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A semi-immersive virtual reality incremental swing balance task activates prefrontal cortex: A functional near-infrared spectroscopy study

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ABSTRACT

Previous functional near-infrared spectroscopy (fNIRS) studies indicated that the prefrontal cortex (PFC) is involved in the maintenance of the postural balance after external perturbations. So far, no studies have been conducted to investigate the PFC hemodynamic response to virtual reality (VR) tasks that could be adopted in the field of functional neurorehabilitation. The aim of this fNIRS study was to assess PFC oxygenation response during an incremental and a control swing balance task (ISBT and CSBT, respectively) in a semi-immersive VR environment driven by a depth-sensing camera. It was hypothesized that: i) the PFC would be bilaterally activated in response to the increase of the ISBT difficulty, as this cortical region is involved in the allocation of attentional resources to maintain postural control; and ii) the PFC activation would be greater in the right than in the left hemisphere considering its dominance for visual control of body balance. To verify these hypotheses, 16 healthy male subjects were requested to stand barefoot while watching a 3 dimensional virtual representation of themselves projected onto a screen. They were asked to maintain their equilibrium on a virtual blue swing board susceptible to external destabilizing perturbations (i.e., randomizing the forward-backward direction of the impressed pulse force) during a 3-min ISBT (performed at four levels of difficulty) or during a 3-min CSBT (performed constantly at the lowest level of difficulty of the ISBT). The center of mass (COM), at each frame, was calculated and projected on the floor. When the subjects were unable to maintain the COM over the board, this became red (error). After each error, the time required to bring back the COM on the board was calculated (returning time). An eight-channel continuous wave fNIRS system was employed for measuring oxygenation changes (oxygenated-hemoglobin, O_2Hb; deoxygenated-hemoglobin, HHb) related to the PFC activation (Brodmann Areas 10, 11 and 46). The results have indicated that the errors increased between the first and the second level of difficulty of the ISBT, then decreased and remained constant; the returning time progressively increased during the first three levels of difficulty and then remained constant. During the CSBT, the errors and the returning time did not change. In the ISBT, the increase of the first three levels of difficulty was accompanied by a progressive increase in PFC O_2Hb and a less consistent decrease in HHb. A tendency to plateau was observable for PFC O_2Hb and HHb changes in the fourth level of difficulty of the ISBT, which could be partly explained by a learning effect. A right hemispheric lateralization was not found. A lower amplitude of increase in O_2Hb and decrease in HHb was found in the PFC in response to the CSBT with respect to the ISBT. This study has demonstrated that the oxygenation increased over the PFC while performing an ISBT in a semi-immersive VR environment. These data reinforce the involvement of the PFC in attention-demanding balance tasks. Considering the adaptability of this virtual balance task to specific neurological disorders, the absence of motion sensing devices, and the motivating/safe semi-immersive VR environment, the ISBT adopted in this study could be considered valuable for diagnostic testing and for assessing the effectiveness of functional neurorehabilitation.

Abbreviations: fNIRS, functional near infrared spectroscopy; PFC, prefrontal cortex; ISBT, incremental swing balance task; CSBT, control swing balance task; COM, center of mass; O_2Hb, oxygenated hemoglobin; HHb, deoxygenated hemoglobin; VR, virtual reality; PI, postural instability; COP, center of pressure; fMRI, functional magnetic resonance; EEG, electroencephalography; SBT, swing balance task; ICBM, International Consortium for Brain Mapping; BAs, Brodmann Areas; HR, heart rate; 3D, 3 dimensional; STAI, State-Trait Anxiety Inventory; LI, laterality index.

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Introduction

Postural instability (PI) and falls are common in old people and in brain damaged patients suffering from motor disabilities (e.g., Parkinson's disease and stroke), and often result in injuries or hospitalization, which can significantly impair the quality of life of these individuals. More specifically, PI consists of alterations in postural control strategies (i.e., changes in both anticipatory feedforward, and compensatory feedback postural reactions) during standing balance tasks; such anomalies may occur either when responding to an unexpected destabilizing perturbation or when performing voluntary destabilizing movements. To date, the functional neural correlates underlying standing balance control and PI are not well known. Standing balance control is a complex sensorimotor action based on automated and reflexive spinal programs under the influence of several distinct and separate supra-spinal centers in the brainstem, cerebellum and cortex (Drew et al., 2004). Concerning the evaluation of standing balance, systems based on force platforms are currently the standard, since they enable to estimate the center of pressure (COP) and the center of mass (COM) distribution by means of pressure sensors in the force platform (Winter, 1995). The ability to voluntarily move the body to positions within the limits of stability is fundamental to mobility tasks such as reaching for objects, transitioning from a seated to a standing position, and walking. The assessment and rehabilitation of standing balance control require a multidisciplinary approach that could maximize functional recovery with the aid of new technologies, such as virtual reality (VR).

In the last few years, there has been increasing research interest in the application of VR technology for neurorehabilitation. In contrast with traditional rehabilitation procedures, which may be tedious, resource-intensive and expensive, VR provides opportunities to engage in enjoyable and purposeful tasks. Recently, the neural correlates of VR experiences have been investigated by neuroimaging techniques (Bohil et al., 2011; Seraglia et al., 2011). The most widely used neuroimaging modalities are functional magnetic resonance imaging (fMRI) (Bandettini, 2007), electroencephalography (EEG) (Kober et al., 2012), and functional near-infrared spectroscopy (fNIRS) (Ferrari and Quaresima, 2012). However, if compared with the other methods, fNIRS represents an optimal cortical imaging monitoring tool to evaluate the patient's motor performance in a VR environment (Holper et al., 2010), given that it does not require stringent physical and motor constraints. fNIRS is a non-invasive neuroimaging technology that measures concentration changes of oxygenated-hemoglobin (O_2Hb) and deoxygenated-hemoglobin (HHb) in cerebral microcirculation blood vessels by means of the characteristic absorption spectra of hemoglobin in the near-infrared range. Cerebral blood flow adequate for brain activity and metabolic demand is maintained through the processes of autoregulation and neurovascular coupling. Coupling between neuronal activity and blood flow is fundamental to brain function. When a specific brain region is activated, cerebral blood flow increases in a temporally and spatially coordinated manner tightly linked to changes in neural activity through a complex sequence of coordinated events involving neurons, glia, arteries/arterioles, and signaling molecules (Kleinfeld et al., 2011). fNIRS, a vascular-based functional brain imaging technique, relies on this coupling to infer changes in neural activity that is mirrored by changes in blood oxygenation in the region of the activated cortical area (i.e., the increase in O_2Hb and the decrease in HHb).

fNIRS has been applied for evaluating the cortical activation during motor tasks as hand grasping (see Leff et al., 2011 for a review), walking (Atsumori et al., 2010; Miyai et al., 2001), stepping (Huppert et al., 2012), and real-world activities realized in a computer simulated artificial environment (Ayaz et al., 2011; Karim et al., 2012; Tachibana et al., 2011). Different cortical areas were found involved in these artificial environment tasks; in particular parietal and temporal cortices were found activated in response to a multimodal dance video game (Tachibana et al., 2011), the prefrontal cortex (PFC) was found activated during spatial navigation learning in virtual mazes (Ayaz et al., 2011), and temporal cortex was found activated during a balance task associated to a video game (Nintendo Wii, Nintendo Co. Ltd, Japan) simulating downhill skiing (Karim et al., 2012). Moreover, fNIRS studies have highlighted the involvement of the PFC and other cortical regions in maintaining postural balance after external perturbation in healthy subjects and patients recovering from stroke (Mihara et al., 2008, 2012). EEG imaging techniques have also emphasized the importance of the fronto-central region for the regulation of the postural equilibrium of standing subjects voluntarily moving continuously in the forward and backward direction (Slobounov et al., 2005, 2008).

So far, no studies have been conducted for investigating the cortical hemodynamic response to VR tasks that could be adopted in the field of functional neurorehabiliation. Moreover, it has been argued that cognitive decline (particularly related to executive functioning) might be a contributing factor to PI and falls: such failure of executive control has been suggested to be associated with changes in the PFC activation (Anstey et al., 2009). However, the relation between changes in the PFC activation and the PI has not yet well understood. It has been reported that the ability to integrate visual and proprioceptive information is required to adaptively modify the postural stability in response to changes of the VR environment and to perform the goal of action (Sober and Sabes, 2003). Moreover, a hemispheric asymmetry in the visual contribution to postural control has been shown in healthy adults, revealing a greater right hemispheric involvement (Pérennou et al., 1997). Previous fNIRS studies have indicated that the PFC is involved in the maintenance of postural control after external perturbations via the allocation of the attention (Mihara et al., 2008, 2012).

The present study was aimed at assessing by fNIRS the PFC hemodynamic response to a swing balance task (SBT), performed either at constant (control swing balance task —CSBT) or incremental (incremental swing balance task — ISBT) difficulty, in a semi-immersive VR environment driven by a depth-sensing camera. During the SBT, the control of the equilibrium over a virtual swing board, by forward-backward postural sways induced by the task, was required. Considering the: 1) PFC involvement in the allocation of the attentional resources to maintain postural control, and 2) the right hemisphere dominance for visual control of body balance, we hypothesized that the PFC would be activated bilaterally by the increase of difficulty of the SBT, and this PFC activation would be greater in the right hemisphere.

Methods

Subjects

Sixteen right-handed healthy male volunteers (mean age: 29.0 ± 4.8 y.; body mass index: 24.0 ± 2.6 kg/m^2) without self-reported balance or mobility disorders participated in the study. Only men were recruited to avoid whichever gender differences in emotional responses. Informed consent was obtained after a full explanation of the protocol and the non-invasiveness of the study. To exclude left-handed subjects, all participants completed the Edinburgh Handedness Inventory (Oldfield, 1971) assessing hand dominance.

Experimental setup

fNIRS instrumentation

An eight-channel fNIRS system (NIRO-200 with the multifiber adapter, Hamamatsu Photonics, Japan) was used to measure changes in O_2Hb and HHb over the PFC area. Two optical fiber bundles (length: 2.5 m; diameter: 3 mm) carried the light to the left and the right PFC, whereas eight optical fiber bundles of the same size (four for each hemisphere) collected the light emerging from the same cortical areas. The illuminating and collecting bundles were assembled into a specifically designed flexible probe holder (Elastomer LCG20R, Chiorino S.p.A, Italy) ensuring that the position of the 10 optodes,

relative to each other, was firmly fixed. The probe holder consisted of two mirror-like units (10 × 8 cm each) held together by a flexible junction. The detector–illuminator distance was set at 3 cm. The optodes were inserted into the elastomer probe holder by fiber optical bundle socket connectors, and then placed over the forehead skin of both hemispheres. The probe holder was placed over the skin forehead in order to include the underlying PFC. In particular, the measurement points (channels) 7 and 4 were centered (according to the International 10–20 system for the EEG electrode placement) at the Fp1 and Fp2 for left and right side, respectively. The relative Brodmann Areas (BAs) of the 8 measurement points have been calculated by a new method based on ICBM152 (International Consortium for Brain Mapping) head surface for probe placement in multichannel fNIRS (Fig. 3) (Cutini et al., 2011) and were: BA 46 (measurement points: 1; 2; 5; 6), BA 10 (measurement points: 2; 3; 4; 6; 7; 8), and BA 11 (measurement points 4; 8).

The probe holder was fixed over the head by a velcro brand fastener, adapting it to the individual size and shape of the different heads. This flexible probe holder and its position on the head allowed the creation of a stable optical contact with the forehead's scalp for all optodes. The accuracy of the contact between the optodes and the scalp was verified at the end of the protocol. The pressure created by the velcro brand fastener was adequate to induce a partial transient blockage of the skin circulation during the fNIRS study, as witnessed by the presence of the well-defined 10 circles over the forehead skin (depressed cutaneous areas associated with the location of the 10 optodes). The 10 circles over the forehead skin started to disappear 15–20 min after the end of the protocol. The adopted procedure would suggest that a consistent reduction of forehead skin blood flow was occurring as a result of this approach (Takahashi et al., 2011).

The O_2Hb and HHb data from the 8 measurement points, which are defined as the midpoint of the corresponding detector–source pairs (distance set to 3 cm), were acquired at 1 Hz. During the data collection procedure, O_2Hb and HHb concentration changes were displayed in real time, and the signal quality and the absence of movement artifacts were verified. The coming out concentration changes in O_2Hb and HHb, calculated according to a modified Beer-Lambert Law, were transferred online from the fNIRS system to a personal computer. The additional quantification of the concentration changes (expressed in ΔμM) of O_2Hb and HHb was obtained by including an age-dependent constant differential pathlength factor ($4.99 + 0.067^{*}Age^{0.814}$) (Duncan et al., 1996). A 0.1 Hz low-pass filter (SigmaPlot Version 10, Systat Software, Inc., San Jose, CA) was applied to attenuate cardiac signal, respiration, and Mayer-wave systemic oscillations.

The subject's heart rate (HR) was monitored by a pulse oximeter (N-600, Nellcor, Puritan Bennett, St. Louis, MO) with the sensor clipped to the right earlobe (Fig. 1).

Semi-immersive virtual reality system

The study was conducted in a quiet and dimly lit room. Subjects were required to stand barefoot on a force platform (Winposture, Medicapteurs, Balma, France) with a firm surface while watching a 3 dimensional (3D) virtual representation of themselves projected onto a screen placed at a distance of 1.3 m (Fig. 1). The semi-immersive VR environment was implemented by connecting and extending three leading technologies: a 3D depth sensing camera, a middleware, and a high performance real time 3D engine. The 3D depth sensing camera (DepthSense™ 311, Softkinetic™, Belgium) provided a depth map (i.e., 3D information) for the identification of the subject and his distance from a viewpoint within the video stream. The camera, positioned on the right side of the subject at a distance of 1.8 m, was used to record his movements. A middleware system (iisu™ development kit, iisu™ SDK, 2011 Bruxelles, Belgium) allowed the communication between the camera and a suitably implemented end-user application. A cross-platform high performance real time 3D engine (Irrlicht Engine, Irrlicht, 2011, http://irrlicht.sourceforge.net/) allowed the rendering of 3D data in a virtual environment. By using the aforementioned technologies, a 3D model, composed by a cloud of 150 spheres of constant density and shape, was projected on a screen at 30 frames/s (Fig. 1). The 3D model was located over a virtual swing board and the COM was calculated. The so called SBT used in this study was designed and implemented by considering that the subject had to maintain his equilibrium standing on a virtual long arm swing. The arms of the swing (not visible to the subject) were used to construct the physical model of the task, as sketched in Fig. 1. The virtual swing board had an invisible node (i.e., pivot), placed at a height of 2.5 m from the floor around which the subject/board rotated. The virtual swing board (width 25 cm and length 70 cm) was subjected to external destabilizing perturbations (i.e., randomizing the forward–backward direction of the impressed pulse force). The SBT required the subject to maintain his equilibrium on the swinging virtual board by tilting forward and backward his body around his ankles (i.e., ankle strategy). The subject was asked to keep his arms along the body, to remain still on his feet, and not to bend his knees and hips (Fig. 1). At each frame, the COM of the subject model was calculated and projected on the floor. Considering that this projection would be obscured by the legs of the subject model, a yellow circle was positioned on the blue virtual board laterally to the subject in correspondence of the projection of the COM. The COM was used by the subject as an indicator of his position on the virtual swing board. When the subject was unable to maintain the COM within the blue board, the board became red (considered as an error). After each error, the time required to bring back the subject's COM on the board was calculated (returning time). The subject was informed that the errors were recorded and that he should have kept his projected COM within the swing board in order to achieve a high score. After each swing of the board, the board returned, autonomously and slowly (0.4 m/s in velocity), to its original equilibrium condition (blue color). The parameters of the virtual SBT were the following: 1) subject body weight; 2) static and dynamic friction of the swing with respect to the pivot ($5\ kg * m/s^2$ and $0.5\ kg * m/s^2$, respectively); 3) difficulty of the task; and 4) task duration (3 min). The difficulty of the task was obtained by changing linearly the impressed pulse force ($F = m\Delta v/\Delta t$, where Δv is the velocity variation after the perturbation and Δt is the time lag in which the pulse force was applied). Considering a 80 kg subject and $\Delta t = 0.1$ s, the minimum and maximum force values were 800 N ($\Delta v = 1$ m/s) and 3200 N ($\Delta v = 4$ m/s), respectively. For the ISBT, Δv was linearly increased from 1 to 4 m/s (corresponding to the four levels of difficulty); for the CSBT, Δv was kept constant at 1 m/s (corresponding to the first level of difficulty of the ISBT). The interval between the perturbations was fixed at 6 s. Moreover, the direction of

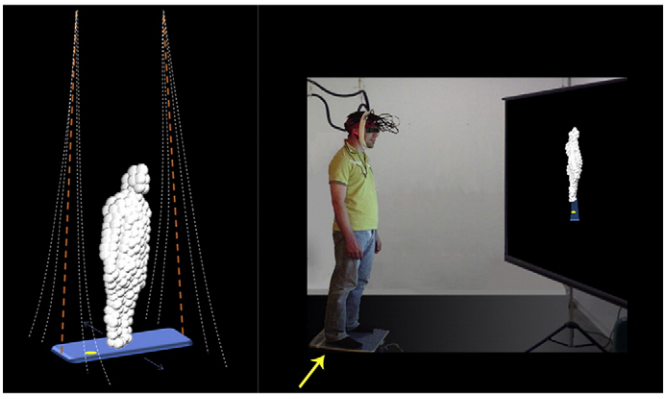

Fig. 1. The experimental setup (right) and the 3D subject model on the virtual swing board (left). The subject, standing on the force platform, observes his body model and the virtual swing board on the screen when performing a semi-immersive virtual reality incremental swing balance task in the forward and backward direction. The arrow indicates the direction of the depth sensing camera framing. Yellow circle: lateral perpendicular projection of the subject's center of mass (COM) with respect to the floor.

the applied force was randomized by choosing the forward or backward direction with a 50% probability. After each perturbation, the board remained still in the most distant point for 2 s, then it returned back to the starting point.

After placing the fNIRS probe over the forehead overlying the prefrontal region of interest, the subject was instructed to move correctly his body during the protocol. Then, the subject performed a short practice trial (around 2 min) at the first level of difficulty of the SBT. Each subject watched his 3D model on the projection screen over a blue virtual swing board turned about 30° with respect to the camera-subject direction, thereby being able to maintain a lateral view with no pronounced head rotation. The reciprocal positions and distances between camera/subject/projection screen are shown in Fig. 1. The presentation of the 3D model over the blue virtual swing board was counterbalanced across subjects for right or left side. The dimension of the scene re-projected on the screen was regulated allowing each subject to view his whole image, including the virtual swing board, without moving his eyes. At a subject-screen distance of 1.3 m, the scene resulted reduced by about 70% with respect to its original dimension (Fig. 1).

Protocol

The protocol included the ISBT and the CSBT; each task lasted 7 min. During the first 2 min (baseline), each subject was asked to stand still observing his image and the blue virtual swing board (including the yellow circle of the COM) represented on the projection screen by the 3D model rendering. Then, an auditory signal indicated the start of a 3-min ISBT or CSBT. The ISBT was divided in four steps (S1; S2; S3; S4) of increasing difficulty (i.e., 1–4 m/s), each 45-s in duration, and each level of difficulty contained 7 random perturbations (forward–backward direction). The CSBT was divided in four steps (S1; S2; S3; S4) of constant difficulty, each 45-s in duration, executed at the lowest level of difficulty of the ISBT (i.e., 1 m/s). Each step contained 7 random perturbations (forward–backward direction). After the end of the last step of ISBT/CSBT, each subject had to observe his image on the projection screen without moving his body for 2 min (recovery time). The interval between the two tasks was 3 min, and the task order was counterbalanced across subjects. During the experiment, the trajectory of the actual COP of the subjects was recorded with the force platform in order to estimate the direction and the amplitude of the COP oscillations during the two tasks. At the end of the study, the subjects completed the Borg rating of perceived exertion scale attributing to the ISBT a value from 6 to 20 (where 6 corresponds to “no exertion”; 9 to “very light”; 13 to “somewhat hard”; 17 to “very hard”; 20 to “maximally hard”) (Borg, 1990). In order to evaluate the “state anxiety”, the subjects completed twenty-items of the State-Trait Anxiety Inventory (STAI) — Form Y-1 before and after the protocol (Spielberger et al., 1983).

Data analysis and statistics

The mean values of the concentration changes in PFC O_2Hb and HHb were calculated over: 1) the last 30-s of the baseline period; 2) the last 10-s of the four steps of the ISBT and CSBT; and 3) every 30-s over the 2-min recovery time. The choice of the last 10-s was driven by the fact that the O_2Hb/HHb signal over the first three steps of the ISBT was stabilized after a transient increase/decrease over the first 25–35 s of each 45-s step. In order to investigate the PFC activation in response to ISBT and CSBT, the repeated measures analysis of variance (ANOVA) was performed for O_2Hb/HHb, HR and performance (number of errors/returning time) mean values. The ANOVA included four factors: channel (4 levels), hemisphere (2 levels), step (5 levels) and task (2 levels). To control for multiple significance tests, the Fisher's LSD adjustment was applied. A one-way repeated measures ANOVA was performed to evaluate the influence of: 1) the steps of the ISBT and CSBT on O_2Hb/HHb, HR and performance (number of errors/returning time) mean values; 2) the channel on O_2Hb/HHb mean values during ISBT and CSBT. To further rule out the presence of a systemic effect as the origin of O_2Hb increase in response to ISBT and CSBT, a series of analysis of covariance (ANCOVA) for the second, third and fourth level of difficulty with HR changes as covariate were performed. The first level of difficulty was not analyzed because the difficulty was the same for ISBT and CSBT. The Pearson's correlation coefficient was calculated to evaluate the relation between: 1) the subjects' performance (mean number of errors/mean returning time for each of the four steps) and O_2Hb/HHb changes (grand average over the 8 measurement points) during ISBT and CSBT; and 2) the subjects' HR and O_2Hb/HHb changes during ISBT and CSBT. Student's t tests were conducted in order to evaluate the presence of any difference between: 1) the anxiety state before and after the protocol; 2) the performance (number of errors/returning time) during ISBT and CSBT for each step; and 3) O_2Hb/HHb changes over the 8 measurement points between the ISBT and the CSBT. To analyze the PFC symmetry/asymmetry in response to the ISBT, a laterality index (LI) was calculated for O_2Hb using the formula $(R - L)/(R + L)$ where R and L indicated O_2Hb mean values of the right (channels 1, 2, 3, and 4) and left side (channels 5, 6, 7, and 8) (Seghier, 2008). $LI > 0$ indicates a greater activation in the right PFC, while $LI < 0$ indicates a greater activation in the left PFC; when the activation of one PFC side is 1.4 times greater than that one found on the other side, the absolute value of LI becomes greater than 0.15. The threshold for establishing the hemispheric dominance was arbitrarily defined as 0.15 (Baciu et al., 2005). All statistical analyses were conducted with SPSS 20.0 (SPSS Inc., Chicago, IL). Data were expressed as mean ± SD. The criterion for significance was $p < .05$.

Results

The behavioral data analysis revealed the following main results. The subject's direction angle, evaluated by monitoring the trajectory of the actual COP with the force platform (Fig. 1), was 30° ± 5°; the amplitude of the forward–backward and the medio-lateral oscillations were 18.3 ± 2.6 cm and 10.0 ± 4.6 cm, respectively. The mean subjective rating of perceived exertion during the ISBT was 10.6 ± 2.3, suggesting that the task was considered by the participants as “light”. There was no significant difference ($t = 1.2$, $p = .24$) in the anxiety state before (31.1 ± 4.5) and after the protocol (29.2 ± 5.2).

The ANOVA analysis for the performance revealed a significant main effect of: 1) the task ($F_{(1, 15)} = 112.76$, $p < .001$; $F_{(1, 15)} = 92.18$, $p < .001$); 2) the step ($F_{(2.09, 31.38)} = 8.15$, $p = .001$; $F_{(2.25, 33.8)} = 6.78$, $p = .002$), and 3) an interaction step * task ($F_{(1.73, 25.88)} = 25.74$, $p < .001$; $F_{(2.52, 37.77)} = 23.08$, $p < .001$) for the errors and the returning time, respectively. The mean values of the errors performed by all subjects in the four levels of difficulty raised between the first and the second level of difficulty of the ISBT, then decreased and remained constant at the third and the fourth level of difficulty (Fig. 2). Concomitantly, the returning time progressively increased during the first three levels of difficulty and remained constant between the third and the fourth levels. During the CSBT, the mean values of the errors and the returning time did not change (Fig. 2). As expected, the number of errors and the returning time were the same at the first step of the ISBT and CSBT ($p > .9$), while in the following three steps the number of errors and returning time related to the ISBT were significantly higher than those ones related to the CSBT (number of errors: $t = 7.283$, $p < .001$; $t = 8.490$, $p < .001$; $t = 5.208$, $p < .001$, respectively; returning time: $t = 3.831$, $p < .001$; $t = 8.476$, $p < .001$; $t = -3.448$, $p = .002$, respectively).

The fNIRS results revealed a typical pattern of cortical activation (characterized by a decrease in HHb accompanied by an increase in O_2Hb of about three-fold of magnitude), which was similarly observed over the 8 measurement points of the PFC in response to the ISBT in all subjects. Specifically, the increase in difficulty during the first three levels was accompanied by a progressive O_2Hb increase and a less consistent HHb decrease over the 8 measurement points of the PFC. In the

fourth level of difficulty of the task, O_2Hb and HHb changes tended to plateau. After performing the task, O_2Hb and HHb changes immediately started to gradually return to their corresponding pre-task levels. As expected, the peak amplitude of the increase in O_2Hb and decrease in HHb was lower during the CSBT with respect to ISBT.

The mean cortical oxygenation changes over the PFC and mean HR changes during ISBT and CSBT observed over the 8 measurement points are shown in Figs. 3 and 4, respectively. The ANOVA analysis, carried out on O_2Hb changes, revealed a significant main effect of: 1) the task ($F_{(1,\ 15)} = 17.55$, $p = .001$); 2) the hemisphere ($F_{(1,\ 15)} = 4.81$, $p = .044$); 3) the step ($F_{(2.57,\ 38.53)} = 36.22$, $p < .001$); an interaction 4) channel * hemisphere ($F_{(2.03,\ 30.44)} = 9.62$, $p = .001$); and 5) step * task ($F_{(2.61,\ 39.10)} = 12.93$, $p < .001$). Specifically, during the ISBT a significant difference was found between: A) the channels 1 and 2, and 2 and 3 within the right hemisphere; and B) the channels 5 and 6 within the left hemisphere. During CSBT a significant difference was found between: A) the channels 2 and 3, and 2 and 4 within the right hemisphere; B) the channels 5 and 6, 5 and 7, and 5 and 8 within the left hemisphere. The ANOVA analysis, carried out on HHb changes, revealed a significant main effect of: 1) the task ($F_{(1,\ 15)} = 8.19$, $p = .012$); 2) the hemisphere ($F_{(1,\ 15)} = 6.17$, $p = .025$); 3) the step ($F_{(1.53,\ 22.90)} = 27.78$, $p < .001$); an interaction 4) channel * hemisphere ($F_{(2.67,\ 40.04)} = 5.93$, $p = .003$; 5) step * task ($F_{(1.94,\ 29.18)} = 8.59$, $p = .001$); and 6) a marginally significant interaction channel * hemisphere * step * task ($F_{(5.84,\ 87.61)} = 1.93$, $p = .087$). Specifically, during the ISBT a significant difference was found between: A) the channels 1 and 4, and 3 and 4 within the right hemisphere; and B) the channels 5 and 7, 6 and 7, and 7 and 8 within the left hemisphere. During CSBT a significant difference was found between the channels 6 and 7 within the left hemisphere.

Subject's HR remained almost unchanged during the ISBT and CSBT. The ANOVA analysis for the HR revealed a significant main effect of the step ($F_{(2.73,\ 41.01)} = 11.41$, $p < .001$), and a significant step * task interaction ($F_{(2.90,\ 43.50)} = 9.33$, $p < .001$). Mean HR values slightly significantly increased at the first level of difficulty (S1) of the ISBT, returned to the baseline value at the second level (S2), and remained unchanged up to the end of the period considered after the end of the task (recovery time) (S3; S4; R1–R4) (Fig. 3). During the CSBT, the mean HR values remained unchanged in the first two steps (S1; S2) and moderately decreased at the third and fourth step (S3; S4) (Fig. 4).

The ANCOVA analysis revealed no covariance HR effect, and a significant main effect for the task ($F_{(1,\ 14)} = 4.89$, $p = .044$; $F_{(1,\ 14)} = 26.77$, $p < .001$; $F_{(1,\ 14)} = 20.51$, $p < .001$) as well as an interaction channel * hemisphere ($F_{(1.76,\ 24.60)} = 9.56$, $p = .001$; $F_{(2.14,\ 29.97)} = 10.44$, $p < .001$; $F_{(2.09,\ 29.22)} = 6.06$, $p = .006$) for the second, third and fourth level of difficulty.

The PFC activation response elicited by the ISBT was confirmed by the fNIRS results obtained from the subtraction of the CSBT O_2Hb/HHb concentration changes from the ISBT O_2Hb/HHb concentration changes (Fig. 5). In particular, O_2Hb increased significantly in all the measurement points, while HHb decreased significantly in the right hemisphere, and only in the channels 5 and 8 of the left hemisphere. The laterality index, calculated on the data of Fig. 5, evidenced a right dominance in 5 subjects (the laterality indexes of the 16 subjects were the following: 0.49, 0.28, 0.19, 0.17, 0.16, 0.14, 0.13, 0.09, 0.05, 0.02, −0.03, −0.06, −0.11, −0.15, −0.23, and −0.90).

The series of channel-wise *t*-tests of O_2Hb revealed a significant difference for all the 8 measurement points in the comparison between ISBT and CSBT in the right ($t = 4.229$, $p = .001$; $t = 3.593$, $p = .003$; $t = 4.048$, $p = .001$; $t = 3.168$, $p = .006$) and left hemisphere ($t = 3.245$, $p = .005$; $t = 4.004$, $p = .001$; $t = 3.435$, $p = .004$; $t = 3.653$, $p = .002$). In particular, the channel 1 of the right hemisphere showed the highest *t* value. For HHb, the channel-wise *t*-tests revealed a significant difference for all the four measurement points of the right hemisphere ($t = -3.067$, $p = .008$; $t = -3.344$, $p = .004$; $t = -3.072$, $p = .008$; $t = -2.564$, $p = .022$), and for 2 measurement points of the left hemisphere ($t = -1.920$, $p = .074$; $t = -1.226$, $p = .239$; $t = -1.230$, $p = .238$; $t = -3.061$, $p = .008$).

In ISBT, a correlation between returning time and the corresponding O_2Hb changes was found ($r = .265$, $p = .034$); the correlations between returning time and the corresponding HHb ($r = -.232$, $p = .065$) and between the errors and the corresponding O_2Hb/HHb changes ($r = .209$, $p = .098$; $r = -.135$, $p = 0.289$, respectively) failed to reach significance. No correlation was found between subjects' HR and PFC O_2Hb/HHb changes during ISBT ($r = .140$ $p = .216$; $r = -.018$, $p = .876$, respectively) and CSBT ($r = .058$, $p = .608$; $r = -.137$, $p = .225$, respectively).

Discussion

To the best of our knowledge this is the first time in which fNIRS has been employed to study the PFC activation response to an ISBT in a semi-immersive VR environment driven by a depth-sensing camera. In all subjects, the increase of the task difficulty over the first three levels of the ISBT was associated with a significant progressive increase in O_2Hb and a concomitant (although less consistent) decrease in HHb over the 8 measurement points of the PFC of both hemispheres. A tendency to plateau in O_2Hb and HHb changes was observed between the third and the fourth level of difficulty of the ISBT concomitantly to a steady number of errors and returning time. Hence, the primary hypothesis of the study was supported only in part by these fNIRS results. In addition, a right hemispheric lateralization was not found. The results of the present study suggest that, during the ISBT, the PFC is bilaterally recruited to integrate visual and proprioceptive information to adaptively modify the PI in response to changes of the virtual environment and perform the goal of action. In addition, these results confirm that

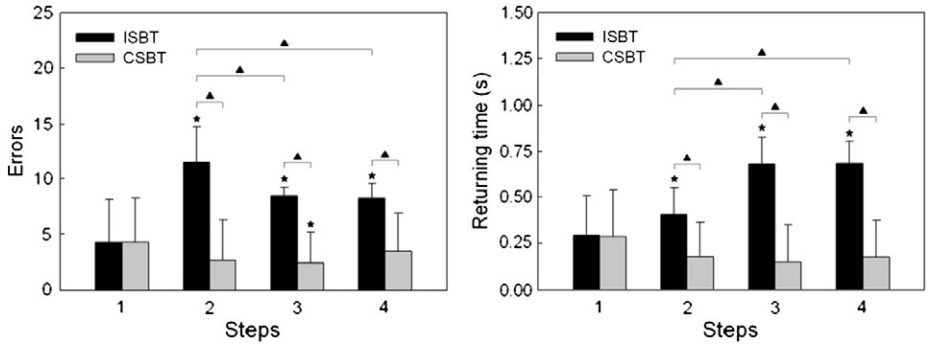

Fig. 2. Mean values of errors (left panel) and returning time (right panel) associated with each 45-s step of the incremental swing balance task (ISBT) and the control swing balance task (CSBT). For the ISBT, the four steps correspond to the levels of difficulty of the task (1–4; see Methods section). For the CSBT, the four steps were executed at the lowest level of difficulty of ISBT (step 1). ($n = 16$; mean ± SD). ★: $p < .05$ with respect to the step 1; ▲: $p < .05$.

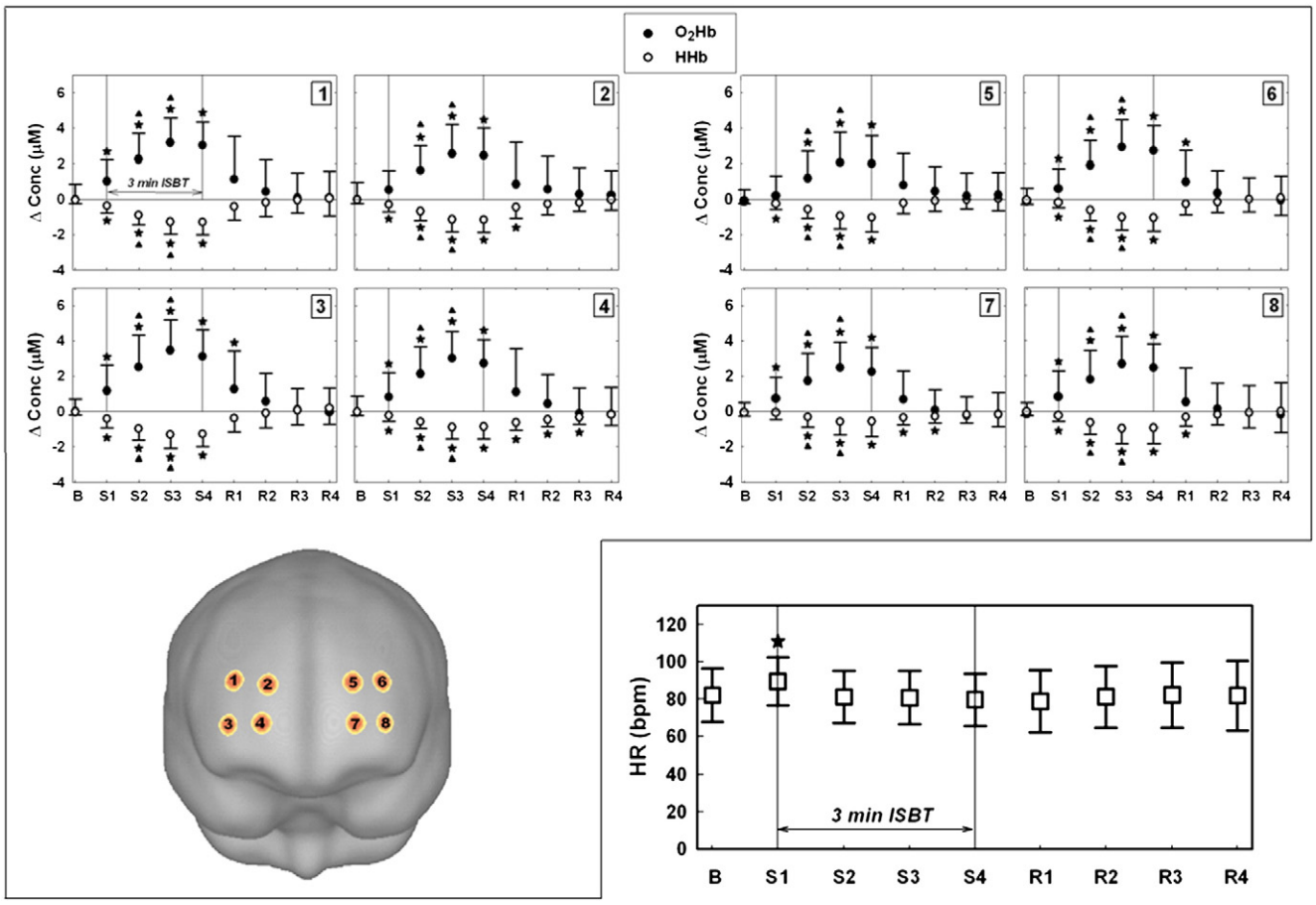

Fig. 3. Mean cortical oxygenation changes (increase in O_2Hb and decrease in HHb) over the prefrontal cortex and mean heart rate (HR) changes (lower right panel) during the 3-min incremental swing balance task (ISBT). The numbers 1–8 of the panels refer to the cerebral projections of the measurement points superimposed on the ICBM152 template brain. The points have been created with a 1-cm Gaussian blurring, to reproduce the spatial resolution of fNIRS. The vertical solid lines limit the task. B: baseline; S(1–4): step (1–4; four levels of difficulty; see Methods section); R(1–4): recovery (1–4); bpm: beats per minute. (n = 16; mean ± SD). ★: $p < .05$ with respect to the baseline. ▲: $p < .05$ with respect to the previous step (level of difficulty).

the PFC is implicated in the adaptation of its response to the changes occurring in the environment, besides its role in the regulation of attention (Miller and Cohen, 2001).

PFC activation

In the last twelve years several studies highlighted fNIRS as a valuable tool for monitoring motor brain functions in healthy subjects and patients during dynamic tasks such as gait and postural changes. Miyai et al. (2001) recorded for the first time the bilateral activation of the medial primary sensorimotor cortex and the supplementary motor area in healthy participants associated with bipedal walking on a treadmill. The involvement of the PFC in locomotor control was evidenced while adjusting the walking speed on the treadmill in healthy adults (Suzuki et al., 2004) and during the recovery process of ataxic stroke (Mihara et al., 2007). Altogether these studies reported an association between the PFC, primary sensorimotor cortex and supplementary motor area with the control of gait, demonstrating the suitability of fNIRS for detecting brain activity during normal and impaired locomotion, and subsequently as being part of a top-down strategy for stroke rehabilitation (Lin et al., 2009).

A relatively recent fNIRS study (Mihara et al., 2008) has reported a bilateral activation response (evidenced by O_2Hb increase only) in the PFC, the supplementary motor cortex and the posterior parietal cortex on healthy standing subjects applying unpredictable and external postural perturbations (brisk forward and backward translations of a moving platform). Mihara et al. (2012), utilizing the same protocol, found that these widespread cortical network activations, including the PFC, are vital for postural control in post-stroke hemiplegic patients.

The results of the present study confirm in part those of Mihara et al. (2008) who first reported the involvement of the PFC in maintaining postural balance. However, in the present study, a novel VR system was utilized to provide visual stimulations to allow subjects to control their COM on the moving board using an ankle strategy, which is different from the proprioceptive stimulations of moving a board under the feet of subjects as used by Mihara et al. (2008, 2012). Therefore, the present study requires more executive control by the PFC to maintain the task demands. More importantly, the results of the present study demonstrate that the PFC activation (evidenced by either O_2Hb increase or HHb decrease) is partly susceptible to the difficulty and learning of the ISBT, which enriches the current knowledge about the role of the PFC in maintaining postural balance.

The PFC activation should reflect its executive/strategic control role in directing/maintaining attention and regulating postural control (Drew et al., 2004; Woollacott and Shumway-Cook, 2002). In the present study, the subjects were requested to control their balance over a virtual swing board by visual feedback without having a direct contact with the board. Therefore, the task adopted in this study tested the ability of the subject to compensate his movements (i.e., lean forward or backward) with those induced by a virtual swing board in the same semi-immersive VR environment (Fig. 1). Bilateral PFC activation was observed in all subjects during the gradually more demanding ISBT (Fig. 3). In the first part of the ISBT, when PFC O_2Hb/HHb increased/decreased consistently, the subjects were

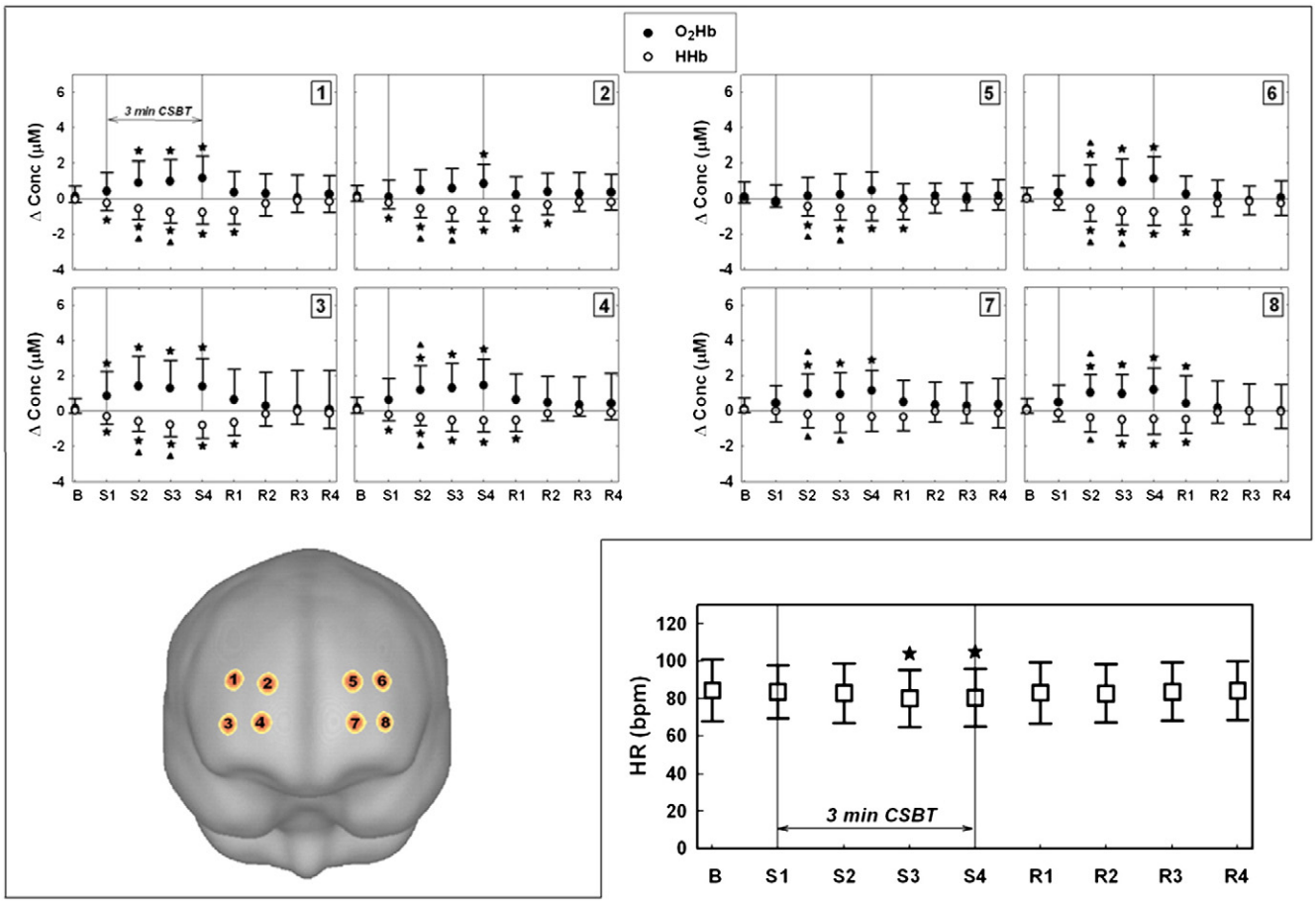

Fig. 4. Mean cortical oxygenation changes (increase in O_2Hb and decrease in HHb) over the prefrontal cortex and mean heart rate (HR) changes (lower right panel) during the 3-min control swing balance task (CSBT). The numbers 1–8 of the panels refer to the cerebral projections of the measurement points superimposed on the ICBM152 template brain. The points have been created with a 1-cm Gaussian blurring, to reproduce the spatial resolution of fNIRS. The vertical solid lines limit the task. B: baseline; S(1–4): step (1–4; the steps were executed at lowest level of difficulty of the incremental swing balance task; see Fig. 2 and Methods section); R(1–4): recovery (1–4); bpm: beats per minute. (n = 16; mean ± SD). ★: $p < .05$ with respect to the baseline. ▲: $p < .05$ with respect to the previous step.

focused to pursue the goal of action recruiting attentional resources to maintain postural balance (Mihara et al., 2008; Woollacott and Shumway-Cook, 2002) and to attain a high level of performance by minimizing errors. The number of errors increased from the first and the second level of difficulty of the ISBT, then partially decreased from the second and the third level of difficulty (Fig. 2). The returning time instead progressively increased from the first up to the third level of difficulty. The number of errors and the returning time were

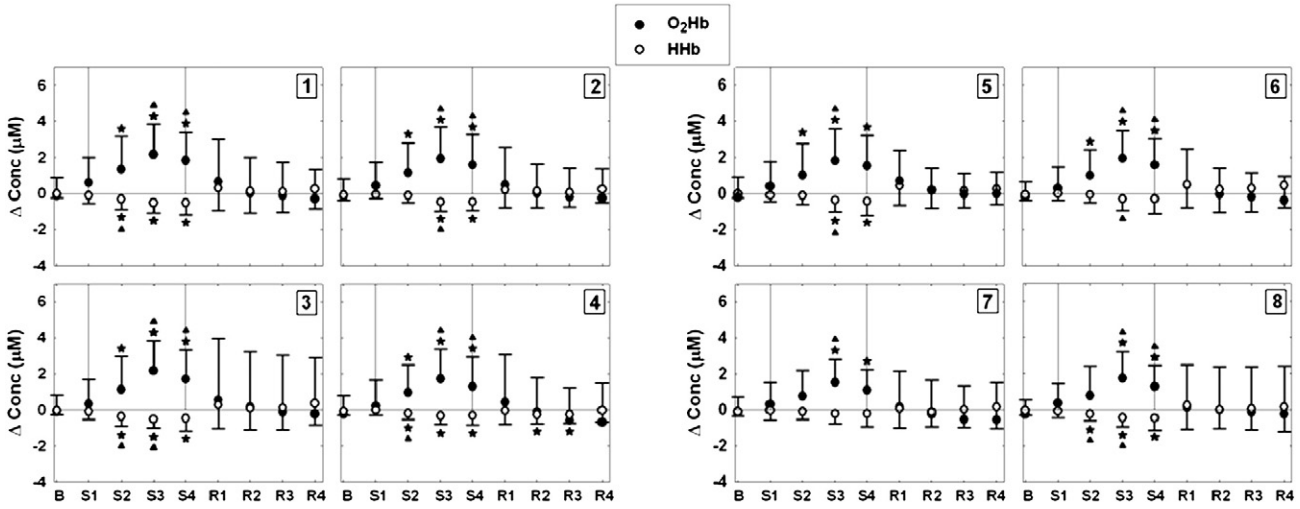

Fig. 5. Mean cortical oxygenation changes over the prefrontal cortex during the 3-min incremental swing balance task after the subtraction of O_2Hb and HHb changes occurring during the control swing balance task (Fig. 4). The vertical solid lines limit the task. B: baseline; S(1–4): step (1–4; four levels of difficulty); R(1–4): recovery (1–4). (n = 16; mean ± SD). ★: $p < .05$ with respect to the baseline. ▲: $p < .05$ with respect to the previous step (level of difficulty).

unchanged from the third up to the fourth level of difficulty. Interestingly, PFC O_2Hb and HHb were also unchanged from the third up to the fourth level of difficulty. This tendency to plateau, observed in the PFC activation in concomitance with an improvement in the task performance and with a steady returning time, could be partly explained by a no further involvement of PFC in performing the ISBT when motor skill adaptation with the task itself occurs (Leff et al., 2008). In the CSBT, as expected, the number of errors and the returning time were constant and lower than those observed in the ISBT. Concomitantly, PFC O_2Hb and HHb, after a small change between the first and the second step of the CSBT, did not change from the second up to the fourth step. Although all the subjects performed many errors in the last level of difficulty of the ISBT, they considered the perceived exertion as "light".

Nevertheless, the PFC activation could be affected by either the physiological or the psychological state of the subjects leading to increased HR and blood pressure. For these reasons, in this study only men were recruited to avoid at least gender differences in emotional responses. Moreover, within the investigated subjects, no significant difference in the anxiety state (before and after the end of the task) was found. As clearly shown in the Figs. 3 and 4, HR significantly increased (with respect to the baseline) only over the first step (S1) in the ISBT, and over the third (S3) and forth (S4) steps in the CSBT. Moreover, the influence of HR changes on the PFC O_2Hb/HHb changes has been ruled out with the ANCOVA analysis results that revealed no covariance of O_2Hb and HHb changes with HR. These results could be enough to disprove the interference of any emotional component on PFC activation.

Although the observed interaction between fNIRS channels and hemisphere suggests a right hemispheric dominance during the ISBT, the results of the laterality index revealed a right dominance in 5 out of 16 subjects only, and a left dominance in 2 out of 16 subjects. Furthermore, the group-averaged analysis did not reveal an explicit hemispheric lateralization, confirming the suboptimal consistency of PFC lateralization. Therefore, the second hypothesis of the study was not fulfilled. This appears to be in contrast with the greater right PFC activation found in previous studies performed in brain damaged patients in whom the right hemisphere functions were found related to the visual control of postural balance (Pérennou et al., 1997, 2008). On top of that, these results might be also related to the neural mechanisms of goal directed visuo-spatial attention, which are typically right-lateralized (Corbetta and Shulman, 2002). On the other hand, previous fNIRS studies on complex movements, such as knot-tying (Leff et al., 2008) and apple peeling (Okamoto et al., 2004) tasks have not revealed a specific PFC hemispheric lateralization. Thus, the bilateral PFC engagement during the ISBT found in the present study might be well explained in terms of executive functions and strategic control. Importantly, this interpretation is also consistent with the fact that PFC activation is positively correlated with task difficulty: the harder the task, the higher the requirement of unspecific cognitive resources (Miller and Cohen, 2001).

The role of the frontal cortical regions in human postural control has been investigated also by EEG. Slobounov et al. (2005) found that the frontal region has an important role for the regulation of the postural equilibrium of standing subjects voluntarily moving continuously in the forward and backward direction as far as they could, or only in the forward direction. The fronto-central region (i.e., Fz, F4, FCz, Cz and C4 sites) was activated when the balance was at risk of compromise (i.e., at the limits of stability). Although this frontal cortical area was not specifically investigated in the present study, these frontal regions are relatively close to the measured BAs (Fig. 3). Nevertheless, postural control seems to be modulated by other cortical areas than those investigated in the present study. Recently, the modulation of the cortical activity by the level of difficulty of a balance task was found in the temporal cortex in response to active balancing during a video game simulating downhill skiing by a 32-channel fNIRS system (Karim et al., 2012).

Semi-immersive VR and fNIRS integration

This study provides novel information regarding the balance control in healthy subjects during a semi-immersive VR balance task (i.e., ISBT). It is well known that the postural control involves somatosensory, visual and vestibular systems and evaluates the ability to remain stable and control the position of COM under different movements and speeds. The ISBT adopted in this study was primarily in the forward–backward direction, which is commonly assessed in balance programs for elderly people prone to falling, including certain age related neurodegenerative disorders such as Parkinson's disease. The present study highlights the potential advantages offered by the combined use of a semi-immersive VR based neurorehabilitation system and fNIRS to assess the PFC oxygenation changes. In contrast with traditional rehabilitation procedures, which may be tedious, resource-intensive and expensive, VR provides opportunities to engage in enjoyable and purposeful tasks. Interactive, functional neurorehabilitation training exercises using visual biofeedback, coupled with sensitive, real-time monitoring of movements motivates patients to achieve better balance control faster. Recently, some studies have investigated in people with Parkinson's disease the advantages of: 1) the balance training on PI (Smania et al., 2010), and 2) the VR-augmented balance training on sensory organization and attentional demand for postural control (Yen et al., 2011). In addition, Mirelman et al. (2011) demonstrated that VR-gait training improved the physical performance and gait in people with Parkinson's disease.

The compatibility of VR systems with neuroimaging techniques, such as fNIRS, allows a multimodal stimulus presentation with a high degree of ecological validity and control while changes in brain activity are monitored (Bohil et al., 2011; Seraglia et al., 2011). Visual and/or auditory feedback can be provided in real time to monitor the subject's performance with more accuracy than traditional therapies. In addition, VR environments for neurorehabilitation can be created in a warm and friendly atmosphere to motivate patients to follow the training without interruptions.

Commercial systems, such as Balance Master system (NeuroCom International Inc., Clackamas, OR) and Nintendo Wii, have been considered in neurorehabilitation programs (Meldrum et al., 2012; Srivastava et al., 2009), but unfortunately they do not allow an accurate interaction between the whole human body and the virtual space. In the Balance Master system and in the Nintendo Wii balance board, the force platforms do not directly measure human posture. In the case of the Nintendo Wii console, the human posture is inferred by motion sensor information distributed on the physical board and integrated with the information collected by low resolution environmental sensors. In addition, the Nintendo Wii system presumes the subject's posture on the basis of the posture suggested on the computer screen by the system itself. In the present study, the use of the depth-sensing camera for capturing the whole subject's motion (which preserves the geometry of the movement with respect to the body and the environment) allowed an accurate mapping of the COM movements of the subject into a semi-immersive VR environment (the subject's movements were not suggested by the system), which was confirmed using a standard force platform.

Limitations

The limitations of fNIRS technique have been previously discussed (Dieler et al., 2012; Quaresima et al., 2012). However, only a few limitations should be noted for an adequate understanding of the current findings. First, differences in the difficulty and duration of the ISBT could have provided different PFC activation patterns. Second, given that the study included only healthy subjects, the effect of the ISBT on subjects with PI remains unclear. Third, a learning effect was possibly associated with the ISBT/CSBT. Although in the design of this study the ISBT and the CSBT were randomized, the effects of

habituation (Loubinoux et al., 2001) and procedural learning (Eliassen et al., 2001) cannot be completely excluded from the current experimental design. Fourth, only a restricted area of the PFC was explored using an 8-channel fNIRS system. In fact, the simultaneous investigation of the other cortical areas involved in balance tasks, such as supplementary motor, parietal and temporal cortices (Karim et al., 2012; Mihara et al., 2008), could be carried out by using fNIRS systems equipped with a larger number of channels (Cutini et al., 2012; Ferrari and Quaresima, 2012). Fifth, it was not possible to correlate PFC activation with muscle activation or postural adjustment strategy because electromyographic and/or kinesiological measurements were not performed. Sixth, the task-evoked changes occurring in forehead skin perfusion could represent an overestimation of the cortical changes as measured by fNIRS. Recent reports have raised a question against the assumption that PFC O_2Hb/HHb changes originated only from the cortical hemodynamic response (Gagnon et al., 2011, 2012; Kirilina et al., 2012; Kohno et al., 2007; Takahashi et al., 2011). Such task-evoked changes could result either from systemic blood pressure changes or from skin-specific regulation mechanisms different from the HR autonomic control. In this study, there was no difference in the anxiety state before and after the protocol; in addition, HR remained almost stable over the ISBT and CSBT (Figs. 3 and 4). However, forehead skin perfusion changes would have occurred during the tasks. This confounder was investigated by simultaneous fNIRS and laser Doppler forehead skin flow meter measurements during cognitive tasks (Kohno et al., 2007; Takahashi et al., 2011). The laser Doppler skin flow meter was not utilized in this study because the technique cannot be applied during movements. To the best of our knowledge, although several instrumental and/or analysis methods have been proposed to separate cortical and extra-cranial components in fNIRS signals (see Kirilina et al., 2012 for a review), no consensus has been reached yet on the best strategy to be adopted in order to minimize this effect and/or separate superficial and cortical fNIRS responses. In terms of data analysis, considering the limited number of measurement points (8) of the present study, a shorter separation channel could not be included in the used probe holder. Therefore, the authors could not be able to suppress the potential superficial artifacts using an additional systemic predictor in the general linear model analysis of the fNIRS data (Gagnon et al., 2011, 2012). In this study, as suggested by Takahashi et al. (2011), the superficial effect was minimized by an accurate "measurement setting" (see Methods section). In particular, the flexible probe holder and its position on the head allowed the creation of a stable optical contact with the forehead's scalp for all optodes. The pressure created by the velcro brand fastener was adequate to induce a partial transient blockage of the skin circulation during the fNIRS study, as witnessed by the presence of the well-defined 10 circles over the forehead skin (depressed cutaneous areas associated with the location of the 10 optodes). The adopted procedure would suggest that, although no correction algorithm has been utilized, the amplitude of the activation responses in the eight measurement points during the ISBT (Fig. 3) compared with the small activation responses in the CSBT, the inconsistent HR changes (Figs. 3 and 4), and the partial transient blockage of the skin circulation under the optodes could support the argument that the observed PFC activation during the ISBT is attributable mainly to cortical oxygenation changes.

On top of that, in this study all the potential confounders/contamination factors for the fNIRS signals have been eliminated by subtracting the PFC oxygenation changes related to the CSBT from those related to the ISBT (Fig. 5). This subtraction procedure eliminated also possible differences related to inter-individual anatomical differences (i.e., scalp depth) over the investigated PFC areas. Therefore, the observed differences in the shape and/or amplitude of the hemodynamic response over the investigated PFC areas are very likely to be related to the increase of the level of difficulty of the ISBT.

Conclusion

Although the ISBT has not been yet applied in the neurorehabilitation field, it has the potential to be adopted in patients with movement disorders due to neurological dysfunction such as Parkinson's disease. Specifically, the advantages of the combined use of a semi-immersive VR based neurorehabilitation system and fNIRS to promote visuo-motor (re)learning for better body movement control can be listed as follows: 1) the task requires the ability to maintain oneself over a swing balance board that is not present in the real world, so the patient with a reduced mobility does not risk falling; 2) the visual feedback can be seen on the computer screen with the objective of knowing the errors and to sustain the motivation for achieving a higher level of performance; 3) the combined system produces fNIRS data for online/offline analysis which can quantify the patient's cortical activation and performance during the motor activity.

In conclusion, this study has demonstrated that oxygenation increased over the PFC of both hemispheres in healthy subjects performing an ISBT in a semi-immersive VR environment. The observed PFC activation was partly modulated by the levels of difficulty of the task suggesting that the PFC is bilaterally involved in attention-demanding balance tasks. Considering the adaptability of this virtual balance task to specific neurological disorders, the absence of motion sensing devices, the motivating/safe semi-immersive VR environment, and the adopted ISBT could be considered valuable for diagnostic testing and for assessing the effectiveness of functional neurorehabilitation.

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Conflict of interest statement

No author has any conflict of interest with respect to this article.

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