UNIVERSITA'
DEGLI STUDI DI
PADOVA

Sede amministrativa: Università degli Studi di Padova
Dipartimento di Psicologia Generale

SCUOLA DI DOTTORANDO DI RICERCA IN SCIENZE PSICOLOGICHE
INDIRIZZO PSICOBIOLOGIA
CICLO XXIII

ACTIVATION AND SELECTION OF COMPETING RESPONSES:

A TMS STUDY OF THE FRONTOPARIETAL NETWORK

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Investigating an effect, rather than cognitive
mechanisms or phenomena,
was the least useful thing I could imagine.
The fascinating thing about the Simon effect,
and the experimental design used to create it,
is that it provides a particularly useful window
into a whole number of central aspects of
human cognition and action.

Bernard Hommel

ABSTRACT

In the every day life, we are continuously presented with multiple opportunities for action. Cognitive models maintain that response conflicts may arise from simultaneous sensorimotor processes: Trough a direct route, response codes that most closely correspond to the stimulus are automatically activated, whereas a slower indirect route is proposed to select responses on the basis of task-relevant stimulus features. In the Simon task an irrelevant spatial code of the stimulus competes with relevant non-spatial information (e.g., the colour of the stimulus). When the appropriate response called by task instruction does not match that primed by stimulus position, a conflict arises at the response selection stage, which has to be resolved before action execution. In the present work, transcranial magnetic stimulation (TMS) was used to investigate the contribution of different cortical areas within a frontoparietal network which is thought to be implicated in response activation and selection during conflict. The results of the first study showed that distinct parietal subregions play a different role in visuomotor transmission which leads to the activation of the response on the basis of irrelevant spatial information. Results revealed that spTMS over posterior parietal cortex (PPC) reduced the Simon effect as if no irrelevant spatial code influenced performance. Our findings suggest that the posterior portion of PPC, as being crucially involved in orienting attention, is essential for a spatial code to the assigned to the stimulus, whereas the anterior portion of PPC, is involved in transforming spatial code into code for action, a process related to motor attention. The second study reported evidence that the frontal eye fields (FEF), which have been characterized for their role in oculomotor control, contribute to the generation of the spatial conflict in the Simon task. Finally results of the third study suggested that response selection in the conflict task is mediated by the dorsal premotor cortex (PMd). The temporal pattern of TMS interference over this area gave new insights about the mechanisms underlying response selection during resolution. Overall the results of the present study contributes not only to detect the locations of active cortical regions in response activation and selection during conflict but also to construct a dynamic physiological map by visualizing the temporal evolution of functional activities in the relevant cortical region.

RIASSUNTO

L’ambiente ci pone spesso di fronte a diverse opportunità di azione. In molte situazioni diversi piani motori possono essere simultaneamente attivati e la competizione tra questi deve essere risolta per l’esecuzione della risposta appropriata. Nel compito Simon, la posizione dello stimolo influenza i tempi di risposta, nonostante l’informazione spaziale sia irrilevante per l’esecuzione del compito. Alcuni modelli cognitivi postulano due vie parallele di elaborazione dallo stimolo alla risposta. Attraverso una via diretta o automatica, il codice spaziale irrilevante dello stimolo attiva la risposta corrispondente mentre una via indiretta, volontaria attiva la risposta corretta. Quando i due codici di risposta non coincidono, si verifica un conflitto che deve essere risolto perché la risposta corretta possa essere eseguita. L’obiettivo del presente lavoro era di valutare, attraverso la stimolazione magnetica transcranica (TMS), il contributo di diverse aree corticali che formano un network frontoparietale, nell’attivazione e nella selezione della risposta in situazione di conflitto. I risultati del primo studio hanno mostrato che distinte sub-regioni della corteccia parietale posteriore (PPC) svolgono un ruolo critico in diversi aspetti della trasmissione visuomotoria attraverso la quale è attivata la risposta sulla base delle informazioni spaziali irrilevanti nel compito Simon. Il secondo studio riporta evidenza del coinvolgimento dei campi dell’occhio frontali (FEF), un’area implicata nel controllo dei movimenti oculari, nella generazione dell’effetto Simon. Infine, i risultati dell’ultimo esperimento suggeriscono che la selezione della risposta e la risoluzione del conflitto sono mediate dalla corteccia premotoria. Questo lavoro fornisce un contributo nello studio delle basi neurali del conflitto attraverso un approccio che si propone, non soltanto di individuare le aree cerebrali coinvolte in un certo processo, ma anche di specificarne il contribuito relativo attraverso lo studio del timing di attivazione.

Summary

THEORETICAL SESSION

CHAPTER 1

CHAPTER 2

EXPERIMENTAL SESSION

CHAPTER 3 Timing the conflict within the posterior parietal cortex

THEORETICAL SESSION

CHAPTER 1

1.1 Introduction: the conflict paradigm

Successful behaviour depends on mechanisms of attention administering the allocation of neural resources on environmental stimuli potentially relevant for response planning. Because the world continuously presents us with multiple opportunities for action, different candidate motor plans may be activated in parallel; thus, a selection between different competing responses has to be performed before action execution (Cisek 2007). Conflict usually arises when simultaneous sensorimotor processes point to different responses, and selection between these responses produces a cost.

Three prototypical representatives of choice reaction time tasks in the conflict paradigm are Stroop, Flanker, and Simon tasks. The signals employed in these tasks are by definition relevant or irrelevant. The relevant information has to be mapped to a response while the irrelevant information has to be ignored. However, irrelevant information can markedly influence performance: Responses are typically slowed down and the percentage of errors is enhanced when some irrelevant feature of the stimulus is associated with the response opposite to that associated with the relevant stimulus feature.

In a Stroop task (Stroop, 1935) participants have to name the color of the ink in which a word is printed. When the word spells out the name of a color, reaction times are slower if the word meaning and the presentation do not match (incongruent condition; e.g., “red” printed in green ink) than in neutral condition (e.g., “chair” printed in red ink) or in a congruent condition (e.g., “red” printed in red ink). In the Eriksen flanker task (Eriksen and Eriksen, 1974) participants respond to a target stimulus that appear among distracters, such a central letter flanked by irrelevant, incongruent, congruent or neutral letter distracters. For instance, participants are required to press one key if a central target is a letter (e.g., H or K) and another key if the target is another letter (e.g., S or C). When the irrelevant information (distracters) is associated with the incorrect response side (i.e., incongruent condition), reaction times are usually prolonged and the percentage of errors is enhanced. When the irrelevant information is associated with the correct response side (i.e., congruent condition), responses are usually shortened and the percentage of errors is reduced compared to a neutral condition in which the irrelevant information is not associated with either of the two response sides.

This effect of interference on response choice is particularly strong and robust when the irrelevant information is “direct,” that is, when it is strongly associated with a dimension of the response (usually its laterality). This is typically the case in two-alternative response tasks with right- and left-hand responses, when the irrelevant information is lateralized, or when it contains directional information, such as arrows or directional words (e.g., right, left). A classical task with lateralized irrelevant stimulus information is the Simon task (Simon and Rudell, 1967). Here a conflict arises because irrelevant spatial information competes for response selection with non-spatial task-relevant information (e.g., Simon and Rudell, 1967; see Lu and Proctor 1995 for a review).

1.1.1 The Simon effect

Simon and Rudell (1967) reported the first Simon-like effect. In this study, participants were asked to press a left- or right-key in response to the word “left” and “right” presented through the left or right speaker of a headphone. The main finding was that participants were unable to ignore the side of stimulus presentation: even if the location was an irrelevant feature with respect to response choice, participants were faster if the location of the word was spatially corresponding with the response. No much later, Simon and Small (1969) observed the same effect by using acoustic but not verbal stimuli. They reported that when participants had to press a left- or right-key in response to low and high tones presented to the left or right ear, they were faster when the tone was presented in the ear spatially corresponding with the key they had to press than when it was presented in the ear spatially non-corresponding with the key they had to press. Craft and Simon (1970) first described this effect in the visual modality. Figure 1.1 represents a scheme of a standard Simon task with visual stimuli.

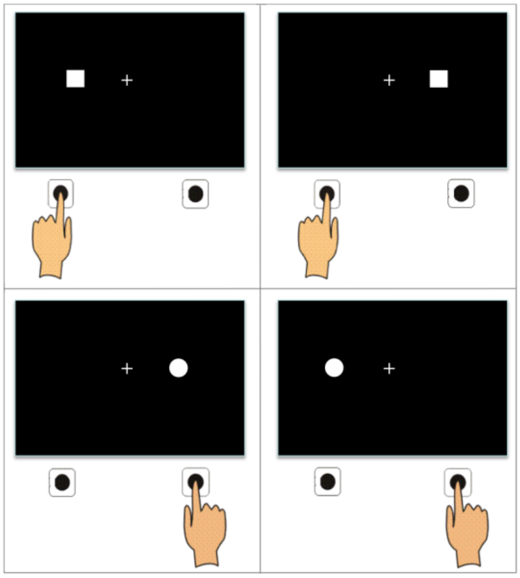

Figure 1.1. In the left column corresponding conditions with right response (right stimulus) and left response (left stimulus). In the right column, non-corresponding condition with left response (right stimulus) and

The participant is required to respond to the square by pressing a left key and to the circle by pressing the right key. Stimuli could appear on the left or on the right with respect to a central point. The task requires participant to maintain the gaze aligned to the center of the screen (fixation point). Although stimulus location is irrelevant to the task, responses are faster and less error-prone when stimulus and response positions spatially correspond than when they do not.

1.1.2 Dual-route models

The Simon task is a particularly clear example of the fact that information on stimulus location is processed even if it is irrelevant to select a response to the task-relevant stimulus attribute.

In cognitive psychology, two main classes of theoretical accounts have been proposed to explain the Simon effect: Translation theories (e.g., Hasbroucq and Guiard, 1991) assume that both stimulus and response positions are cognitively represented by mean of spatial codes (e.g., right and left) which are matched during response selection. Responses are speeded up by corresponding codes and decelerated by non-corresponding codes. Activation theories (e.g., Kornblum, et al., 1990; Simon, 1969) maintain that the stimulus spatial code automatically activates (primes) a congruent response, namely the response on the same side. Finally, the basic assumptions of these theories have been integrated in the so-called dual-route models (Kornblum et al. 1990; De Jong et al. 1994; Proctor et al. 1995). Dual route models (Figure 1.2), which have been proposed explicitly for the Simon task (De Jong et al. 1994), have been introduced to explain mechanisms underlying conflict in a variety of conflict tasks (e.g., the flanker task; Ridderinkhof, van der Molen, and Bashore, 1995). These models postulate that two parallel pathways, a direct automatic and an indirect controlled one, are involved in response preparation and selection processes in the Simon task. Via the fast direct route, the irrelevant stimulus information is thought to activate its spatially corresponding response. Through a controlled indirect route, the appropriate response is intentionally selected based on task-relevant stimulus information (Kornblum et al. 1990; Wascher, Schatz, Kuder, and Verleger, 2001). The direct route may arise from long-term associations between perceptual and motor processes, which may depend on genetic factors or on the synaptic consolidation of stimulus-response associations widely over-learned during lifetime (Cohen, Dunbar, and McClelland, 1990; Tagliabue, Zorzi, Umilta, and Bassignani, 2000).

The Simon effect has been explained in terms of a cost of conflict between the direct route (carrying the response linked to the spatial position of the stimulus) and the indirect one (holding the task demands). When the two routes generate the same response codes (i.e., in the corresponding condition) reaction times (RTs) are speeded up, whereas when the two routes generate different response codes (i.e., in the non-corresponding condition), a conflict must be resolved which leads to slower RTs.

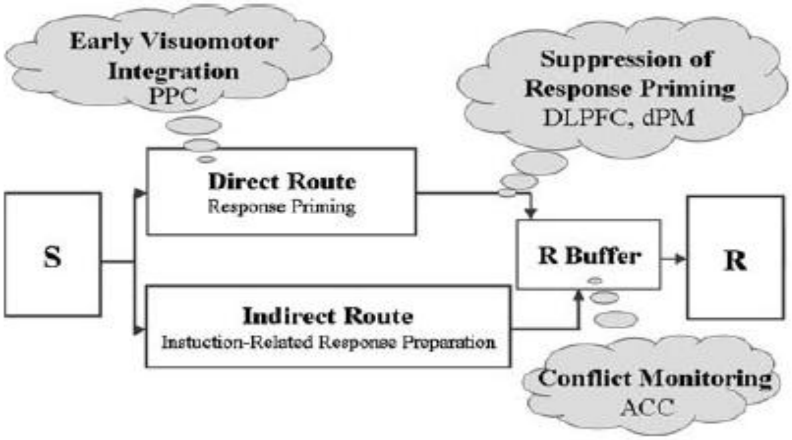

Figure 1.2. A stretch of the dual-route model of response preparation indicating brain structures involved in response priming and control. From Sturmer et al. (2007)

Even though many researchers tend to treat Simon, Stroop, and flanker effects alike, commonly referring to the fact that all three tasks involve irrelevant stimulus information that in one way or another induce response conflict, it seems important to note some differences with respect to the processes that might be responsible for these effects (see Hommel, in press). In the flanker task, flanker stimuli may impair performance because of a direct conflict between stimulus-codes of target and flanking letters (e.g., H code and S code) and/or because of a conflict between response-codes the stimuli are activating or priming. In the standard Stroop design, in which participants have to name the color of the stimulus, conflict might not only arise between the codes of the two stimulus features (ink color and semantic information) and the two responses, but the code of the irrelevant color word might also interact and interfere with the activation of the code of the correct response. Systematic manipulations have revealed separable contributions of stimulus and response conflict in flanker and Stroop tasks (Fournier, Scheffers, Coles, Adamson, and Villa Abad, 1997; De Houver, 2003). In contrast, the Simon effect does not originate with incompatibility between stimulus dimensions but with a direct interference of an irrelevant stimulus dimension with the response selection process (Acosta and Simon, 1976; Simon, 1982). Conflict in the Simon task is therefore held to represent a purely response-based conflict (Kornblum et al., 1990; Zhang et al., 1999).

1.1.3 Orienting attention and the spatial stimulus code

A common assumption in many accounts of the Simon effect is that a spatial code of the irrelevant stimulus location is formed and that this code either facilitates or interferes with task-relevant processing at response-related stages. To explain the mechanisms underlying the generation of the irrelevant stimulus spatial code, the attention-shift hypothesis proposed that the critical process is the direction of the attention shift toward the location of the imperative stimulus (Nicoletti and Umiltà, 1994; Stoffer and Umiltà, 1997). Thus, a stimulus that appears on the left of a currently attended location (i.e., the center in a standard Simon task) is coded as “left” because attention needs to the shifted to the left in order to focus on that stimulus. Nicoletti and Umiltà (1994) provided converging evidence that attention orienting yields the spatial code that causes the Simon effect by showing that the Simon effect if prevented from moving towards the stimulus location. In this study, participants were presented with a display as shown in Figure 1.3 were a small letter was presented below the central fixation point while lateralized target stimuli appeared. This letter was to be reported and the assumption was that this required focused attention on that letter, thus preventing an attention shift towards the stimulus. As expected, no Simon effect was obtained in this condition.

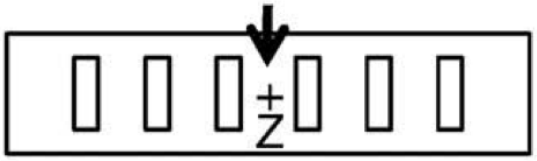

Figure 1.3. The boxes indicate the possible target locations and the arrow indicates the to-be-attended location. From Nicoletti and Umiltà

To explain why the stimulus spatial code would be formed in the Simon task, the attention-shifting approach refers to the premotor theory of attention (Rizzolatti, Riggio, Dascola, and Umiltà, 1987; Umiltà, Riggio, Dascola, and Rizzolatti, 1991). In a Simon task, when the peripheral stimulus is presented, attention covertly shifts toward its position. Accordingly to the premotor model, an attention shift occurs because a motor program for the corresponding saccade is prepared regardless of whether or not the saccade is subsequently executed (overt orienting) or not (covert orienting). The motor program specifies the direction of the saccade, hence, the stimulus spatial code is formed, and it generates the Simon effect by priming the corresponding manual response (Rizzolatti et al. 1987; Umiltà et al. 1991).

1.2 Activation of a frontoparietal network during conflict tasks: fMRI studies

Neuroimaging studies showed that activation and selection of potential response plans in conflict tasks involve a large frontoparietal network (e.g., Egner, Delano, and Hirsch, 2007; Bunge, Hazeltine, Scanion, Rosen, and Gabrieli, 2002). Here, different brain regions might play distinctively different roles in conflict situations. While some may be the site in which competing responses are activated by environment stimuli, other brain regions might act selectively to resolve conflict by reducing the impact of irrelevant information and/or by enhancing the impact of task-relevant information. Prefrontal regions, including the anterior cingulate gyrus, and the dorsolateral prefrontal cortex, receive information from the ventral visual pathway (Goodale and Milner, 1992) and seem to play a crucial role in the selection of the appropriate response and in the resolution of conflicts (e.g., Botvinick et al. 2004; Egner and Hirsch 2005; Ridderinkhof, 2002; Kerns, 2006). The posterior parietal cortex (PPC), as part of the dorsal visual stream (Goodale and Milner 1992) is thought to be implicated in both visuospatial attention (e.g., Ashbridge et al. 1997; Chambers et al. 2004) and in transforming sensory information into motor outputs (e.g., Rizzolatti et al. 1987; Mattingley et al. 1998; Passingham and Toni, 2001).

Early visuomotor integration in the PPC has been suggested to produce competing representations of potential responses in a flanker task with pointing arrows (Bunge et al, 2002; Coulthard, Nachev, and Husain, 2008). In a recent study, Bunge and coworkers (2002) sought to distinguish between brain areas involved in the representation of candidate responses and brain areas involved in the selection of competing response alternatives. In this study, participants performed a flanker task with pointing arrows during functional imaging. Brain activations associated with the number of responses, which are brought to mind, and brain activation related to the selection between competing responses were separately analyzed. Results showed that left parietal cortex was activated by either two task manipulations that increased the need to maintain a representation of possible responses: activation in parietal cortex was greater for incongruent then congruent trials but even for congruent then neutral trials. Because congruent trials were assumed to be associated with the activation of more S-R associations than neutral trials (both target and distracters activate the same response), this finding supports the idea that parietal cortex is involved in activating motor plans on the basis of S-R associations. In contrast, prefrontal areas and the anterior cingulate cortex were activated in incongruent vs. congruent trials comparison supporting the idea that prefrontral cortex is recruit when there is a need to select between competing responses. The view that two systems are involved in situations of conflict, with PPC being crucial site for automatic activation of competing motor plans and prefrontal regions acting to inhibit action plans irrelevant to current task goals was also supported by recent findings on parietal neglect patients and patients with frontal lesions (Coulthard et al., 2008).

In the spatial variation of the flanker task used in these studies, both relevant (target) and irrelevant (distracters) information are spatial in nature (stimuli are arrows pointing a right/left position), thus it is not surprising that competing motor plans activated by these signals occurs in the PPC

Few fMRI studies investigated the neural bases of the Simon task. Liu and coworkers (2004) mapped the neural substrates of the Simon and spatial Stroop tasks and reported for each task the areas that were more active in the non-corresponding relative to corresponding condition (i.e., the areas contributing to Simon and Stroop interference). In the spatial variation of the Stroop task, the word meaning designates a spatial location or direction (i.e., "right" or "left"). Both tasks activated brain regions that serve as a source of attentional control (dorsolateral prefrontal cortex) and posterior regions that are sites of attentional control (the visual processing stream, middle occipital and inferior temporal cortices). In addition, there was also a specific brain network activated to a significantly greater degree by one task and/or only by a single task. The brain regions significantly more activated by the Simon task were those sensitive to detection of response conflict, response selection, and planning (anterior cingulate cortex, supplementary motor areas, and precuneus), and visuospatial (PPC) and motor association areas. The posterior parietal area activated by the Simon non-corresponding condition, as compared with the Simon corresponding condition, had its center in the left supramarginal gyrus, the most anterior portion of the PPC, which has been associated with motor attention (i.e., attentional processes related to the preparation and/or the priming of a movement with a specific effector; Rushworth et al., 2001).

In another study, Egner, Delano, and Hirsch (2007) investigated the neural bases of conflict resolution in a modified color-naming Stroop task with lateralized stimuli. Here two different sources of conflict were available: conflict arising from incompatibility between the task-relevant and an irrelevant stimulus feature (stimulus-based or Stroop conflict), and conflict arising from incompatibility between an irrelevant stimulus feature and response features (response-based or Simon conflict). Results showed that control mechanisms recruited by stimulus-based conflict resolve stimulus-based conflict, but do not affect the resolution of response-based conflict, and vice versa. The resolution of response-based conflict (the Simon conflict) was distinguished by modulation of activity in premotor cortex, whereas resolution of stimulus-based conflict was distinguished by the modulation of activity in parietal cortex. These results suggest that the human brain flexibly adopts, and independently controls, conflict-specific resolution strategies, biasing motor programming to resolve response-based conflict. These findings are in line with the view that resolution of response conflict in the Simon task operates on later motor-related stages of information processing probably by inhibit response primed by spatial information when inappropriate (e.g., Stürmer et al., 2007).

1.3 The posterior parietal cortex and the direct route

The PPC has been indicated as a site of visuomotor transmission because of anatomy and physiology: anatomically it is poised between the visual and motor cortices; physiologically, PPC neurons do not posses the receptive fields properties that would be consistent with higher visuo-visual role. Posterior parietal areas carry neuronal signals that are related to the preparation of eye and arm movements. It has been suggested that visuomotor integration in the PPC is the neurophysiological correlative of the direct route, which is the precondition for response conflict in dual route models of the Simon task (De Jong et al., 1994). From this hypothesis, a prediction was made regarding the behavioural effect induced by interference on the neural activity in PPC. Only two studies sought to establish a causal role of the PPC in the generation of the correspondence effect in the Simon task. Stürmer and coworkers (2007) applied repetitive transcranial magnetic stimulation (rTMS) over PPC for 200 ms (5 pulses, 20 Hz) starting with the onset of the visual stimulus while participants were performing a Simon task with targets appearing above and below a central fixation point (vertical stimulus-response arrangement). The authors were expecting to abolish or reduce the Simon effect due to a suppression of response priming through the direct route. Results showed a reduction of the Simon effect when rTMS was applied to the right PPC but not to the left PPC with regard to responses of the contralateral (left) hand.

Following the same logic, Rusconi, Turatto, and Umiltà (2007) applied rTMS over the anterior and the posterior portion of the PPC of both hemispheres, lying along the intraparietal sulcus during a combined Simon-SNARC task (Figure 1.4). In this task, subjects were required to perform a parity judgment with lateralized digits. Stimulation was delivered simultaneously with the presentation of the target stimulus for 500 ms (for a total of 5 TMS pulses, 10 Hz).

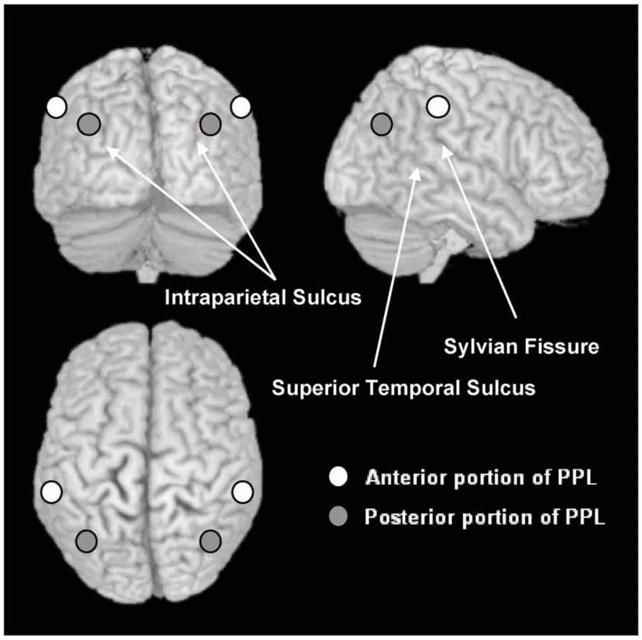

Figure 1.4. Site of TMS stimulation in the study by Rusconi et al. (2007)

The effects of magnetic stimulation on Simon and SNARC correspondence were separately analyzed. Results suggested a causal role of both anterior and posterior portions of PPC of both hemispheres in the Simon effect. The Simon effect was in fact abolished after stimulation compared to the non-stimulation condition as if no irrelevant spatial code influenced performance. Overall these outcomes allowed establishing a causal role of the PPC in the generation of the Simon effect.

1.4 Orienting and motor attention

The posterior parietal lobule, as part of the dorsal visual stream (Goodale and Milner 1992) has long been thought to play an important role in visuospatial attention (Ashbridge et al. 1997; Chambers et al. 2004). Recently, there is increasing interest in dissociating the role of different parietal subregions in different, altrough related functions. It has been noticed that in the macaque brain, regions of the intraparietal sulcus show preparatory activity that is selective for different effectors: The lateral intraparietal (LIP) area is concerned with the control of gaze (Snyder et al., 1997), represents space in a body centered reference frame (Snyder et al., 1998) and is strongly interconnected with parts of the oculomotor system including Frontal Eye Fields (FEF) and the superior colliculus (Paré and Wurtz, 2001). The medial intraparietal (MIP) area is involved in arm reaching actions (Ferraina and Bianchi, 1994; Snyder et al., 1997), represents target location with respect to the current hand location (Graziano et al., 2000; Bune et al., 2992) and is interconnected with frontal regions that play a critical role in motor preparation such as the dorsal premotor cortex (Jonhson et al., 1996; Marconi et al., 2001).

It has been proposed that, in the human brain, different parietal subregions are specialized for orienting attention in the visual field, a function that is closely connected to eyes control and in motor attention, a function related to hand-response. This latter term is used to refer to attention processes concerned with motor execution: We know that responses can speeded up if subjects covertly attend to motor response that they will make instead of directing attention towards the expected visual stimulus. The critical region involved in visuospatial attention appears to be in and around the posterior intraparietal sulcus (Gitelman et al., 1999; Corbetta and Shulman, 1998; Corbetta et al., 1993; Nobre et al., 1997). A more anterior part of PPC, corresponding to the supramarginal gyrus would be concerned with motor attention (Rushworth et al., 2001).

Moreover, there is growing evidence supporting the view that not only do different areas within the parietal cortex have different relative specializations for orienting and motor attention, there are also different patterns of hemispheric lateralization associated with the different attention processes. In human subjects, the right hemisphere plays the preeminent role in controlling visuospatial attention (Kinsbourne, 1987; De Renzi, 1982; Mesulam, 1981; Hecaen and Angelergues, 1963). Recent neuroimaging studies have confirmed that it is also a right posterior parietal cortical region that is most prominently activated during covert orienting tasks. The ability to represent extrapersonal space and to direct attention within extrapersonal space is compromised when tissue in the parietal region, particularly in the right hemisphere, is damaged (e.g., Vallar, Perani, Cappa, Messa, Lnzi, and Fazio, 1988). Motor attention is predominantly associated with the activation in the left rather than right parietal cortex even when movements of the ipsilateral left hand are being prepared (see Rushworth et al., 2003). Left parietal damages are mostly associated with praxis deficits (Goldenberg 2009).

Rushworth and coworkers (2001) used rTMS to interfere with neural activity in a more anterior part of PPC, the right or left angular gyri (ANG) and in a more anterior part (supramarginal gyrus) during performance in two tasks in which either orienting or motor attention processes were primarily involved. In the orienting attention task, a cue (valid, invalid or neutral) predicted the location of a subsequently target. In the motor attention task, the cue instructed about the finger to be use in responding. Results showed that rTMS of right but not left ANG selectively disrupted orienting attention while left but not right SMG disrupted performance in the motor attention task.

These findings suggest that motor attention may involve a distinct mechanism that depends on a distinct parietal cortical area. It appears to be the left rather than the right parietal cortex that is dominant for motor attention (Rushworth et al., 1997; 2001). Moreover, the TMS results suggest that the critical region may lie more anteriorly within the parietal cortex than that concerned with covert orienting attention.

Both orienting attention and motor attention seem to be implicated in the generation of the Simon effect. Ivanoff and Peters (2000) showed that the Simon effect is not the result of a reflexive attention orienting, as stimulus position has to be mapped to a manual response for the Simon effect to occur. They found that the Simon effect is present when visuospatial attention is oriented toward a target stimulus in a manual choice RT task but it is absent when visuospatial attention is reflexively attracted by the sudden onset of a task-irrelevant peripheral stimulus. They conclude that a shift of attention is necessary but not sufficient for generating the Simon effect, because attention has to be oriented toward the target of manual response for the Simon effect to occur.

1.5 The Frontal Eye Fields

The Frontal Eye Fields (FEF) have been defined in non human primates as an area in the frontal cortex from which low-threshold electrical stimulation elicit eye movements and where oculomotor activity can be recorded in single units (Bruse et al., 1985). Three main categories of neurons have been identified in FEF region: visual, motor, and visuomotor, discharging respectively at the onset of a visual target, when the saccade is executed, or both (Schall, 1997). Thus the FEF in monkeys can be viewed as an interface between visual processing and motor production, dedicated to the orienting system. In humans, the frontal eye fields (FEF) have typically been investigated in terms of their role in the generation of eye movements. Lesions to this area, either accidental or experimental, disrupt saccades and electrical stimulation elicits eye movements (e.g., Godoy, Luders, Dinner, Morris, and Wyllie, 1990; see Schall and Thompson, 1999; Schall and Bichot, 1998 for reviews).

Recently, there has been an increasing interest in the involvement of this area in visual processes, including tasks where eye movements are not required or precluded. Brain imaging studies showed that task requiring shift of attention without eye movements as well as tasks requiring focused attention activate the frontal cortex in the region of the FEF (e.g., Corbetta, Shulman, and Petersen, 1993). FEF are activated in orienting paradigms whether or not an eye movement is required. In the latter case, this activity is commonly interpreted in terms of the premotor theory of attention (Rizzolatti et al., 1987). FEF activation is attributed to the generation of saccade programs that are not overtly executed, rather than to visual analytic processes in the FEF (see, however, Donner et al., 2000). This confirms a functional overlap for visuospatial attention and eye movements, already observed in PPC (Corbetta et al., 1998).

Different studies directly addressed the role of FEF in space representation and covert attention orienting. These studies have reported roles for the FEF in contralateral visual stimulus analysis (Blanke et al., 1999), preparatory vision (Grosbras & Paus, 2002), and target detection in conjunction visual search (Muggleton, Juan, Cowey, & Walsh, 2003; O'Shea, Muggleton, Cowey, Walsh, 2004; Kalla, Muggleton, Juan, Cowey, Walsh, 2008). Grosbras and Paus (2002) applied single pulse TMS over the FEF during performance of a visuospatial attention task. In this task, a central cue (valid, invalid or neutral) directed shift of attention and the subject responded by a key press to a subsequent visual peripheral target without moving the eyes from the central fixation. They observed a decrease of performance when stimulating the right hemisphere and when the cue was invalid that is, when attention had to be disengaged and moved to the opposite hemifield. O'Shea and coworkers (2004) used double-pulse TMS to investigate the timing of target discrimination during visual conjunction search. They applied dual TMS pulses separated by 40 ms over the right FEF and vertex. These were applied in five timing conditions to sample separate time windows within the first 200 ms of visual processing. TMS impaired search performance. This effect was limited to a time window between 40 and 80 ms after search array onset. These parameters correspond with single-cell activity in FEF that predicts monkeys' behavioural reports on hit, miss, false alarm, and correct rejection trials. These findings demonstrate a crucial early role for human FEF in visual target discrimination that is independent of saccade programming. Kalla and coworkers (2008) directly compared the timing of involvement of FEF (Figure 1.5) and PPC in visual search by applying double pulse TMS delivered at different times over FEF and PPC during performance of a visual search task.

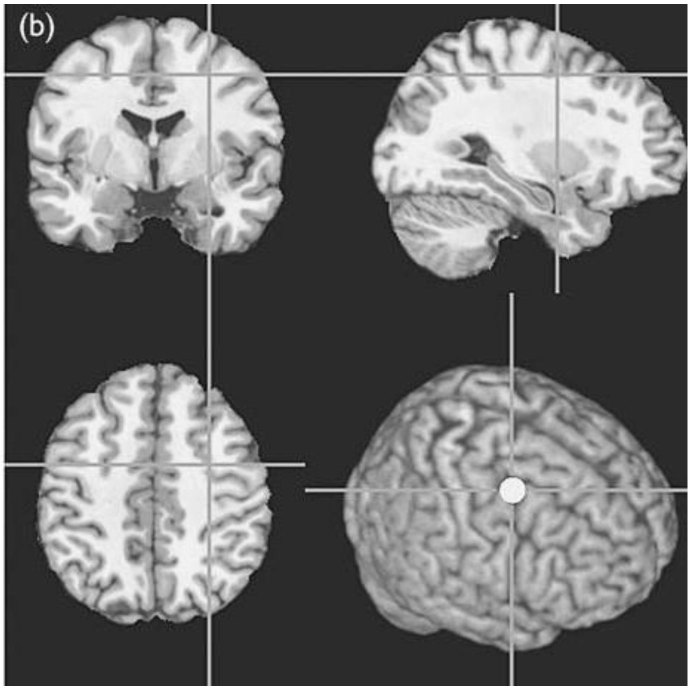

Figure 1.5 Frontal Eye Fields (FEF) as targeted in a participant' magnetic resonance image in the TMS study by Kalla et al. (2008). The site is above the posterior middle frontal gyrus, just in front of the junction of the precentral sulcus and the superior frontal sulcus.

Disruption of performance was earlier (0/40ms) with FEF stimulation than with PPC stimulation (120/160ms), revealing a clear and substantial temporal dissociation of the involvement of these two areas in conjunction visual search. In conclusion, the FEF seem to have a role, independent eye movements, in the control of visuospatial attention. FEF and PPC have been indicated as being part of the same frontoparietal attentional network (Corbetta and Shulman, 2002).

1.6 Dynamics of direct response activation

As above described, the PPC has been suggested to be the neural substrate of the direct route. Parietal areas are implicated in both visuospatial attention and in the preparation of manual responses as being strongly connected with premotor and motor cortices. Central to dual route models of the Simon task is the notion that a privileged (dorsal) visuomotor pathway mediates automatic response activation based on spatial irrelevant information. In corresponding trials, the automatic response activation supports the selection that is called for by the spatial attribute of the stimulus. In non-corresponding trials, an inappropriate response tendency toward stimulus position competes with the activation of the task-based correct response.

The support adduced for the automatic activation of the corresponding response and response competition includes evidence from movement-related EEG potentials which reveals that the corresponding response is briefly activated when the correctly executed response if spatially non-corresponding. The Lateralized Readiness Potential (LRP; Figure 1.6) is based on readiness potential (RP), which exhibits the increase of EEG negativity over the motor cortex contralateral to a planned movement a few hundred milliseconds before overt response onset. To compute the LRP from the RP recorded over left and right primary motor cortex (M1) from electrode C3 and C4 (10-20 International System of electrodes placement), respectively, the follow method is commonly used. Let the potentials recorded at sites C3 and C4. If the stimulus demands a right-hand response, the difference waveform C3-C4 is calculated whereas the difference C4-C3 is calculated when a left-hand response is demanded. Difference waveforms are then averaged over all trials within each task condition. The resulting LRP provides a specific index to trace the time course of selective motor activation.

In the Simon task, an early deflection of the LRP is observed at around 150 ms after stimulus onset. This deflection, named Gratton-dip (Gratton et al., 1988), is thought to reflect the location-based priming of the corresponding response whereas a later component would reflect the activation of the response specified by task instruction (e.g., De Jong et al., 1994; Eimer, 1995; Valle-Iclán, 1996). The Gratton-dip would occur when information is partially transmitted from perceptual to motor processes before the end of stimulus evaluation (Gratton, Coles, and Donchin, 1992). If the pre-activated response indexed by this early LRP is correct, the LRP continues to grow until response execution. If the pre-activated response does not correspond to the required one, incorrect early LRP lessens, and an LRP of contrary polarity will develop in the direction of the required response. For correct response trials, the LRP showed an initial activity dip, indicating location-based activation of the incorrect response when stimulus and response location were in the opposite sides (2003; Valle-Iclan, 1996; Vallesi et al., 2005). This early incorrect response activation is taken as a sign of the direct route response priming (De Jong et al., 1994).

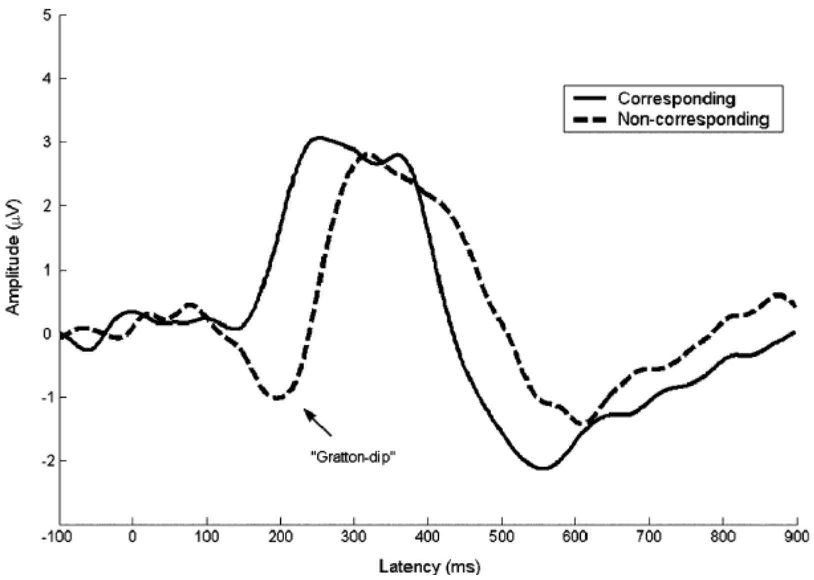

Figure 1.6. Grand average lateralized readiness potential (LRP) waveforms in a Simon task. From Vallesi et al. (2005).

It is known from visual search studies (e.g., Luck & Hillyard, 1994) that, for bilateral stimulus arrangements, the N2 component over posterior electrodes exhibits larger amplitude contralateral to the side of the target between 200 and 300 ms after stimulus onset. This N2pc component is assumed to reflect the spatially selective processing of visual target stimuli in multi-stimulus displays and/or the attention suppression of surrounding detractors. Different authors recorded the N2pc in spatial compatibility tasks in which the presentation of the peripheral target stimulus was accompanied by the presentation of a filler in the other hemifield. These authors have observed that the N2pc in this kind of task can be accompanied by a deflection over central electrodes that is of the same polarity as the N2pc ad coincident in time with the N2pc (Praamstra and Plat, 2001; Praamstra and Oostenveld, 2003; Praamstra, 2006). Praamstra and coworkers have designated this deflection as N2cc (N2 central-contralateral) and proposed that it reflects attention-related motor cortex activation. Interestingly the N2cc is not fully determined by the attentional shift that accompanies the visuospatial selection represented in N2pc. That is, the N2pc is absent or attenuated when the selected target does not map onto a response or when the task not involve competing response alternatives defined at opposite hands (Praamstra and Oostenveld, 2003). Based on these features and based on source EEG analyses, it was suggested that the N2cc reflect activation of the dorsal premotor cortex that is invoked to prevent the direction of attention determining response choice (Praamstra and Oostenveld, 2003; Praamstra, 2006).

1.7 Response selection and conflict resolution

A widely accepted assumption is that the Simon effect is a phenomenon related to response election. On trials in which the automatically activated response matched that called by the relevant stimulus feature, there is no competition at the response selection stage. When the two responses activated by direct and indirect way differ (i.e., in non-corresponding trials), the response activated by irrelevant spatial information has to be inhibited to allow the correct response is executed.

Dual route models of the conflict (De Jong et al., 1994) proposed that competing responses activated on the basis of task-irrelevant information are checked through inhibitory control, exercised by an executive system that supervised the flow of information through subordinated mechanisms (Stürmer et al., 2007).

However, how response selection and conflict resolution is implemented in the brain during the Simon task has not been extensively studied. Neuroimaging studies showed that prefrontal regions, such as the anterior cingulate gyrus and the dorsolateral prefrontal cortex, receive information from the ventral visual pathway and play a crucial role in the selection of the correct response and in the resolution of conflicts (Botvinick et al. 2004; Egner and Hirsch 2005; Ridderinkhof 2002; Kerns, 2006). Moreover, control mechanisms over response conflict in the Simon task have been shown to recruit premotor cortex (Egner, Delano, Hirsch, 2007). This network was proposed to be the main neural substrate for the indirect route, which is responsible for elaborate task instructions.

Praamstra, Kleine, and Schnitzler (1999) applied rTMS over dorsal premotor cortex (PMd), as that area could serve the inhibitory control of automatic response activation in non-corresponding trials. This area is involved in response preparation of non-standard stimulus-response mappings when a predominant correspondence between visuospatial stimuli and responses has to be overcome (Wise, Di Pellegrino, and Boussaoud, 1996). Moreover, the PMd plays a role in suppressing prepared movements that should not be executed (Koch et al., 2006). Praamstra and coworkers (1999) predicted that temporary interference with the PMd would release the automatic activation of the corresponding response from inhibition and thereby enhance the Simon effect. Results were not straightforward, for the expected effects of TMS were actually confined to those trials that followed a non-corresponding trial.

Another study that investigated the neural mechanism of control over response priming in the Simon task by using TMS focused on sequential modulation of the correspondence effect. The sequential modulation of the Simon effect refers to the fact the correspondence effect is modulated by the prior task context (e.g., Leuthold and Schröter, 2006; Stürmer et al., 2002; Valle-Iclán et al., 2002). The Simon effect is commonly abolished after a non-corresponding trial. Dual-route models assume that response priming via the direct route is suppressed after a response conflict in the preceding trial. The direct route suppression account receives strong support in event-related brain potentials (ERP) studies. Stürmer and

Leuthold (2002) reported that the LRP over motor cortex is modulated by the correspondence in the preceding trial. Like the Simon effect in behavioural performance, incorrect LRP activity in non-corresponding condition was observed only after a corresponding trial and was abolished after a non-corresponding predecessor. This effect is localized on the level or response preparation (LRP over motor cortex) and they contrast with lateralized activity over PPC. This activity, which reflects early visuomotor integration, is not modulated by the correspondence condition of the preceding trial.

Overall, these outcomes support the view that the suppression of direct route priming, carrying irrelevant information, operates on later motor-related stages of information processing.

CHAPTER 2

Transcranial magnetic stimulation

2.1 Introduction

Transcranial magnetic stimulation (TMS) is an established investigative tool in the cognitive neurosciences used to study all cognitve functions as perception, attention, learning, language and cortical plasticity. TMS operates on Faraday’s principle of electromagnetic induction. Faraday showed that an electrical current passed through one coil could induce a current in a second nearby coil. The current in the first coil produces a magnetic field that in turn causes current to flow in the second coil. In TMS the second coil is replaced by brain tissue and the induced electric field elicits neuronal activity (Walsh and Cowey, 2000).

The TMS machine delivers a large current in a short period of time; the current in the TMS coil then produces a magnetic field, which, if changing rapidly enough, will induce an electric field sufficient to stimulate neurons. Figure 2.1 shows the sequence of events in TMS from pulse generation to cortical stimulation. A large current (up to 8kA) is generated by the capacitor and discharged into the coil, which in turn produces a magnetic pulse of up to 2 Tesla. The pulse has a very short rise time (approximately 100-200 s) and has an overall duration of less than 1 ms.

TMS stimulate neurons or change the resting membrane potentials in the underlying cortex. Thus TMS can be used t induce a transient interference with the normal activity in a relatively restricted area.

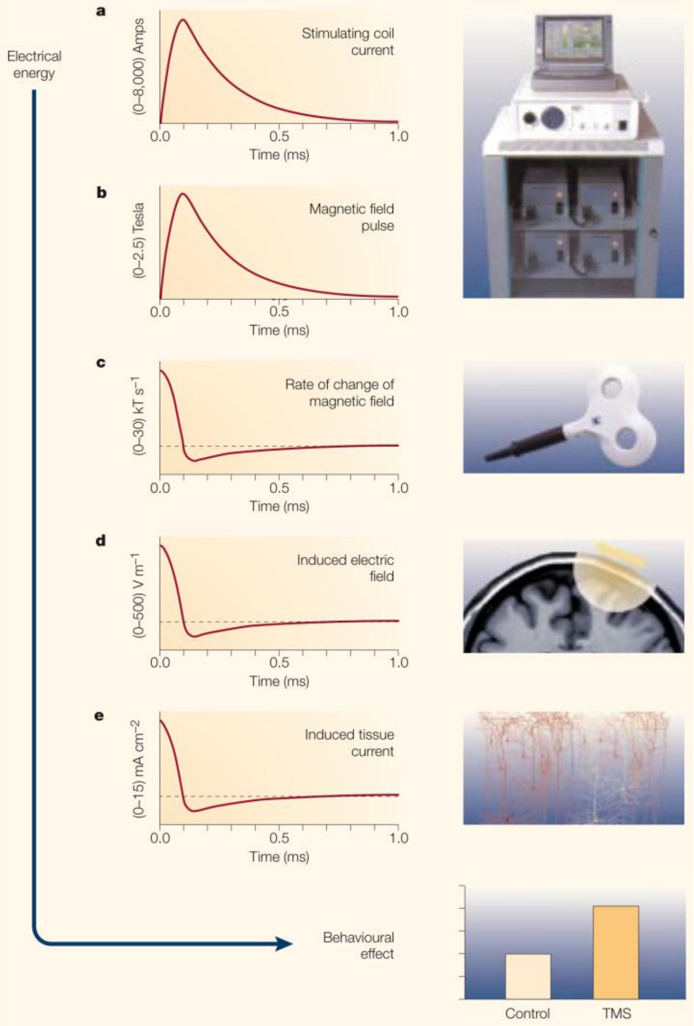

Figure 2.1: The sequence of events in TMS. An electrical current is generated by a capacitor and discharged into a figure-of-eight-shaped coil, which in turn produces a magnetic pulse of up to 2 tesla. The pulse has a rise time of approximately 200 μs and duration of 1 ms and changes at a rapid rate due to its intensity and brevity. The changing magnetic fields generate an electric fields, resulting in neural activity or changes in resting potentials (from Walsh and Cowey, 2000).

2.2. Mechanisms of interference

TMS data from the study of cognitive functions have traditionally been interpreted in term of ‘‘virtual brain lesion’’ (Walsh and Cowey, 1998). The terminology has been proposed by analogy with neuropsychological and animal lesion studies and TMS has been described as techique capable to induce a temporary, reversible lesion in the stimulated area, avoiding problems related to cortical plasticity and functional reorganisation (Walsh and Pascual-Leone, 2003). Based on this interpretation, TMS has been utilised to define the putative role of areas during the execution of cognitive tasks. The term ‘‘virtual lesion’’ identifies the effect induced by TMS, which temporarily disrupts the function of a population of neurons in the selected areas. Nevertheless, the TMS pulse induces a depolarisation of a group of neurons that in turn might activate other neurons, and the behavioural outcome depends on a number of different factors. The effect of stimulation may depend, for instance, on the role of the stimulated area in relation to the network engaged in such a task (Sack and Linden, 2003) and/or on the actual activity state of that area at a certain time (in which stimulation is applied). Single-pulse TMS over the primary motor cortex has commoly reported to induce a facilitatory effect, inducing a Motor Evoked Potential (MEP) recorted at the body periphery but may worse performance in many cognitive tasks (e.g., Ashbridge et al,., 1997; Chambers et al., 2004). Thus, based on these observations, the effect of TMS can be thought of as inducing ‘noise’ into neural processes. If a group of neurons are involved in a given task (for example, identifying a shape or searching for a stimulus in a complex array), introducing a TMS pulse is highly unlikely to selectively stimulate the same coordinated pattern of neural activity as performance of that task. Rather, TMS induces activity that is random with respect to the goal-state of the area stimulated. In other words, TMS induces disorder into the information processing system, thereby disrupting task performance. This ‘neural noise’ concept underpins what has become known as the ‘virtual patient’ approach.

2.3 TMS coils

The simplest TMS coil, and historically the first to be used, forms a circle. Typically the coil is 8–15 cm in outer diameter. As shown in Figure 2.2, a changing current in the coil induces an antiparallel, circular current flow of opposite direction in the underlying brain.

The induced current tends to be maximum near the outer edge of coil. In contrast, the magnetic field is maximum directly under the centre of the coil. This discrepancy is an occasional source of confusion, and may lead to the erroneous assumption that the site of magnetic stimulation is beneath the coil centre as well. Because of their size, most circular TMS coils have good penetration to the cerebral cortex. They are commonly placed at the cranial vertex, where they can stimulate both hemispheres simultaneously.

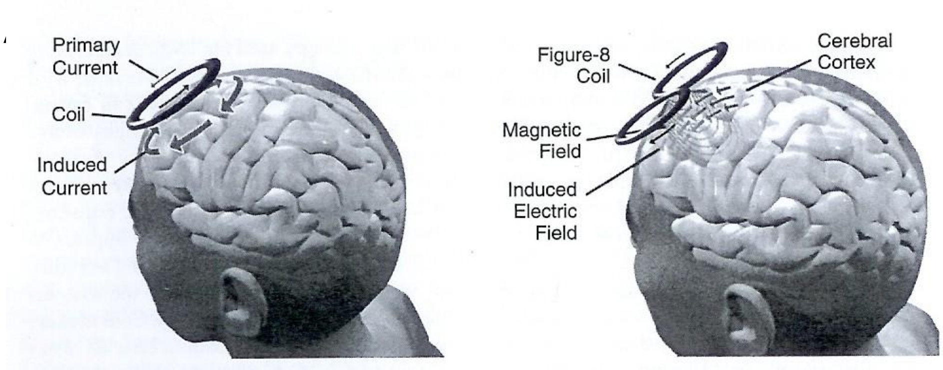

Figure 2.2. Circular stimulation coil (left). Magnetic and electric fields produced by a figure-of-eight coil (right).

If two round coils are placed side by side, so that the currents flow in the same direction at the junction point, the induced electric fields will add together and be maximum below the junction (Figure 2.2). Because of this greater focality, compared to the circular coil, most of the most studies of cognitive functions use the figure-of-eight coil. This design allows focal stimulation at a limited and clearly definable location.

2.4 TMS parameters

In the single-pulse TMS (spTMS), stimulation is applied with a single pulse at a time. A pulse may be followed by another at a distance of about 3 seconds. This approach is particularly useful for the mapping of motor cortical representations, the study of cortical plasticity, in motor rehabilitation. Allowing relatively high temporal resolution, spTMS represents a unique tool for the study of the chronometric of information processing. In the paired-pulse TMS (ppTMS) two pulses may be applied over two areas at the same time or at short intervals in order to study cortico-cortical interactions. In the repetitive TMS (rTMS) a train of pulses is applied either during the execution of a task (on-line stimulation) or before the execution of a task (off line) inducing a modulation of cortical excitability. By convention, “slow” TMS refers to stimulation at 1 Hz or less, and “fast” or “rapid” TMS refers to stimulation at greater than 1 Hz. Slow rTMS decreases (Chen et al, 1997) the excitability, while fast TMS increases (Pascual-Leone et al, 1994) the excitability of the motor cortex.

2.5 Spatial and temporal resolution

The magnetic field produced by TMS is not spatially focal (in theory it is of infinite extent, like the earth’s gravitational field). However, the distribution of the induced electric field has been modelled (Gamba and Delpy, 1998; Tofts, 1990), and progress has been made in relating the induced currents to specific sites of activation with a resolution of a few millimetres. resolution of a few millimetres. Detailed measurement of induced fields can be made in model heads, and several mathematical models of TMS have been proposed (Tofts 1990; Davey et al. 2003; Miranda and Basser, 2003; Wagner 2004).

The figure 2.3 shows a comparison between different techiques in temporal and spatial resolution. The spatial and functional localization of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are achieved, in part, by comparing the effects on blood flow of different task conditions. Similar inferences can be applied to TMS as this technique allows to compare the effect of stimulation over different sites on the same task. With TMS, however, the number of sites that can be compared is more restricted. This limitation provides a conceptual constraint on the application of TMS because a hypothesis is required for every comparison. The subtraction approach follows the logic of lesion analysis in humans and non-human primates, and that of functional neuroimaging. Compared with other techniques, one limitation of TMS is that the effects of stimulation are limited to superficial cortical regions and cannot be used to investigate functions of medial cortex or subcortical structures.

When a TMS pulse is delivered over an area of cortex, the effect is to simultaneously activate many neurons. At the point of maximal activation, the stimulated area will have its lowest signal-to-noise ratio with respect to the task it is performing. However, as neurons recover, the signal will increase, and whether or not TMS continues to have an effect will depend on the level of signal required for the task. Note that the interaction between the TMS signal and the contribution of an area to a task makes it highly unlikely that the time at which TMS has its maximal effect will correspond with the peak times reported in event-related potential (ERP) experiments. An effectively disruptive pulse will interfere with processes that contribute to the build up of the ERP signal, so if the signal represents a neural event that is essential to the task, the time of TMS interference will typically precede ERP peaks and is more likely to coincide with single unit dat. In other words, where an ERP result reports a peak at, say 300 ms, this may reflect the contribution of more than one neural event with a group maximum at 300 ms. When TMS is applied over the areas that contribute to this signal, it may disrupt processing of the individual components that may be maximal before, at, or after the reported peak at 300 ms.

EXPERIMENTAL SESSION

CHAPTER 3

Timing spatial conflict within the posterior parietal cortex

3.1 Introduction

The posterior parietal cortex (PPC), as part of the dorsal visual stream (Goodale and Milner 1992), is thought to be implicated in both visuo-spatial attention (Ashbridge et al. 1997; Chambers et al. 2004) and in transforming sensory information into motor outputs (Goodale and Milner 1992; Rizzolatti et al. 1987; Mattingley et al. 1998). Early visuomotor integration within the PPC has been suggested to produce competing representations of potential responses in spatial conflict tasks (e.g., Eriksen flanker task; Bunge, Hazeltine, Scanlon, Rosen, and Gabrieli, 2002; Coulthard, Nachev, and Husain, 2008; Cisek, 2009). Furthermore, PPC has been indicated as the neural substrate of the direct route in the Simon task (Stürmer et al. 2007; Rusconi et al. 2007).

Recently, lateralized neural mechanisms within the PPC were proposed as being responsible for different, although related, attentional processes (Rushworth et al. 2001; Rushworth and Taylor 2006): the right PPC is thought to be responsible for orienting attention in space, while the left PPC is suggested as being involved in attentional processing directed towards motor selection (i.e., motor attention). Rushworth and colleagues (2001) used the transcranial magnetic stimulation (TMS) technique to dissociate between the roles of the right angular gyrus (AG) and the left supramarginal gyrus (SMG) in covert visuospatial orienting attention and in the selection of overt finger movements. They found that the right AG was critically involved in a task which required orienting attention, while the left SMG was involved in a task which entailed motor attention and response selection (Rushworth et al. 2001). This anatomo-functional dichotomy is supported by neuropsychological findings, which showed that lesions in the right PPC are associated with hemi-spatial neglect (Vallar et al. 1988), whereas left parietal damage is mostly associated with praxis deficits (Goldenberg 2009).

However, the role of the PPC in situations of spatial stimulus-response conflict has not been extensively studied. Only one study investigating the role of the anterior and posterior portions of the PPC in a conflict task failed to clearly dissociate between different and/or asymmetrical contributions of these areas to different attentional mechanisms (Rusconi et al. 2007). Thus, it is still unknown how orienting and motor attention processes are related to the spatial conflict created by the direct route during choice reaction task. On the other hand, the proposed dichotomy between orienting and motor attention was based on results obtained from different tasks (Rushworth et al. 2001) and a direct comparison of the involvement of the different parietal subregions in a single task is still lacking.

Interestingly, behavioural findings on the Simon effect revealed a peculiar result in which may help to reveal the neural substrates of orienting and motor attention processes during conflicting conditions. Usually, the correspondence effect is greater for right-hand responses compared to left-hand responses (Tagliabue, 2007). This phenomenon was supposed to depend on the dominance of the left hemisphere in motor attention and response selection and it has been argued that visuomotor processing through the direct (automatic) pathway might be more efficient for the dominant hand in right-handed subjects (Rubichi et al. 2006; Tagliabue, Vidotto, Umilta, Altoe, Treccani, and Spera, 2007). Recently, a computational model by Spironelli and colleagues (2009) was proposed to explain the asymmetry in the correspondence effect through differently lateralized neural mechanisms in the PPC for orienting attention (involving both the left and right AG) and motor attention (carried out by the left SMG). However, only behavioural data inspired such a model, and validation from a neurofunctional point of view is lacking. Moreover, it is still unknown whether the conflict created by the direct route is related to either attention orienting or response selection processes.

The present study examined the different contributions of the angular and supramarginal gyri (AG and SMG) of both hemispheres while dealing with a spatial conflict task. In two experiments, participants performed a Simon task with laterally presented stimuli as a single-pulse TMS (spTMS) was delivered. In the first experiment, spTMS was applied over the left or right AG at various time intervals after stimulus onset, whereas in the second experiment spTMS was delivered over the left or right SMG. In both experiments the vertex was stimulated as control site. If stimulation of these areas generated a reduction of the Simon effect, then it can be assumed that a region involved in the direct route had been hit, since the Simon effect is due to the interference of the direct route on the task-driven indirect route.

In our hypothesis, if the right and left PPC are involved in different attentional processes related to the direct route, a different timing of the TMS effect should be revealed by the stimulation of the right and left hemispheres. We predicted that if the right AG is involved in the generation of the stimulus spatial code, which is the precondition of the conflict in the Simon task, a reduction of the Simon effect would be induced by TMS in an early time window at that site. A later effect could instead be associated with the stimulation of the left hemisphere, which is thought to be involved in transforming stimulus spatial information into codes for action (Rushworth et al. 2001; 2006).

Furthermore, we hypothesized that the asymmetry in the correspondence effect between right and left hand responses would be suppressed only after stimulation of the parietal region involved in motor attention.

3.2 Experiment 1

3.2.1 Materials and Methods

Participants

Eleven healthy undergraduate students of the University of Padua (all right-hand handed, mean age of 24 years ± 3) with normal or corrected-to-normal visual acuity took part in the first experiment. All subjects were checked for TMS exclusion criteria (Wassermann 1998) and gave their written informed consent before participation. The intensity of stimulation and the duration of the TMS sessions were in accordance with the safety guidelines established by Wassermann (1998), and the Ethics Committee of the Department of General Psychology, University of Padua, approved the procedure. The subjects were reimbursed with cash for participating in the two sessions of each experiment. All participants were naive as to the purpose of the study.

Apparatus and stimuli

The participants were seated in a dimly-lit and soundproof room with their head held by a fixed head-and-chin rest at a distance of 50 cm from a 17-inch monitor controlled by a Pentium 4 PC programmed with E-prime (Psychological Software Tool, Pittsburgh, USA). The targets were the letters ‘N’ and ‘H’ subtending 1.4° × 1.8° (width × height) of a visual angle presented for 200 ms in white on a black background, 3.5° laterally with respect to a fixation cross.

Procedure and experimental design

Each participant was tested in two experimental sessions lasting approximately 2 hours each. The participants completed a block of 40 practice trials followed by the experimental blocks. A trial started with the presentation of a central fixation cross (subtending 0.5° × 0.5° of visual angle) lasting 400 ms. Then a stimulus was presented for 200 ms at a visual angle of 4.6° either to the left or to the right of the central fixation point. A contralateral filler ‘#’ was also presented. The maximum response time was 1200 ms. The inter-trial interval varied randomly between 1500 and 2500 ms. After an incorrect response, a tone (600 Hz) was delivered to provide feedback on the wrong answer. At the end of each block, feedback concerning mean RT and accuracy was displayed on the screen. A schematic representation of the trial sequence is depicted in Figure 3.1. The participants were instructed to maintain their gaze on the fixation point during the whole experimental session. Half of the participants were asked to respond, as quickly as possible, by pressing the leftmost key (‘Z’) on the keyboard with the index finger of the left hand when the target letter was an ‘N’ and the rightmost key (‘M’) with the right hand when it was an ‘H’. The other half of the participants received the opposite hand-target assignment.

The design of the two TMS experiments involved within-subject manipulation of sites of stimulation, stimulus-response correspondence and the time intervals between the onset of the target and the application of the TMS pulse (SOA). Each session was divided into three experimental blocks, one for each stimulation site. Each block was composed of 480 trials in which stimulus position (left or right), response position (left or right), and SOA (70, 100, 130, 160, 190, 220, 250 ms) were fully crossed to produce the same number of trials for each possible combination, presented in a random order. No TMS pulse was delivered in 60 trials of each block (randomly intermixed). A pause was given to the participants every 160 trials. The order of blocks (i.e., site of stimulation) was counterbalanced across participants.

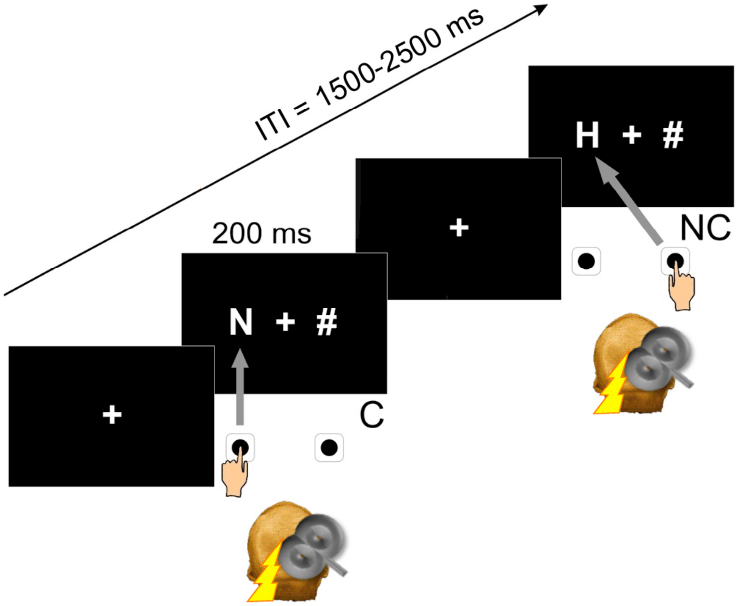

Figure 3.1. A schematic representation of the trial sequence of the Simon task. Single-pulse TMS were randomly delivered in each trial at different SOAs (70, 100, 130, 160, 190, 220, 250 ms).

Localization of brain targets for TMS stimulation

The TMS coil was placed on the skull of each subject using MRI images of the participants with the Brainsight stereotaxic neuronavigator (Rogue Research Inc, Montreal, Canada) coupled with a Polaris Vicra infrared camera system (NDI, Waterloo, Canada). The coil position was monitored on-line during all experiments. An individual T1-weighted MR scan was obtained from each participant using a Signa 3T system GE Healthcare, Milwaukee, WI, USA (1.3 × 1.3 × 1.3 mm, sagittal acquisition).

The right AG was identified by means of the hunting procedure described by Ashbridge et al. (1997), which has been employed in several previous studies (Ellison et al. 2004; Rushworth 2001; Walsh et al. 1999). A 3 × 3 cm grid was applied with the central square on the position of the scalp which corresponded to electrode P4 of the international 10-20 system for electrodes placement (oriented 45° away from the midsagittal line). After a practice block of 40 trials, the participants performed 9 blocks of a conjunction visual search task consisting of 20 trials each. Single-pulse TMS were applied 100 ms after stimulus onset to one of the 9 marked sites of the grid (the order was randomized between subjects). The right AG site used for the experimental session was defined as the site where single-pulse TMS increased the mean RTs of about 50 ms in the visual search task compared with the other 8 stimulation sites of the grid. Previous studies showed that this procedure accurately pinpoints the position of the posterior part of the PPC, specifically the part corresponding to the right AG (Rushworth et al. 2001; 2006). See Figure 3.2 for a description of the visual search task and of the hunting procedure. The left AG stimulation site was defined as the point on the left hemisphere, which corresponded to the right AG site. The vertex was used as the control site. The vertex was defined as a point midway between the inion and the nasion and equidistant from the left and right pre-auricular points (10-20 International system). Correspondence between the anatomical region and the spot obtained from the hunting procedure was confirmed in five subjects by using their own individual MRI. Mean and standard deviations of stimulation sites were reported, according to the MNI system (standard deviation in brackets): for the left AG were X=-40(5), Y=-72(3), Z=44(6), while for the right AG were X=44(6), Y=-68(6), Z=40(4).

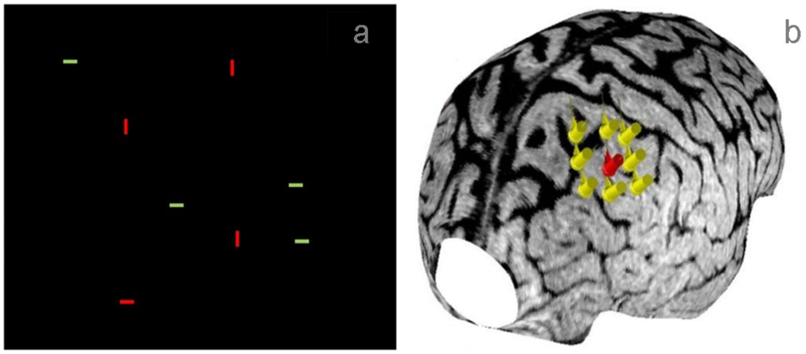

Figure 3.2. A representative frame of the conjunction visual search array (i.e. colour and orientation) adopted in the procedure for the localization of the right AG, with psTMS applied 100 ms after stimulus presentation (Panel A). A 3D MRI brain reconstruction of a representative subject with the 3 × 3 cm grid depicted around the P4 site used in functional localization of the right AG (Panel B).

TMS parameters

Transcranial magnetic stimulation was applied with a Magstim Super Rapid2 system (Magstim Company Ltd, Spring Gardens, Wales, UK). The intensity of the magnetic stimulation was set separately for each participant 10% above the individual motor threshold (MT). The MT was defined as the minimum percentage of the stimulator output which could evoke a visually detectable twitch in a tense muscle of the hand of each participant contralateral to the stimulated motor cortex. In Experiment 1, the resulting mean intensity was around 69 ± 1.7% of the maximum stimulator output.

3.2.2 Results

A repeated measures ANOVA was performed on the mean RTs of TMS trials with the stimulation site (left and right AG and vertex), Stimulus onset asynchronous (SOAs; 70, 100, 130, 160, 190, 220, 250 ms) and correspondence (corresponding vs. non-corresponding trials) as within subjects factors. Paired-sample t-tests (two-tailed) were then performed to compare the magnitude of the correspondence effect (difference between non-corresponding and corresponding trials) obtained after stimulation of the experimental sites and the vertex at specific stimulus onset asynchronous (SOA).

A main effect of correspondence was found [$F(1,10) = 36.375$, $p < 0.001$, $\eta^2_p = 0.78$], where corresponding trials were faster than the non-corresponding ones. Overall, the correspondence effect amounted to 15 ms. The site × correspondence interaction [$F(2,20) = 4.197$, $p < 0.05$, $\eta^2_p = 0.30$] revealed that a spTMS produced a significant reduction of the correspondence effect when applied to the right AG (10 ms) with respect to both the left AG (17 ms) and the vertex (18 ms). However, the three-way interaction between site × SOA × correspondence [$F(12,120) = 2.117$, $p < 0.05$, $\eta^2_p = 0.18$] allowed a further description of the TMS effects. Figure 3.3 shows the mean RTs for the corresponding and the non-corresponding conditions at each SOA, separately for the three stimulated sites. Pairwise comparisons aimed to qualify the interaction revealed that a suppression of the correspondence effect was obtained when TMS was applied to the left and right AG compared to the vertex, but only when pulses were delivered 130 ms and 160 ms after stimulus onset to the right AG [t(10) = 2.834, $p < 0.05$] and to the left AG [t(10) = 3.997, $p < 0.01$], respectively (Figure 3.5).

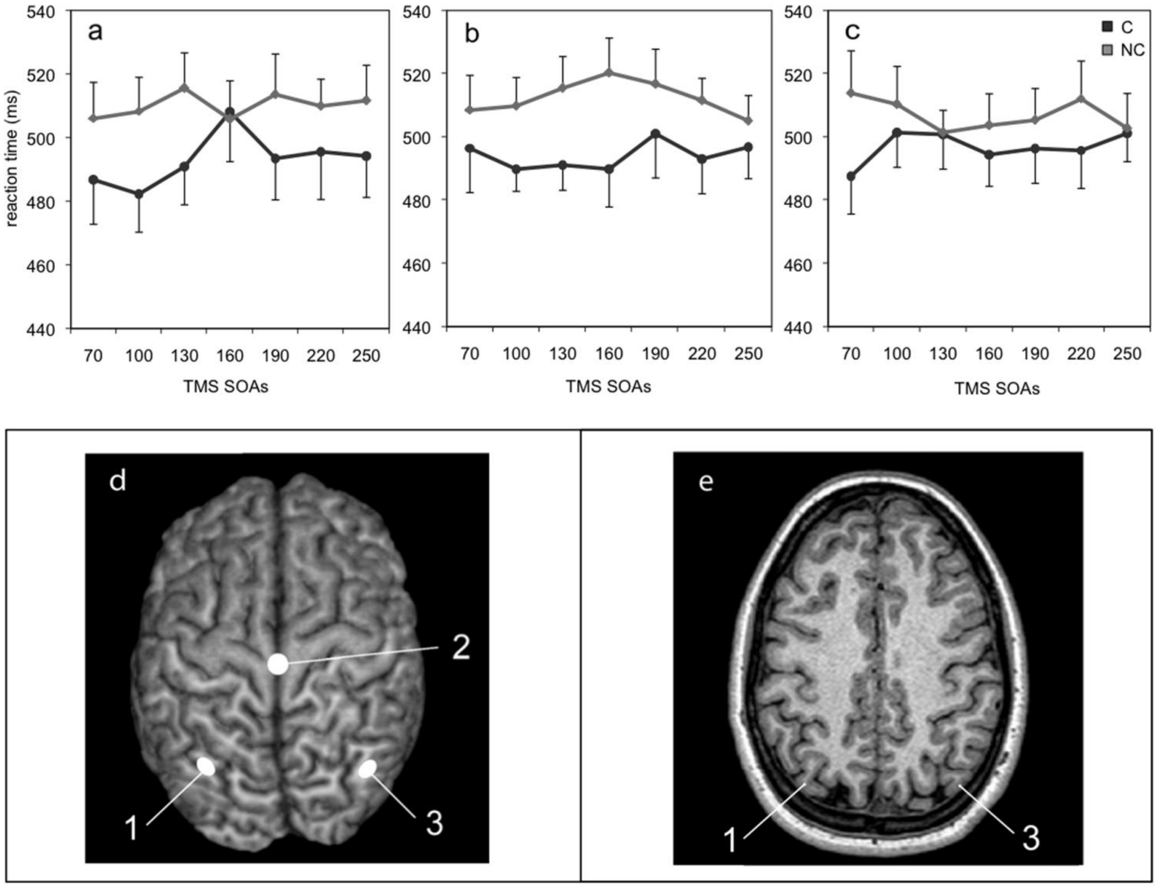

Figure 3.3. In Experiment 1, the left and right AG and the vertex were stimulated with single-pulse TMS at different SOAs (70, 100, 130, 160, 190, 220, 250 ms). Results of ANOVA on the correspondence effect highlighted a suppression of the Simon effect when spTMS was applied to the left AG (1) 160 ms after stimulus onset (panel A), and to the right AG (3) 130 ms after stimulus onset (Panel C). No suppression of the Simon effect was observed when TMS was applied to the Vertex (2) (Panel B). The locations of stimulated sites in experiment 1 are depicted on a 3D rendered surface (Panel D) and on a MRI slide (Panel E).

Effect of AGs stimulation on the correspondence asymmetry

The time course of these effects are close to that of the orienting attention process, as previously found in visual search tasks (Ashbridge et al. 1997; Walsh et al. 1998). Thus, we hypothesize that in these time windows, both the right and left AG are performing a spatial analysis of the incoming visual information which caused attention to be oriented toward the target position. Since behavioural asymmetry between the right and left-hand correspondence effect was supposed to arise from motor attention and response selection processes, attributed to the left SMG (Rushworth et al. 2001), we expected that stimulation over the right and left AG would not affect such asymmetry. Therefore, we analysed the data by considering response position as an additional factor on the SOAs where TMS had an effect. A series of repeated measures ANOVAs were performed on the mean RTs including site (experimental vs. control), correspondence (corresponding vs. non-corresponding condition) and response position (left vs. right hand) as factors.

The comparison between right AG and vertex stimulation showed a very similar pattern to the comparison between the left AG and the vertex. The main effects of correspondence [right AG: $F(1,10) = 5{,}759$, $p < 0.05$, $\eta^2_p = 0.36$; left AG: $F(1,10) = 12{,}065$, $p < 0.01$, $\eta^2_p = 0.55$] and response position [right AG: $F(1,10) = 13{,}740$, $p < 0.01$, $\eta^2_p = 0.58$; left AG: $F(1,10) = 41.053$, $p < 0.001$, $\eta^2_p = 0.80$], showed that the right hand responses were faster than the left hand responses. The significant correspondence × response position interaction [right AG: $F(1,10) = 6{,}263$, $p < 0.05$, $\eta^2_p = 0.38$; left AG: $F(1,10)= 20{,}680$, $p < 0.001$, $\eta^2_p = 0.67$] showed that the correspondence effect for right-hand responses was greater than the correspondence effect for left-hand responses. The significant site × correspondence interaction showed a reduction of the correspondence effect with respect to vertex [right AG: $F(1,10) = 8{,}519$, $p < 0.05$, $\eta^2_p = 0.46$; left AG: $F(1,10) = 17{,}312$, $p < 0.01$, $\eta^2_p = 0.63$]. The lack of an interaction between response position, correspondence and site revealed that stimulation did not affect the right/left hand asymmetry (Figure 3.6 right and middle columns).

3.3 Experiment 2

3.3.1 Materials and Methods

Participants

Eight (all right- handed, mean age of 23 years ± 2), with normal or corrected-to-normal visual acuity, took part in the second experiment.

Apparatus and stimuli

Apparatus and stimuli were the same of experiment 1.

Procedure and experimental design

The procedure and experimental design were the same of experiment 1.

Localization of brain targets for TMS stimulation

Single-pulse TMS was applied to the experimental sites (right and left SMG, as well as to the vertex), identified on the individual MRI images (Figure 3.4). Anatomical landmarks were used for SMG, which was defined as the region adjacent to the dorsolateral projection of the lateral sulcus, posterior to the post-central sulcus and anterior to the superior temporal sulcus (Rushworth et al. 2001; Chambers et al. 2004). Mean coordinates according to the MNI system (standard deviation in brackets): for the left SMG were X=-

53(3), Y=-48(2), Z=41(4), while for the right SMG were X=55(5), Y=-46(9), Z=39(2).

TMS parameters

TMS parameters were the same of experiment 1. The resulting mean stimulation intensity was around 65 ± 2.1% of the maximum stimulation output. During the experiments, single-pulse TMS was delivered in each trial after the target 'at the onset of one out of seven asynchronies.

3.3.2 Results

A repeated measures ANOVA was performed on the mean RTs of TMS trials with the stimulation site (left and right SMG and vertex), stimulus onset asynchronous and correspondence as within subjects factors. Paired-sample t-tests were then performed to compare the magnitude of the correspondence effect (difference between non-corresponding and corresponding trials) obtained after stimulation of the experimental sites and the vertex at specific stimulus onset asynchronous (SOA).

The results showed a main effect of correspondence [$F(1,7) = 8.518$, $p < 0.05$, $\eta^2_p = 0.55$] where the corresponding trials were faster than the non-corresponding ones. Besides the main effect of SOA [$F(6,42) = 2.357$, $p < 0.05$, $\eta^2_p = 0.25$], a three-way interaction between site × SOA × correspondence was also found [$F(12,84) = 1.867$, $p < 0.05$, $\eta^2_p = 0.21$]. When applied 160 ms after stimulus onset, TMS on the left SMG produced a suppression of the correspondence effect (Figure 3.4, Figure 3.5). The magnitude of the correspondence effect at this point was significantly different compared to the vertex [$t(10) = 2.993$, $p <$

0.05]. When TMS was applied over the right SMG, no difference in the correspondence effect with respect to the vertex was found at any SOA (Figure 3.4, Figure 3.5).

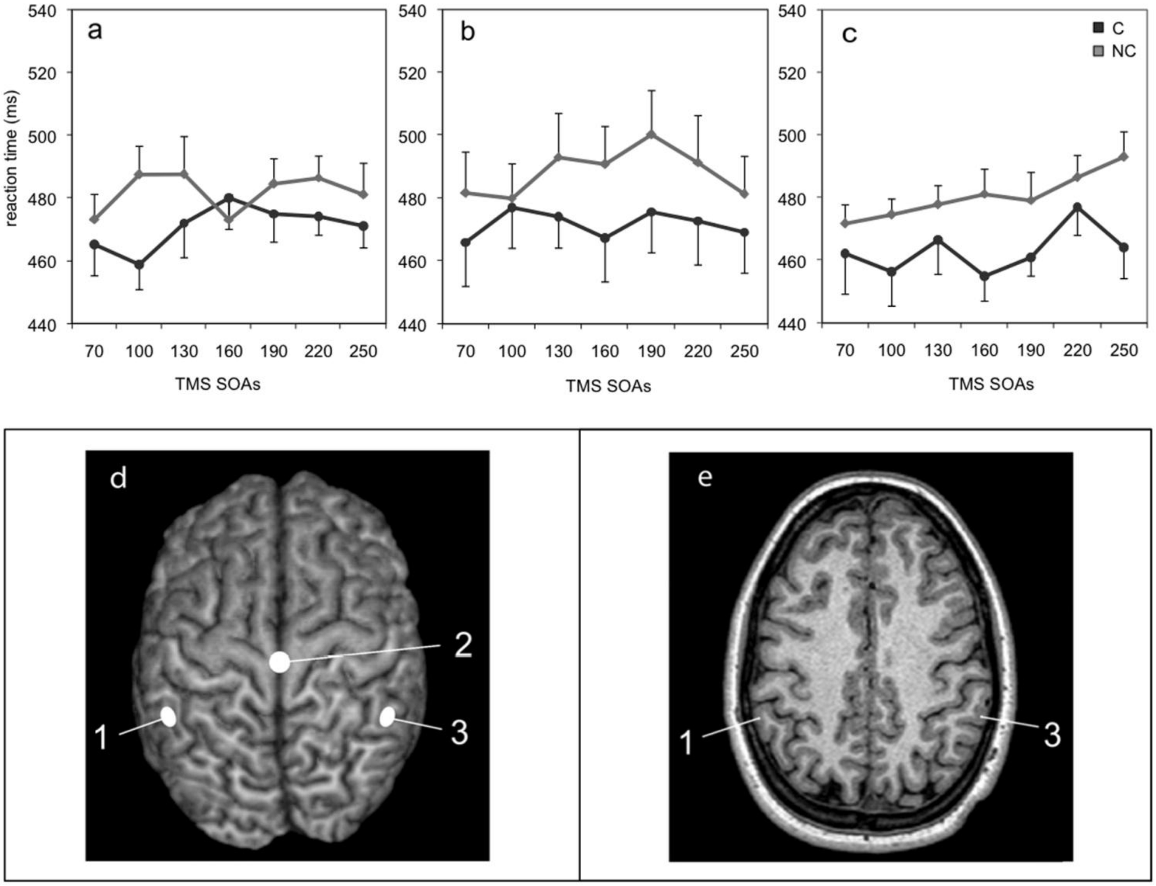

Figure 3.4. In Experiment 2, RTs for the left and right supramarginal gyri (SMG) and the vertex were represented as a function of different SOAs (70, 100, 130, 160, 190, 220, 250 ms, abscissa). A suppression of the Simon effect was found when stimulating the left SMG (1) 160 ms after stimulus onset (Panel A) No suppression of the Simon effect was observed when TMS was applied to either the vertex (2) (Panel B) or the right SMG (3) (Panel C). The locations of stimulated sites in experiment 2 are represented by the white dots on a 3D rendered surface (Panel D) and on a MRI slice (Panel E).

Effect of SMGs stimulation on the correspondence asymmetry

Since the right and left AG were implicated in orienting of attention, and thus in generation of the spatial stimulus code in the Simon task, the left SMG is thought be implicated in transforming spatial information into codes for action and thus in motor attention. To test this hypothesis, an analysis on asymmetry in the correspondence effect was performed as in the previous experiment.

The comparison between the stimulations of left SMG and the vertex showed a close to significance main effect of response position [$F(1,7) = 4.936$, $p = 0.06$, $\eta^2_p = 0.41$], where right-hand responses were faster that left-hand responses. The significant site × correspondence interaction [$F(1,7) = 8{,}129$, $p < 0.05$, $\eta^2_p = 0.54$] confirmed that the suppression of the correspondence effect only occurred when TMS was applied over the left SMG, 160 ms after stimulus onset. Moreover, the lack of a significant interaction between response position and correspondence [$F(1,7) = F(1,7) = 2.064$, $p = 0.194$, $\eta^2_p = 0.23$] suggested that the right and left hand asymmetry in the magnitude of the correspondence effect was eliminated. The Figure 3.5 (left columns) show that when stimulating the vertex, the correspondence effect amounted to 17 ms for left-hand responses and to 26 ms for right-hand responses, whereas when stimulation was applied over the left SMG this difference was suppressed (i.e., correspondence effect amounted to -7 ms for left-hand responses and to -6 ms for right-hand responses).

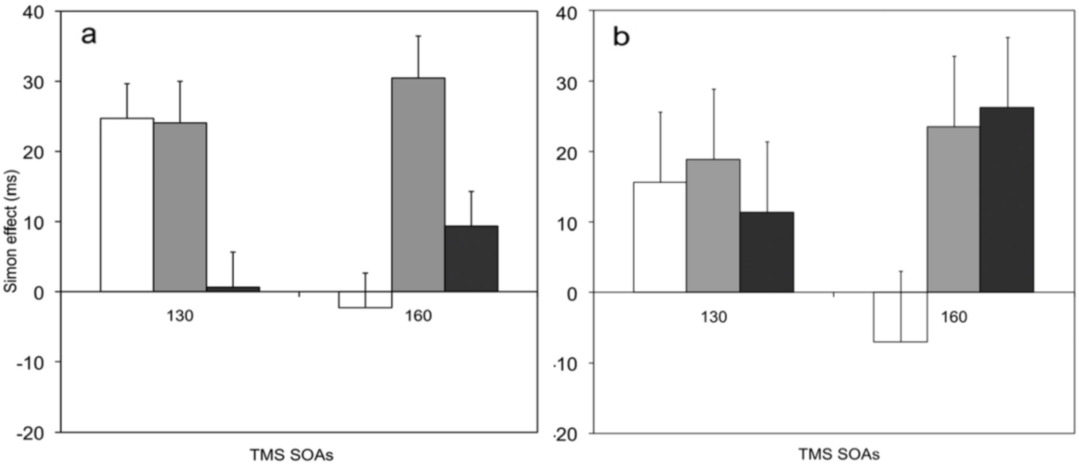

Figure 3.5 (Panel A) The magnitude of the Simon effect for the SOAs and sites where a modulation of conflict was found in experiment 1 (Panel A) and experiment 2 (Panel B). A suppression of the correspondence effect was obtained when spTMS was applied to the right AG 130 ms after stimulus onset and to the left AG 160 ms after stimulus onset compared to the vertex (spTMS on the vertex). An inversion of the correspondence effect was obtained only when spTMS was applied to the left SMG 160 ms after stimulus onset.

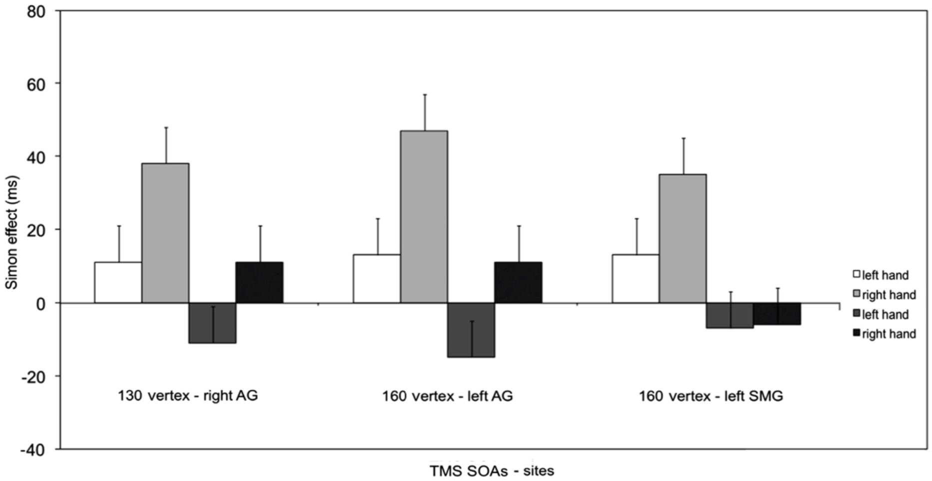

Figure 3.6. Left and right-hand correspondence effects are depicted separately for each site and for the SOAs where TMS modulated the overall correspondence effect. The graph shows that even when the correspondence effect was suppressed for the stimulation of the left AG and SMG and for the right AG, the asymmetry in the correspondence effect between the right and left-hand responses was only eliminated after left SMG stimulation.

3.4 Discussion

In the present study we investigates the role of the angular and supramarginal gyri (AG and SMG, respectively) of both the hemispheres in visual and motor attention, while participants are engaged in the execution of a visual Simon task. It is well known that, in the Simon task, conflict arises when spatial information, associated with stimulus and response positions do not correspond. In two experiments, single-pulse transcranial magnetic stimulation (spTMS) was adopted to modulate the activity of these areas in different time windows (ranging between 70 and 250 ms) during task execution.

The results of the two experiments showed a suppression of the conflict when spTMS was applied on the right AG 130 ms after stimulus onset, and when applied on the left AG and left SMG 160 ms after stimulus onset. No effect of stimulation was found after right SMG stimulation.

The left AG gets involved right after the homologue area (i.e., 160 vs. 130 ms), probably receives information from the right AG via callosal connection. The callosal connection from the right to the left AGs is a fundamental component in the above-described computational model of Spironelli and colleagues (2009) for simulating the Simon effect and its right and left hand asymmetry. This connection was thought to convey information from the right orienting attention system to the orienting and motor attention systems in the left hemisphere. The dominant role of the right AG in orienting attention has been widely supported by studies which showed that, in right-handed subjects, the right parietal orienting mechanism spans both the right and left hemispaces, while the left parietal system contributes mainly to attentional processes in the contralateral hemispace (Nobre et al.

1997; Corbetta and Shulman 2002; Mesulam 1981). Our data further support the dominant role of right AG in orienting attention, in fact, the correspondence effect showed a reduction also when TMS was applied to the right AG 250 ms after stimulus onset, but this value was not significant when compared to vertex stimulation (Figure 2). This later effect is in line with previous data reported by Chambers et al. (2004). In their study, TMS was applied over the right AG in a task that required re-orienting of spatial attention. The right AG was crucial at two distinct time points during spatial attention shifts, namely between 90 and 120 ms and again between 210 and 240 ms after the cue onset. One interpretation of these findings is that the first temporal window was associated with the fast retinotectal visual pathway while the second window was related to the slower geniculostriate visual pathway. Both pathways are assumed to convey attentional information to the inferior parietal lobe (Chambers et al. 2004). Our data further suggest that in the early phase, orienting attention is related to the fast activation of the retinotectal pathway, since this is the basis of automatic processing through the direct route. In contrast, in the later phase, attention should be voluntarily oriented towards the relevant information via the slower geniculostriate pathway.

The suppression of the correspondence asymmetry between right and left hand responses after stimulation of the left SMG suggests a selective involvement of this region in priming irrelevant spatial information to the motor system of the dominant hand. These results are the first important verification of the hypothesized role of the left SMG in producing spatial code at the basis of asymmetry between right and left hands in correspondence magnitude. In support to this view, recently, Rushworth and co-workers (2006) investigated, with diffusion-weighted imaging, the connection pattern of the different parietal subregions. In their study the SMG was found to have a high probability of connection with the premortor cortex, while the AG was found to be connected with higher probability with visual areas within the ventral stream (i.e. the parahippocampal gyrus).

In conclusion, the present data allowed us to dissociate between the functional roles of right/left AGs and that of the left SMG during spatial conflict. While the AGs are involved in orienting attention, the left SMG is a critical region for transforming spatial information into code for action (i.e., motor attention, Rushworth et al. 2001; 2003). These results provide a new step towards a description of the roles played by different PPC sub-regions in spatial conflict; furthermore, these data bridge the gap between dual route models of information processing and the attention orienting and motor attention dichotomy (Cisek 2008). Nevertheless, further experiments are necessary to study the neural substrate of the indirect route, which was not directly investigated in the present study. Evaluation of the prefrontal system during visuomotor transmission in conflict tasks seems particularly important in order to describe how conflict resolution of competing visual information is implemented. The analysis of the time course of cerebral modulation produced by TMS was convincingly shown to be an important method in cognitive neuroscience for the chronometric study of brain circuit activation (Walsh and Covey 2000).

CHAPTER 4

The role of the Frontal Eye Fields in the Simon effect

4.1 Introduction

There is unanimous consensus that the control of visuospatial attention involves a large cortical network, which specially includes posterior parietal and frontal areas (Corbetta and Shulman, 2002). The frontal eye fields (FEF), which have been characterized for their role in oculomotor control, have recently been shown to play an important role in the allocation of attention in space, whether or not eye movements are required (Corbetta et al., 1998; Nobre et al., 1997; Gosbras and Paus, 2002). In the latter case, this activity is commonly interpreted in terms of the premotor theory of attention (Rizzolatti et al., 1987). FEF activation is attributed to the generation of saccade programs that are not overtly executed. Space representation and covert orienting attention involve FEF with the control of either bilateral (e.g., Grosbras and Paus, 2002) or contralateral control (Corbetta and Shulman, 2002).

Recent studies reported that, like PPC (Ashbridge et al., 1997; Walsh et al., 1998), TMS delivered over FEF disrupted performance in conjunction visual search tasks (e.g., Kalla, Miggleton, Juan, Cowey, and Walsh, 2008; O'Shea, Muggleton, Cowey, & Walsh, 2004; Muggleton et al, 2003). Interestingly, the contribution of the FEF and PPC to visual search has been dissociated in the temporal domain. Kalla and coworkers (2008) directly compared the effect of TMS over the FEF and PPC in the same visual search task. They reported that magnetic stimulation over the FEF disrupted performance when applied in an earlier time period compared to PPC. The FEF TMS effect occurred in a 0-40 ms range after stimulus onset while the same effect was obtained by TMS over PPC at 120 and 160 ms. O’Shea and coworkers (2004) found that the disruption of visual search task performance with FEF TMS occurred when a pair of pulses were delivered in a 40-80 ms time range after stimulus onset. These outcomes are consistent with response latency to target visual stimuli of FEF neurons in monkeys (Bullier, 2001). These early response times of the FEF, together with anatomical investigations of connectivity of FEF neurons within the visual hierarchy and the reports of FEF neurons showing selectivity for visual features and target (Bichot, Thompson, Chenchal Rao, and Schall, 2001) has led to the suggestion that FEF may be considered as part of an early or fast stage of visual processing in addition to its traditional post-perceptual role in programming saccade (More and Fallah, 2001).

Most theoretical accounts of the Simon effect share two basic assumptions. The first assumption is that a spatial code is generated for the irrelevant stimulus location attribute. The second is that the spatial code automatically activates its spatially corresponding response code (e.g., De Jong et al., 1994). The irrelevant spatial code is thought to be generated by the direction of the last attention shift before a response is selected (Nicoletti and Umiltà, 1994; Stoffer and Umiltà, 1997), through a mechanisms suggested by the premotor theory of attention shift (Rizzolatti et al., 1987; Umiltà et al., 1991). In line with the premotor theory of attention, in stimulus-response tasks, a motor program for the corresponding saccade is automatically generated every time there is an attention shift. The motor program contains the final target coordinates of the shift, i.e., the stimulus position (Rizzolatti et al., 1987). Hence, the stimulus spatial code is formed and it generates the Simon effect by priming the corresponding response.

It may be predicted that a neural correlate for encoding the attention-driven stimulus spatial coordinates is activated in cerebral areas devoted to both visuospatial attention and motor control.

The aim of the present study was to investigate if the FEF have a role in coding the irrelevant stimulus spatial attribute, which is the precondition of the conflict in the Simon effect. To this end, double-pulse TMS was delivered to both the right and the left FEF while participants were performing a Simon task. We predict that if the FEF contribute to the generation of the Simon effect, temporally interfering with the neural activity in this area should reduce the correspondence effect at least for stimuli presented in the visual hemifield contralateral to the stimulated area.

We expected that TMS applied over the FEF during the Simon task would disrupt the allocation of attention to the contralateral visual field and thereby prevent the irrelevant stimulus spatial code to be formed. This should result in a suppression of the Simon effect for stimuli presented in the visual field contralateral to the stimulation site. In order to qualify the timing of the involvement of the FEF, double-pulse TMS was applied over FEF at various time intervals after stimulus onset. On the basis of previous data on visual search tasks, we predict that TMS will interfere in the Simon task in an early timing after the onset of stimulus presentation.

4.2 Materials and Methods

Participants

Nine healthy undergraduate students of the University College London (all right-hand handed, mean age of 23 years ± 2) with normal or corrected-to-normal visual acuity took part in this experiment. All subjects were checked for TMS exclusion criteria (Wassermann 1998) and gave their written informed consent before participation. The local Ethics Committee approved the procedure. The subjects were reimbursed with cash for participating in the experiment. All participants were naïve as to the purpose of the study.

Apparatus and stimuli

The participants were seated in a dimly lit and soundproof room with their head held by a fixed head-and-chin rest at a distance of 60 cm from a 17-inch monitor. The experiment was programmed with Matlab Psychtoolbox (Brainard, 1997). The target stimulus was either a red or a green square subtending 1.5° × 1.5° (width × height) of visual angle presented for 200 ms on a black background.

Procedure and experimental design

Each participant was tested in one experimental session lasting approximately 1 hour and half. Participants completed a block of 20 practice trials followed by the experimental blocks. A trial started with the presentation of a central fixation point (a circle subtending 0.5° of visual angle) lasting 400 ms. Then a stimulus was presented for 200 ms at a visual angle of 4.5° either to the left or to the right of the central fixation point. The inter-trial interval was of about 3000 ms. After an incorrect response, a tone (600 Hz) was delivered to provide feedback on the wrong answer. Participants were instructed to maintain their gaze on the fixation point during the whole experimental session and were asked to maintain their eyes on the central point. Participants were instructed to respond, as quickly as possible, by pressing the leftmost key (‘F’) on the keyboard with the index finger of the left hand when the target square was red and the rightmost key (‘J’) with the right hand when the target square was green.

The design involved within-subject manipulation of sites of stimulation, stimulus-response correspondence and the time intervals between the onset of the target and the application of the double-pulse TMS (SOA). Participants performed a baseline condition without TMS of 64 trials followed by 12 experimental blocks, four for each stimulation site (right FEF, left FEF, and control site). Each block was composed by 64 trials in which stimulus position (left or right), response position (left or right), and TMS timing (0-40, 40-80, 80-120, 120-180 ms) were fully crossed to produce the same number of trials for each possible combination, presented in a random order. A total of 256 trials were given for each stimulation site. The order of the site of stimulation was counterbalanced across participants.

Localization of brain targets for TMS stimulation

TMS applied over the right and the left FEF. Right and left FEF were localized for TMS using the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada). The stimulation sites was identified on each subject’s T1-weighted MRI scan and was then co registered with scalp coordinates over which TMS was applied (see Figure 3.7). The probabilistic location of each subject's right and FEF was determined according to anatomical landmarks. Stimulation was applied over the posterior middle frontal gyrus, just rostral of the junction of the precentral sulcus and the superior frontal sulcus (Blanke et al., 2000). For some participants, the site of stimulation was also referenced to each individual motor hand area (Ro, Cheifet, Ingle, Shoup, and Rafal, 1999; Yousry et al., 1997). Using this method, on average, TMS was applied 5 cm lateral of the sagittal midline and 3–4 cm rostral of each subject's motor hand area. This site corresponds well with scalp coordinates used in other TMS studies of the FEF (Leff, Scott, Rothwell, and Wise, 2001; Wipfli et al., 2001; Muri, Hess, & Meienberg, 1991). After registration of the MRI images to the Montreal Neurological Institute series average (Evans, Collins, and Holmes, 1996), mean Talairach coordinates for the sites stimulated were ±32, -2, 57 (Talairach & Tournoux, 1988). These coordinates correspond well with mean Talairach coordinates for the FEF derived from a review of PET imaging studies (Paus, 1996). As control site, the point on the scalp corresponding to CPZ in the 10-20 international system for electrodes placement was chosen. TMS over a control site was chosen for the nonspecific effects of TMS, such as somatosensory and acoustic artifacts.

Figure 4.1. The left FEF stimulation site shown in coronal, sagittal and transverse sections of a participant's magnetic resonance. The location, targeted in the coronal corresponding to the standard coordinates -32, -2, 57 was indentified for each participant by application of a normalized procedure.

TMS parameters

TMS was delivered by means of a Magstim Super Rapid2 machine (Magstim Company, Dyfed, UK) was used to deliver two magnetic pulses at a frequency of 25 Hz during the task over either right FEF, left FEF and CPZ. A fixed level of 60% of the maximum machine output was employed. The level selected was used as it has previously proved effective in TMS studies of FEF (e.g., Kalla et al., 2008). A series of figure of eight TMS coils (70 mm) were used to apply stimulation over the cortical sites of interest. Coils were cooled before use to prevent overheating during a trial block and were replaced after two blocks. For all the stimulation sites, the experimenter clamped the coil with the handle running in an anterior–posterior direction

4.3 Results

Statistical analyses were performed on the magnitude of the Simon task (non-corresponding *minus* corresponding trial) calculated as a function of stimulus position (i.e., for left- and right-side stimuli separately). The Simon effect for left-side stimuli was obtained by subtracting left-side responses to left-side stimuli (corresponding trials) from right-side responses to left-side stimuli (non-corresponding trials). The Simon effect for right-side stimuli was calculated by subtracting right-side responses to right-side stimuli (corresponding trials) from left-side responses to right-side stimuli. A repeated measures ANOVA was performed on the magnitude of the Simon effect with TMS site (left FEF, right FEF, CPZ), TMS timing condition (0-40, 40-80, 80-120, and 120-160 ms) and stimulus position (left, right) as within-subjects factors. Pairwise comparisons were then performed to qualify the interaction by comparing the magnitude of the Simon effect obtained after stimulation of the experimental sites and the control site (CPZ).

Results showed a significant interaction of site × stimulus position [$F(2, 16) = 8{,}633$, $p < 0.01$, $\eta^2_p = 0.52$]. Left FEF TMS reduced the Simon effect for right-side stimuli compared to both the right FEF and the control site ($Ps < 0.05$) and an increase of the Simon effect for left-side stimuli compared to the control site ($p<0.01$) (Figure 4.2).

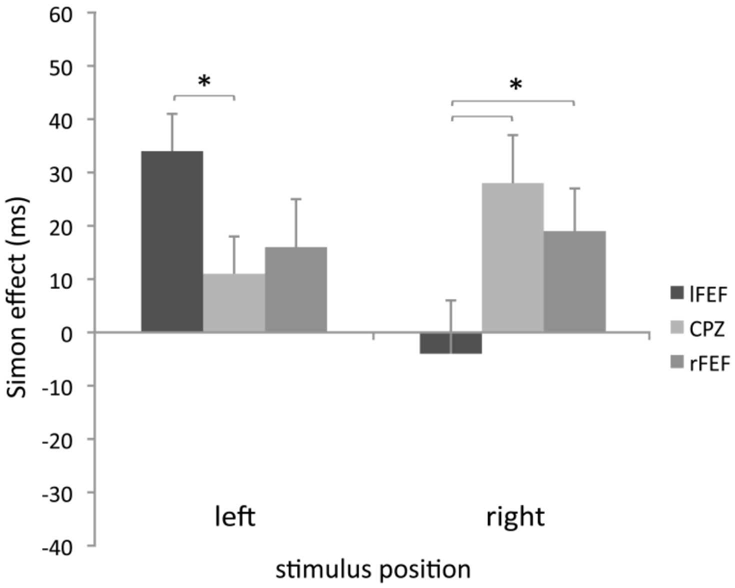

Figure 4.2. The magnitude of the Simon effect (non-corresponding-corresponding trials) is represented for left and right hemifield separately. Left FEF TMS resulted in a suppression of the Simon effect for right-side stimuli. An increase of the Simon effect has been observed for left-side stimuli. These effects have been obtained irrespective of the TMS timing.

Furthermore, the effect of double-pulse TMS over the left FEF was better qualified by the site × TMS timing × stimulus position interaction close to significance [$F(6, 48) = 2,207$, p = 0.058, $\eta^2_{\mathrm{p}} = 0.22$]. This outcome revealed that the TMS interference had different effect in subsequent time windows. TMS reduced the Simon effect for right-side stimuli when applied over the left FEF in two early time windows (0-40 and 40-80 ms) after stimulus onset. In the 0-40 ms time window, the Simon effect was reduced by TMS over left FEF (5 ms) compared to the control site (33 ms; $p < 0.05$). In the 40-80 ms time window, a reversed Simon effect (-34 ms) for right-side stimuli was obtained after TMS over left FEF. The magnitude of the Simon on this site was significantly different both compared to the control site (35 ms) and to the right FEF (18 ms) (Ps < 0.01). In the 80-120 ms time window, stimulation of the left FEF got increased the Simon effect for left-side stimuli compared to the right FEF ($p < 0.05$).

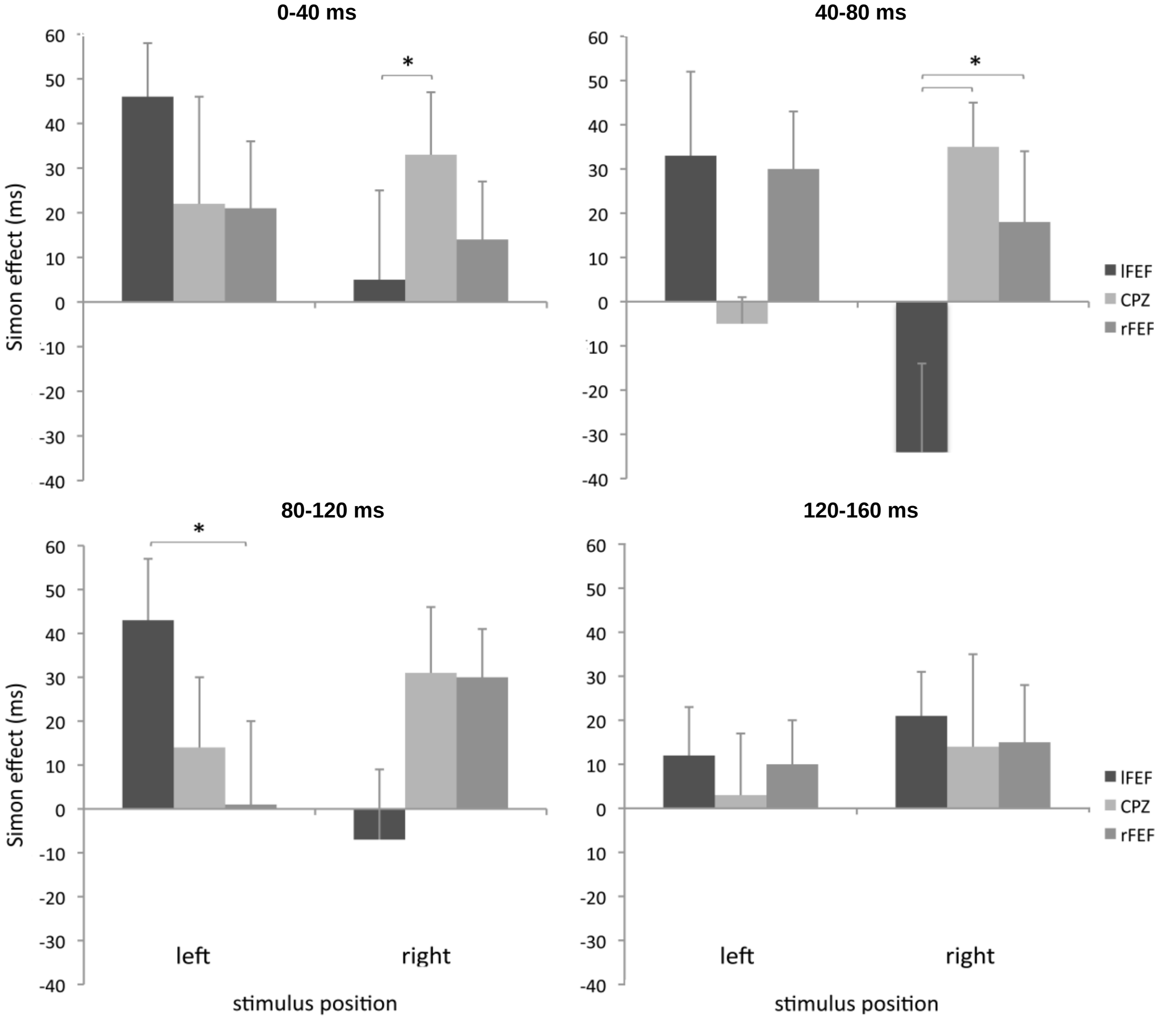

Figure 4.3. The magnitude of the Simon effect (non-corresponding-corresponding trials) is represented for left and right hemifield separately. Double-pulse TMS caused a suppression of the Simon effect for right-side stimuli when applied in the 0-40 and 40-80 ms time window after stimulus onset. An increase of the Simon effect has been observed for left-side stimuli when applied in the 80-120 ms timing after stimulu onset.

4.4 Discussion

Previous studies suggest that the FEF play an important role in the control of visuospatial attention, which may be independent of eye movements. TMS over the FEF interfere with performance in orienting paradigm in which eye movements are not required or prevented. However no studies investigated the contribution of the FEF in conflict task. In the Simon task, a conflict arises because irrelevant spatial information competes for response selection. This study was aimed at evaluating is the FEF contribute in priming motor response on the basis of stimulus position (spatially corresponding response).

The main result of this study is that left FEF TMS caused a suppression of the Simon effect for stimuli presented in the hemifield contralateral to the stimulation site (right-side stimuli) when applied in a early timing after stimulus onset (in the 0-40, 40-80 ms ranges). The simplest explanation for this result is that TMS interfered with the allocation of attention towards right-side stimuli, thus suppressing the Simon effect as no stimulus spatial code influence performance. This result is in line with the view that the left FEF exert control of orienting attention towards the right hemifield (Cosbras and Paus, 2007). The timing of the TMS effect is in line with previous data on visual search tasks reporting that FFF are involved in this task in a earlier time window compared to PPC. FEF TMS disrupts visual search task performance when applied in a 40-80 ms range after stimulus onset (O’Shea et al., 2004) or in a 0-40 ms range (Kalla et al., 2008). Moreover Taylor and co-workers (2007) found that the FEF exert top-down control over early visual processing as revealed by the combination of TMS over FEF and EEG recording over occipital areas.

The second result of this experiment is that left FEF TMS got increased the Simon effect for stimuli presented in the left visual hemifield when applied in the 80-120 ms range. In order to explain this result, different explanations might be proposed. The first maintains that the stimulation facilitated the allocation of attention in the ipsilateral hemifield, thus increasing the impact of irrelevant spatial information (i.e., the stimulus spatial code) in response selection. This effect might have been caused through a modulation of neural activity in the contralateral homologue area (i.e., the right FEF) induced by the stimulation over the left hemisphere. It has been previously reported that the inhibition of an area can lead to increase of activity on the omologue area in the contralateral hemisphere. Thus, the interference induced over the left FEF could have released the right FEF from interemispheric inhibition leading to a facilitation of attention orienting toward stimuli appearing in the left hemifield. This could have speeded up corresponding response and/or delayed non-corresponding response, resulting in an increase of the Simon effect.

A candidate alternative explanation of the increase of the Simon effect for the left hemifield could originate in the FEF's role in inhibition. The FEF have been extensively studied for their role in oculomotor control (Schiller and Chou, 1998; Tehovik et al, 2000). In humans, electrical stimulation evokes saccades (Godoy et al., 1990; Rasmussen and Penfield, 1948) as well as in monkeys (Russo and Bruce, 1993) and TMS to the region interferes with saccades (Muri et al., 1991; Thickbroom et al., 1996). Moreover the FEF have been studies more specifically in relation to the competition between reflexive and the voluntary system testing inhibition and execution of reflexive and voluntary saccades in prosaccade and antisaccade tasks. In the prosaccade task the participant fixates a central point and then makes a saccade to a peripheral stimulus that abruptly appears. In the antisaccade task the participant is supposed to inhibit the reflexive saccade toward the stimulus and to saccade in the opposite direction. In one study using TMS to investigate oculomotor function, Muri and coworkers (1991) applied TMS to the FEF during an antisaccade task and found an increase of antisaccade latency by triggering TMS 50-100 ms after stimulus onset. Terao and coworkers (1998) found a delay of antisaccades when TMS was applied 100 ms after stimulus onset to both right and left FEF irrespective of antisaccade direction.

For antisaccades, attention had to be disengaged from the stimulus and moved to the opposite visual hemifield. Compromising antisaccades could indicate insufficient suppression of an automatic motor program and the TMS effects indicate that the FEF play a critical role in such a process. Based on these observation, it is conceivable to hypothesize that the increase of the conflict (i.e., the Simon effect) observed after TMS in the 80-120 ms time period, is due to an induced interference on the inhibition of the irrelevant spatial stimulus code and/or of the priming of the corresponding response. If this explanation holds, we should expect that TMS induced a delay of non-corresponding trials in which the inhibition of the task-irrelevant information is necessary for the correct response to be executed.

Overall, the present study provides the fist evidence of the involvement of the FEF in a conflict task. Moreover, the evidence presented here that the left but not the right FEF are involved in the Simon task provides some insight into the hemispheric asymmetries of the FEF, which have been less well explored than asymmetries in the parietal lobe. Regions in the left hemisphere such as the supplementary motor area (Rushworth et al., 2003; Kennerley et al., 2004) and intra-parietal sulcus (Rushworth et al., 2001) are important for attention to action, action selection and action sequencing and it seems reasonable to suggest that the left FEF forms a component of this left hemisphere choice-action system.

FEF are, in fact strictly connected with premotor and supplementary motor areas, which are devoted to action selection (Rushworth et al., 1997; Schluter et al., 1998; O’Shea et al., 2007.

CHAPTER 5

Response activation and response selection in the dorsal premotor cortex

5.1 Introduction

The execution of the correct response in situations of conflict may require the inhibition of irrelevant information competing for motor planning. In the Simon task, a conflict arises in non-corresponding trials because irrelevant spatial information interferes with the execution of the correct response by priming the inappropriate, spatially corresponding response. Response activation thought automatic direct way (De Jong et al., 1994), found its neuropsychological correlative in the analysis of movement-related EEG potentials. This analysis revealed brief activation of the corresponding response when the overt non-corresponding response is correctly executed (Valle-Iclán, 1996; Stürmer et al., 2002). This early motor cortex activation provides an example of how partial stimulus information can lead to preliminary response activation that is subsequently aborted when the called response is inappropriate.

Dual route models of the conflict (De Jong et al., 1994) proposed that competing responses are checked through inhibitory control, exercised by an executive system that supervised the flow of information through subordinated mechanisms (Stürmer et al., 2007). Frontal regions, such the dorsolateral prefrontal cortex and premotor areas seem to play a crucial role in response selection and conflict resolution (e.g., Kerns, 2006).

However, how response selection and conflict resolution is implemented in the brain in situations of conflict has not been extensively studied. Praamstra and coworkers (1999) applied rTMS over dorsal premotor cortex (PMd) during the execution of a Simon task as that area could subserve the inhibitory control of automatic response activation in non-corresponding trials. Praamstra and coworkers (1999) predicted that temporary interference with the PMd would release the automatic activation of the corresponding response from inhibition and thereby enhance the Simon effect. Results were not straightforward, for the expected effects of TMS were actually confined to those trials that followed a non-corresponding trial. This result suggests that the premotor cortex play a role in the trial-by-trial adjustments by modulating the impact of irrelevant information when a conflict occurs in the previous trial (i.e., the sequential effect). However, on the basis of this outcome, it is no clear whether premotor cortex is critical for resolution of the conflict in the current trial, or only for monitoring conflict.

The activation of the corresponding response along the direct route may be subject to spontaneous decay as well as to more active forms of inhibition. The activation-suppression hypothesis (Ridderinkhof, 2002) maintains that the behavioral response activated by the irrelevant stimulus features is selectively inhibited in the current trial.

According to previous studies, PMd might exert top-down control over sensorimotor systems to mediate the selection between alternative responses. For instance, Schluter and colleagues (1998) reported that temporary interference in PMd, induced by single-pulse TMS, delay responses in a choice reaction-time task when stimulation was applied at short interval from stimulus onset. Moreover, this area is involved in response preparation of non-standard stimulus-response mappings when a predominant correspondence between visuospatial stimuli and responses has to be overcome (Wise, Di Pellegrino, and Boussaoud, 1996) and seems to play a role in suppressing prepared movements that should not be executed (Koch et a., 2006).

The present study was aimed at investigating if PMd play a role in response selection in the current trial in the Simon task. We predict that, if PMd is recruit in response selection to inhibit the automatic activation of the corresponding response when inappropriate (i.e., in the non-corresponding trials), a release from the inhibition, due to TMS interference would result in an increase of the Simon effect due to delay of non-corresponding trials, that in the condition in which a conflict between competing responses has to be resolved.

5.2 Materials and Methods

Participants

Eighteen healthy undergraduate students of the University of Padua (all right-hand handed, mean age of 23 years ± 2) with normal or corrected-to-normal visual acuity took part in this experiment. All subjects were checked for TMS exclusion criteria (Wassermann 1998) and gave their written informed consent before participation. The intensity of stimulation and the duration of the TMS sessions were in accordance with the safety guidelines established by Wassermann (1998), and the Ethics Committee of the Department of General Psychology, University of Padua, approved the procedure. The subjects were reimbursed with cash for participating in the experiment. All participants were naïve as to the purpose of the study.

Apparatus and stimuli

The participants were seated in a dimly lit and soundproof room with their head held by a fixed head-and-chin rest at a distance of 50 cm from a 17-inch monitor controlled by a Pentium 4 PC programmed with E-prime (Psychological Software Tool, Pittsburgh, USA). The targets were the letters ‘N’ and ‘H’ subtending 1.4° × 1.8° (width × height) of a visual angle presented for 200 ms in white on a black background, 3.5° laterally with respect to a fixation cross.

Procedure and experimental design

The procedure and the experimental design were identical to those of the study 1 of this work except as follow. The design of the TMS experiment involved within-subject manipulation of sites of stimulation, stimulus-response correspondence and the time intervals between the onset of the target and the application of the TMS pulse (SOA). Each session was divided into three experimental blocks, one for each stimulation site. Each block was composed of 480 trials in which stimulus position (left or right), response position (left or right), and SOA (100, 130, 160, 190, 220, 250, 280, 310 ms) were fully crossed to produce the same number of trials for each possible combination, presented in a random order. No TMS pulse was delivered in 60 trials of each block (randomly intermixed). A pause was given to the participants every 160 trials. The order of blocks (i.e., site of stimulation) was counterbalanced across participants.

Localization of brain targets for TMS stimulation

The location of each subject's PMd was firstly determined by reference to each subject's motor hand area. The motor cortex 'hot spot' was determined as the optimal scalp position at which the lowest intensity TMS evoked a visually detectable twitch in a tense muscle of the hand of each participant contralateral to the stimulated motor cortex. This site was then marked on the subject' scalp. PMd site was marked 2 cm anterior and 1 cm medial to the motor 'hot spot'. This procedure for targeting PMd has been used in a number of previous studies, which have shown that single-pulse TMS at these coordinates slows RT on choice-reaction time tasks (Schluter et al., 1998; O'Shea et al., 2007). We verified the cortical location of this site anatomically on T1-weighted MRI scan of 6 participants using Brinsight framless stereotaxy (Rogue Research, Montreal; Canada). After registration of the MRI images to the Montreal Neurological Institute series average (Evans, Collins, & Holmes, 1996), mean Talairach coordinates for the site stimulated were ± 28, -5, 71 (standard error: ± 1.24, 4.07, 2.55) (Talairach & Tournoux, 1988). This confirmed that TMS was applied just anterior to the dorsal branch of the precentral sulcus. This coordinates correspond well with published probabilistic coordinates for PMd (e.g., Fink et al., 1997; O'Shea et al., 2007). For all the sites, the coil was held tangentially to the scalp and parallel to the medial sagittal line with the coil handle oriented backward.

TMS parameters

Transcranial magnetic stimulation was applied with a Magstim Super Rapid2 system (Magstim Company Ltd, Spring Gardens, Wales, UK). The intensity of the magnetic stimulation was set separately for each participant 10% above the individual motor threshold (MT). The resulting mean intensity was around 68 ± 1.6% of the maximum stimulator output.

5.3 Results

A repeated measures ANOVA was performed on the mean RTs of TMS trials with the stimulation site (left and right AG and vertex), Stimulus onset asynchronous (100, 130, 160, 190, 220, 250, 280, 310 ms) and correspondence (corresponding vs. non-corresponding trials) as within subjects factors. Paired-sample t-tests were then performed both to compare the magnitude of the Simon effect (the difference between corresponding and non-corresponding condition) and the mean RTs for corresponding and non-corresponding conditions obtained after stimulation of the experimental sites and the control site at specific stimulus onset asynchronous (SOA).

A main effect of correspondence was found [$F(1,17) = 43.958$, $p < 0.001$, $\eta^2_p = 0.72$], being corresponding trials (mean ± SEM = 469.2 ± 7.2) faster than the non-corresponding trials (mean ± SEM = 486.2 ± 6.8). Overall, the correspondence effect amounted to 17 ms. Moreover, a three-way interaction site × SOA × correspondence [$F(1,238) = 2.143$, p <

0.05, $\eta^2_p = 0.12$] was found. Figure 5.1 shows the mean RTs for the corresponding and the non-corresponding conditions at each SOA, separately for the three stimulated sites. The difference between corresponding and non-corresponding trials (i.e., the Simon effect) was significant for all stimulation conditions A suppression of the correspondence effect was obtained when TMS was applied to the left PMd compared to the control site when the TMS pulse was delivered at 160 ms after stimulus onset ($p<0.05$). An increase of the Simon effect was observed at 220 ms compared to the control site ($p<0.05$). Pairwise comparisons between left PMd and CPZ separately performed on corresponding and non-corresponding conditions, showed a delay of corresponding trials when TMS was applied over left PMd at 160 ms ($p<0.05$) and a delay of non-corresponding trials at 220 e 250 ms SOA ($Ps<0.05$).

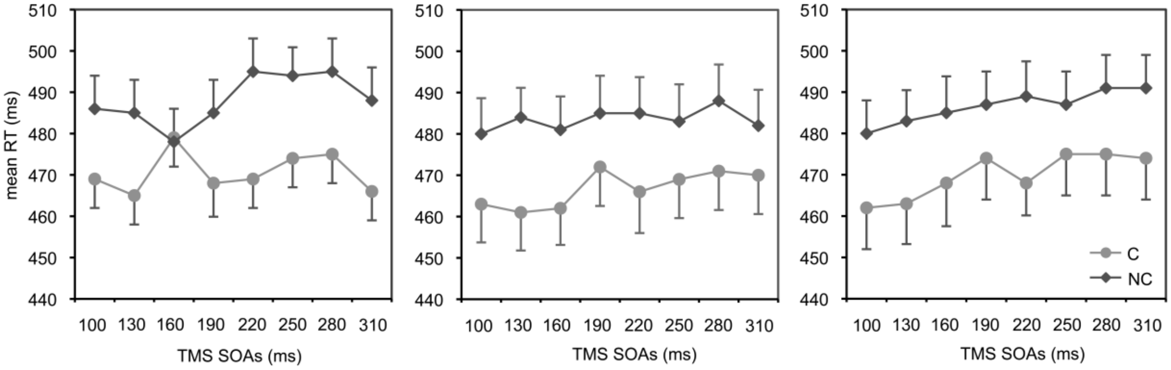

Figure 5.1: Mean RTs for the left and right PMd and CPZ were represented as a function of different SOAs (100, 130, 160, 190, 220, 250, 280, 310 ms, abscissa). A suppression of the Simon effect was found when stimulating the left PMd 160 ms after stimulus onset (left) No suppression of the Simon effect was observed when TMS was applied to either CPZ (middle) or the right PMd (right).

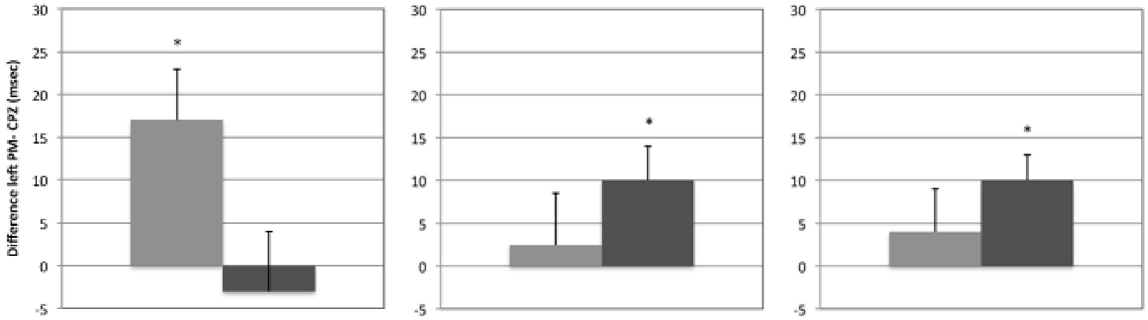

Figure 5.2. Mean RTs for corresponding and non-corresponding conditions in the three SOAs in which TMS over left PMd produced an effect. A delay of corresponding responses was observed when TMS was applied 160 ms after stimulus onset (left). TMS at 220 (middle) and 250 ms (right) induced a delay of non-corresponding conditions.

5.4 Discussion

The results of the present study suggest that conflict resolution and response selection in the Simon task are mediated by the PMd. Single-pulse TMS modulated the magnitude of the conflict by inducing a suppression of the Simon effect when applied at 160 ms and an increase of the Simon effect when applied in a later time window (220 ms after stimulus onset). Interestingly, these effects have been qualified in term of correspondence conditions in the two time windows.

The first result is that TMS affected only corresponding trials when applied at 160 ms from stimulus onset suggesting that PMd might contribute response priming on the basis of irrelevant spatial information at this time. This timing in fact corresponds with the timing in which the same effect occurred over left PPC in our previous study. Previous EEG studies suggested that in spatial compatibility tasks, there is activation, coincident in time, of both posterior and motor cortical areas, which has been qualified as a sign of automatic response activation through the direct route. In the Simon task, an early deflection of the LRP is observed whish is thought to reflect the location-based priming of the corresponding response whereas a later component would reflect the activation of the response specified by task instruction (e.g., De Jong et al., 1994; Eimer, 1995; Valle-Iclán, 1996). This deflection would occur when information is partially transmitted from perceptual to motor processes before the end of stimulus evaluation (Gratton et al., 1992) and is observed at around 150 ms after stimulus onset; a time that is consistent with the timing of the TMS effect on corresponding trials reported here and in the previous study on the PPC.

The second result is that TMS caused a delay of non-corresponding trials when applied at 220-250 ms after stimulus onset. This result is in line with our hypothesis, which maintains that PMd is recruited for response selection when a conflict between competing responses occurs. In non-corresponding trials, the response primed by the irrelevant stimulus code does not match that called on the basis of task instruction. Thus, the corresponding response has to be inhibited for the execution of the correct response.

Finally, the results presented here, support the previous observation that the left hemisphere is dominant for response selection. In fact, although it has been reported that PMd is activated bilaterally during choice-reaction time tasks, imaging and TMS studies suggested that the left PMd exerts dominance over the right (Schluter et al., 1998; Schluter et al., 2001; Johansen-Berg et al., 2002). Functional imaging studies showed that, when subjects have to select between left and right hand movements, the right PMd is active only for movements executed by the left hand, whereas the left PMd is active for movements of either hand (Schluter et al., 2001). Similarly, TMS of the right PMd only disrupts the selection of left hand movements, whereas TMS of the left PMd disrupts the selection of movements that will be executed by either hand (Schluter et al., 1998; Johansen-Berg et al., 2002). This pattern of dominance is similar to that observed in apraxia, where left hemisphere lesions disrupt performance with the ipsilateral hand but right hemisphere lesions do not (Rushworth et al., 1998).

CONCLUSIONS

In the study 1 we evaluated the time-course and the role played by distinct right and left subregions of the posterior parietal cortex which have been suggested to be differently involved in orienting and motor attention. In fact, a possible different contribution of these processes when visual information competes for different motor response was steel undiscovered. To deal with this issue, single-pulse TMS was applied over the angular (AG) and the supramarginal (SMG) gyri of both the hemispheres, at various time intervals during the execution of a Simon task. We reported evidence that the posterior parietal cortex (PPC) is critically involved in the generation of the Simon effect. Results revealed that spTMS over PPC reduced the Simon effect as if no irrelevant spatial code influenced performance. Our findings support the hypothesis that the bilateral posterior portion of PPC (right and left angular gyri), as being crucially involved in orienting attention, is essential for a spatial code to the assigned to the stimulus, whereas the left anterior portion of PPC (left supramarginal gyrus) is involved in transforming spatial code into code for action, a process related to motor attention (Rushworth et al., 2001). A suppression of the conflict between stimulus and response positions (i.e. the Simon effect) was found when TMS pulse was applied 130 ms after stimulus onset over the right AG and after 160 ms when applied over the left AG and SMG. Interestingly, only stimulation of the left SMG suppressed the asymmetry in conflict magnitude between left and right hand responses, normally observed in the Simon task. The present data show that orienting attention and motor attention processes are temporally, functionally and spatially separated in the posterior parietal cortex, and both contribute to prime motor response during spatial conflict. Moreover, our results confirm the importance of visuospatial orienting and manual response selection in the generation of the Simon effect (Ivanoff and Peters, 2000).

The second study was aimed at investigating the contribution of the frontal eye fields (FEF) in the generation of the irrelevant spatial code that primes the corresponding response. TMS applied over left FEF caused a suppression of the Simon effect for stimuli presented in the visual hemifield contralateral to the stimulated site indicating that the FEF play a critical role in the generation of the Simon effect.

PPC and FEF are thought to be part of the same frontoparietal network for visuospatial attention. Dissociation of the roles of these two areas is particularly important because of the degree of overlap of some of the processes typically ascribed to them, for example, both have been suggested to have representations of saliency maps with respect to a search target and both have been associated with top-down modulation of extrastriate cortex (Moore and Fallah, 2001; Taylor et al., 2007). At our current state of knowledge, there is a certain deal of overlap in the descriptions of FEF and PPC functions and begin to identify the extent to which their functions overlap and differ in the Simon effect requires further experiment. However, the temporal domain seems to be a useful place from which to start to probe differential contributions of the two regions. The outcomes reported in the study 1 and 2 revealed that the contribution of the FEF and PPC in the Simon effect can be temporally dissociated. The suppression of the Simon effect caused by FEF TMS occurs at an earlier time point than the same effect caused by PPC TMS, consistent with the timing of the responses of these areas in visual search tasks (Kalla et al., 2008).

In the third study, spTMS has been applied to the dorsal premotor cortex to evaluate the role of this area in response selection during conflict. Previous studies suggested that premotor cortex in recruited in suppressing prepared movements that should not be executed (Koch et a., 2006). Moreover, dPM has been indicated as responsible for the inhibition of response priming through the direct route. The application of a single pulse in different timing after stimulus onset allowed us to indentify two specific time in which dPM seems to be involved in the response selection process. TMS over dPM modulated the Simon effect by inducing a delay of corresponding trials when applied at 160 ms while a delay of non-corresponding trials has been observed when TMS was applied at 220 and 250 ms. These results indicated that dPM is implicated in both priming the corresponding response and in resolution of the conflict when the automatically activated response is inappropriate.

Overall these results allowed us not only to detect the locations of active cortical regions during conflict task performance but also to construct a dynamic physiological map by visualizing the temporal evolution of functional activities in the relevant cortical region.

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