

Cortical Connections Between Dorsal and Ventral Visual Streams in Humans: Evidence by TMS/EEG Co-Registration

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Abstract Parietal cortex subserves various cognitive tasks, ranging from attention to visuo-motor skills. It is part of a parieto-frontal network involved in attention, and part of the visual dorsal stream, opposed to the visual ventral stream, although increasing evidence suggests interchange of information between them. In this study, co-registration of Transcranial Magnetic Stimulation (TMS) and Electroencephalographic activity (EEG) has been used to investigate the spreading of cortical connections from the parietal cortex in healthy volunteers. TMS on the left parietal cortex activated a network of prefrontal regions in the contra-lateral hemisphere in a time range of 102–167 ms after the stimulus. Moreover, activation in the ipsilateral middle temporal and fusiform gyri was observed at 171–177 ms after delivery of TMS. Findings suggest the existence of late driven connections between parietal and prefrontal regions that could partially represent the neural pathway related to attention, even if, in this experiment, no attentional processing was requested. Late connections between dorsal and ventral streams were also evident, confirming previous evidence about interchange of information between them. Conclusively, the present investigation confirms that a great amount of information spreads from parietal cortex to different regions in the brain, supporting the idea that connections are more complex and articulated than those proposed. Present findings also

suggest that the simultaneous recording of EEG during the application of TMS is a promising tool for the study of connections in the brain.

Keywords Dorsal stream · Cortical connection · sLORETA · TMS/EEG · Ventral stream

Introduction

Parietal cortex is an important cortical region that occupies about the 25% of a cerebral hemisphere (Culham et al. 2006; Damasio 2005) and, apart from the somatosensory cortex, it is normally viewed as an association region where multimodal elaboration of information takes place (Rizzolatti et al. 1997). More specifically, the posterior parietal cortex is usually involved in various cognitive tasks, as for example re-direction of attention (Rushworth et al. 2003), visuo-spatial behaviour (Babiloni et al. 2006; Thayer and Johnson 2006) or integration of visuo-motor information (Berndt et al. 2002; Holz et al. 2008; MacKay and Mendonça 1995; Praeg et al. 2006). It is principally involved in planning and execution of actions and it is considered as part of the visual dorsal stream for action (Milner and Goodale 2006). On the other hand, there also exists a visual ventral stream (Milner and Goodale 2006), involving mainly temporal regions in the brain. The ventral stream is thought to be mainly involved in elaborating the information related to object perception (Milner and Goodale 2006).

Dorsal and ventral streams have been preferentially thought as independent (Cavina-Pratesi et al. 2007; Shmuelof and Zohary 2005; see also Bruno et al. 2008 for a review), even if evidence of interchange of information between them exists, both in monkeys (Borra et al. 2008;

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Felleman and Van Essen 1991) and humans (Mahon et al. 2007; Schenk and Milner 2006). However, the dimension of the latter possibility is still strongly debated, and no definitive evidence is available.

Anatomical studies in monkeys and structural and functional studies in humans have demonstrated that the posterior parietal cortex spreads a number of fibres toward different regions in the brain, ranging from temporal to frontal lobes (Borra et al. 2008; Hagmann et al. 2008; Matelli and Luppino 2001; Tannè-Gariepy et al. 2002). For example, there is evidence suggesting the existence of reciprocal connections between parietal and frontal areas in humans, as well as between parietal and temporal areas (Hagmann et al. 2008).

It has also been demonstrated that fibres leaving the posterior parietal cortex are mainly directed to the premotor cortex, probably to allow the transformation of visuo-spatial information into motor commands (Hagmann et al. 2008; Matelli and Luppino 2001; Tannè-Gariepy et al. 2002).

In spite of the large amount of information on cortico-cortical fibres leaving the parietal cortex, the number of these connections and when they are really used has been insufficiently investigated.

Electroencephalography (EEG) has been largely used to investigate which brain regions participate in a cognitive task, as well as their timing and pattern of activation. For example, the existence of complex patterns of activation during attention and/or visuo-spatial and visuo-motor tasks have been reported (Berndt et al. 2002; Holz et al. 2008; Praeg et al. 2006; Thayer and Johnson 2006), indicating the involvement of both parietal and frontal areas but not clarifying the involvement and amount of functional connections among them (Berndt et al. 2002; Holz et al. 2008; Praeg et al. 2006).

Transcranial Magnetic Stimulation (TMS) has been used to investigate the role that an area plays in a given task, facilitating or disturbing its activation (Walsh and Pascual-Leone 2003). In this sense, the time window of TMS delivery during the cognitive processing of the stimulated area has been proposed to be crucial in order to define facilitatory or inhibitory effects of stimulation (Silvanto and Pascual-Leone 2008). Moreover, TMS has been largely used to investigate the role of areas such as those in the parietal and frontal cortices, especially in attention tasks and/or visuo-motor integration (Desmurget et al. 1999; Lee and van Donkelaar 2006; Van Donkelaar et al. 2000, 2002), and a number of studies indirectly suggest an interchange of information between these regions (see Sack and Linden 2003 for a review). In this sense, the combination of TMS and EEG seems to be the best approach to investigate this issue.

In fact, in recent years, the recording of brain electric activity has been performed simultaneously with TMS, adding new possibilities to the study of the dynamics of brain functions. The combination of these two techniques (TMS/EEG approach) was first used to study the connectivity of different regions of the brain and cortico-cortical interactions, mapping the spread of activation caused by TMS and taking advantage from the extraordinary temporal resolution offered by EEG (Ilmoniemi et al. 1997). Successively, TMS/EEG approach has been applied for several other purposes both in the EEG time- and frequency-domain. TMS/EEG approach can be used to study the reactivity to magnetic stimulation of different brain areas or different cortical state, such as during sleep (Massimini et al. 2005) or after the ingestion of alcohol (Komssi et al. 2002). An other interesting possibility is to evaluate how TMS can modify the EEG rhythm in one or more frequencies that might play particular roles in cognitive processes such as attention (Thut and Miniussi 2009).

In the context of this article, TMS/EEG approach is viewed as an interesting technique that allows to observe not only direct effects of TMS, but also its indirect ones on areas situated far from the stimulated one (Ilmoniemi et al. 1997; Komssi and Kahkonen 2006; Miniussi and Thut 2009). As a matter of fact, TMS interacts not only with the cortical region underlying the coil, but the activation of this area spreads along its efferent fibres and influences brain regions that are the target of these projections, so as to discover areas which are functionally related to the original point of stimulation (Brignani et al. 2008; Fuggetta et al. 2005, 2008; Komssi et al. 2002; Massimini et al. 2005; Schutter and van Honk 2006). In this sense, it should be indicated that cortical connectivity may depend on the physiological state of the neurons in the stimulated cortex (Massimini et al. 2005). Consequently, in a theoretical frame, the study of brain connections by means of TMS/EEG co-registration could bring to different conclusions when the brain is stimulated during sleep or when awake, when subjects lie in a resting state with closed eyes, or when they are performing a cognitive task. In this sense, besides the well known and diffuse change from alpha to beta activity when passing from a closed to an open eyes condition, a greater variability was reported when EEG was recorded in a closed eyes condition with respect to an open eyes condition, but it must be noted that this was evident only in the primary visual cortex (Thuraisingham et al. 2007).

In this study we investigated cortical connections of parietal cortex by means of TMS/EEG co-registration and EEG source analysis. On the basis of the reported literature, when stimulating parietal cortex, activation should diffuse mainly to the ipsi-lateral premotor and/or temporal

cortex, in compliance with the idea of a cortical connection among parietal cortex and these areas (Massimini et al. 2005; Mahon et al. 2007). Consequently, we expected to directly confirm the existence of a link between parietal and premotor cortex in humans, and/or give useful suggestions about the possibility of an interchange of information between different streams, namely the dorsal and the ventral ones in the brain. Moreover, the TMS/EEG approach should be useful also to obtain additional information about the specific time-course needed to activate these links and to accomplish information delivery.

Materials and Methods

Participants

Ten healthy volunteers (5 males and 5 females; age-range 20–26 years, mean age and standard deviation 23.8 ± 2.1 years) took part to the experiment. All subjects were right-handed accordingly to the Oldfield test (Oldfield 1971; mean score of handedness and standard deviation $91.7\% \pm 7.9$) and gave written informed consent after receiving information about TMS/EEG co-registration and related risks of magnetic stimulation, in accordance with the Declaration of Helsinki. The safety guidelines for TMS were strictly observed (Wassermann 1998). Permission from the Local Ethic Committee was also obtained. Subjects could leave the study at any point, nevertheless they all completed the experiments.

TMS Protocol

During experiments, each subject was comfortably seated and was asked to close her/his eyes for the entire duration of stimulation blocks in order to reduce eye-blinks or saccades during the experiments.

Single biphasic TMS pulses (Medtronic MagPro R30; pulse duration: 280 μ s) were delivered on the left parietal cortex on a scalp location determined according to the 10–20 EEG coordinate system (Okamoto et al. 2004) and marked with stickers on the EEG cap. This position corresponded to a parietal region that was situated at 15% of the bicaudal distance to the left of CPz point, near electrode CP3. The rationale for stimulating this point in the left parietal cortex with respect to other points in left or right parietal cortex was related to the fact that it has been individuated as a region involved in the elaboration of visuo-motor information by previous evidence obtained by our research group (Busan et al. 2009).

A figure-8 coil (each wing measuring seven cm; Medtronic C-B60) tangentially oriented to the scalp was used for the stimulation. The coil handle was positioned perpendicular to the interhemispheric scissure. This position was chosen because it caused the minor stimulation artefact on the surrounding electrodes. Position of the stimulated point with the presumed underlying main sulci are illustrated in Fig. 1.

Before the experiment, the best cortical point activating the first dorsal interosseous (FDI) muscle was determined in each subject, and motor threshold was set as the stimulus intensity triggering at least 50 μ V response on EMG recording in at least 50% of 10 consecutive stimulations (Rossini et al. 1994). Intensity of TMS pulses was then set at 110% of the FDI motor threshold.

During the experiments, real TMS delivery was intermingled with sham stimulation. In the sham condition, the same coil for real stimulation was used, but the effect of magnetic field produced from the stimulating coil was attenuated by applying a thickness of about 3.5 cm of polystyrene, in order to avoid that magnetic field reached cerebral cortex. Thus, coil placement in the sham condition was identical to that of the real stimulation, making it indistinguishable with respect to coil's weight and position

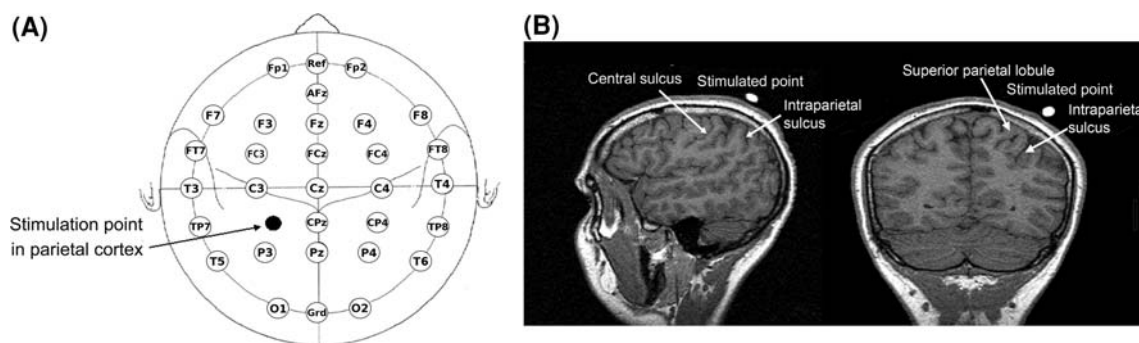


Fig. 1 Location of electrodes and point of stimulation. **a** Location of the stimulated point on a simplified drawing of the skull where the position of the EEG electrodes is also reported. **b** Location of the stimulated point on anatomical magnetic resonance scanning of one

subject, revealed by vitamin E pill. Sagittal and coronal sections are presented. Anatomical locations were identified according to Duvernoy (1999)

on the scalp. Additionally, the sound clicks produced in the two conditions were identical. Consequently, the comparison of real and sham TMS permitted also to check for current density effects related to acoustic cerebral activations.

Each subject participated to six stimulation blocks, with alternating real and sham TMS. The first type of stimulation was pseudo-randomly defined among subjects. Subjects were not informed about the type (sham or real) of stimulation. In every block a total of 60 single-pulse stimulations were delivered on the scalp. Between two consecutive stimulations, a random period from 4 to 6 s was introduced in order to avoid prediction of the delivery of the stimuli. The different blocks of stimulation were separated by stimulus-free intervals of at least 2 min duration.

Anatomical Localization

To validate the correspondence between point of stimulation on the scalp and underlying cortical areas, one subject underwent T1-weighted anatomical magnetic resonance (MR) scanning (slide thickness 1.5 mm, TR 10.26 ms, ET 4.6 ms, fov 240×240 , acquisition matrix 256×256 pixels, pixel spacing 0.93×0.93). Point of interest in parietal cortex, individuated on the basis of the 10–20 EEG system (Okamoto et al. 2004), was marked with a vitamin E pill.

EEG Recordings

Recordings were conducted in an electrically shielded and sound attenuated room. The EEG was recorded with a MIZAR-SIRIUS system (EBNeuro, Italy), using an amplifier BASIS BE (EBNeuro, Italy) and the acquisition software GALILEO_NT (EBNeuro, Italy). In order to minimize overheating of the electrodes in the vicinity of the stimulating coil, TMS compatible Ag/AgCl-sinterized electrodes were used.

A cap (Electro-Cap Center BV, Nieuwkoop, NL) with 29 Ag/AgCl-sinterized electrodes placed according to the Extended 10–20 International System was used (see Fig. 1 for electrodes used). Electrode CP3 was eliminated from the standard set-up since it was located too close to the coil and the interference caused by the stimulation on this electrode also affected the surrounding electrodes.

Additional electrodes were used as ground and reference. The ground electrode was positioned in Oz, in order to have a good distance from the stimulating coil, while the active reference was placed on FPz electrode. Blinks and other eye movements were recorded with a single bipolar channel constituted by two skin electrodes placed diagonally above and below the right eye. Electrode impedance

was kept below 10 k Ω . EEG signals were amplified and digitized at a rate of 512 Hz, and filtered analogically with a low-pass filter set at 230.4 Hz to avoid aliasing. Nevertheless these parameters could be not sufficient to assure a fast decay of the TMS induced artefact and avoid rippling.

The epoching of the real TMS- and sham TMS-evoked EEG responses was performed off-line.

EEG Data Analysis

EEG traces were analysed with the commercial software Scan 4.3 (Compumedics Neuroscan Inc., El Paso, USA), in order to characterize the real TMS- and sham TMS-related EEG responses. Before epoching, data were digitally filtered with a band-pass filter set at 0.01–150 Hz. Successively, epochs were computed, starting 100 ms before and ending 500 ms after the stimulus onset. Epochs with excessively noisy EEG or with eye-movements artefacts (startle reflexes or saccades) were rejected and the remaining ones were divided into two groups according to the type of stimulus (real or sham TMS). The average number and standard deviation of EEG epochs considered for statistical analysis was 93.3 ± 14.6 for real TMS condition and 93.5 ± 21.0 for sham TMS condition. In this sense, it is evident that more than half of the trials were normally discarded, because the presence of eye-movement artefacts, slow decay of the signal and/or rippled traces forced the elimination of a high number of EEG epochs. Finally, in order to analyze evoked potentials, the epochs were averaged in order to obtain real TMS-evoked potentials (real TEPs) and sham TMS-evoked potentials (sham TEPs).

As reported by other authors (Taylor et al. 2008), the TMS artefact influences the recording of scalp potentials in a period of a few tens of milliseconds after the delivery of the magnetic field. In the present data, TMS artefact resulted higher on electrodes positioned near the coil than on more distant ones, sometimes causing a TMS artefact lasting till to 30 ms. Moreover, a potential with a slow decay was still evident in some electrodes and in some subjects, more than 30 ms after the TMS delivery. This potential did not affect the shape of the TEP waves, but it disturbed the correct and natural realignment of the TEP trace on the baseline. This was a serious problem for the correct localization of the current density sources. For this reason, a “linear detrend” function, available in the Scan 4.3 software (Compumedics Neuroscan Inc., El Paso, USA), was applied to these electrodes, in order to correct real and sham TEPs. This function allows to eliminate slow potentials without affecting the TEP shape, and realign traces on the baseline in the time-range of interest. The “linear detrend” function was applied only in the time-range comprised between 30 ms and 300 ms after the TMS

delivery, in order to avoid problems linked to the presence of the fast rising-falling peak of the TEP. As a consequence, all successive analysis was carried out in a time period ranging between 30.5 ms and 300 ms after the stimulation.

sLORETA Analysis

sLORETA (Pascual-Marqui 2002) was used to compute the cortical three-dimensional distribution of current density for real and sham TMS stimulation in every experiment, on the basis of the distribution of the scalp-recorded electric potential.

It permits to solve the non-unique EEG inverse problem by assuming similar activation of neighbouring neuronal sources. This is obtained by an appropriate standardization of the current density and, consequently, by producing images of electrical activity without localization bias (Lorenzo-Lopez et al. 2008; Pascual-Marqui 2002; Sekihara et al. 2005).

Previous version of sLORETA (LORETA, Pascual-Marqui et al. 1994) received considerable validation from reports combining it with other more reliable localization methods as, for example, functional Magnetic Resonance Imaging (fMRI; Mulert et al. 2004; Vitacco et al. 2002). These results also validate sLORETA, since it is an improved version of the original LORETA method (Lorenzo-Lopez et al. 2008). Moreover, reliability of sLORETA is further validated by the increasing number of published studies using it and LORETA for their experimental aims (e.g., Pascual-Marqui et al. 2002; Abe et al. 2008; Lorenzo-Lopez et al. 2008; Praeg et al. 2006).

The sLORETA software was used to perform a voxel-by-voxel within group comparison of real vs. sham TMS cortically induced current density distribution. Specifically, in order to identify possible differences in the brain electrical activity within group, non parametrical statistical analyses (Statistical non-Parametric Mapping: SnPM) were performed employing a *t*-statistic for each voxel, for corrected $P < 0.05$. The SnPM methodology is used to correct for multiple comparisons, and does not require any assumption about normality of distribution (Nichols and Holmes 2002). For this reason no correction or normalization has been conducted on the raw data.

Computations have been performed in a realistic head model (Fuchs et al. 2002), using the MNI 152 template (Montreal Neurological Institute, Montreal, Canada), with the three dimensional solution space restricted to the cortical gray matter. In the model used by sLORETA, intracerebral volume is partitioned in 6239 voxels at 5 mm spatial resolution. Moreover, anatomical labels corresponding to Brodmann areas are reported thanks to an appropriate correction from MNI 152 (Montreal

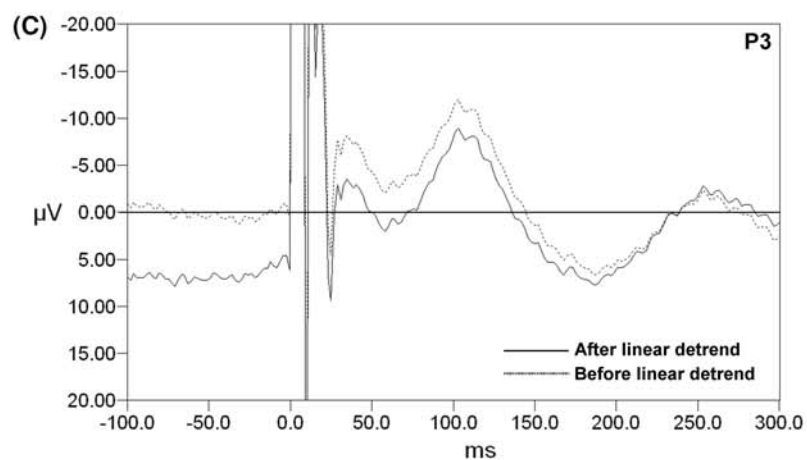
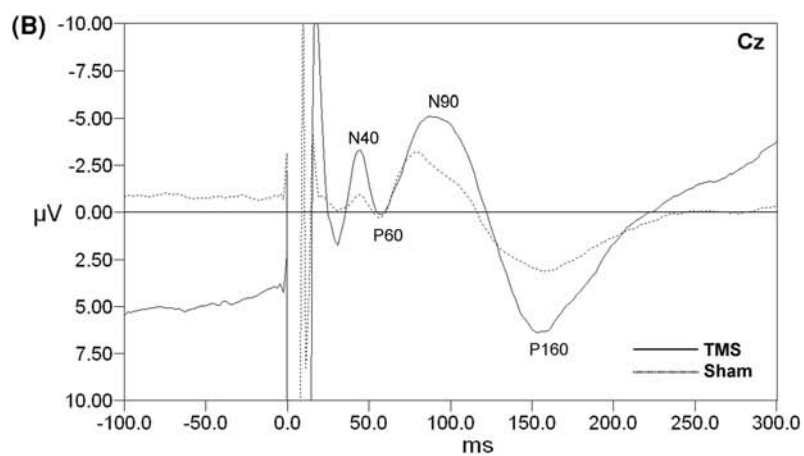
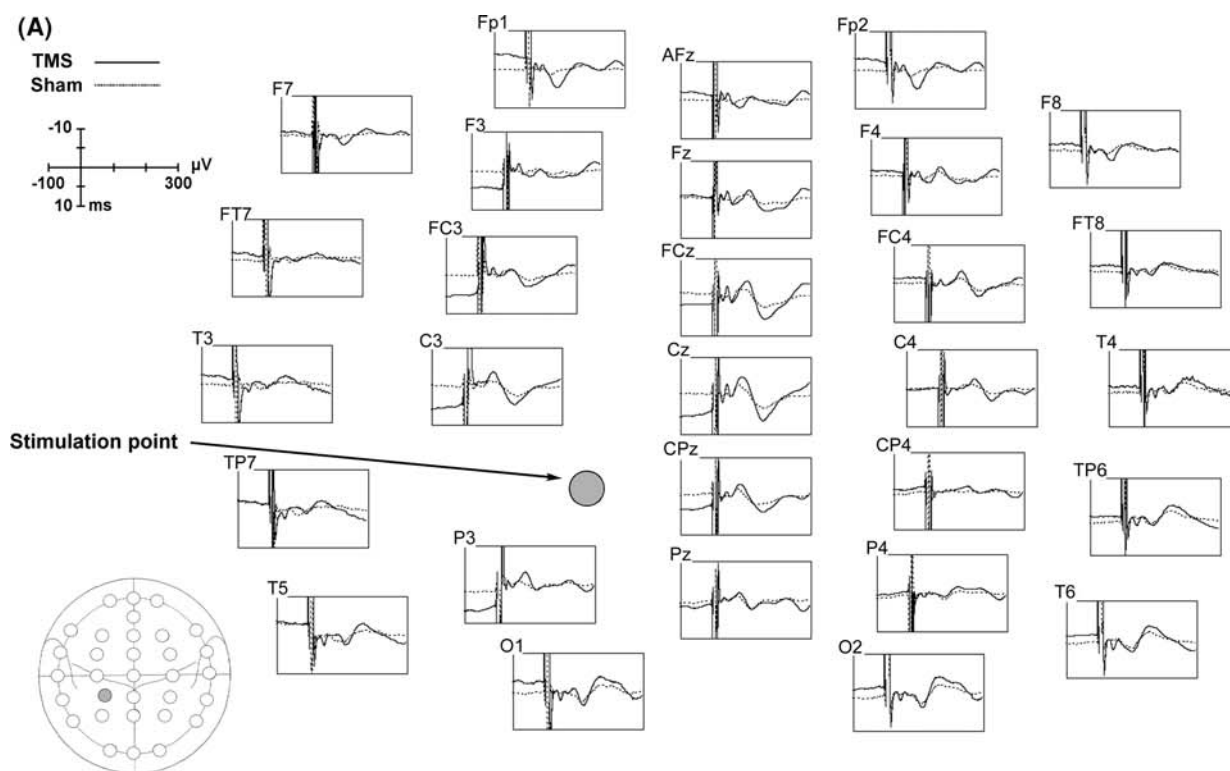
Neurological Institute, Montreal, Canada) to Talairach coordinates (Talairach and Tournoux 1988) performed by the software.

Results

The EEG activity evoked by means of real TMS and sham TMS conditions resulted in a sequence of alternating positive and negative deflections of EEG traces. Figure 2a displays the mean real TEPs (grand average) of the 10 subjects with respect to the mean sham TEPs waveform. Specifically, four peaks were identified in real TEPs (Fig. 2b), two with positive polarity and two with negative polarity. In particular, every deflection was defined considering its amplitude and latency (mean \pm SD), calculated on the Cz electrode. The first component was a negative deflection ($-4 \pm 3 \mu\text{V}$), peaking at 43 ± 3 ms, followed by a positive one ($1 \pm 2 \mu\text{V}$) peaking at 59 ± 6 ms. The last two components showed amplitudes of $-7 \pm 2 \mu\text{V}$ and $7 \pm 2 \mu\text{V}$, peaking at 91 ± 12 ms and 158 ± 12 ms, respectively. Also in sham TEPs several components were identified (Fig. 2b), but they had lower amplitudes. Indeed, although some early deflections could be recognized in the grand average potential, these early components were not identified in all the single subjects. For this reason, only the amplitudes and latencies of the two latest components are reported: the former was an up-going deflection of $-4 \pm 1 \mu\text{V}$ at 81 ± 11 ms, while the latter had a positive peak of $4 \pm 1 \mu\text{V}$ at 155 ± 15 ms.

Figure 2c illustrates corrections performed with the “linear detrend” function. Specifically, TEPs recorded at electrode P3 of a representative subject are shown before (dotted line) and after (solid line) the application of the function. The solid EEG trace is not aligned with baseline before the stimulus onset because of the application of the “linear detrend” function that, as previously indicated, permits to re-align the trace considering only a particular time-range of interest. Before this function was used, the pre-stimulus traces laid on baseline indicating that no artefacts were present in the EEG response before the stimulus onset. Finally, the “linear detrend” function did not change the sequence of positive and negative components that were evoked by stimulation.

Real TMS showed that parietal cortex is connected with several brain regions: bilateral frontal, parietal, and temporal lobes resulted diffusely activated, as well as limbic lobe and insula, but differences between real and sham TMS conditions were generally not significant. Real TMS activated in a statistically significant way a series of contralateral frontal regions in the right hemisphere in a time range comprised between 102 and 167 ms after the delivery of the stimulus (Table 1).



◀ **Fig. 2** Real and sham TEPs in 10 healthy subjects. **a** Grand average of TEPs ranging from 100 ms before to 300 ms after the stimulation, showing all recorded electrodes. Real TEPs (*solid line*) are superimposed on sham TEPs (*dotted line*). Site of stimulation in parietal cortex is also shown. **b** Grand average of real TEPs (*solid line*) and sham TEPs (*dotted line*) recorded at the Cz electrode, showing the main deflections described in the text. **c** Correction performed by means of “linear detrend” function on a representative electrode placed near the coil (P3): corrected waveform (*solid line*) is superimposed on the waveform recorded before the application of the function (*dotted line*)

Real TMS on the left parietal cortex significantly activated also a series of left temporo-occipital regions in a time range comprised between 171 ms and 177 ms after the delivery of the stimulus (Table 1 and Fig. 3).

Anatomical Localization

In one subject, a vitamin E pill was positioned over the stimulated location in left parietal cortex. MR imaging (Fig. 1b) showed that, in this prototypical subject, this point was situated over the parietal lobe in correspondence to the intraparietal sulcus. Due to coil orientation, in this case stimulation probably involved the immediately adjacent part of the superior parietal lobule (Brodmann area 7) rather than the cortex of the intraparietal sulcus or the inferior parietal lobule. Taking into account the anatomical variability in parietal regions (Ryan et al. 2006), and a range of ± 8 mm when using the 10–20 EEG system to individuate the correspondence between position of electrodes and underlying cortex (Okamoto et al. 2004), the stimulation probably involved a region of cortex in the superior parietal lobule, presumably situated nearby the intraparietal sulcus.

Discussion

In this study, we report a distributed and complex pattern of activation obtained by means of TMS, when delivered in the left parietal cortex. More specifically, it has been observed that magnetic stimulus activated various brain

regions situated in the right prefrontal cortex in a time range comprised between 100 ms and 167 ms, and in the left middle temporal and fusiform gyri between 171 ms and 177 ms after the delivery of real TMS. No evidence of the expected cortical connections between parietal and premotor cortex have been highlighted (Hagmann et al. 2008; Tannè-Gariepy et al. 2002).

Posterior parietal cortex has been reported to play a role in some complex cognitive tasks as, for example, attention (Bundesen et al. 2002; Thomsen et al. 2005), but it is more properly considered as an associative region where visuo-spatial and visuo-motor information are integrated (Babiloni et al. 2006; Berndt et al. 2002; Holz et al. 2008; MacKay and Mendonça 1995; Praeg et al. 2006; Thayer and Johnson 2006).

In this sense, it should be primarily noted that, in the present study, no cognitive or motor tasks were performed by the subjects. Specifically, they were asked to remain in a rest position and with closed eyes for the entire duration of the experiment. Consequently, the particular experimental procedure performed in the present investigation could induce a specific state in the subject that could modify connectivity (Massimini et al. 2005), even if the closed eyes condition has been reported to increase EEG variability mainly in primary visual cortex (Thuraisingham et al. 2007). Therefore, in the present investigation, it is difficult to draw a clear conclusion about specific functional connectivity among parietal and other cortical regions, in relation to specific cognitive or motor tasks. On the other hand, useful information about cortical connectivity spreading from parietal cortex and its timing of involvement might be clearly described.

In this sense, the present spreading of activation toward right prefrontal regions might represent part of a circuit that might intervene in the elaboration of attention information (Grosbras et al. 2005; Thomsen et al. 2005), helping to explain also the presence of contra-lateral rather than ipsi-lateral cortical connections spreading from the left parietal cortex. In this sense, it could be also speculated that the specific region of the stimulated parietal cortex might be in connection mainly with contra-lateral prefrontal regions, or

Table 1 Locations of current source density activations observed when comparing real and sham TMS conditions

Anatomical region (Brodmann area)	MNI coordinates (x,y,z)	Activation after real TMS (ms)	Statistical values
Right middle frontal gyrus (46)	(40,50,20)	102	$t = 6.81, P < 0.05$
Right superior frontal gyrus (9)	(20,50,40)	110	$t = 7.34, P < 0.05$
Right medial frontal gyrus (9)	(20,40,20)	140	$t = 7.65, P < 0.05$
Right precentral gyrus (9)	(40,25,40)	167	$t = 7.55, P < 0.05$
Left middle temporal gyrus (37)	(−55,−65,−5)	171	$t = 7.87, P < 0.05$
Left fusiform gyrus (20)	(−40,−40,−25)	175	$t = 7.41, P < 0.05$
Left fusiform gyrus (36)	(−45,−40,−30)	177	$t = 7.16, P < 0.05$

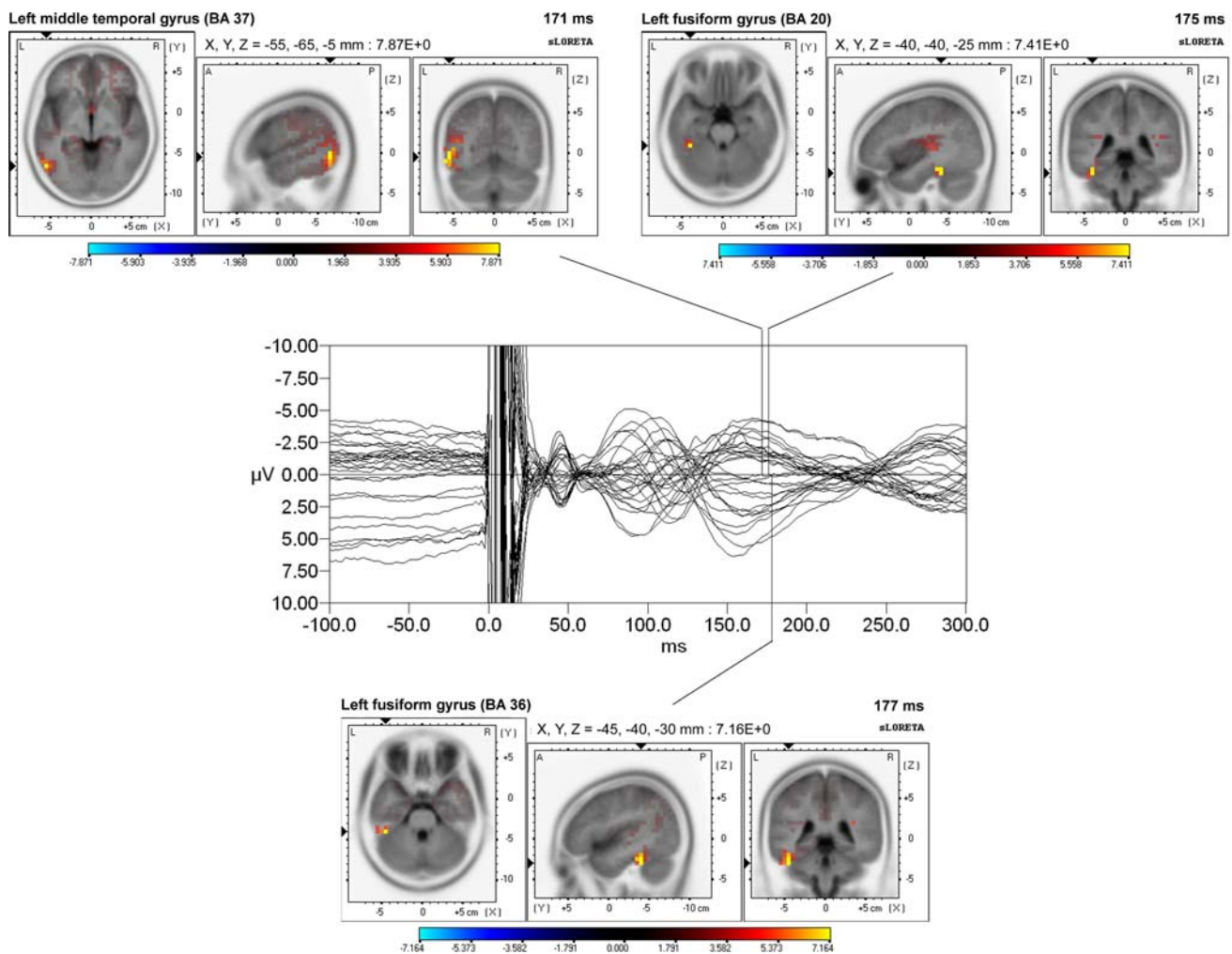


Fig. 3 sLORETA images showing standardized current density of real vs. sham TMS conditions. Activation obtained in left middle temporal gyrus (Brodmann area 37) and in left fusiform gyrus (Brodmann areas 20 and 36, respectively) is shown relatively to

grand-averaged TEPs recorded at all electrodes. Middle temporal and fusiform gyri were activated at 171, 175, and 177 ms after the delivery of the stimulus, respectively

that the particular position of the coil and the current direction of the stimulation were not able to stimulate fibres directed toward the ipsi-lateral prefrontal cortex. In any case, the presence of a very specific state in subjects (closed eyes) in the present experiment should be again considered in order to correctly drive interpretation. However, it has been clearly reported that both parietal and frontal cortices are involved in visuo-spatial tasks (Oliveri et al. 2001), which might request attentive elaboration (Bundesen et al. 2002; Oliveri et al. 2001) or shifted and sustained attention (Grosbras et al. 2005; Slagter et al. 2007; Thomsen et al. 2005).

The already indicated lack of evidence of connections between parietal and premotor cortex could be surprising, but it might be related to the very long TMS artefact present in this study. In fact, the first 30.5 ms after the delivery of the stimulus were eliminated from the analysis

and it may well be the case that parietal cortex sends information toward premotor regions very early, as already suggested (Massimini et al. 2005), and as it should be the case to control planning and execution of on-going movements. Alternatively, in the present experiment, a region of left parietal cortex that has no connections with premotor cortex might have been stimulated, or, again, the particular position of the coil and the current direction of the stimulation were not able to stimulate fibres directed toward the premotor cortex. In this case, the influence of the closed eyes condition on cortical connectivity should be less important because a parietal–premotor connection that should, however, subserve mainly visuo-motor integration (Hagmann et al. 2008; Matelli and Luppino 2001; Tannè-Gariepy et al. 2002), has been individuated to exist in humans also during a particular physiological state like sleep (Massimini et al. 2005).

Perhaps more interestingly, present findings suggest the existence of a cortical connection between parietal and ipsi-lateral temporo-occipital cortex, specifically the middle temporal and fusiform gyri. It is widely accepted that the parietal cortex is part of the dorsal visual stream, normally involved in the planning and execution of movements in peripersonal space and in its elaboration (Culham et al. 2003; Ellison and Cowey 2006; Milner and Goodale 2006; Oliveri et al. 2001; Valyear et al. 2006), as for example reach-to-grasp movements toward a target located in space. On the other hand, temporo-occipital regions, as the middle temporal and fusiform gyri, are usually reported as part of the ventral visual stream, preferentially involved in the perception of objects and the elaboration of their features (Milner and Goodale 2006; Oliveri et al. 2001; Valyear et al. 2006), as for example shape (Ellison and Cowey 2006; Op de Beeck et al. 2000) or motion attributes (Kable et al. 2005). Middle temporal and fusiform gyri have been also suggested to be activated in response to manipulable objects, suggesting a role also in the processing of knowledge associated with tools (Kellenbach et al. 2003; Mahon et al. 2007).

Consequently, in order to successfully interact with and percept a 3D object in the peripersonal space, the intervention of both streams and the combination of their information is requested, and it is probable that the cortical connectivity individuated in the present findings could subserve this type of task. There is to say that dorsal and ventral streams have been initially reported as possibly segregated, and that they can work in an autonomous way (Cavina-Pratesi et al. 2007; Shmuelof and Zohary 2005; see also Bruno et al. 2008 for a review). However, it has also been suggested that processing in the two streams occurs largely in parallel (Fang and He 2005). Moreover, the evidence of an interchange of information between streams is also increasing, especially when referring to monkeys data (Borra et al. 2008; Felleman and Van Essen 1991). In this sense, direct anatomical connections have been demonstrated to exist between anterior intra-parietal area (devoted to the visuo-motor transformations needed for grasping) and ventral visual stream areas of the lower bank of the superior temporal sulcus and the middle temporal gyrus (Borra et al. 2008). This study suggests that visuo-motor transformation for object-oriented actions does rely on dorsal visual stream information, however it also relies on ventral visual stream information related to object identity (Borra et al. 2008). Consequently, a situation of continuous interchange of information between the two streams is necessary in order to accomplish a different series of tasks. This may be also true in humans (Mahon et al. 2007; Schenk and Milner 2006), where it has been proposed that an interaction between the two streams is present in order to product adaptive behaviour (Goodale

2008; Keizer et al. 2008), but no agreement has been reached yet on this issue.

In this context, a connection among the left fusiform gyrus, the left middle temporal area and the inferior parietal lobe has been suggested to exist in humans, when referring to neural activity elaborating tools and manipulable objects (Mahon et al. 2007).

Furthermore, the novelty of the present findings relies not only on the indication of current source data and, consequently, on the areas that should be in connection with parietal cortex in humans, but also on the precise time windows in which these areas are activated after the excitation of the parietal cortex. Consequently, it is evident that these late driven connections spreading from parietal cortex activate prefrontal areas earlier than ventral stream areas (102–167 ms vs. 171–177 ms), suggesting that processes involving a parieto-frontal circuit (probably attention) should be performed before cognitive processes requesting an interchange of information between dorsal and ventral streams. In this sense, it might be suggested that the late temporal window (171–177 ms) individuated for the spreading of information from parietal cortex toward ventral stream regions might be useful to transmit complete and elaborated visuo-motor information to a semantic and perception system, in order to successfully accomplish, for example, an executing action toward an object.

In conclusion, present findings suggest that there may be communication between dorsal and ventral visual streams, likely favouring the interchange of information between the two systems. This should be needed in order to successfully accomplish the processing of visuo-motor and visuo-spatial information (for example, in order to elaborate the position in space and the shape of a 3D object). This implies the possibility of more complex, late and long-lasting flow of information between different areas in the brain than those previously suggested.

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