A novel semi-immersive virtual reality visuo-motor task activates ventrolateral prefrontal cortex: A functional near-infrared spectroscopy study

Article *in* Journal of Neural Engineering · June 2016

DOI: 10.1088/1741-2560/13/3/036002

10 authors, including:

Sara Basso Moro
University of Padova

Danilo Avola
Sapienza University of Rome

Sabrina Brigadoi
University of Padova

Stefania Lancia
Università degli Studi dell'Aquila

A novel semi-immersive virtual reality visuo-motor task activates ventrolateral prefrontal cortex: a functional near-infrared spectroscopy study

2016 J. Neural Eng. 13 036002

(http://iopscience.iop.org/1741-2552/13/3/036002)

IOP Publishing Journal of Neural Engineering
J. Neural Eng. **13** (2016) 036002 (14pp) doi:10.1088/1741-2560/13/3/036002

A novel semi-immersive virtual reality visuo-motor task activates ventrolateral prefrontal cortex: a functional near-infrared spectroscopy study

Sara Basso Moro[1,4], Marika Carrieri[1,4], Danilo Avola[1], Sabrina Brigadoi[2], Stefania Lancia[1], Andrea Petracca[1], Matteo Spezialetti[1], Marco Ferrari[3], Giuseppe Placidi[1] and Valentina Quaresima[1]

[1] Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[2] Department of Developmental Psychology, University of Padova, Padova, Italy
[3] Department of Physical and Chemical Sciences, University of L'Aquila, L'Aquila, Italy

E-mail: valentina.quaresima@univaq.it

Received 21 September 2015, revised 4 February 2016
Accepted for publication 2 March 2016
Published 22 March 2016

Abstract

Objective. In the last few years, the interest in applying virtual reality systems for neurorehabilitation is increasing. Their compatibility with neuroimaging techniques, such as functional near-infrared spectroscopy (fNIRS), allows for the investigation of brain reorganization with multimodal stimulation and real-time control of the changes occurring in brain activity. The present study was aimed at testing a novel semi-immersive visuo-motor task (VMT), which has the features of being adopted in the field of neurorehabilitation of the upper limb motor function. *Approach.* A virtual environment was simulated through a three-dimensional hand-sensing device (the LEAP Motion Controller), and the concomitant VMT-related prefrontal cortex (PFC) response was monitored non-invasively by fNIRS. Upon the VMT, performed at three different levels of difficulty, it was hypothesized that the PFC would be activated with an expected greater level of activation in the ventrolateral PFC (VLPFC), given its involvement in the motor action planning and in the allocation of the attentional resources to generate goals from current contexts. Twenty-one subjects were asked to move their right hand/forearm with the purpose of guiding a virtual sphere over a virtual path. A twenty-channel fNIRS system was employed for measuring changes in PFC oxygenated–deoxygenated hemoglobin (O_2Hb/HHb, respectively). *Main results.* A VLPFC O_2Hb increase and a concomitant HHb decrease were observed during the VMT performance, without any difference in relation to the task difficulty. *Significance.* The present study has revealed a particular involvement of the VLPFC in the execution of the novel proposed semi-immersive VMT adoptable in the neurorehabilitation field.

Keywords: visuo-motor task, functional near-infrared spectroscopy, LEAP Motion Controller, neurorehabilitation, ventrolateral prefrontal cortex, virtual reality

(Some figures may appear in colour only in the online journal)

1. Introduction

In recent years, novel strategies for the lower and the upper limb motor rehabilitation have been developed in order to

[4] These authors contributed equally to this work.

take advantage of the brain reorganization aspects of neuroplasticity. For example, current clinical guidelines for stroke rehabilitation (see Belda-Lois *et al* 2011, Langhorne *et al* 2011 for reviews) are based on the increasing evidence of neuroplasticity potentials for motor relearning and brain remodeling, which occur within defined plastic time windows during stroke recovery (Kleim and Jones 2008, Wahl and Schwab 2014). However, training has to respect some specific principles in order to induce neuroplasticity to occur and to maximize its potentialities. Basic neuroscience research suggested that training has to be repetitive, challenging, specific, intense, transferable to similar behaviors, and it has also to take into account the timings for neuroplasticity to occur, the training salience and the age of the patient (Kleim and Jones 2008). The research into robotic-assisted therapies (see Chang and Kim 2013, Basteris *et al* 2014 for reviews), the development of haptic interfaces, and the advent of virtual reality (VR) technologies (Langhorne *et al* 2009, Buma *et al* 2013) have introduced new promising scenarios for rehabilitation trainings, which allow for the implementation of the suggested proposals to enhance brain remodeling. VR is a computer-based technology that allows the creation of multisensory simulated environments, in which users can interact and receive real-time feedbacks on their performance. The possibility to have multi-sensorial (visual, auditory, and/or tactile) feedbacks, typical of the VR environments, could address the improvement and the facilitation of the motor relearning processes (Subramanian *et al* 2010). There are three types of VR systems: non-immersive, semi-immersive and total immersive. In non-immersive techniques, the virtual environment is visualized through conventional computer monitors or projector screens. In semi-immersive techniques, subjects can perform activities both in the real and virtual environment and can perceive a strong involvement in the virtual environment. In immersive techniques the virtual environments are simulated through head-mounted displays, three- dimensional (3D) glasses, or similar equipment. In comparison with the non-immersive and the immersive techniques, the semi-immersive VR systems represent a good compromise between the degree of possible virtual involvement of the participant and the inconvenience of the equipment needed to make happen the virtual environment. In particular, the LEAP Motion Controller (https://leapmotion.com) is a high-resolution 3D hand-sensing device, which allows a freehand natural interaction necessary for the implementation of realistic semi-immersive VR systems. This low cost non-bulky small device has an extremely accurate reactivity (Weichert *et al* 2013).

With respect to the lower limb motor function, the recovery of the upper limb motor function is more challenging (Buma *et al* 2013), given its complex organization within the motor cortex that, together with the related descending spinal pathways and the biomechanical features, provide humans with the vast repertoire of all possible postures and gestures achievable. In addition to the primary motor cortex, other cortical regions are involved in the upper limb motor control, such as the prefrontal cortex (PFC). The PFC is a region of the cerebral cortex strongly involved in the top-down control of behavior and in the activation of the networks finalized at the temporal organization of goal-directed actions, in order to adapt to the changes that occur in the environment and/or to adapt to the mental images of new programs of action (Wise *et al* 1996, Miller and Cohen 2001, Fuster 2008, Tanji and Hoshi 2008, Passingham and Wise 2012). In particular, the ventrolateral PFC (VLPFC) shows a main involvement in visuo-motor learning tasks (Tanji and Hoshi 2008, Yamagata *et al* 2012, Hoshi 2013), as in the case of the rehabilitation tasks conducted in VR environments. In addition, the left VLPFC seems to be engaged in maintaining and retrieving the goal-relevant information for the action control (Badre and Wagner 2007, Souza *et al* 2009), whereas the right VLPFC seems to be engaged mainly in the inhibition of the motor responses (Aron *et al* 2004) and in the reflexive orienting (Corbetta and Shulman 2002, Corbetta *et al* 2008). Nevertheless, the neural mechanisms underlying the innovative VR rehabilitation strategies and the specific effects of the rehabilitation trainings have not been clearly understood yet (Wahl and Schwab 2014).

The compatibility of VR systems with neuroimaging techniques offers a great opportunity of monitoring the cortical dynamics in response to the rehabilitation trainings, thus allowing the investigation of brain reorganization and neuroplasticity with multimodal stimulation and real-time control of the changes occurring in the brain (Bohil *et al* 2011). To predict long term outcome in neurorehabilitation and to monitor plasticity enhancements in response to behavioral trainings, the most widely used neuroimaging modality is represented by functional magnetic resonance imaging (fMRI) (Bandettini 2007, Wilde *et al* 2012). However, unlike fMRI, functional near-infrared spectroscopy (fNIRS) (Boas *et al* 2014, Fishburn *et al* 2014), with relatively low physical constraints and high degree of ecological validity, represents an optimal tool for the cortical monitoring in healthy subjects and patients (see Ferrari and Quaresima 2012, Scholkmann *et al* 2014 for reviews), and for evaluating the effects of neurorehabilitation therapies as well as the functional reorganization after brain damage (Mihara and Miyai 2012, Obrig 2014). fNIRS is a non-invasive neuroimaging technology that measures concentration changes in oxygenated–deoxygenated hemoglobin (O_2Hb/HHb, respectively) of the cerebral microcirculation blood vessels by means of the characteristic absorption spectra of hemoglobin in the near-infrared range. When a specific brain region is activated, cerebral blood flow increases in a temporally and spatially coordinated manner through a complex sequence of coordinated events, tightly linked to changes in neural activity (i.e., neurovascular coupling). The coupling between neuronal activity and cerebral blood flow is fundamental to brain function, and fNIRS relies on this coupling to infer changes in neural activity, which is mirrored by the blood oxygenation changes of the activated cortical region (i.e., the increase in O_2Hb and the decrease in HHb). fNIRS has been already utilized in combination with VR technologies for evaluating the cortical activation during upper and lower limb motor tasks such as grasping (Holper *et al* 2012), standing balance control (Basso Moro *et al* 2014, Ferrari *et al* 2014), or walking (Sangani *et al* 2015).

Since previous studies have reported positive effects in the upper limb motor function recovery and in neural adaptation after brain damage with trainings executed in VR environments (e.g., Adamovich *et al* 2005, Jang *et al* 2005, Merians *et al* 2009, Turolla *et al* 2013, Tsoupikova *et al* 2014), in the present study the potentialities of a novel visuo-motor task (VMT), performed in a semi-immersive VR environment, have been tested. Therefore, this study was aimed at investigating, first in a healthy population, the feasibility of the novel VMT in eliciting a focalized cortical hemodynamic response (used as testing metric for the present study). The achievement of reasonable results in the present study could encourage the use of this proposed novel VMT in a clinical population (e.g., patients with stroke and/or cerebral palsy, who need a neuro-rehabilitation treatment dedicated to the recovery of the upper limb motor function, such as motor planning, motor coordination, motor reflex, and visuo-motor function, etc). The concomitant VMT-related PFC response was monitored non-invasively by a twenty-channel fNIRS system. The VMT was executed at three different levels of difficulty and required: (1) the control of the hand and forearm movement function; (2) the adaptation to the virtual stimuli; (3) the active interaction with the virtual environment through the hand/forearm motor actions; and (4) the real-time visuo-motor integration of the visual feedbacks. Considering the PFC involvement in the motor action planning and in the allocation of the attentional resources to generate goals from current contexts or events, it was hypothesized that the PFC would be activated bilaterally in response to the VMT, with an expected greater level of activation in the VLPFC.

2. Materials and methods

2.1. Subjects

Twenty-one right-handed healthy male volunteers (age: 26.1 ± 2.9 y; level of education: 14.9 ± 2.5 y) participated in the study. In order to avoid whichever gender differences in emotional responses (Matud 2004, Leon-Carrion *et al* 2006) and in visuo-motor abilities (Wang *et al* 2015), only men were recruited. Only subjects who, in a preliminary familiarization session, correctly completed two out of three levels of difficulty of the task (see the 'protocol' section) were included in the study. According to the tenets of the latest Declaration of Helsinki, written and informed consent was obtained from each participant prior to the recording after a full explanation of the protocol and the non-invasiveness of the study. The study was approved by the University Ethics Committee. To exclude left-handed subjects, all participants completed the Edinburgh Handedness Inventory (Oldfield 1971) assessing hand dominance.

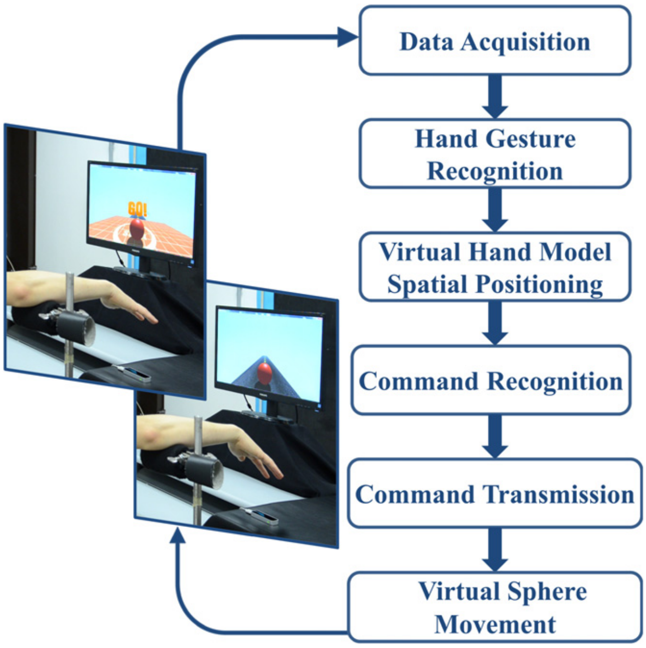

Figure 1. VMT experimental setting (left image) and schematic description of the VMT implementation (right image). See 'material and methods' section for details.

2.2. Experimental setup

2.2.1. Semi-immersive VR system. The semi-immersive VR environment was implemented by connecting and extending two leading technologies: a 3D hand sensing device, and a high performance real-time 3D engine. As a 3D hand-sensing device, the LEAP Motion Controller (LEAP Motion, Inc., San Francisco, CA) was utilized (figure 1). It provides both a 3D hand model and real-time hand tracking information to enable subjects to transpose their hand movements within the virtual 3D VMT. The LEAP Motion Controller is a small (1.3 cm × 3.2 cm × 8 cm) depth sensing camera that uses built-in infrared LEDs to detect objects within a dome of approximately 0.22 m^3 above it. It is connected to a computer via a USB cable and is designed specifically to detect, in real-time, hand and finger motion and gestures, such as pinching fingers, closing hand, tapping, etc. The device, positioned under the palm center of the subjects right hand at a distance of about 25 cm (figure 1), was used to: (1) capture the movements of the hand, (2) associate these movements to a virtual hand model, and (3) translate the movements of the virtual hand model to a set of commands in order to drive a virtual sphere (VS) within a virtual environment. The aim of the VMT was to move the VS over a virtual path (VP), avoiding its fall out of the VP. The Torque 3D Engine (http://garagegames.com/products/torque-3d), a cross-platform high performance real-time 3D engine, was used both for the editing and the rendering of the whole virtual 3D VMT. By using the aforementioned technologies, a controllable VS and a 3D VP, managed through a browser, were created by using a customized version of Marble Motion, a well-known game available on the web (http://mit.garagegames.com/MarbleMotion-1-0b.zip). In particular, the whole native source code was rewritten and enriched in accordance with a rehabilitation therapist, in order to fulfill the requirements of the VMT. With respect to the original implementation, the following tools were added: (1) a time driven version of the task in which both the start and the end of the VMT were established by a fixed time interval; (2) the possibility of storing information related to the subjects-task interaction process (including the number of times in which the VS had fallen out of the VP, the position of the VS falls over the VP, and the time necessary to complete each VMT). The software allowed also the calculation of: (1) the 'force' applied on the VS by the user along the VP, and (2) the VS movement parameters (trajectory, speed, and acceleration). Although these last parameters were not directly linked with the hand force applied on the VS (since the VS could not impose any tactile resistance to the hand movements), they have provided information about the VS speed and the subject dexterity over the task (as explained below). Moreover, to increase the subject concentration and motivation during the VMT, all the technical aspects, including elements of the VP (textures and materials), were redefined utilizing some predefined aspects of the 3D engine editor (Torque 3D Editor; www.garagegames.com/products/torque-3d/overview/editor). The whole source code of the developed VMT-application can be freely provided by the authors.

The VMT was preceded by the locking phase during which the right hand was open over the LEAP Motion Controller. The subjects were asked to place their right forearm on a fixed and firm support in order to allow the hand to be captured. This support ensured the maintenance of the correct position of the forearm, and consequently of the hand, during the performance of the whole VMT. The VMT protocol started with a stationary VS placed at the beginning of the VP. Subjects had to maintain their right hand open over the LEAP device by keeping their forearm on the support with the palm center perpendicular to the center of the device and with all the five fingers extended (figure 1). At the beginning of the task, the subjects had to guide the VS over the VP by using four commands. The first command (flexion) allowed the VS to proceed forward; the second command (extension) allowed the VS to decrease the speed (up to stop the VS) and to proceed backward; the third and the fourth commands (rotations of the wrist, for a maximum of about 80°, in the clockwise and counter-clockwise direction, starting from pronation) moved the VS to the left or to the right side, respectively. Note that the LEAP Motion Controller was designed to allow a freehand natural interaction, and that it is an extremely accurate and reactive device (Weichert *et al* 2013). The movements of the hand (e.g., degree of flexion/extension, degree of rotation of the wrist) had a proportional impact on the behavior of the VS, in real-time. More specifically, the command chosen by the subject transmitted the direction and the 'force' to the VS (e.g., a low hand downward flexion corresponded to a low 'force' application to the VS in the forward direction), where the VS speed depended on the inclination degree of the downward flexion and the time period during which the subject was maintaining the same hand position. Thus, the VMT was purposely designed to combine the four main commands, and, when the subjects took a pose of their hand halfway between two commands, the system merged both directions and 'force' amplitude. In this way, the subjects had the feeling of guiding the VS without restrictions or constraints. Moreover, the virtual environment allows the change of the VS physical properties, setting different values of the VP friction and the VS mass. In addition, the time and the 'force' required to stop the moving VS depended on its speed and its VP friction (considering fixed the VS mass).

In the present virtual 3D VMT, subjects were required to face three different levels of difficulty, generated by using three diverse VS mass values (18 kg, 12 kg, and 8 kg), corresponding to VMT_1, VMT_2, VMT_3, respectively. The $VMT_{1,}$ $VMT_{2,}$ and VMT_3 corresponded to the lowest, medium and highest level of the VMT difficulty, respectively.

Moreover, within each VMT level, the VP consisted of four segments each characterized by the constant inclination and a different friction value with respect to the ground. Consequently, the subjects were requested to apply a different entity of 'force' with the feeling of moving a solid sphere over a given path with a different friction.

The three levels of difficulty have been previously evaluated on different healthy subjects.

2.2.2. fNIRS instrumentation and data processing. A twenty-channel continuous wave fNIRS system (Oxymon Mk III, Artinis Medical Systems, The Netherlands) was employed to map the changes in O_2Hb and HHb over the bilateral PFC. This device measures changes in light attenuation at two wavelengths, 764 and 856 nm. The O_2Hb/HHb concentration changes (expressed in $\Delta\mu$M), obtained by using the modified Beer–Lambert law (Delpy *et al* 1988, Duncan *et al* 1996), are displayed in real-time. Eight optical fiber bundles (length: 3.15 m; diameter: 4.5 mm) were utilized to carry out the light to the left and the right PFC (four for each hemisphere), whereas ten optical fiber bundles of the same size (five for each hemisphere) were utilized to collect the light emerging from the same cortical areas. The illuminating and collecting bundles were assembled into a specifically designed flexible probe holder ensuring that the position of the 18 optodes, relative to each other, was firmly fixed. The probe holder consisted of two mirror-like units (9.7 cm × 8.9 cm each) held together, along the longest side, by three flexible junctions (figure 2). In sixteen of the twenty measurement points (or channels) the detector-illuminator distance was set at 3.5 cm, while in four measurement points the detector-illuminator distance was set at 1 cm (short-separation channels or SS channels). The optodes were inserted into a polyoxymethylene probe holder by connectors. The probe holder was appropriately placed over the head in order to include the underlying PFC. In particular, the two frontopolar fibers bundles collecting light at the bottom of the holder were centered (according to the International 10–20 system for the electroencephalography (EEG) electrode placement) on the Fp1 and Fp2 locations for the left and right side, respectively. The Montreal Neurological Institute coordinates of the

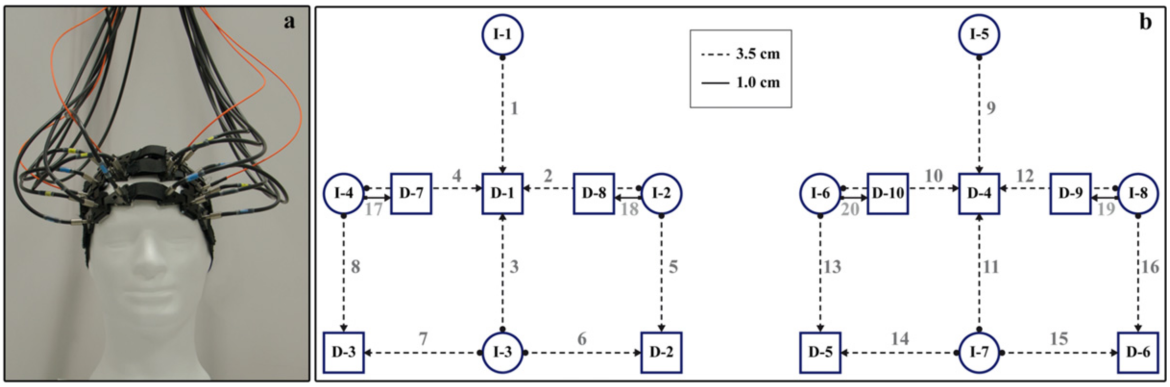

Figure 2. Eighteen optical fiber bundles (8 carrying and 10 collecting the NIR light to and from brain, respectively) mounted on the probe holder which is placed over the head in order to investigate the underlying VLPFC, dorsolateral PFC and frontopolar PFC areas (panel (a)). Schematic illustration of the optodes (end part of optical fiber bundles) placement in the probe holder (panel (b)). The 8 illuminators (I-1,…, I-8) and the 10 detectors (D-1,…, D-10) are evidenced by circles and squares, respectively. The numbers (from 1 to 16) between circle and square boxes correspond to the measurement points, while the numbers from 17 to 20 correspond to the SS channels measurement points. More specifically, the measurement points 6 and 14 refer to the frontopolar PFC of the right and left hemisphere, respectively; the measurement points 7 and 15 refer to the VLPFC of the right and left hemisphere, respectively. The solid and dashed lines indicate the distance of each I-D couple. See 'material and methods' section for details.

optodes and the relative sixteen measurement points were calculated using a probe placement method (Cutini *et al* 2011) based on a physical model of the ICBM152 head surface (Mazziotta *et al* 2001). For the details of the procedure, see Basso Moro *et al* (2014). The resulting matching Brodmann areas (BAs) of the sixteen measurement points are: BA 46 (measurement points: 1, 2, 3, 9, 10, 11), BA 10 (measurement points: 5, 6, 13, 14), and BA 45 (measurement points: 4, 7, 8, 12, 15, 16). Moreover, these BAs correspond to three major subregions of the PFC: the dorsolateral PFC (BA 46), the frontopolar cortex (BA 10), and the VLPFC (BA 45). The probe holder was fixed over the head by a Velcro brand fastener, adaptable to the individual size and shape of the head. This flexible probe holder and its position on the head provided a stable optical contact with the scalp for all the 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 18 well-defined circles over the PFC skin (i.e., depressed cutaneous areas corresponding with the location of the 18 optodes). The 18 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/HHb data from the twenty measurement points, which are defined as the midpoint of the corresponding detector-illuminator pairs, were acquired at 10 Hz. During the data collection procedure the signal quality as well as the absence of movement artefacts was verified. 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 index finger of the left hand.

The data processing was carried out using some of the Homer2 (http://nmr.mgh.harvard.edu/PMI/resources/homer2/home.htm) NIRS processing package functions (Huppert *et al* 2009) based in MATLAB (Mathworks, Natick, MA). For every subject, channels with a very low optical intensity were discarded from the analysis using the function enPruneChannels. The remaining raw optical intensity data were then converted into changes in optical density (OD). Motion artefacts were corrected applying the Wavelet motion correction method implemented into Homer2 (iqr parameter set to 0.1), which is based on the method developed by Molavi and Dumont (2012). Then, the corrected OD data were converted into concentration changes using the modified Beer–Lambert law. The hemodynamic response for each task was recovered using a general linear model (GLM) approach (with the hmrDeconvHRF_DriftSS function), which simultaneously regressed the SS channel signals to correct for physiological noise contamination. A set of Gaussian functions with standard deviation (SD) of 3 s and with their means separated by 2 s was used as temporal basis functions in an interval between −20 and 210 s before and after the starting of the VMT, respectively (Gagnon *et al* 2011). For each standard channel, the SS channel signal with the greatest correlation was chosen and its signal was added in the design matrix of the GLM. The iterative weighted least square method proposed by Barker *et al* (2013) was selected for solving the GLM matrix equation. This produced three hemodynamic response functions (HRFs), one per condition type (i.e., level of the VMT difficulty), for each channel and for each subject.

2.3. Protocol

Prior to the study, subjects were informed about the procedures and familiarized with the protocol. The study was conducted in a quiet and dimly lit room. Subjects were asked to sit on a comfortable high-backed chair in front of a 17″ PC monitor placed at a distance of 70 cm. The VMT protocol included three blocks lasting 4 min each. Each block consisted of a 1 min baseline, a 2 min VMT and a 1 min recovery.

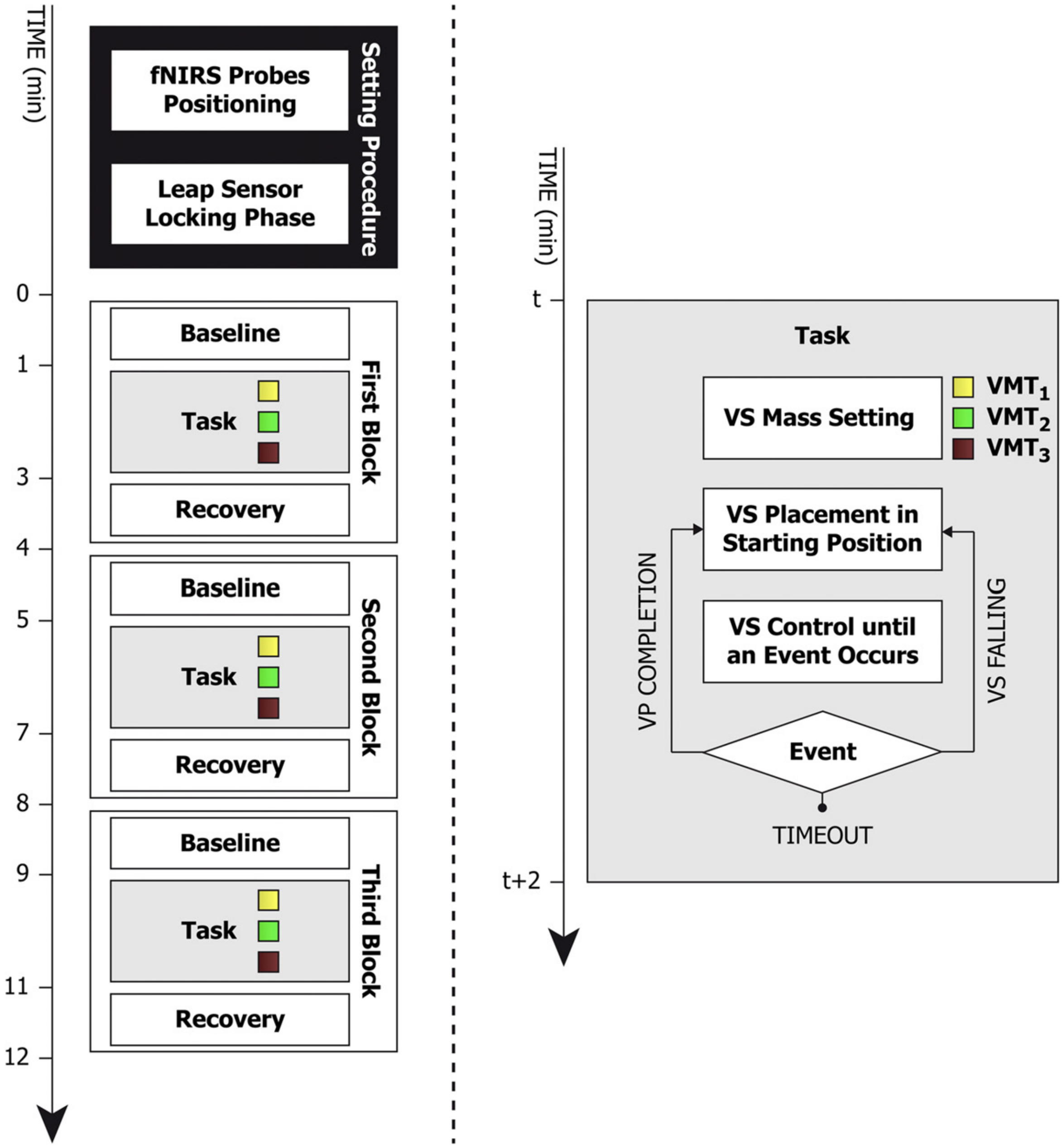

Figure 3. Temporal diagram of the experimental protocol. The task of each block could be VMT_1 or VMT_2 or VMT_3. The order of presentation of the VMTs (1, 2 and 3 corresponding to the incremental levels of difficulty) was randomized within the protocol. However, for each subject it was made possible to perform all the 3 levels of difficulty. For details, see 'material and methods' section.

Over the protocol, the order of presentation of the VMT_1, VMT_2, and VMT_3 was randomized and counterbalanced across subjects. The experimental design is shown in figure 3. Specifically, during the first min (baseline period) of each block, subjects had to maintain their forearm on the firm support with the right hand open over the LEAP device (see the 'semi-immersive VR system' section) (figure 1), and they were asked to relax observing a white fixation cross presented on a black screen in order to obtain fNIRS signals as stable as possible. Immediately after the VMT refreshing screen, a stationary VS at the beginning of a VP appeared on the PC monitor and a visual instruction advised subjects that the 2 min VMT was starting. During the VMT, subjects had to interact with the VS, guiding it over the VP through the four hand movements (see the 'semi-immersive VR system' section), starting from the wrist. The aim of the VMT was to guide the VS over the whole length of the VP, the end of which was indicated by the inscription 'finish'. Within each block, when the subject failed in guiding the VS over the VP, or the subject completed the VP in a time shorter than the allocated timeframe, the VS was repositioned at the starting point, and the task restarted. The number of times that the VS correctly reached the end of the VP (completed paths) within the 2 min VMT was considered as index of the subject's performance. After the end of the VMT, each subject had to observe the white fixation cross, presented on a black screen for a 1 min recovery period. Immediately after the end of the recovery period of the block, a 1 min baseline period of the following block started. The 12 min protocol ended immediately after the end of the recovery period of the third block. In order to evaluate the perceived physical and/or psychological discomfort caused by the probe holder during the protocol, subjects completed a visual analogue scale (VAS) (Jensen *et al* 2003), rating the perceived discomfort by making a mark somewhere on a 100 mm line, which indicates the discomfort intensity (where 0–4 mm can be considered no discomfort; 5–44 mm, mild discomfort; 45–74 mm, moderate discomfort; 75–100 mm, severe discomfort). In order to evaluate the 'state anxiety', subjects completed the 20-items of the STAI-Form Y-1 before and after the protocol (Spielberger *et al* 1983).

2.4. Data analysis and statistics

The integral value of the O_2Hb/HHb ($_{INT}O_2Hb/HHb$) changes of the HRFs were calculated from the beginning of the VMT_1, the VMT_2, and the VMT_3 (at 0 s) until the end of each task period (at 120 s), for each channel and subject, and were used as testing metric for the following statistical analysis. The mean values of the HR changes (analyzed as percentage of control) were calculated from the beginning of the VMT_1, the VMT_2, and the VMT_3 (at 0 s) until the end of each task period (at 120 s). Both the $_{INT}O_2Hb/HHb$ changes and the HR mean values of the task periods were normalized to the baseline periods, calculated over the last 20 s before the starting of the VMT_1, the VMT_2, and the VMT_3 (i.e., from −20 s to 0 s), respectively. This procedure permitted to remove the basal signal from the $_{INT}O_2Hb/HHb$ hemodynamic responses (i.e., obtaining normalized task periods), and to bring all the traces to a zero starting value. The HR values underwent the same 'correction for the baseline' procedure, for coherence with the hemodynamic data processing. The HR values were statistically analyzed in order to evaluate possible HR changes occurring during the execution of each VMT and/or between the three levels of difficulty of the VMT. However, it is important to mention that the $_{INT}O_2Hb/HHb$ changes were calculated from the HRFs corrected from the physiological noise contaminations (see 'materials and methods' section).

The statistical analysis's design was characterized by the following structure. Primarily, in order to investigate the presence of any effect produced by the difficulty levels of the VMT (i.e., VMT_1, VMT_2, and VMT_3) on the overall PFC activation, the omnibus repeated measures analysis of variance (ANOVA) was performed for the $_{INT}O_2Hb/HHb$ changes, for the HR mean values, and for the performance (mean of the number of paths completed by the subjects). Specifically, the ANOVA for the $_{INT}O_2Hb/HHb$ changes included four factors: channel (8 levels), hemisphere (2 levels), cortical hemodynamic response (CHR; 2 levels i.e. normalized task period versus zero) and the difficulty of the VMT (3 levels). The ANOVA for the HR mean values included two factors: task (2 levels) and difficulty of the VMT (3 levels). The ANOVA for the performance included one factor: difficulty of the VMT (3 levels). To control for multiple significance tests, the Fisher's LSD adjustment was applied. The Student's *t* test was conducted to investigate the presence of any difference in the anxiety state before and after the protocol, in order to exclude any influence of the anxiety in the hemodynamic response. Secondly, in order to investigate which specific region of the PFC was involved in the cortical activation elicited by the VMT, *post hoc* statistical analyses were conducted, motivated by the results of the previous omnibus ANOVAs. The $_{INT}O_2Hb/HHb$ changes were averaged across the three levels of VMT difficulty, and the following statistical analyses were conducted on the resulting $_{INT}O_2Hb/HHb$ changes. In order to investigate trends and patterns of the hemodynamic response across channels, and the activation associated to specific channels, a two-way ANOVA for the channels (16 levels) and the CHR (2 levels) and a series of channel-wise Student's *t* tests for the CHR were performed for the $_{INT}O_2Hb/HHb$ changes. Specifically, the Student's *t* tests were conducted only for the channels 7 and 8, and the channels 15 and 16, chosen as descriptive channels for the right and left hemisphere's hemodynamic activity, respectively.

All statistical analyses were conducted with SPSS 20.0 (SPSS Inc., Chicago, IL). Data were expressed as mean ± SD. The criterion for significance was $p < .05$.

3. Results

The behavioral data analysis revealed the following main results. The mean subjective rating of the perceived physical and/or psychological discomfort caused by the probe holder during the VMT was 19.4 ± 16.5. There was no significant difference ($t = 1.2$, $p = .24$) in the anxiety state before (31.1 ± 7.5) and after the protocol (29.8 ± 6.9).

The performance (mean number of completed paths) was 1.5 ± 0.6 for the VMT_1, 1.5 ± 1 for the VMT_2, and 0.8 ± 0.9 for the VMT_3. The ANOVA analysis for the performance revealed a significant main effect of the difficulty of the VMT ($F_{(2, 40)} = 8.76$, $p = .001$). In particular, there was a significant difference between the VMT_2 and the VMT_3 ($p = .002$), and between the VMT_1 and the VMT_3 ($p = .002$).

The fNIRS data evidenced a heterogeneous O_2Hb/HHb response over the mapped area during the VMT. Figure 4 shows the hemodynamic response over the sixteen measurement points during the execution of the three levels of VMT difficulty (i.e., VMT_1, VMT_2, and VMT_3). Since the beginning of the task, a consistent and progressive increase of the O_2Hb and a concomitant progressive decrease of the HHb were observed in the measurement point #8 and #16, accompanied by a gradual return at the O_2Hb/HHb baseline value since about 15 s after the end of the task. To a minor extent, a progressive O_2Hb increase accompanied by a progressive HHb decrease was observed also in the measurement point #7 and #15, with a major degree of hemodynamic response in the measurement point #15 (i.e., left hemisphere).

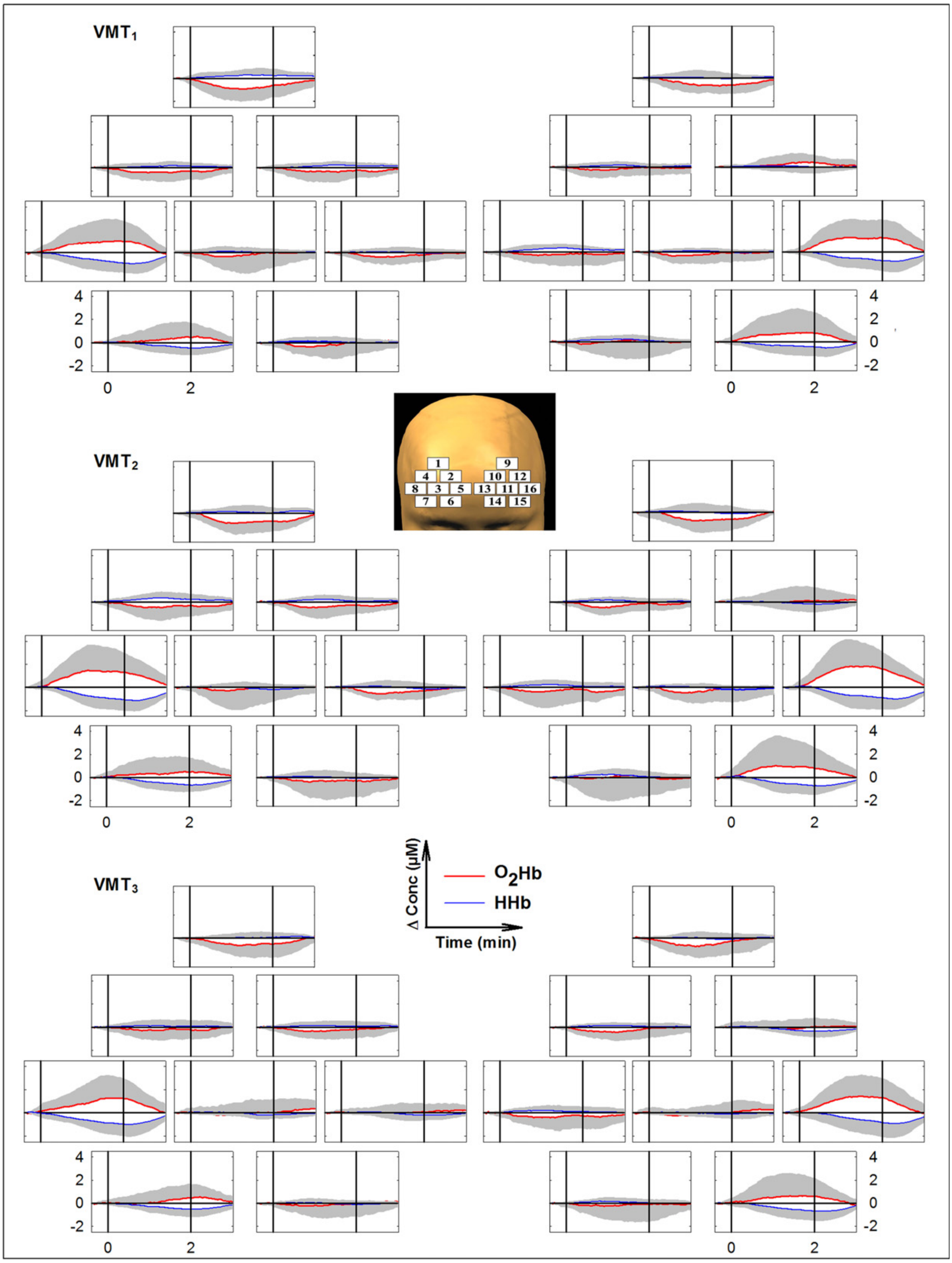

Figure 4. Grand average (mean ± SD, $n = 21$) of the PFC O_2Hb and HHb changes in response to the VMT$_1$, the VMT$_2$, and the VMT$_3$. The vertical solid lines limit the duration of the task execution. The layout of the 16 fNIRS measurement points over the right (numbers from 1 to 8) and left (numbers from 9 to 16) hemisphere is graphically represented. The major cortical hemodynamic response was observed in the bilateral VLPFC (measurement point #7, #8, #15, and #16), as confirmed by the significant O_2Hb increase and HHb decrease found in the measurement point #8 and #16 independently from the level of the VMT difficulty. VMT$_1$, VMT$_2$, VMT$_3$: visuo-motor task first, second, third level of difficulty, respectively.

The statistical analysis revealed the following main results. The omnibus ANOVA analysis, carried out on the $_{INT}O_2Hb$ changes, revealed a significant main effect of the channel ($F_{(1.93,38.59)} = 18.35$, $p < .001$), and the channel * CHR interaction ($F_{(1.93,38.59)} = 18.35$, $p < .001$). The omnibus ANOVA analysis, carried out on the $_{INT}HHb$ changes, revealed a significant main effect of the channel ($F_{(1.83,36.53)} = 20.08$, $p < .001$), and the channel * CHR ($F_{(1.83,36.54)} = 20.08$, $p < .001$), channel * hemisphere ($F_{(3.14,62.74)} = 2.89$, $p = .040$), and channel * hemisphere * CHR ($F_{(3.14,62.74)} = 2.89$, $p = .040$) interactions. There were no significant main effects of the difficulty of the VMT (*ps* > .05).

The further two-way ANOVAs, carried out on the pooled $_{INT}O_2Hb/HHb$ changes, revealed a significant main effect of the channel ($F_{(3.38,67.62)} = 10.45$, $p < .001$; $F_{(3.29,65.84)} = 12.36$, $p < .001$), and the channel * CHR ($F_{(3.38,67.62)} = 10.45$, $p < .001$; $F_{(3.29,65.84)} = 12.36$, $p < .001$) interaction. In particular, the main significant differences were found: (A) within the right hemisphere, between the channel #7, #8 and all the others (*ps* < .05); (B) within the left hemisphere, between the channel #15, #16 and all the others (*ps* < .05). The series of channel-wise *t* tests, carried out on the $_{INT}O_2Hb$ changes of the channel #7, #8, #15, and #16, revealed a significant activation in channels 8 ($t = -2.850$, $p = .010$) and 16 ($t = -4.278$, $p < .001$), while the series of channel-wise *t* tests carried out on the $_{INT}HHb$ changes of the channel #7, #8, #15, and #16 revealed a significant activation in all the channels ($t = 3.817$, $p = .001$; $t = 5.512$, $p < .001$; $t = 3.140$, $p = .005$; $t = 3.358$, $p = .003$).

Subject's HR remained almost unchanged during the VMT. The omnibus ANOVA analysis for the HR mean values revealed a significant main effect of the task ($F_{(1.00,20.00)} = 22.64$, $p < .001$), and no significant main effect of the difficulty of the VMT ($p > .05$).

4. Discussion

To the best of our knowledge, this is the first time in which a high-resolution and low cost 3D hand-sensing device (i.e., LEAP Motion Controller) combined with the non-invasive fNIRS investigation of the PFC hemodynamic changes has been utilized with the aim of reproducing a novel semi-immersive VMT adoptable for the upper limb motor function rehabilitation. During the VMT, the sixteen measurement points fNIRS system revealed a significant bilateral VLPFC activation. The major engagement of the VLPFC could be explained by the cognitive demand requested to perform the VMT, and its involvement in the association of the visual information with the motor responses. In order to perform the VMT, the control of the hand and forearm movement function, through the visuo-motor integration of the real-time virtual stimuli and feedbacks, was required. In addition, both the adaptation to the virtual stimuli and the active interaction with the virtual environment through the hand/forearm motor actions were needed.

4.1. VLPFC activation

The performance of the VMT elicited a heterogeneous pattern of hemodynamic response over the sixteen measurement points (figure 4), underlined by the main effect of the channel. A significant activation was found in the right and left hemisphere in correspondence to measurement point #8 and #16, respectively. However, the O_2Hb/HHb time traces in the measurement points #7 and #15, also belonging to the VLPFC, presented a clear trend of activation. This trend of activation was confirmed by the two-way ANOVA, showing that in the measurement point #7 and #15 the O_2Hb/HHb increase/decrease was significantly higher with respect to the O_2Hb/HHb increase/decrease found in all the other measurement points within the relative hemisphere.

The principal involvement observed in the bilateral VLPFC could be explained by its role in human cognition. The VLPFC, because of its connections, is thought to play a key role in associating visual information with motor responses (Bussey *et al* 2001, Fuster 2008, Tanji and Hoshi 2008). More specifically, the VLPFC receives information about the visual and auditory signals from the inferior and superior temporal cortex (Webster *et al* 1994), and seems to be part of a network (i.e., inferior/superior temporal cortex-VLPFC) involved in determining the behavioral goals associated with the visual signals that compose a present context (Yamagata *et al* 2012, Hoshi 2013). This is in line with the cognitive demand requested in order to perform the VMT. In fact, the adopted VMT required subjects to integrate the contextual visual information to adaptively modify the hand/forearm motor actions and, moreover, to actively interact with the VR environment, generating selective motor goals in order to correctly guide the VS over the VP. Thus, the learning and the maintaining of selective associations between visual cues and spatial motor actions were needed to perform the VMT.

The VLPFC activation was not modulated by the three levels of VMT difficulty, as evidenced by the absence of a main effect of the difficulty. However, a significant main effect of the difficulty in the number of paths completed by the subjects (performance) was observed. Therefore, the difficulty of the VMT was enough to influence the behavioral performance but it was not enough to induce a difficulty-related modulation in the hemodynamic changes. This could be partially explained by the fact that the VP features during the three levels of difficulty were identical. Furthermore, the sequences of motor actions requested to the subjects, in order to bring the VS to the end of the VP, were the same. However, the 'force' that they had to apply to guide the VS changed with the increasing difficulty of the VMT. Indeed, it is possible that the changes implemented in the VS mass values in order to increase the task difficulty were not adequate to involve the VLPFC to a progressively higher extent. In fact, even if the VLPFC seems to have a role in maintaining and retrieving the goal-relevant information (Badre and Wagner 2007, Souza *et al* 2009), it is especially activated during the learning of new associations between visual contextual cues and motor goal behaviors (Bussey *et al* 2001) but this specificity (i.e., the novelty of the associations to be learned) could have been lost during the performance of the second and the third blocks. On the other hand, it is also possible that a learning effect occurred during the performances of the VMT_1, VMT_2 and VMT_3. In fact, although during the experimental protocol the VMT_1, VMT_2 and VMT_3 were randomized, the influence of the increased automaticity in the task performance cannot be completely excluded (e.g., Floyer-Lea and Matthews 2004).

In addition, the left VLPFC seems to have a role in accessing, maintaining and retrieving the goal-relevant information for the action control (Badre and Wagner 2007, Souza *et al* 2009), whereas the right VLPFC seems to be engaged in the inhibition of the motor responses (Aron *et al* 2004) and in the reflexive orienting (Corbetta and Shulman 2002, Corbetta *et al* 2008). However, no effect of the hemisphere was found in the VLPFC activation observed in the present study, even though, for the execution of the VMTs, the movements of the right hand/forearm only were requested.

4.2. Semi-immersive VR technology and fNIRS

In the last few years, there has been increasing research interest in the application of VR technology in neurorehabilitation. In contrast with the traditional rehabilitation procedures, which may be tedious, resource-intensive and expensive, VR provides opportunities to engage in enjoyable and purposeful tasks. In addition, VR environments for neurorehabilitation can be created in a warm and friendly atmosphere, motivating patients to follow the training without interruptions. Studies in computational neuroscience have demonstrated that VR technology, if compared with traditional trainings, can improve motor relearning providing real-time feedbacks on the performance (Holden 2005, Laver *et al* 2015). Moreover, when considering, for example, the upper limb treatment, many studies indicated that the VR approach yielded better motor and functional outcomes than conventional therapies (e.g., Cameirao *et al* 2008, Merians *et al* 2009, Turolla *et al* 2013, Tsoupikova *et al* 2014). In the present study, the fNIRS and the VR technology for neurorehabilitation have been combined implementing a semi-immersive VR environment through a LEAP Motion Controller device, with the aim of evaluating the feasibility of this system for the rehabilitation of the upper extremity. The main advantage of this device is the freehand interaction offered to the subjects while practicing their fine motor control, without wearable sensors or uncomfortable gloves. Moreover, this low cost device (≈\$80) is a small high-resolution motion controller, which requires an easy installation. This type of touch-less device can be used for the sick and the healthy arm, thus allowing the objective evaluation of the functional recovery after rehabilitation (e.g., Placidi 2007, Avola *et al* 2013, Placidi *et al* 2013, Khademi *et al* 2014). It is noteworthy to underline that Virtualware, a Spanish technology company specialized in the development of hardware and software solutions based on immersive and interactive technologies, recently commercialized VirtualRehab Hands; this system incorporates the LEAP Motion Controller and eight very simple games that help fine motor skills of the hands through customized physical rehabilitation programs (www.virtualrehab.info). In the present study, the VMT-application has been implemented using free and open source platforms without any additional cost to install and to utilize the prototype, and it has been also designed to send remotely (via internet) a report about the performance of the patient who is executing the VMT protocol. In the last years, the interest for remote healthcare solutions has increased, due to their numerous advantages. In fact, these solutions allow for the reduction of healthcare costs and, support promotion of home rehabilitation training, giving benefit to those patients who do not have conventional access to hospital or care centers (e.g., non-autonomous patients, with limited mobility, or geographically isolated) (Garrido Navarro *et al* 2014, Su *et al* 2014). Importantly, the VMT-application has been preliminary but successfully utilized, with the supervision of a rehabilitation therapist, on some patients under rehabilitation treatment. The patients were capable of performing a 2 min VMT several times and they found the device very comfortable and friendly, thanks both to the advantage of moving the hand without wearing haptic interfaces (e.g., haptic gloves), and to the possibility of personalizing the task on the basis of their residual potentialities. The rehabilitation therapist also found the system very adequate and effective, and the degree of patients' involvement observed during the rehabilitation sessions was high. The proposed combined application of the VMT with the LEAP cannot be utilized in all kind of patients, for instance in those ones with severe hand/forearm mobility limitations. Indeed, the proposed VMT has the features to be easily adaptable to the residual capabilities of patients who need upper limb neurorehabilitation. Therefore, the resulting personalized VMT could match the requirements for the so called individualized treatment.

fNIRS has already been utilized to evaluate the cortical activation during motor tasks in healthy subjects and in patients during neurorehabilitation procedures (see Miyai *et al* 2001, Mihara *et al* 2008, , Haraguchi *et al* 2009 and Atsumori *et al* 2010 and Leff *et al* 2011, for reviews; Mihara *et al* 2012a, Huppert *et al* 2013, Koenraadt *et al* 2014, Perrey 2014, for review, Piper *et al* 2014). Moreover, fNIRS has been also utilized in combination with VR technologies in upper and lower limb motor tasks (Holper *et al* 2012, Basso Moro *et al* 2014, Ferrari *et al* 2014, Sangani *et al* 2015), in real-world activities realized in computer simulated artificial environments (Takeuchi 2000, Kojima *et al* 2005, Tomioka *et al* 2009, Tsunashima and Yanagisawa 2009, Ayaz *et al* 2011, Seraglia *et al* 2011, Tachibana *et al* 2011, Karim *et al* 2012), in the observation, imagination and imitation of motor actions (Holper *et al* 2012), in dance simulations (Ono *et al* 2014), in lathe operations (Hou and Watanuki 2012), and in spatial navigation (virtual maze) (Kober *et al* 2013). In particular, some of these VR activation paradigms could be adopted for the neurorehabilitation of the limb motor function (Holper *et al* 2012, Basso Moro *et al* 2014, Ferrari *et al* 2014). Basso Moro *et al* (2014) and Ferrari *et al* (2014) implemented two novel semi-immersive VR balance tasks, which involved mainly the lower limbs. These studies showed a PFC involvement to integrate the visual and proprioceptive information in order to perform the goal of action. In addition, both studies suggested the adaptability of the proposed semi-immersive VR tasks in diagnostic testing and neurorehabilitation.

To the best of our knowledge, fNIRS and VR technologies have never been utilized on patients during motor neurorehabilitation. The present study highlights the potential advantages offered by the combined use of a semi-immersive VR based upper limb neurorehabilitation system and fNIRS, in order to assess the impact of the motor rehabilitation on brain plasticity. With respect to other neuroimaging methods, fNIRS presents some advantages that make this technique more suitable to be used in the clinical and neurorehabilitation fields, and in combination with VR systems. During fNIRS measurements fewer constraints are required, and fNIRS equipment is transportable, completely safe and non-invasive. These advantages allow for the investigation of brain activity in natural conditions (e.g., bedside or while sitting on a chair), during daily life activities (e.g., standing and/or walking) and during neurorehabilitation procedures (Mihara and Miyai 2012). In addition, it is possible to adapt treatment resources in order to meet the needs of each patient and optimize the recovery process. Another neuroimaging method largely used in combination with VR technologies is EEG (e.g., Bohil *et al* 2011, Snider *et al* 2013, Comani *et al* 2015, Slobounov *et al* 2015). Although the last generation of the commercial high-density EEG systems has overcome the spatial resolution of the last generation of fNIRS instruments, the resolution of the utilized fNIRS system was good enough for investigating the selected cortical areas and the movements were well tolerated.

4.3. Strengths and limitations

The strengths and the limitations of the fNIRS technique have been previously discussed in detail (see Ferrari and Quaresima 2012, Scholkmann *et al* 2014 for reviews). In the present study, the fNIRS data could have been corrupted by subtle and hardly identifiable head motion artefacts. In order to correct for these, the Wavelet motion correction method (Molavi and Dumont 2012), which has been shown to be one of the best motion correction techniques (Cooper *et al* 2012, Brigadoi *et al* 2014), was applied to the fNIRS data. Physiological noise contamination is another fundamental issue in the analysis of fNIRS data since it can elicit spurious activation (Kirilina *et al* 2012). Several studies have demonstrated the importance of acquiring SS channel signals in order to reduce these superficial systemic oscillations and recover true brain activity (Saager and Berger 2005, Gagnon *et al* 2011). Therefore, in the current study the SS signals were regressed from standard channel signals to avoid physiological confounds to be interpreted as functional activation of the brain. The method developed by Barker *et al* (2013) was chosen to solve the GLM since it takes into account the serially correlated physiological noise present in the fNIRS data. Therefore, both the suppression of the subtle motion artefacts and the reduction of the physiological noise contamination (e.g., the possible influence of the HR in the O_2Hb/HHb changes suggested by the main effect of the CHR) were achieved in this study, supporting the argument that the described PFC hemodynamic changes were indeed mainly related to the VMT. Moreover, the PFC is also involved in pain perception and modulation (Lorenz *et al* 2003), therefore it is important that during the fNIRS studies the probe holder, equipped with the optodes, does not cause any discomfort to the subjects. In the present study, in order to avoid any PFC activation induced by discomfort and/or pain, the subjects were properly instructed to alert the researchers whenever they experienced any discomfort and/or pain during the fNIRS measurement. In addition, subjects reported a mean rating, corresponding to 'mild discomfort', by completing the VAS (Jensen *et al* 2003) at the end of the fNIRS measurement. Therefore, discomfort and/or pain did not interfere with the observed VMT-related O_2Hb/HHb changes. The right VLPFC seems to be associated also with anxiety (e.g., Koric *et al* 2012); however, in the present study, no difference was found in the anxiety state before and after the protocol.

For an adequate understanding of the current findings, some limitations should be pointed out: (1) the study has been conducted only in healthy subjects, thus the effect of the adopted VMT on the PFC hemodynamic response of patients with neurological impairments remains almost unknown, with the exception of some, though preliminary, results; (2) a connectivity investigation over the PFC was not possible, given the relatively small cortical area that could be monitored with the employed twenty-channel fNIRS system. For the same reason, the premotor, the motor, and the somatosensory cortical areas, although have been supposed to play a pivotal role in performing VMT, were not investigated; (3) the fNIRS system software does not provide data stream mining i.e. real-time input that allows an interactive user interface to adapt its behavior, thus improving user performance and experience (Mihara *et al* 2012b); (4) although a multi-sensorial stimulation, which includes haptic other than visual feedbacks, may benefit motor rehabilitation, the utilized VR technologies did not make possible to include a real sphere in the experimental setting. The possibility of a rehabilitation training, without any physical contact with real objects, permits completely freehand movements. Moreover, the utilized low cost VR technologies could allow patients to perform self-rehabilitation at home; (5) during the VMT, the participants were not filmed, and a kinematic analysis was not performed, neither during the VMT nor offline. In addition, the hemodynamic analysis was focused on the activation elicited by the VMT. The four distinct movements requested for performing the VMT were not analyzed separately. Considering the importance, particularly when patients are involved, of having an assessment of the precise movements performed by the subjects, as well as the degree of engagement and the effort applied, these procedures will be adopted in future studies and (6) only men were included in the study. Since women, as much as men, are potential VMT users, their inclusion in the experimental sample would have been important. Nevertheless, it was decided to include only men in order to reduce the sample variability related to emotional responses (Matud 2004, Leon-Carrion *et al* 2006), and visuo-motor abilities (Wang *et al* 2015) associated to gender.

5. Conclusion

The present study has demonstrated that the VLPFC is activated (O_2Hb increase and concomitant HHb decrease) when healthy subjects perform a VMT in a semi-immersive VR environment simulated through a 3D hand-sensing device (i.e., LEAP Motion Controller). However, this VLPFC activation was not found to be modulated by the levels of the VMT difficulty, suggesting that the bilateral VLPFC is involved in attention-demanding VMTs only until the task requires the learning of new associations between visual cues and spatial motor goals. Moreover, given: (1) the advantages offered by the combined use of fNIRS and VR technologies, (2) the absence of wearable motion sensing devices, (3) the motivating-safe and customizable semi-immersive VR environment, and (4) the positive feedback of both the rehabilitation therapist and the patients, the present VMT appears potentially adoptable to assess the impact of the motor neurorehabilitation on the brain plasticity of neurological patients with upper limb impairments.

Acknowledgments

This study has been performed in the framework of the Interdepartmental Research Centre for Molecular Diagnostics and Advanced Therapies. This work was partially funded by: (1) the 2014 grant from the Fondazione Cassa di Risparmio della Provincia dell'Aquila, and (2) the Abruzzo Earthquake Relief Fund (Toronto, ON). The authors wish to thank Dr Simone Cutini, Department of Developmental Psychology and Socialization, University of Padua, Italy for helping in the identification of the relative Brodmann's Areas. The authors declare that they have no conflict of interest.

References

Adamovich S V, Merians A S, Boian R, Tremaine M, Burdea G C, Recce M and Poizner H 2005 A virtual reality (VR)-based exercise system for hand rehabilitation after stroke *Presence* **14** 161–74

Aron A R, Robbins T W and Poldrack R A 2004 Inhibition and the right inferior frontal cortex *Trends Cogn. Sci.* **8** 170–7

Atsumori H *et al* 2010 Noninvasive imaging of prefrontal activation during attention-demanding tasks performed while walking using a wearable optical topography system *J. Biomed. Opt.* **15** 046002

Avola D, Spezialetti M and Placidi G 2013 Design of an efficient framework for fast prototyping of customized human–computer interfaces and virtual environments for rehabilitation *Comput. Meth. Progr. Bio.* **110** 490–502

Ayaz H, Shewokis P A, Curtin A, Izzetoglu M, Izzetoglu K and Onaral B 2011 Using MazeSuite and functional near infrared spectroscopy to study learning in spatial navigation *J. Vis. Exp.* **56** e3443

Badre D and Wagner A D 2007 Left ventrolateral prefrontal cortex and the cognitive control of memory *Neuropsychologia* **45** 2883–901

Bandettini P 2007 Functional MRI today *Int. J. Psychophysiol.* **63** 138–45

Barker W, Aarabi A and Huppert T 2013 Autoregressive model based algorithm for correcting motion and serially correlated errors in fNIRS *Biomed. Optics Express* **4** 1366–79

Basso Moro S, Bisconti S, Muthalib M, Spezialetti M, Cutini S, Ferrari M, Placidi G and Quaresima V 2014 A semi-immersive virtual reality incremental swing balance task activates prefrontal cortex: a functional near-infrared spectroscopy study *Neuroimage* **85** 45–60

Basteris A, Nijenhuis S M, Stienen A H A, Buurke J H, Prange G B and Amirabdollahian F 2014 Training modalities in robot-mediated upper limb rehabilitation in stroke: a framework for classification based on a systematic review *J. Neuroeng. Rehabil.* **11** 111

Belda-Lois J M *et al* 2011 Rehabilitation of gait after stroke: a review towards a top-down approach *J. Neuroeng. Rehabil.* **8** 66

Boas D A, Elwell C E, Ferrari M and Taga G 2014 Twenty years of functional near-infrared spectroscopy: introduction for the special issue *Neuroimage* **85** 1–5

Bohil C J, Alicea B and Biocca F A 2011 Virtual reality in neuroscience research and therapy *Nat. Rev. Neurosci.* **12** 752–62

Brigadoi S, Ceccherini L, Cutini S, Scarpa F, Scatturin P, Selb J, Gagnon L, Boas D A and Cooper R J 2014 Motion artifacts in functional near-infrared spectroscopy: a comparison of motion correction techniques applied to real cognitive data *Neuroimage* **85** 181–91

Buma F, Kwakkel G and Ramsey N 2013 Understanding upper limb recovery after stroke *Restor. Neurol. Neurosci.* **31** 707–22

Bussey T J, Wise S P and Murray E A 2001 The role of ventral and orbital prefrontal cortex in conditional visuomotor learning and strategy use in rhesus monkeys *Behav. Neurosci.* **115** 971–82

Cameirao M S, Bermudez I Badia S and Verschure P F M J 2008 Virtual reality based upper extremity rehabilitation following stroke: a review *J. Cyber. Ther. Rehab.* **1** 63–74

Chang W H and Kim Y H 2013 Robot-assisted therapy in stroke rehabilitation *J. Stroke* **15** 174–81

Cooper R J, Selb J, Gagnon L, Phillip D, Schytz H W, Iversen H K, Ashina M and Boas D A 2012 A systematic comparison of motion artifact correction techniques for functional near-infrared spectroscopy *Front. Neurosci.* **6** 147

Comani S, Velluto L, Schinaia L, Cerroni G, Serio A, Buzzelli S, Sorbi S and Guarnieri B 2015 Monitoring neuro-motor recovery from stroke with high-resolution EEG, robotics and virtual reality: a proof of concept *IEEE Trans. Neural Syst. Rehabil. Eng.* **23** 1106–16

Corbetta M, Patel G and Shulman G L 2008 The reorienting system of the human brain: from environment to theory of mind *Neuron* **58** 306–24

Corbetta M and Shulman G L 2002 Control of goal-directed and stimulus-driven attention in the brain *Nat. Rev. Neurosci.* **3** 201–15

Cutini S, Scatturin P and Zorzi M 2011 A new method based on ICBM152 head surface for probe placement in multichannel fNIRS *Neuroimage* **54** 919–27

Delpy D T, Cope M, van der Zee P, Arridge S R, Wray S and Wyatt J S 1988 Estimation of optical pathlength through tissue

from direct time of flight measurement *Phys. Med. Biol.* **33** 1433–42
Duncan A, Meek J H, Clemence M, Elwell C E, Fallon P, Tyszczuk L, Cope M and Delpy D T 1996 Measurement of cranial optical path length as a function of age using phase resolved near infrared spectroscopy *Pediatr. Res.* **39** 889–94
Ferrari M, Bisconti S, Spezialetti M, Basso Moro S, Di Palo C, Placidi G and Quaresima V 2014 Prefrontal cortex activated bilaterally by a tilt board balance task: a functional near-infrared spectroscopy study in a semi-immersive virtual reality environment *Brain Topogr.* **27** 353–65
Ferrari M and Quaresima V 2012 A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application *Neuroimage* **63** 921–35
Fishburn F A, Norr M E, Medvedev A V and Vaidya C J 2014 Sensitivity of fNIRS to cognitive state and load *Front. Human Neurosci.* **8** 76
Floyer-Lea A and Matthews P M 2004 Changing brain networks for visuomotor control with increased movement automaticity *J. Neurophys.* **92** 2405–12
Fuster J M 2008 *The Prefrontal Cortex* (New York: Academic)
Gagnon L, Perdue K, Greve D N, Goldenholz D, Kaskhedikar G and Boas D A 2011 Improved recovery of the hemodynamic response in diffuse optical imaging using short optode separations and state-space modeling *Neuroimage* **56** 1362–71
Garrido Navarro J E, Ruiz Penichet V M and Lozano Pérez M D 2014 Movement-based interaction applied to physical rehabilitation therapies *J. Med. Internet Res.* **16** e281
Haraguchi M, Kikuchi T, Mihara M, Hatakenaka M, Miyai I and Furusho J 2009 Development of evaluation system of the motor function for upper limbs using 3-D rehabilitation robot 'EMUL' and near-infrared spectroscopy 'NIRS' *IEEE Int. Conf. on Rehabilitation Robotics* pp 566–70
Holden M K 2005 Virtual environments for motor rehabilitation: review *Cyberpsychol. Behav.* **8** 187–211
Holper L, Kobashi N, Kiper D, Scholkmann F, Wolf M and Eng K 2012 Trial-to-trial variability differentiates motor imagery during observation between low versus high responders: a functional near-infrared spectroscopy study *Behav. Brain Res.* **229** 29–40
Hoshi E 2013 Cortico-basal ganglia networks subserving goal-directed behavior mediated by conditional visuo-goal association *Front. Neural Circuits* **7** 158
Hou L and Watanuki K 2012 Measurement of brain activity under virtual reality skills training using near-infrared spectroscopy *J. Adv. Mech. Des. Syst.* **6** 168–78
Huppert T J, Diamond S G, Franceschini M A and Boas D A 2009 HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain *Appl. Opt.* **48** D280–98
Huppert T J, Schmidt B, Beluk N, Furman J and Sparto P 2013 Measurement of brain activation during an upright stepping reaction task using functional near-infrared spectroscopy *Hum. Brain Mapp.* **34** 2817–28
Jang S H, You S H, Hallett M, Cho Y W, Park C M, Cho S H, Lee H Y and Kim T H 2005 Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study *Arch. Phys. Med. Rehabil.* **86** 2218–23
Jensen M P, Chen C and Brugger A M 2003 Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain *J. Pain* **4** 407–14
Karim H, Schmidt B, Dart D, Beluk N and Huppert T 2012 Functional near-infrared spectroscopy (fNIRS) of brain function during active balancing using a video game system *Gait Posture* **35** 367–72
Khademi M, Hondori H M, McKenzie A, Dodakian L, Lopes C V and Cramer S C 2014 Free-hand interaction with leap motion controller for stroke rehabilitation *Proc. 32nd Annual ACM Conf. on Human Factors in Computing Systems (CHI EA '14)* pp 1663–8
Kirilina E, Jelzow A, Heine A, Niessing M, Wabnitz H, Brühl R, Ittermann B, Jacobs A M and Tachtsidis I 2012 The physiological origin of task-evoked systemic artefacts in functional near infrared spectroscopy *Neuroimage* **61** 70–81
Kleim J A and Jones T A 2008 Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage *Speech Lang. Hear Res.* **51** S225–39
Kober S E, Wood G and Neuper C 2013 Measuring brain activation during spatial navigation in virtual reality: a combined EEG-NIRS study *Virtual Environments: Developments, Applications and Challenges* ed S Trautman and F Julien (New York: NOVA Publisher) pp 1–24
Koenraadt K L, Roelofsen E G, Duysens J, Keijsers N L, Kojima T and Tsunashima H 2014 Cortical control of normal gait and precision stepping: an fNIRS study *Neuroimage* **85** 415–22
Kojima T, Tsunashima H, Shizawa T, Takada H and Sakai T 2005 Measurement of train driver's brain activity by functional near-infrared spectroscopy (fNIRS) *Opt. Quantum Electron.* **37** 1319–38
Koric L, Volle E, Seassau M, Bernard F A, Mancini J, Dubois B, Pelissolo A and Levy R 2012 How cognitive performance-induced stress can influence right VLPFC activation: an fMRI study in healthy subjects and in patients with social phobia *Hum. Brain Mapp.* **33** 1973–86
Langhorne P, Bernhardt J and Kwakkel G 2011 Stroke rehabilitation *Lancet* **377** 1693–702
Langhorne P, Coupar F and Pollock A 2009 Motor recovery after stroke: a systematic review *Lancet Neurol.* **8** 741–54
Laver K E, George S, Thomas S, Deutsch J E and Crotty M 2015 Virtual reality for stroke rehabilitation *Cochrane Database Syst. Rev.* **2**
Leff D R, Orihuela-Espina F, Elwell C E, Athanasiou T, Delpy D T, Darzi A W and Yang G Z 2011 Assessment of the cerebral cortex during motor task behaviours in adults: a systematic review of functional near infrared spectroscopy (fNIRS) studies *Neuroimage* **54** 2922–36
Leon-Carrion J, Damas J, Izzetoglu K, Pourrezai K, Martìn-Rodrìguez J F, Barroso y Martin J M and Dominguez-Morales M R 2006 Differential time course and intensity of PFC activation for men and women in response to emotional stimuli: a functional near-infrared spectroscopy (fNIRS) study *Neurosci. Lett.* **403** 90–5
Lorenz J, Minoshima S and Casey K L 2003 Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation *Brain* **126** 1079–91
Mazziotta J *et al* 2001 A probabilistic atlas and reference system for the human brain: international consortium for brain mapping (ICBM) *Phil. Trans. R. Soc.* B **356** 1293–322
Matud M P 2004 Gender differences in stress and coping styles *Personality Individual Differences* **37** 1401–15
Merians A S, Tunik E, Fluet G G, Qiu Q and Adamovich S V 2009 Innovative approaches to rehabilitation of upper extremity hemiparesis using virtual environments *Eur. J. Phys. Rehabil. Med.* **45** 123–33
Mihara M and Miyai I 2012 Applications of near infrared spectroscopy in neurorehabilitation *Infrared Spectroscopy—Life and Biomedical Sciences* ed T Theophanides (Rijeka: InTech) pp 41–56
Mihara M, Miyai I, Hatakenaka M, Kubota K and Sakoda S 2008 Role of the prefrontal cortex in human balance control *Neuroimage* **43** 329–36
Mihara M, Miyai I, Hattori N, Hatakenaka M, Yagura H, Kawano T and Kubota K 2012a Cortical control of postural balance in patients with hemiplegic stroke *Neuroreport* **23** 314–9

Mihara M *et al* 2012b Neurofeedback using real-time near-infrared spectroscopy enhances motor imagery related cortical activation *PLoS One* **7** e32234
Miller E K and Cohen J D 2001 An integrative theory of prefrontal cortex function *Annu. Rev. Neurosci.* **24** 167–202
Miyai I, Tanabe H C, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T and Kubota K 2001 Cortical mapping of gate in humans: a near-infrared spectroscopic topography study *Neuroimage* **14** 1186–92
Molavi B and Dumont G A 2012 Wavelet-based motion artifact removal for functional near-infrared spectroscopy *Physiol. Meas.* **33** 259–70
Obrig H 2014 NIRS in clinical neurology—a 'promising' tool? *Neuroimage* **85** 535–46
Oldfield R 1971 The assessment and analysis of handedness: the Edinburgh inventory *Neuropsychologia* **9** 97–113
Ono Y, Nomoto Y, Tanaka S, Sato K, Shimada S, Tachibana A, Bronner S and Noah J A 2014 Frontotemporal oxyhemoglobin dynamics predict performance accuracy of dance simulation gameplay: temporal characteristics of top-down and bottom-up cortical activities *Neuroimage* **85** 461–70
Passingham R E and Wise S P 2012 *The Neurobiology of the Prefrontal Cortex: Anatomy, Evolution and the Origin of Insight* (Oxford: Oxford University Press)
Perrey S 2014 Possibilities for examining the neural control of gait in humans with fNIRS *Front. Physiol.* **5** 204
Piper S K, Krueger A, Koch S P, Mehnert J, Habermehl C, Steinbrink J, Obrig H and Schmitz C H 2014 A wearable multi-channel fNIRS system for brain imaging in freely moving subjects *Neuroimage* **85** 64–71
Placidi G 2007 A smart virtual glove for the hand telerehabilitation *Comput. Biol. Med.* **37** 1100–7
Placidi G, Avola D, Iacoviello D and Cinque L 2013 Overall design and implementation of the virtual glove *Comput. Biol. Med.* **43** 1927–40
Saager R B and Berger A J 2005 Direct characterization and removal of interfering absorption trends in two-layer turbid media *J. Opt. Soc. Am.* A **22** 1874–82
Sangani S, Lamontagne A and Fung J 2015 Cortical mechanisms underlying sensorimotor enhancement promoted by walking with haptic inputs in a virtual environment *Prog. Brain Res.* **218** 313–30
Scholkmann F, Kleiser S, Metz A, Zimmermann R, Pavia J M, Wolf U and Wolf M 2014 A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology *Neuroimage* **85** 6–27
Seraglia B, Gamberini L, Priftis K, Scatturin P, Martinelli M and Cutini S 2011 An exploratory fNIRS study with immersive virtual reality: a new method for technical implementation *Front. Hum. Neurosci.* **5** 176
Slobounov S M, Ray W, Johnson B, Slobounov E and Newell K M 2015 Modulation of cortical activity in 2D versus 3D virtual reality environments: an EEG study *Int. J. Psychophysiol.* **95** 254–60
Snider J, Plank M, Lee D and Poizner H 2013 Simultaneous neural and movement recording in large-scale immersive virtual environments *IEEE Trans. Biomed. Circuits Syst.* **7** 713–21
Souza M J, Donohue S E and Bunge S A 2009 Controlled retrieval and selection of action-relevant knowledge mediated by partially overlapping regions in left ventrolateral prefrontal cortex *Neuroimage* **46** 299–307
Spielberger C D, Gorsuch R L, Lushene R, Vagg P R and Jacobs G A 1983 *Manual for the State-Trait Anxiety Inventory* (Palo Alto, CA: Consulting Psychologists Press)
Su C J, Chiang C Y and Huang J Y 2014 Kinect-enabled home-based rehabilitation system using dynamic time warping and fuzzy logic *Appl. Soft Comp.* **22** 652–66
Subramanian S K, Massie C L, Malcolm M P and Levin M F 2010 Does provision of extrinsic feedback result in improved motor learning in the upper limb poststroke? A systematic review of the evidence *Neurorehabil. Neural Repair* **24** 113–24
Tachibana A, Noah J A, Bronner S, Ono Y and Onozuka M 2011 Parietal and temporal activity during a multimodal dance video game: an fNIRS study *Neurosci. Lett.* **503** 125–30
Tanji J and Hoshi E 2008 Role of the lateral prefrontal cortex in executive behavioral control *Physiol. Rev.* **88** 37–57
Takahashi T, Takikawa Y, Kawagoe R, Shibuya S, Iwano T and Kitazawa S 2011 Influence of skin blood flow on near-infrared spectroscopy signals measured on the forehead during a verbal fluency task *Neuroimage* **57** 991–1002
Takeuchi Y 2000 Change in blood volume in the brain during a simulated aircraft landing task *J. Occup. Health* **42** 60–5
Tomioka H, Yamagata B, Takahashi T, Yano M, Isomura A J, Kobayashi H and Mimura M 2009 Detection of hypofrontality in drivers with Alzheimer's disease by near-infrared spectroscopy *Neurosci. Lett.* **451** 252–6
Tsoupikova D, Stoykov N S, Corrigan M, Thielbar K, Vick R, Li Y, Triandafilou K, Preuss F and Kamper D 2014 Virtual immersion for post-stroke hand rehabilitation therapy *Ann. Biomed. Eng.* **43** 467–77
Tsunashima H and Yanagisawa K 2009 Measurement of brain function of car driver using functional near-infrared spectroscopy (fNIRS) *Comput. Intell. Neurosci.* **2009** 164958
Turolla A, Dam M, Ventura L, Tonin P, Agostini M, Zucconi C, Kiper P, Cagnin A and Piron L 2013 Virtual reality for the rehabilitation of the upper limb motor function after stroke: a prospective controlled trial *Neuroeng. Rehabil. J.* **10** 85
Wahl A S and Schwab E M 2014 Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment *Front. Human Neurosci.* **8** 1–13
Wang L, Krasich K, Bel-Bahar T, Hughes L, Mitroff S R and Appelbaum L G 2015 Mapping the structure of perceptual and visual-motor abilities in healthy young adults *Acta Psychologia* **157** 74–84
Webster M J, Bachevalier J and Ungerleider L G 1994 Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys *Cereb. Cortex* **4** 470–83
Weichert F, Bachmann D, Rudak B and Fisseler D 2013 Analysis of the accuracy and robustness of the leap motion controller *Sensors* **13** 6380–93
Wilde E A, Hunter J V and Bigler E D 2012 Neuroimaging in neurorehabilitation *NeuroRehabilitation* **31** 223–6
Wise S P, Murray E A and Gerfen C R 1996 The frontal cortex-basal ganglia system in primates *Crit. Rev. Neurobiol.* **10** 317–56
Yamagata T, Nakayama Y, Tanji J and Hoshi E 2012 Distinct information representation and processing for goal-directed behavior in the dorsolateral and ventrolateral prefrontal cortex and the dorsal premotor cortex *J. Neurosci.* **32** 12934–49