only nutritional counseling and others ONC and a few IDPN. However, according to the literature the different nutrition methods have equivalent efficacy and the prescription of the type of nutritional support will follow actual guidelines. If this current clinical trial can highlight the expected effects of exercise to reverse PEW, at least for a part, it would be a strong argument for implementing an exercise program in this high-risk population and even in the whole dialysis population in order to prevent the occurrence of PEW.

Competing interests

Authors declare that there is no competing interest.

Authors' contributions

DH has conceived and designed the research protocol, DH and AP contributed in patients' inclusion–exclusion criteria and submission of the protocol to the ethics committee, while JM and TD have suggested important aspects for exercise protocol, functional measures and quality of life. The manuscript was prepared by DH, JM, and TD. All authors revised the manuscript critically for important intellectual content and approved the final version to be published.

Acknowledgements

The study was sponsored by the University Hospital of Nantes.
The research is also sponsored in part by the ACTICLAN prize provided by Fresenius Kabi France.
The Body Composition Monitor is graciously provided by Fresenius Medical Care, France.
The Reck moto med ergometers are provided by Echo Nantes, Dialysis Association.

Sponsor's role

The study was financially supported by the Nantes University Hospital and by the ACTICLAN association. The sponsor had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Author details

[1]University of Nantes, Laboratory "Motricité, Interactions, Performance" (UPRES EA 4334), F-44000 Nantes, France. [2]ECHO Nantes, Centre de dialyse Laënnec, 23, rue des Piliers de la Chauvinière, 448000 Saint Herblain, France.

Received: 31 May 2013 Accepted: 8 November 2013
Published: 26 November 2013

References

1. Grassmann A, Gioberge S, Moeller S, Brown G: **ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends.** *Nephrol Dial Transplant* 2005, **20:**2587–93.
2. O'Hare AM, Tawney K, Bacchetti P, Johansen KL: **Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2.** *Am J Kidney Dis* 2003, **41:**447–454.
3. Lopes AA, Bragg-Gresham JL, Elder SJ, Ginsberg N, Goodkin DA, Pifer T, Lameire N, Marshall MR, Asano Y, Akizawa T, *et al*: **Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the dialysis outcomes and practice patterns study (DOPPS).** *J Renal Nutr* 2010, **20:**224–234.
4. Sietsema KE, Amato A, Adler SG, Brass EP: **Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease.** *Kidney Int* 2004, **65:**719–724.
5. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA: **Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function.** *Kidney Int* 2003, **63:**291–297.
6. Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH: **Uremic myopathy limits aerobic capacity in hemodialysis patients.** *Am J Kidney Dis* 1993, **22:**277–287.
7. Cheema BS, Smith BC, Singh MA: **Rationale for intradialytic exercise training as standard clinical practice in ESRD.** *Am J Kidney Dis* 2005, **45:**912–916.
8. Johansen KL: **Exercise in the end-stage renal disease population.** *J Am Soc Nephrol* 2007, **18:**1845–1854.
9. Johansen KL, Chertow GM, Ng AV, Mulligan K, Carey S, Schoenfeld PY, Kent-Braun JA: **Physical activity levels in patients on hemodialysis and healthy sedentary controls.** *Kidney Int* 2000, **57:**2564–2570.
10. Painter P, Moore GE, Carlson L, Paul S, Myll J, Phillips W, Haskell W: **Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life.** *Am J Kidney Dis* 2002, **39:**257–265.
11. Mustata S, Chan C, Lai V, Miller JA: **Impact of an exercise program on arterial stiffness and insulin resistance in hemodialysis patients.** *J Am Soc Nephrol* 2004, **15:**2713–8.
12. Cheema B, Abas H, Smith B, O'Sullivan A, Chan M, Patwardhan A, Kelly J, Gillin A, Pang G, Lloyd B, *et al*: **Randomized controlled trial of intradialytic resistance training to target muscle wasting in ESRD: the progressive exercise for anabolism in kidney disease (PEAK) study.** *Am J Kidney Dis* 2007, **50:**574–84.
13. Kong CH, Tattersall JE, Greenwood RN, Farrington K: **The effect of exercise during haemodialysis on solute removal.** *Nephrol Dial Transplant* 1999, **14:**2927–2931.
14. Farese S, Budmiger R, Aregger F, Bergmann I, Frey FJ, Uehlinger DE: **Effect of transcutaneous electrical muscle stimulation and passive cycling movements on blood pressure and removal of urea and phosphate during hemodialysis.** *Am J Kidney Dis* 2008, **52:**745–752.
15. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Tourkantonis A, Deligiannis A: **The effects of exercise training on muscle atrophy in haemodialysis patients.** *Nephrol Dial Transplant* 1998, **13:**685–99.
16. Ouzouni S, Kouidi E, Sioulis A, Grekas D, Deligiannis A: **Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients.** *Clin Rehabil* 2009, **23:**53–63.
17. Heiwe S, Jacobson SH: **Exercise training for adults with chronic kidney disease.** *Cochrane Database Syst Rev* 2011, **5**, CD003236.
18. Giannaki CD, Stefanidis I, Karatzaferi C, Liakos N, Roka V, Ntente I, Sakkas GK: **The effect of prolonged intradialytic exercise in hemodialysis efficiency indices.** *ASAIO J* 2011, **57:**213–218.
19. Maheshwari V, Samavedham L, Pandu Rangaiah G, Loy Y, Hsi LL, Sethi S, Lau L: **Comparison of toxin removal outcomes in online hemodiafiltration and intra-dialytic exercise in high-flux hemodialysis: a prospective randomized open-label clinical study protocol.** *BMC Nephrol* 2012, **13:**156.
20. Oh-Park M, Fast A, Gopal S, *et al*: **Exercise for the dialyzed: aerobic and strength training during hemodialysis.** *Am J Phys Med Rehabil* 2002, **81:**814–821.
21. Canaud B, Tong L, Tentori F, Akiba T, Karaboyas A, Gillespie B, Akizawa T, Pisoni RL, Bommer J, Port FK: **Clinical practices and outcomes in elderly hemodialysis patients: results from the dialysis outcomes and practice patterns study (DOPPS).** *Clin J Am Soc Nephrol* 2011, **6:**1651–62.
22. Fung F, Sherrard DJ, Gillen DL, Wong C, Kestenbaum B, Seliger S, Ball A, Stehman-Breen C: **Increased risk for cardiovascular mortality among malnourished end-stage renal disease patients.** *Am J Kidney Dis* 2002, **40:**307–314.
23. Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, Young EW: **Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS.** *Kidney Int* 2002, **62:**2238–2245.
24. Aparicio M, Cano N, Chauveau P, Azar R, Canaud B, Flory A, Laville M, Leverve X: **Nutritional status of haemodialysis patients: a French national cooperative study: French study group for nutrition in dialysis.** *Nephrol Dial Transplant* 1999, **14:**1679–1686.
25. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, *et al*: **A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease.** *Kidney Int* 2008, **73:**391–8.
26. Fouque D, Vennegoor M, ter Wee P, Wanner C, Basci A, Canaud B, Haage P, Konner K, Kooman J, Martin-Malo A, *et al*: **EBPG guideline on nutrition.** *Nephrol Dial Transplant* 2007, **22:**ii45–87.
27. Cano NJ, Fouque D, Roth H, Aparicio M, Azar R, Canaud B, *et al*: **Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study.** *J Am Soc Nephrol* 2007, **18:**2583–91.
28. Kopple JD, Wang H, Casaburi R, Fournier M, Lewis M, Taylor W, Storer T: **Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle.** *J Am Soc Nephrol* 2007, **18:**2975–2986.
29. Kouidi E, Grekas D, Deligiannis A, Tourkantonis A: **Outcomes of long-term exercise training in dialysis patients: comparison of two training programs.** *Clin Nephrol* 2004, **61:**S31–S38.
30. Pupim LB, Flakoll PJ, Levenhagen DK, Ikizler TA: **Exercise augments the acute anabolic effects of intradialytic parenteral nutrition in chronic hemodialysis patients.** *Am J Physiol Endocrinol Metab* 2004, **286:**E589–E597.
31. Majchrzak KM, Pupim LB, Flakoll PJ, Ikizler TA: **Resistance exercise augments the acute anabolic effects of intradialytic oral nutritional supplementation.** *Nephrol Dial Transplant* 2008, **23:**1362–9.
32. Copley JB, Lindberg JS: **The risks of exercise.** *Adv Ren Replace Ther* 1999, **6:**165–171.
33. Moissl U, Wabel P, Chamney PW, Renders L, Bosy-Westphal A, Korth O, Müller MJ: **Validation of a bioimpedance spectroscopy method for the assessment of fat free mass.** *NDT plus* 2008, **1:**ii215.
34. Wieskotten S, Heinke S, Wabel P, Moissl U, Becker J, Pirlich M, Keymling M, Isermann R: **Bioimpedance-based identification of malnutrition using fuzzy logic.** *Physiol Meas* 2008, **29:**639–54.
35. Theodorakis Y, Laparidis K, Kioumourtzoglou E, Goudas M: **Combined effects of goal setting and performance feedback on performance and physiological response on a maximum effort task.** *Percept Mot Skills* 1998, **86:**1035–1041.
36. Segura-Ortí E: **Exercise in haemodyalisis patients: a literature systematic review.** *Nefrologia* 2010, **30:**236–46.
37. Verschell M: **Low intensity exercise as a treatment intervention in obese adults**. In *Handbook of obesity intervention for the lifespan.* Edited by James LC, Linton JC, Linton C. New York: Springer; 2009:103–114.
38. Ninot G: **Psychological outcome of exercise in patients with chronic disease.** *Science & Sport* 2013, **28:**1–10.
39. American Thoracic Society: **ATS statement: guidelines for the six-minute walk test.** *Am J Respir Crit Care Med* 2002, **166:**111–117.
40. Ware JE, Sherbourne CD: **The MOS 36-item shortform health survey (SF-36): I. conceptual framework and item selection.** *Med Care* 1992, **30:**473–483.
41. McHorney CA, Ware JE, Raczek AE: **The MOS 36- item shortform health survey (SF-36): II. psychometric and clinical tests of validity in measuring physical and mental health constructs.** *Med Care* 1993, **31:**247–263.
42. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT: **The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS.** *BMJ* 1993, **306:**1437–1440.
43. Mingardi G, Cornalba L, Cortinovis E, Ruggiata R, Mosconi P, Apolone G: **Health-related quality of life in dialysis patients: a report from an Italian study using the SF-36 health survey: DIA-QOL group.** *Nephrol Dial Transplant* 1999, **14:**1503–1510.

44. Deschamps T, Magnard J, Cornu C: **Postural control as a function of time-of-day: influence of a prior strenuous running exercise or demanding sustained-attention task.** *J Neuroeng Rehabil* 2013, **10:**26.
45. Huynh H, Feldt LS: **Conditions under which mean square ratios in repeated measures designs have exact F-distributions.** *J Am Stat Assoc* 1970, **65:**1582–1589.
46. Huynh H, Mandeville GK: **Validity conditions in repeated measures design.** *Psychol Bull* 1979, **86:**964–973.
47. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C: **Increased risk of hip fracture among patients with end-stage renal disease.** *J Am Soc Nephrol Kidney Int* 2000, **58:**396–399.

doi:10.1186/1471-2369-14-259
Cite this article as: Magnard *et al.*: Effects of a six-month intradialytic physical ACTIvity program and adequate NUTritional support on protein-energy wasting, physical functioning and quality of life in chronic hemodialysis patients: ACTINUT study protocol for a randomised controlled trial. *BMC Nephrology* 2013 **14**:259.