

Primary Sensory and Motor Cortex Activities During Voluntary and Passive Ankle Mobilization by the SHADE Orthosis

Simone Pittaccio,¹ Filippo Zappasodi,² Stefano Viscuso,¹ Francesca Mastrolilli,³ Matilde Ercolani,³ Francesco Passarelli,³ Franco Molteni,⁴ Stefano Besseghini,¹ Paolo Maria Rossini,^{5,6} and Franca Tecchio^{7,6*}

¹CNR-IENI, Unità di Lecco, Italy

²Department of Clinical Sciences and Bioimaging, 'G. D'Annunzio' University, Chieti, Italy

³AFaR, Ospedale Fatebenefratelli, Isola Tiberina, Rome, Italy

⁴Ospedale Valduce, Clinica Villa Beretta, Costamasnaga, Italy

⁵Department of Neurology, 'Campus Bio-Medico' University, Rome, Italy

⁶Casa di Cura SAN RAFFAELE Cassino and IRCCS SAN RAFFAELE PISANA, Italy

⁷CNR-ISTC, Unità MEG, Ospedale Fatebenefratelli, Isola Tiberina, Rome, Italy

Abstract: This study investigates cortical involvement during ankle passive mobilization in healthy subjects, and is part of a pilot study on stroke patient rehabilitation. Magnetoencephalographic signals from the primary sensorimotor areas devoted to the lower limb were collected together with simultaneous electromyographic activities from tibialis anterior (TA). This was done bilaterally, on seven healthy subjects (aged 29 ± 7), during rest, left and right passive ankle dorsiflexion (imparted through the SHADE orthosis, O-PM, or neuromuscular electrical stimulation, NMES-PM), and during active isometric contraction (IC-AM). The effects of focussing attention on ankle passive movements were considered. Primary sensory (FS_{S1}) and motor (FS_{M1}) area activities were discriminated by the Functional Source Separation algorithm. Only contralateral FS_{S1} was recruited by common peroneal nerve stimulation and only contralateral FS_{M1} displayed coherence with TA muscular activity. FS_{M1} showed higher power of gamma rhythms (33–90 Hz) than FS_{S1} . Both sources displayed higher beta (14–32 Hz) and gamma powers in the left than in the right hemisphere. Both sources displayed a bilateral reduction of beta power during IC-AM with respect to rest. Only FS_{S1} beta band power reduced during O-PM. No beta band modulation was observed of either source during NMES-PM. Mutual FS_{S1} - FS_{M1} coherence in gamma2 band (61–90 Hz) showed a slight trend towards an increase when focussing attention during O-PM. Somatosensory and motor counterparts of lower limb cortical representations were discriminated in both hemispheres. SHADE was effective in generating repeatable dorsiflexion and inducing primary sensory involvement similarly to voluntary movement. *Hum Brain Mapp* 32:60–70, 2011. © 2010 Wiley-Liss, Inc.

Key words: ankle movement; sensorimotor; attention; rehabilitation; magnetoencephalography

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*Correspondence to: Franca Tecchio, CNR-ISTC, Unità MEG, Ospedale Fatebenefratelli; 00186 Isola Tiberina; Rome (Italy).

E-mail: franca.tecchio@istc.cnr.it

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INTRODUCTION

This study deals with the response of the central nervous system (CNS) to passive mobilization of the ankle joint in healthy subjects. This topic certainly has intrinsic basic research interest in that it may deepen our understanding of the mechanisms by which sensorimotor activation in the brain can be elicited, not by voluntary motor planning or execution, but rather by perceptual and cognitive attention. However, there are also clinical reasons that support the undertaking of such investigation, e.g. in the field of post-stroke care and rehabilitation, where passive mobilization could gain great importance in the recovery of lost motor functions—particularly in severely affected patients either unable to voluntarily move the plegic limb or entirely neglecting it—and notions about the concurrent central involvement could be of help in honing early rehabilitation interventions.

Passive mobilization is already a fundamental part of physical rehabilitation programs for post-acute stroke. In fact, it is a means to limit the motor impairment due to paresis after stroke as a consequence of immobilization-dependent tissue biomechanical deterioration [Gracies, 2005; Harvey and Herbert, 2002; O'Dwyer et al., 1996; Singer et al., 2004]. This is why clinical practice and rehabilitation guidelines suggest that rehabilitation should support patients even at a time when they cannot work out actively [Brass, 1992; NINDS, 2002]. Moving from tissue property preservation on to clinical outcome, there is strong evidence that greater intensity of leg rehabilitation can improve functional recovery and health-related functional status [Kwakkel et al., 1999, 2004]. For all these reasons the application of robotic rehabilitation extending therapeutic sessions in a standardized way could be of some advantage to the patients.

All these items of evidence speak in favor of passive mobilization sustaining motor recovery. In developing more suitable interventions, added value can be provided by a comparative analysis of the central correlates and their contributions to recovery as induced by different procedures, the most common being neuromuscular electrical stimulation, NMES, [Sheffler and Chae, 2007; Yan et al., 2005] and operator- or robot-induced passive mobilization [Masiero et al., 2007; Pittaccio et al., 2007]. It is thought that they may contrast deafferentation and learned nonuse (i.e., directly address impairment of the cortical pathways involved in active limb control). The SHADE orthosis (Shape-memory-alloy-based Haptic Dorsiflexion Exerciser), used to provide repeatable ankle flexion is a simple device for passive mobilization of the ankle joint. This robotic tool was developed to assist in the post-acute rehabilitation treatment of stroke patients. As such, it is an example of a currently much-studied approach to hemiparesis care aiming at preserving tissue viscoelastic properties and fighting movement somatosensory deprivation [Lum et al., 2002; Kwakkel et al., 2008]. SHADE was previously proven to be very well accepted by patients and effective in promoting suitable

movement ranges at appropriate speeds [Pittaccio et al., 2007, 2009]. Because of its being activated through shape memory alloy wires it has the advantage of being fully compatible with MEG environment and recordings.

Investigating central correlates during passive mobilization in comparison with active movements can be done with great advantages if the participations of primary sensory (S1) and primary motor (M1) areas can be clearly discriminated. This can be achieved by a new source extraction method [Functional Source Separation (FSS), Tecchio et al., 2007a] recently developed at our laboratory, which adds functional constraints to the statistical contrast function of a standard independent component analysis algorithm (ICA). FSS is capable to provide the activity of a particular source in a variety of different experimental conditions based on specific information about that source, which can be gained by exploiting a “fingerprint behavior” arising under a limited-time experimental condition. The ability of FSS in discriminating S1 from M1 was previously proven for the hand representation [Porcaro et al., 2008; Tecchio et al., 2008]. Moreover, the powers of these two sources and their mutual coherence in the high gamma band selectively depended on the performance level constituting a sensorimotor feedback efficiency index estimating the continuous functional balance between primary sensory and motor areas devoted to hand control [Tecchio et al., 2008].

This study aims at describing, by means of magnetoencephalographic techniques, the neural circuits activated in healthy subjects undergoing passive mobilization of the ankle joint as produced by NMES or the application of the SHADE orthosis. Previous studies on the index finger provided evidence that MEG can be used in connection with mechanical passive mobilization to assess cortical sensorimotor involvement [Alary et al., 2002; Xiang et al., 1997]. The choice of studying healthy subjects before approaching stroke survivors makes it possible to compare cortical activation induced by passive mobilization of the ankle directly with the physiological pattern during active movement.

SUBJECTS AND METHODS

Subjects

Seven healthy subjects (mean age 29 ± 7 years, five men, six right-handed: Edinburgh Inventory $94 \pm 3\%$, one left-handed: Edinburgh Inventory -100%), participated in the study. The experimental protocol was approved by the Hospital Ethical Committee, and all subjects signed a written informed consent.

The exclusion criteria were any neurological, muscular, or articular disorders particularly those affecting the lower limb function.

MEG Investigation

Brain magnetic fields were recorded by means of a 28-channel MEG system [Tecchio et al., 1997] covering a

scalp area of about 180 cm², operating inside a magnetically shielded room (Vacuumschmelze). The MEG probe was centered 2.5 cm posterior to the Cz position of the 10–20 International EEG system (see Fig. 1). Electromyograms (EMG) from the tibialis anterior (TA) and gastrocnemius muscles were acquired by two pairs of Ag/AgCl cup electrodes (8 mm in diameter), whose active electrode was placed on the skin over the belly of the muscle, referred to a point located 2.5 cm more distally (see also

Fig. 1). MEG and EMG data were sampled at 1,000 Hz (presampling analogical bandpass filtering 0.48–256 Hz), and collected for off-line processing.

MEG activity was recorded during different conditions, namely

- rest (2 min, open eyes, REST);
- somatosensory electrical stimulation to the common peroneal nerve (CPN), delivered through surface

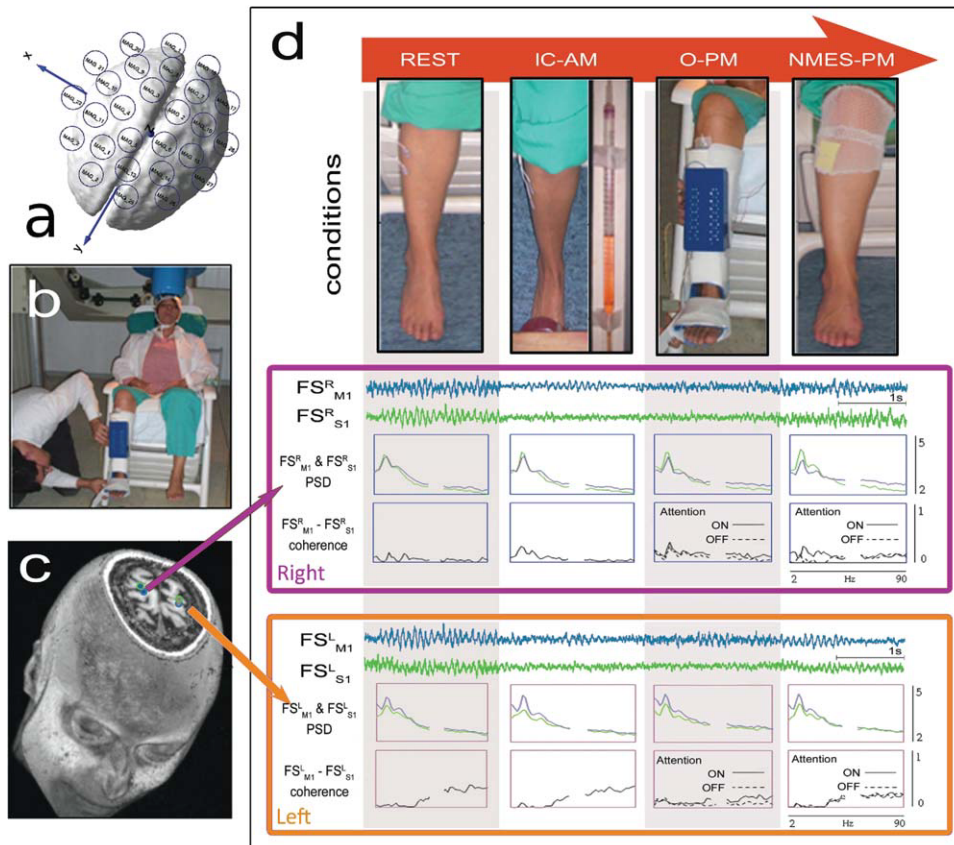


Figure 1.

Experimental set up and FS characteristics in a representative subject (a) Positioning of the MEG probe: centered 2.5 cm posterior to the point Cz and covering an area of ca. 180 cm². The positioning of the MEG sensors is show with respect to the subject brain. (b) The subjects were sitting during the acquisitions, with their heads resting on a cushion and stabilized. (c) The locations of the sensory and motor functional sources devoted to contra-lateral ankle control are shown in the left (FS_{S1}^L, FS_{M1}^L) and right (FS_{S1}^R, FS_{M1}^R) hemispheres projected on a suitable MR transverse section. Those were monitored across the different conditions, as shown for a representative subject: (d) top, general set-up and details for the four experimental conditions (shown for the right foot, the experiment was performed separately also with the left foot): resting state (REST), isometric contraction active movement

(IC-AM), passive movement induced by SHADE (O-PM) and neuromuscular electric stimulation (NMES-PM); bottom, the functional source activities in the left (orange box) and right (purple box) hemispheres are represented during contra-lateral foot tasks. Two-second time evolutions from the subject are shown for both FS_{M1} (blu) and FS_{S1} (green) in each experimental condition applied to the contra-lateral foot, together with their power spectral densities (PSD—ln fT/√Hz) and spectral coherences between the two sources (coherence, dimensionless). It can be appreciated that power values in the left hemisphere are higher than in the right (bottom PSD boxes [left] vs. upper [right]), as well PSD blu traces [FS_{M1}] in the gamma band (50–90 Hz) are above green ones [FS_{S1}]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

disks (cathode proximal), 0.2-ms long electric pulses, 631 ms interstimulus interval, stimulus intensity just inducing a painless foot twitch (total duration 3 min);

- isometric dorsiflexion (active condition) of the ankle at 5% of the maximal voluntary contraction (MVC) for periods of 20 s intermingled with 20 s periods of rest while pressing a water sphygmomanometer under visual feedback to facilitate maintaining a constant isometric contraction (IC-AM). A total of 4 min of contraction were collected. The MVC force of tibialis anterior muscle was estimated as the mean of three measurements taken during 500 ms contractions;
- passive movement of the ankle by neuromuscular electrical stimulation (NMES-PM), which was applied through a pair of 3 mm thick saline-soaked synthetic sponge electrodes. A 20 mm side square anode was placed on the skin covering the CPN at the knee and the cathode (about $70 \times 30 \text{ mm}^2$) was applied above the belly of tibialis anterior muscle. The 3 s on, 3 s off stimulation was delivered for a total of 8 min in the form of square impulse trains at a frequency in the 40–50 Hz range and an impulse duration around 300 μs , both optimized on an individual basis. The stimulus intensity was set just above the motor threshold at a painless level;
- passive repeated dorsiflexion of the ankle by the use of the active orthosis SHADE (O-PM), for 10 min. Each repetition included 7 s of passive dorsiflexion and 30 s during which the foot returned to its resting position in extension due to sheer gravity. The movement ranged approximately from 15° of plantarflexion to 5° of dorsiflexion.

Both types of passive mobilizations were divided into two phases alternating distraction and attention to the movement (5 min ON +5 min OFF). During the distraction periods, the subjects were required to quietly sing in their minds. For the attention condition the subject was required to concentrate on feeling the movement and no line of sight was available. In particular, subjects had to tap, with their hand contralateral to the stimulated limb, on their seat armrest both at onset and offset of dorsiflexion. The whole procedure was repeated on both sides for all subjects.

SHADE Orthosis

The SHADE active orthosis was chosen as a means of obtaining passive dorsi-plantarflexion repeatedly and repeatably for long periods of time.

SHADE is based on the use of thin shape memory alloy wires. Shape memory wire recovery forces and displacements can provide appropriate mobilization for the purpose of this study [Pittaccio et al., 2006] and are very biocompatible. These alloys (typically NiTi alloys, with Nickel content less than 50.6%at) are metal compounds

with the unique characteristic of being very deformable at room temperature and full-recovering up to 8% of deformation once heated. This behavior is due to a crystallographically reversible phase transformation occurring in the solid state, from martensite (stable at lower temperatures, more deformable) to austenite (stable at higher temperatures, stiffer). Shape recovery occurs if the alloy is heated over certain transformation temperatures, while cooling down the material transforms again into martensite. During shape recovery, these alloys produce force and thus can be utilized to make work. For this application, a shape memory NiTi 250- μm -diameter commercial wire, stabilized for actuation, was utilized, to ensure lasting performance for SHADE. This wire is wound inside a non-magnetic cartridge structure and is activated by electric current injection at 20 W. The materials are therefore completely magnetically transparent. Switching the current on and off (square wave pulses) produces magnetic signal artifacts, which are however very easily recognizable and can be straightforwardly eliminated by standard signal processing techniques.

Data Analysis

A semiautomatic ICA-based procedure [Barbati et al., 2004] was applied off line to identify cardiac and/or ocular artifacts and remove them from contaminated trials, without any need to exclude the cerebral signal in those periods from further analysis. Saturated epochs were rejected by visual inspection.

MI and SI FSS

The FSS procedure [Tecchio et al., 2007b] was applied to identify the cortical neural networks devoted to the ankle muscle representation in primary motor (FS_{M1}) and primary sensory (FS_{S1}) areas. In the FSS algorithm, additional information is added to the contrast function of a standard ICA model to bias the algorithm search towards a single solution that satisfies the physiological assumptions (functional source, FS). The FS_{S1} and FS_{M1} sources were extracted by exploiting the functional constraints related to specific time portions of the experiment, respectively CPN electrical stimulation and ankle voluntary isometric dorsiflexion. In particular for FS_{M1} extraction, in the IC-AM condition EMG signal was high-pass filtered at 5 Hz and rectified (i.e., by applying a moving average on a time window of 10 ms to the filtered EMG absolute values). The functional constraint was the maximization of coherence between the source and the rectified EMG in the beta band (between 14 and 32 Hz). For FS_{S1} extraction, the functional requirement was the maximal power in a window of about 5 ms centered on the maximal amplitude at around 40 ms of the response evoked by electrical CPN stimulation. Evoked responses were obtained by averaging the signal on stimulus occurrence. It is known that the

response at 40 ms (M40) is the standardized marker of the arrival of a sensory input from lower limb to the contralateral primary sensory cortex in the brain.

Source Validation

The extracted sources were validated through their location and activity. The generated field distribution of FS_{S1} and FS_{M1} was obtained by retro-projecting the source activities in the sensor space and was used as the input for inverse-problem solution. An equivalent current dipole (ECD) in a homogeneous conductive sphere was used. Location was expressed in a coordinate system defined on the basis of anatomical landmarks: y -axis originating at the mid point between the two preauricular points and directed through the nasion, positive x -axis rightward on the plane including nasion and preauricular points, thus positive z -axis directed upward. The x coordinate of the left hemisphere was mirrored on to the right. The locations of the two sources were compared submitting the 3D coordinates (x, y, z) to a repeated-measure analysis of variance (ANOVA) with Source (FS_{S1}, FS_{M1}) and Hemisphere (Left, Right) as within-subjects factors.

The activities of FS_{S1} and FS_{M1} were estimated during the control extraction conditions, i.e. voluntary movement and sensory stimulation. In particular, we checked whether coherence with the EMG activity was selectively present for contralateral primary motor areas and whether responsiveness to the CPN stimulation was selectively present for the earliest component of the contralateral sensory source. During voluntary contraction, we evaluated the maximal value of cortico-muscular coherence in the 14–32 Hz band (CMC) of FS_{S1} and FS_{M1} contra- and ipsilateral to the movement. These values of maximal CMC were submitted to a repeated-measure ANOVA with Source (FS_{S1}, FS_{M1}), Contraction side (Right, Left), and Hemisphere (Left, Right) as within-subject factors, so that both sources ipsi-lateral and contra-lateral to the movement could be taken into account. A similar model was applied to the maximal amplitude value at around 40 ms of the responses of FS_{S1} and FS_{M1} sources as evoked ipsi- and contra-laterally by CPN stimulation using Stimulation side (Left, Right) factor instead of Contraction.

Involvement of Sensorimotor Areas in Different Motion Tasks

We used the FS_{S1} and FS_{M1} time-courses during the whole experimental session to describe the selective involvement of the sensory and motor foot representations during active and passive ankle mobilizations. In particular, FS_{S1} and FS_{M1} involvement was assessed through their band power distributions and the coherence between them. The Power Spectral Densities (PSD) of both FS_{S1} and FS_{M1} were estimated by the Welch procedure (Hanning window, 60% overlap), by averaging 512 ms estimates,

resulting in a frequency resolution of about 1.95 Hz. The coherence between FS_{S1} and FS_{M1} (Coh) was estimated for each frequency bin as the squared magnitude of the cross-spectrum between the two sources, normalized by the FS_{S1} and FS_{M1} PSDs. The estimate was obtained separately for each condition: for REST the 512 ms windows were consecutive along the whole acquisition period; for IC-AM, NMES-PM, and O-PM analyses, windows were selected only from the dorsiflexion phases. The same number of time epochs (about 150) was chosen to estimate the band power and coherence between sources in the four conditions for all subjects.

Band spectral powers and coherences were evaluated by PSD and Coh mean values in the classical (IFSECN 1974) frequency bands, characteristic of the cortical network responsiveness of primary sensorimotor representation, i.e. alpha (α [8, 13] Hz), beta (β [14, 32] Hz), gamma1 (γ_1 [33, 60] Hz) and gamma2 (γ_2 [61, 90] Hz) bands. In the gamma1 band, four frequency points were excluded to eliminate the mains noise contamination.

We used the term “reactivity” whenever a spectral power reduction was found during the motion tasks (IC-AM, NMES-PM, and O-PM) with respect to REST. This reduction is indeed similar to the transient block (desynchronization) of alpha and beta background electroencephalographic or MEG activity during movement or stimulation in rolandic regions [Gastaut, 1952, Niedermeyer, 1999]. However, we preferred to use different terminology in order to draw attention to the fact that we are actually disregarding the temporal aspect (onset, duration, ...) of those same transient desynchronizations (often referred to as Event Related Desynchronization, ERD) [Hari and Salmelin, 1997; Pfurtscheller and Lopes da Silva, 1999] to focus outright on the fact that an average power modulation occurs during the stationary state of tasks.

Statistical Analysis

All band power values were log-transformed to best-fit the Gaussian distribution (Kolmogorov-Smirnoff test $P > 0.700$ consistently).

The activities at REST of FS_{S1} and FS_{M1} were studied submitting band power values to an ANOVA design with Source (FS_{S1} and FS_{M1}) and Band (alpha, beta, gamma1, gamma2) as within-subject factor: this was done to test possible spectral differences among the sensory and motor lower limb representations via the Source*Band interaction factor.

To estimate the spectral properties of the primary sensory and motor sources and their modulations in different experimental conditions, repeated-measure ANOVA was applied separately to each power band of the source activities with Source (FS_{S1}, FS_{M1}), Hemisphere (Left, Right), and Condition (REST, IC-AM, NMES-PM and O-PM) as within-subject factors. The main factor of interest was the

TABLE I. Functional source FS_{S1} and FS_{M1} locations

	Left hemisphere			Right hemisphere		
	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)
FS _{M1}	-7.4 (5.4)	10.3 (3.1)	92.3 (9.5)	3.9 (8.1)	4.7 (11.8)	98.1 (6.9)
FS _{S1}	-18.9 (3.4)	-0.6 (4.8)	109.1 (8.0)	14.3 (5.1)	-15.7 (8.7)	101.4 (10.0)
M40	-15.1 (3.9)	-7.3 (2.9)	98.1 (6.6)	13.7 (5.3)	-8.7 (8.3)	104.0 (5.9)

Mean (Standard Error) locations of the FS_{S1} and FS_{M1} sources expressed in the coordinate system defined in the text. The location of M40 generator as estimated by an equivalent current dipole (ECD) in a homogeneous conductive sphere is reported for comparison with the FS_{S1} site.

Condition*Source interaction effect, expressing source selectivity in reacting during the sensorimotor tasks. The same analysis was repeated for each FS_{S1}-FS_{M1} coherence band value, with Hemisphere (Left, Right) and Condition (REST, IC-AM, NMES-PM, and O-PM) as within-subject factors.

An additional factor was studied for NMES-PM and O-PM: Attention (ON, OFF) to study the effect of concentrating vs. not concentrating on the passively imparted ankle motion. An effect was reported as a result only if it was statistically significant. In the case of a significant effect, we considered the post-hoc contrasts.

RESULTS

The results are organized in two sections. The first one (Validation of the identified sources) shows the goodness of the left and right sources devoted to the sensory and motor representations of the contra-lateral feet. To this aim their relative positions in relationship with homuncular organization was estimated. Moreover, their responsiveness to the CPN stimulation and their coherence with TA muscular activity during isometric contraction was quantified, which are the standard conditions to activate constraints for the source identification.

In the second section (Primary cortical involvement in different motion conditions), the core results are presented,

dealing with the separate involvement of primary sensory and motor cortices during active and passive mobilizations.

Validation of the Identified Sources

FSS1 and FSM1 locations agree with the relative anatomical locations of the primary sensory and motor areas. Functional sources FSS1 and FSM1 respectively devoted to the cortical representations of lower limb sensory and motor counterparts were suitably identified in both hemispheres for all subjects. The FSS1 and FSM1 locations were spatially distinct in both hemispheres, as indicated by the Source factor in the ANOVA on 3D (x, y, z) coordinates [$F(3,4) = 13.692; P = 0.014$]. Post-hoc comparison showed a more frontal (y -coordinate $P = 0.006$, Bonferroni-corrected) and medial (x -coordinate $P = 0.035$) location for FSM1 with respect to FSS1, in agreement with the precentral and postcentral positioning of M1 and S1 (Fig. 1c, Table I).

FSS1 and FSM1 activities: among bilateral sources, only contralateral FSM1 displayed beta band cortico-muscular coherence during movement and only contra-lateral FSS1 displayed evoked response to CPN stimulation. FSS1 and FSM1 reacted differently to CPN stimulation and displayed different coherence levels with muscular activity (see Fig. 2). In fact, cortico-muscular coherence was

Figure 2.

FS_{S1} and FS_{M1} activities In one representative subject: (a) spectral distribution of the cortico-muscular coherence (CMC) for FS_{S1} and FS_{M1} of right (RH) and left hemisphere (LH) during contra- and ipsi-lateral lower limb tasks. Significant CMC levels appeared only for FSM1 during contralateral isometric contraction; (b) time evolution of each source is shown after averaging repeated measures in the [-20, 100] ms window, time-zero corresponding to common peroneal nerve (CPN) stimulation. Source activity amplitudes are expressed in the same dimensionless units, as they are comparable thanks to the FSS method. Only FS_{S1} responded to contralateral nerve stimulation. (c) Box-and-Whiskers plot of maximal CMC amplitude in beta band (14–32 Hz) for each source in the left and right hemispheres, during contra- and ipsi-lateral contractions. The thick line corre-

sponds to the median of the distribution, while the box corresponds to the interquartile range. Whiskers at the ends of the box show the distance from the end of the box to the largest and smallest observed values that are less than 1.5 box lengths from either end of the box. Outliers (full circles) are above 1.5 box lengths from the end of the box. Horizontal broken lines indicate the CMC significance level, as obtained in Hallyday et al. [1995] (d) Box-and-Whiskers plot of ECD strength of the earliest component (M40) of each source after contra and ipsi-lateral CPN stimulation. Asterisks indicate significant differences between the conditions shown in the graph. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

significantly different from the baseline value only for FSM1 in the hemisphere contra-lateral to the movement (Fig. 2a,c, strong main factor Source [$F(1,6) = 55.734$; $P <$

0.001] in spite of triple interaction factor Source*Hemisphere*Contraction side [$F(1,6) = 23.057$; $P = 0.003$]). Maximal coherence between FSM1 and contra-lateral TA EMG

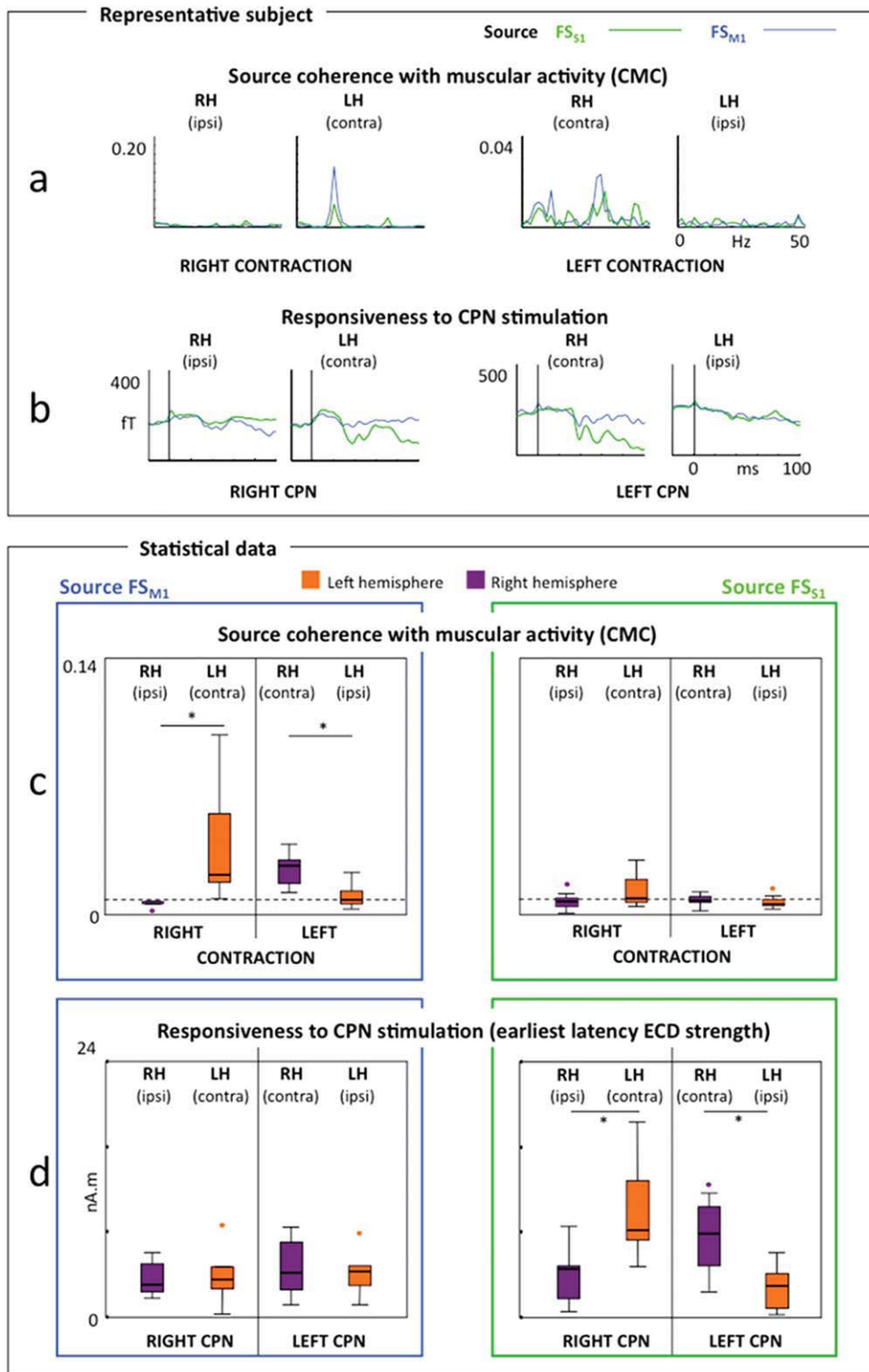


Figure 2.

activity appeared consistently in the beta band in both hemispheres, at mean frequency values 22.3 ± 3.4 Hz in the left and 27.6 ± 7.6 Hz in the right, without statistical differences. In a similar way, only contra-lateral FSS1 responded to the nerve stimulation (Fig. 2b,d, main factor Source [F(1,6) = 8.024; $P = 0.030$] in spite of triple interaction factor Source*Hemisphere*Stimulation side [F(1,6) = 12.106; $P = 0.013$]). Mean latencies of the earliest components of the contralateral FSS1 were 35.1 ± 2.9 ms for the left hemisphere and 35.7 ± 3.1 ms for the right one.

Primary Cortical Involvement in Different Motion Conditions

FS_{S1} and FS_{M1} background activity: FS_{M1} displayed higher gamma band power than FS_{S1} and the two sources in the left hemisphere showed higher power than those in the right. Different spectral components characterize the background activity of the two sources, with higher REST gamma1 and gamma2 powers for FS_{M1} than FS_{S1} [Source factor F(1,6) = 5.438, $P = 0.058$ and F(1,6) = 8.312, $P = 0.028$, respectively]. Both sources displayed higher power in the left hemisphere [Hemisphere factor F(1,6) = 6.314, $P = 0.046$]. Post-hoc comparison showed significant inter-hemispheric differences in bands above beta (beta, $P = 0.042$; gamma1, $P = 0.017$; gamma2, $P = 0.015$, Fig. 1).

FS_{S1} and FS_{M1} task-related activity: both sources reacted selectively in beta band during IC-AM, only FS_{S1} reacted during O-PM, no source reacted during NMES-PM. Considering the sources contralateral to the movement, a Condition*Source effect [F(3, 18) = 16.860, $P < 0.001$, Fig. 3, top] was found selectively in beta band. Post-hoc comparisons indicated that both FS_{S1} and FS_{M1} reacted during IC-AM with respect to REST in both hemispheres ($P = 0.014$ for FS_{S1} and $P = 0.005$ for FS_{M1}). During O-PM, solely FS_{S1} was reactive ($P = 0.036$, $P = 0.843$ for FS_{M1}). No reactivity was found in connection with NMES-PM. FS_{S1} and FS_{M1} ipsilateral to the tested ankle showed a Condition*Source effect [F(1.8, 10.7) = 4.962, $P = 0.033$, Fig. 3 bottom] with post-hoc comparisons indicating FS_{S1} was involved during IC-AM ($P = 0.041$, Fig. 3 bottom). No main or interaction effects were detected in other frequency bands.

No modulation during different sensorimotor tasks was observed for FS_{S1}–FS_{M1} coherence levels in any frequency band, either contra- or ipsi-laterally.

Focusing Attention May Enhance FS_{M1}–FS_{S1} Coherence in Gamma2 Band

During passive mobilizations, neither FS_{S1} or FS_{M1} displayed a power modulation in any spectral band due to attention levels. Conversely, when focusing attention on O-PM a slight increase of FS_{M1}–FS_{S1} coherence selectively in gamma2 band was found with respect to the condition of silent singing (Attention factor [F(1,6) = 4.653, $P = 0.074$]; ON: 0.137 ± 0.084 , OFF: 0.117 ± 0.082).

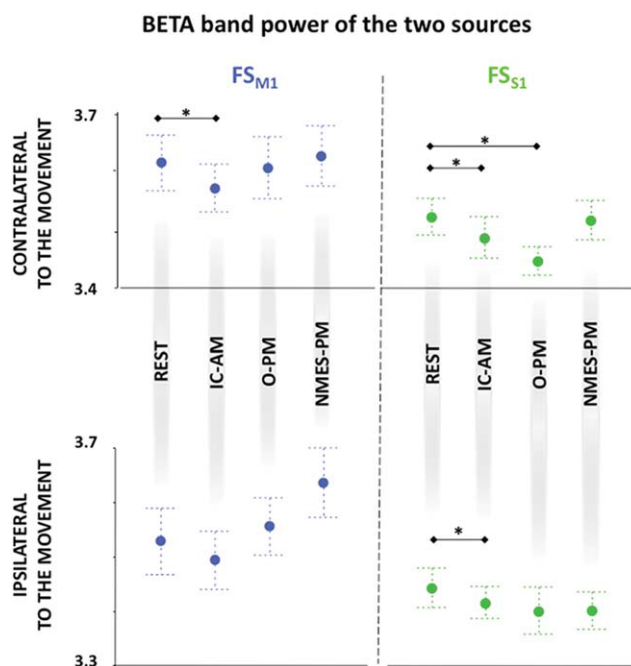


Figure 3.

FS_{S1} and FS_{M1} in voluntary and passive movements Mean across subjects of beta band power of the two sources during REST and voluntary isometric contraction (IC-AM), orthosis and neuromuscular electric stimulation induced passive movements (O-PM and NMES-PM). Error bars indicate standard error. Asterisks indicate significant differences with respect to the REST condition (* $P < 0.050$, + $P < 0.100$). Band powers are expressed in the same dimensionless units, as they are comparable thanks to the FSS method. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

DISCUSSION

This work was intended as a pilot study in healthy controls for comparison with future results on post-stroke subjects. The final aim is investigating the relationship between sensorimotor stimulation provided by passive mobilization of the ankle and the functional recovery of its active control after stroke.

Results provide insights in the activation patterns produced by passive ankle/foot mobilization on the healthy cerebral cortex. Some aspects could have peculiar importance also with respect to possible clinical implications. The recognition of afferent information about the imparted movement by the primary somatosensory cortex, in a way similar to voluntary movement, could provide a foundation for the use of passive exercise as a means to hinder the insurgence of movement pattern forgetfulness and support more efficient cortical rearrangement during the flaccid phase of limb paralysis. This effect was proved for SHADE but it was absent for NMES passive mobilization.

We believe that a partial explanation of why the effect of attention failed to reach full significance in the present tests may lie the limited number of subjects studied so far. That number is indeed going to be improved in future in order to strengthen the present findings. Nonetheless, this effect was deemed worth reporting, as it was observed for the same oscillatory activity, which previous literature indicates as a key code for cognitive involvement and focusing of attention during motor tasks [Cardin et al., 2009; Dalal et al., 2009; Fries et al., 2001; Steinmetz et al., 2000]. Furthermore, in the logical scheme of this work, also aiming at the study of clinical protocols based on passive mobilization, this type of results, if supported by further evidence, stress the importance of creating appropriate conditions during therapy, in which patient's attention is drawn to the passively mobilized limb to maximize beneficial outcomes. Of course maintaining focused attention or lack of it for long periods of time requires strong cognitive involvement, likely inducing mental fatigue and is probably not recommended. This stimulates the idea that also carefully organizing distraction periods may bring some advantage to concentrate better when required.

Apart from clinical considerations, most results are applicable to a description of the healthy brain per se. For the first time, it was possible to discriminate within primary cortical areas devoted to lower limb control the sensory and motor counterparts by analyzing their neural electric activity. Earliest responsiveness to CPN stimulation was present only for FS_{S1} and only for contralateral stimulation. As for the motor side, cortico-muscular coherence was significant across subjects only for FS_{M1} and only during contralateral movement. Bilateral modulations were on the contrary observed in different tasks, in agreement to data by Müller et al. [2003], who reported a beta event-related desynchronization (ERD), i.e. a decrease in spectral power amplitude lasting about 1-2 s after the "trigger" event, starting bilaterally after active, passive, and NMES-induced movement onsets. The main result of that article contrasting active vs. passive conditions was the quite expectable absence of ERD typical of active movement preparation prior to passive or stimulation-induced movement onsets. In this work, although anticipatory ERDs were not considered. We were able to document, more interestingly, that selectively primary sensory areas had a similar activity during passive and voluntary movements of the lower limb. The primary motor areas were significantly involved only during active movements. Müller-Putz et al. [2007] reported that the Cz derivation displayed ERD in the beta frequency range for both active and passive lower limb movements. In our study all relevant effects appeared in the beta band for both primary sensory and motor areas. Previous studies on lower limb movements indicated an ERD of rhythms within alpha and lower beta bands bilaterally over the sensorimotor areas after voluntary movements [Pfurtscheller et al., 1998; Müller et al., 2003], passive movements [Müller et al., 2003], and movement imagination [Rossi et al., 2002].

ler et al. [2003] descriptively reported about ERD phenomena (no statistics were presented) also during passive movements of the hand induced by neuromuscular electrical stimulation. In our study, the oscillatory rhythm reactivity of either FS_{S1} or FS_{M1} did not reach a significant level in any band during NMES. This discordance could be due to longer intervals considered for the power estimate in our study than ERD dynamics, or differences in controlling the lower instead of the upper limb.

The oscillatory activity in the gamma band of primary motor areas devoted to ankle control was stronger than for the primary sensory counterpart. A similar spectral pattern was previously shown for the hand representation [Tecchio et al., 2008]. Oscillatory brain activity with prevalent high-frequency spectral components has been already observed in frontal motor areas with respect to the parietal sensory ones [Crone et al., 1998; Ohara et al., 2000, 2001; Schoffelen et al., 2005].

A clear left prevalence appeared for the right lower limb representation, with the left hemispheric activity of both primary sensory and motor areas showing higher power than the right one in beta and gamma bands. This suggests looking into the possibility that a wider neural area is devoted to the right foot sensory representation. An example of this for FS_{S1} comes from Figure 2d, where the mean value of responsiveness to CPN stimulation is higher for the right than the left ankle. While for the hand representation, at all ages [Zappasodi et al., 2006], wider and more synchronized recruitment was consistently found both in sensory [Jung et al., 2003; Theuvsenet et al., 2005; Zappasodi et al., 2006] and motor areas [Cantello et al., 1991; McDonnell et al., 1991], such an asymmetry for the lower limb was never documented before. Considering that those quoted hand studies needed much larger cohorts to confirm this datum, statistical significance of the observed asymmetry in the lower limb will be similarly sought through more extensive experiments in future.

Although our results on primary relativities were largely significant, hardly anything can be inferred from this study about the secondary, supplementary and premotor cortices, which may play an important role in functional recovery after stroke, but cannot be sufficiently well observed with the present channel scheme. Those areas, involved more in movement planning, recognition, preparation, initiation and control, rather than execution, could have, on deeper observation, some intriguing involvement during passive mobilization of the ankle, such as was demonstrated for the index finger [Alary et al., 2002]. Alary et al. stressed the important role of SII cortices (alongside S1) in processing mechanical passive mobilization and proprioception and observed an interhemispheric asymmetry with left dominance for SII activation in passive index finger extension. Left lateralized sizes of the posterior parietal operculum, in parallel to pronounced left lateralized dipole strengths in response to median nerve somatosensory stimulation indicated both structural and functional asymmetries in the human parietal

operculum closely related to each other [Jung et al., 2009]. These evidences may suggest interhemispheric interplays in controlling the upper limb which should be studied also for the lower limb with a more extensive coverage.

The strength of the current results lies, among other things, in the choice to carry out mobilization by the use of the SHADE orthosis, which made it possible to provide highly repeatable movement ranges and speeds to the ankle joint, thus avoiding the intertrial variability which is typical, for instance, of manual passive mobilization and providing a more solid basis for longitudinal studies. The absence of a human operator also helped avert individual influences on the subjects' psychological attitude. The angular range spanned by SHADE is self-adapting to the individual ankle characteristics but in this case it was possible to preset the chosen limits to a certain extent.

It is interesting to notice that good results were obtained with much higher speeds in previous studies [Alary et al., 2002; Xiang et al., 1997] than we used for the present one. It can be inferred that higher speeds and accelerations could provoke increased response leading to improved signal-to-noise ratios during acquisition. Nevertheless, it is unlikely that speeds applicable to the fingers are feasible for the ankle joint, given the different inertial properties. The study by Alary et al. anyway supports the fact that even low speeds (such as the ones they measured in the finger flexion direction) can provide sufficient stimulation. The specific maximal range and speed of dorsiflexion selected for this study were set at a suitable level to avoid stretch and tension reflexes from the ankle plantarflexors which, for distal segments, may have a long-loop counterpart involving supraspinal circuits, including cortical relays. It could be interesting to study in future also the influence of relatively higher stretches on cortical involvement.

Also NMES generated motion in a repeatable way but it was experienced as a nuisance by many and never produced something that the subjects themselves recognized as a natural ankle dorsiflexion, which makes it a less suitable means of providing passive motion of the ankle for the purposes of this study. In consideration of the fact that most NMES results demonstrated non-significant, it may well be that cerebral processing did not show any characteristics in common with voluntary movement in the same way as subjective opinions did not assimilate those somatosensory perceptions to the ones felt during active tasks, but rather to unnatural and sometimes unpleasant sensations. What was found is that, besides the expected lack of primary motor area involvement (since mobilization was passive), no sign of primary sensory area participation was registered in connection with NMES. This was in stark opposition e.g. to the SHADE orthosis application findings, where S1 reacted in a way similar to the voluntary movement case. The difference between mechanical and electric stimulation could even extend beyond primary areas: a hint of this is provided by Alary et al.'s observation that whereas mechanical proprioception produces asymmetric (left) SII response, electric stimula-

tion has been described as characterized by bilateral SII activation.

CONCLUSIONS

The FSS procedure suitably discriminated the sensory and motor functional sources devoted to the ankle cortical representation in healthy volunteers. The spectrally specific contributions of sensory and motor regions were separately investigated in different foot sensorymotor tasks. Passive mobilization by the use of SHADE stimulated sensory involvement similarly to active movement. Focusing attention on the movement may enhance mutual coherence between the motor and somatosensory sources in the high gamma band. Some of these results may have clinical implications to the effect that passive mobilization of the ankle joint could provide beneficial stimulation of the central sensorimotor areas during their functional recovery period after a cerebrovascular stroke.

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