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Research report

Contribution of frontal cortex to the spatial representation of number

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ABSTRACT

Neuropsychological and neurophysiological studies have suggested that prefrontal cortex may be involved in non-verbal number processing, when relevant for current behavioural goals. More precisely, it has been suggested that an intact right inferior frontal gyrus (rIFG) in humans may be necessary to the use of a spatial representation of numbers, also known as mental number line. In a popular model of spatial functions (e.g., Corbetta et al., 2008), rIFG is part of a right-lateralised ventral fronto-parietal network that conveys signals to a dorsal network supporting attentional orienting in contralateral space. Within the dorsal network, the frontal eye fields (FEF) are known to contribute to visual scene analysis and visual conjunction search tasks when eye movement commands are not required. In the present study, we hypothesised they might also be involved in exploring a conceptual space, such as the mental number line. We examined the proposed functions of the human rIFG and right Frontal Eye Field (rFEF) by interfering with their normal functioning with repetitive Transcranial Magnetic Stimulation (rTMS) while participants performed numerical tasks. The results suggest that, when number magnitude is relevant to the task, rIFG supports orienting to the entire mental number line while rFEF are crucial for contralateral orienting (that is towards small numbers).

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Normal numerical cognition builds on a core numerosity representation which is then enriched with more and more sophisticated tools in the course of education (Butterworth, 1999; Feigenson et al., 2004). It can also benefit from the support of independent symbolic and representational domains, such as language and space (Gelman and Butterworth, 2005; Dehaene, 2009). In particular, the relationship between numbers and space has been fundamental to the development of mathematics at least since Pythagoreans, and the Babylonians before them, showed the numerical relationship between the sides of a triangle. Spatial representations play

a major role in current educational curricula (e.g., by using blocks and the number line to introduce numerical concepts and calculations). Spatial mental models of numbers and other spatial concepts seem to be a particularly natural and effective way of understanding numerical concepts. One possible reason is that the mental representation of numbers is intrinsically spatial (see e.g., Dehaene, 1997 and Walsh, 2003). Alternatively, the connection between numbers and space might be the product of experience and a cultural achievement. For example, it has been speculated that a structural representation of the finger series (e.g., Kinsbourne and

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Warrington, 1962; Rusconi et al., 2009), characterized by a fix order of bodily elements that can be used as placeholders, may precede in the representation of number magnitude, and eventually give way to, an homologous spatial representation: the mental number line (see e.g., Fias and Fischer, 2005; Fischer, 2008; Rusconi et al., 2005). Or that brain circuits that were originally devoted to spatial maps have come to subserve numerical representations via a culture-dependent process of neuronal recycling (Dehaene, 2009). In the present study, we will bring new evidence about the neural basis of number-space interactions in the healthy human brain and extend the range of areas that are known to contribute to the preferential mapping of numbers onto spatial responses during a magnitude comparison task. We will do so by employing repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive stimulation technique by which it is possible to test causal brain-behaviour relationships in healthy humans (for recent discussions on the use – and misuse – of Transcranial Magnetic Stimulation – TMS in cognitive neuroscience see Rusconi and Bestmann, 2009; Siebner et al., 2009; Wagner et al., 2009). Our TMS-induced manipulation of brain states was specifically targeted to interfere with the spatial representation of numbers, as inferred via one of its characteristic behavioural markers (see below). rTMS was here delivered on two well-known prefrontal areas, previously localized on individual brain scans via anatomical landmarks, and vertex as a control site.

Francis Galton observed that some people possess a mental image of the number sequence, which he termed “number form”, that is spatially distributed and can be used to carry out calculations (Galton, 1880; see also Seron et al., 1992 and Sagiv et al., 2006). In Western cultures, people without an explicit number form nevertheless represent numbers spatially, with small numbers towards the left of mental space and large numbers towards the right (e.g., Zorzi et al., 2002). According to a popular proposal (Dehaene and Changeaux, 1993; for a more recent and comprehensive model, see Verguts and Fias, 2004), the mental number line is logarithmically compressed, so that discrimination between contiguous numbers becomes more and more difficult with increasing magnitude (i.e., by travelling further to the right on the mental number line). This property, which has now been directly related to the neural properties of core analogue number representations in human and macaques (e.g., Dehaene, 2003; Nieder and Miller, 2003; Piazza et al., 2004), might be at the origin of the so-called size effect. According to the size effect, the speed of a comparison process between numbers decreases as a function of the size of the two to-be-compared numbers, when distance between them is equated (e.g., Antell and Keating, 1983). A related effect is the *distance* effect, reported by Moyer and Landauer (1967) in number comparison. Precisely, Moyer and Landauer reported that speed of response increases as a function of the numerical distance between the numbers to be compared (e.g., participants were faster at deciding that 8 was larger than 2 than they were at deciding it was larger than 6, and the speed was intermediate for 8 and 4). The explanation provided was that in performing the comparison task the two numbers were located in their correct positions on the number line and the speed of the comparison process was modulated by the distance that

separated the two numbers on the mental number line. The fact that responses to small numbers are faster when the effector is in left space, while responses to larger numbers are faster when the effector is in right space, is often interpreted as a direct consequence of such mental representation. This effect, denominated Spatial-Numerical Association of Response Codes (SNARC; Dehaene et al., 1993; Wood et al., 2008), has also been replicated with lateralised oculomotor and foot responses (e.g., Schwarz and Keus, 2004; Schwarz and Müller, 2006). Even in the absence of lateralised responses, however, number magnitude can influence performance by triggering attentional orienting to either the left or the right side of visual space (e.g., Fischer et al., 2003; Galfano et al., 2006).

Although all of these hallmarks may in principle be ascribed to a genuine spatial representation of numbers (Walsh, 2003; Hubbard et al., 2005; Dehaene, 2009), alternative interpretations have been recently put forward (for the SNARC effect, see Santens and Gevers, 2008; Fitousi et al., 2009). According to Santens and Gevers (2008), the SNARC effect is tricky because it does not necessarily reflect a direct mapping from numerical magnitudes onto response positions. At least an intermediate stage is interposed in which stimulus attributes become categorised into the two extremities of a dipole and give rise to preferential mapping effects based on linguistic markedness (see Proctor and Cho, 2006). Their claim was supported by showing that, with an appropriate manipulation of response arrangement in a magnitude comparison task, stimulus–response (S–R) correspondence effects are determined by linguistic markedness rather than by spatial homology between the supposed mental number line and external response alternatives. On the other hand, Fitousi et al. (2009) showed that access to number magnitude (as measured by Size Congruity and Garner effects) can be bypassed in certain numerical tasks, like parity detection. Hence, the SNARC effect that is found in such tasks would not reveal the workings of a mental number line that is automatically evoked by accessing number semantics as much as a learned association between specific number stimuli and lateralised manual responses. The finding of a SNARC effect with eye movements (Schwarz and Keus, 2004) is interpreted by Fitousi et al. (2009) not as a proof for the non-exclusivity of number-hand association, on the contrary, they claim that the oculomotor effect is secondary to the hand effect, since ‘people look the way that their hands reach!’ (p. 155).

In the context of the present study, we will maintain a spatial representation perspective on the SNARC effect and use it as a heuristic to predict the involvement of anterior attentional areas in the processing of number space. Visual attention areas with a role in oculomotor functions, however, can also be thought of as response preparation areas (see e.g., the influential premotor theory of attention; Sheliga et al., 1994). Therefore our conceptual framework does not necessarily contradict Fitousi et al.’s (2009) proposal.

It is generally claimed that the connection between number and space is a specialized function of posterior parietal cortex, where the processing of physical space and number semantics takes place (for reviews see Hubbard et al., 2005; Sandrini and Rusconi, 2009). In fact it could originate from an interaction between the core representation of

number magnitude in the horizontal intraparietal sulcus (hIPS; Castelli et al., 2006; Piazza et al., 2004) and the contiguous posterior circuits for spatial attention (e.g., Colby and Goldenberg, 1999; Macaluso and Driver, 2003). Rusconi et al. (2007), for example, reduced significantly the SNARC effect in a parity judgment task, when delivering rTMS over left or right posterior parietal cortex. However, space representation and covert orienting to it involve other brain areas including right Frontal Eye Field (rFEF) with either bilateral (e.g., Grosbras and Paus, 2002; Muggleton et al., 2003) or contralateral (Corbetta and Shulman, 2002) role, and right Inferior Frontal Gyrus (rIFG) with bilateral role (Corbetta and Shulman, 2002; Corbetta et al., 2005). Indeed, contralateral hemi-neglect due to right frontal and fronto-parietal lesions can induce distortions of number space, while leaving numerical processing and mental calculation largely intact (e.g., Doricchi et al., 2005; Vuilleumier et al., 2004; Zorzi et al., 2002).

It is also generally assumed that any task involving numbers automatically elicits the same kind of representation. However, there are differences in the shape of the SNARC effect depending on task (precisely, in magnitude vs parity judgments; Gevers et al., 2006), the number–space association can be reversed by instructions (Bächtold et al., 1998; Galfano et al., 2006; Vuilleumier et al., 2004), TMS can differentially affect magnitude and parity tasks (Rusconi et al., 2005), and neglect distorts spatial representations in number bisection, not in parity judgment (Priftis et al., 2006). In summary, there is evidence suggesting that (partially) different neural mechanisms may be recruited when the spatial representation of numbers is involved, depending on its relevance to the task at hand. In addition, the canonical association between number and space, which is likely to be elicited by the mere view of numbers, can be either replaced or overcome by instruction-induced representations.

The above considerations suggest that numbers could be mapped on spatial representations (at the level of either mental images or of lateralised responses) and/or spatial attention could be oriented to number space by means of partially different brain substrates depending on the context. Nieder and Miller (2003) found a much higher proportion of frontal lobe neurons, compared to the fundus of the intraparietal sulcus (IPS), that were broadly tuned to specific numerosities between 1 and 5 in macaque monkeys trained with numerosity judgments in a delayed match-to-sample task. Nieder (2004) speculates that neurons in the prefrontal region might have been flexibly adapted, during the training phase, to perform the particular numerical task at hand. They may constitute adjustable neuronal ensembles that reorganize according to different requirements (a prefrontal neural circuitry guiding executive functions). “Such neuronal numerical representations may not be established automatically (as seems to be the case in IPS), but they are nevertheless genuine and absolutely necessary for the monkey’s behaviour” (Nieder, 2004, p. 408). In the present study, we hypothesised that frontal, in addition to parietal, circuits could subservise representation of and orienting to number space in humans, which is assumed to be tightly connected to the processing of number magnitude (Dehaene et al., 1993).

Precisely, we predicted that if numerical and physical space were processed through similar brain circuits,

temporarily disabling the rIFG should modify the SNARC effect bilaterally, and disabling the rFEF should affect SNARC at least on the contralateral side (i.e., for small numbers), if not bilaterally. To test our hypothesis, we applied rTMS to both of these regions while participants were performing a magnitude or a parity judgment task with two-choice key-press responses. Since frontal lobes have been repeatedly shown to provide a substrate for behaviourally relevant features only (i.e., their contribution to the processing of specific attributes of a stimulus strongly depends on current behavioural goals and strategic encoding; e.g., Bor et al., 2003), we manipulated the relevance of number magnitude for the task at hand. That is, we contrasted the effect of rTMS on SNARC in a context where participants had to judge the magnitude of a number (i.e., the attribute which is directly related to the spatial representation of number was relevant to the task) with the effect of rTMS on SNARC in a context where participants had to judge its parity (i.e., the attribute which is directly related to the spatial representation of number was irrelevant to the task). Differences in task-dependent representation would be indexed by different effects of rTMS on SNARC in magnitude and parity judgments.

1. Method

1.1. Participants

Ten healthy participants (5 females and 5 males) took part in the investigation. All were naïve to its purpose. They were all right handed and had a mean age of 30.1 years. The study was in line with safety guidelines and was approved by the local ethics committee. Participants gave informed written consent before taking part in the experiment.

1.2. TMS parameters

rTMS was administered with a Magstim Super Rapid stimulator (Magstim Company, Whitland, UK). The pulses were triggered remotely with a computer connected to the stimulator and using E-Prime software 1.1.4.1. Custom made figure-of-eight coils with 50-mm diameter across each wing were used. The intensity of stimulation was individually adjusted to 110% of individual motor threshold (MT). MT was assessed while participants performed a slight tonic contraction of the left First Dorsal Interosseous (FDI) and Flexor Pollicis Longus (FPL) muscles. MT was defined as the minimum stimulator intensity at which a single TMS pulse over the hot spot of the FDI elicited a visible twitch in the FDI muscle in five out of ten consecutive trials (Pridmore et al., 1998). Since the frontal eye field (FEF), defined as the region causing a delay in the initiation of overt saccadic movements, is placed in the depth of the superior frontal sulcus (SFS) about 2 cm anterior to the motor strip in correspondence with the spot controlling hand movements (e.g., Paus, 1996; Nagel et al., 2008; Ro et al., 1999; Thickbroom et al., 1996), this criterion allowed us to ascertain the spatial resolution of rTMS which was delivered at 110% of individual MT. If the major effects of rTMS were not confined to the rFEF, then the participant’s left hand would have twitched before and during the experiment. Participants’

verbal reports and inspection before and after each rTMS block confirmed that no visible muscle twitches were elicited in the contralateral FDI muscle when a train of pulses at 5 Hz for 400 msec was applied over the rFEF, rIFG or over the vertex. Of course it is still possible that our rTMS protocol induced some functional modulations in the ipsilateral primary motor cortex, hence only the right hand was used as response effector. During the experiment, the coil was fixed in place by using a mechanical coil holder (Manfrotto, Bassano del Grappa, Italy), and for the vertex and rFEF sites the coil was held anterior to the handle and oriented parallel to the sagittal midline. For the rIFG site, the coil was held ventral to the handle and its orientation was, on average, perpendicular to the midline, although slight adjustments were introduced on a subject-by-subject basis, to avoid visible muscle twitches and/or reported painful sensations.

1.3. TMS localization

Site localization was performed on each participant's T1-weighted Magnetic Resonance Imaging (MRI) scan, which was co-registered with the participant's scalp through frameless stereotaxy (see below). rTMS was applied over the right posterior middle frontal gyrus, at the junction of SFS and ascending limb of precentral sulcus (PCS) in each individual, a location that corresponded with the anatomical delineation of rFEF. The IFG was stimulated in correspondence with BA 45/

47, and precisely in the area comprised between the pars triangularis and the inferior frontal sulcus (see Figs. 1 and 2). It is important to note that this area does not correspond to the dorsolateral prefrontal node (in BA46), which is both more anterior and more dorsal (middle frontal gyrus) and is part of the frontal dorsal oculomotor circuit (e.g., Hamidi et al., 2008; Nagel et al., 2008). These sites were preliminarily localized by adapting MNI coordinates on individual brain scans through SPM2 (Wellcome Department of Imaging Neuroscience, University College London, UK). The procedure involved normalizing each participant's T1-weighted MRI scan against a standard template. The description of each resulting transformation was then used to convert the appropriate MNI coordinates [rFEF (31, -4.5, 51) – derived from Paus, 1996 and rIFG (50, 22, 22) – derived from Doricchi et al., 2005] to the untransformed (structural) space coordinates, yielding subject specific localization of the sites. These coordinates were then used to guide frameless stereotaxy, through which individual brain scans were co-registered with scalp coordinates (Brainsight, Rogue Research, Montreal, CA). Vertex was used as an additional stimulation site to control for non-specific effects of rTMS (see e.g., Muggleton et al., 2003).

1.4. Procedure

On each trial, participants fixated the centre of a computer display where a white digit (range: 1–9, 5 excluded; font and

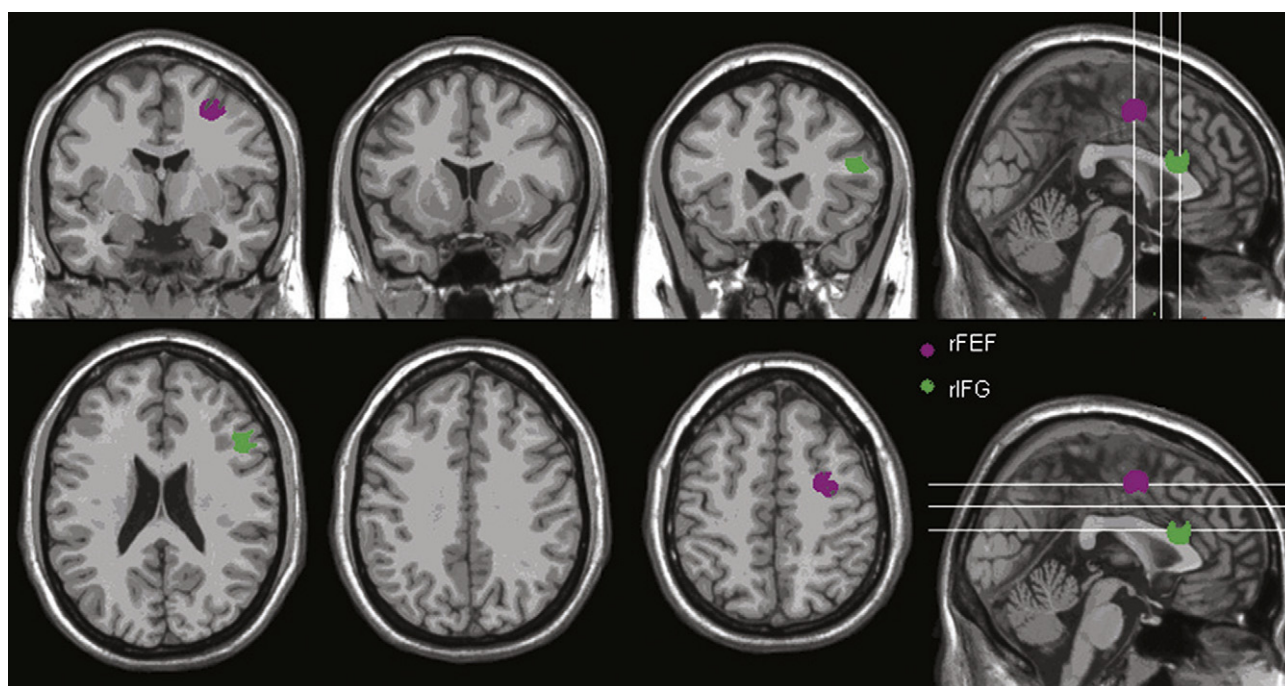


Fig. 1 – Sites of interest were localized in Brainsight™ on individual scans, which were co-registered with the participant's head by frameless stereotaxy (Polaris™ infrared tracking device). During the experiment, the coil centre was held tangential to the scalp in constant position over vertex, rFEF – at the junction of PCS and SFS – or rIFG. MNI coordinates from Paus (1996) and Doricchi et al. (2005) were adapted to individual scans through SPM™ (see Muggleton et al., 2006), to select the sites that have been previously related to visuo-spatial attention, saccade programming and execution (rFEF; see, e.g., Corbetta et al., 1998; Ruff et al., 2006) and to a selective rightward bias in numerical space (Doricchi et al., 2005). Coronal and transversal sections are here shown in the upper and bottom row respectively, with regions of interest centred on stimulation coordinates for the experiment on the ch2 MRIcro template. Vertex was also stimulated and served as a control site (Muggleton et al., 2003).

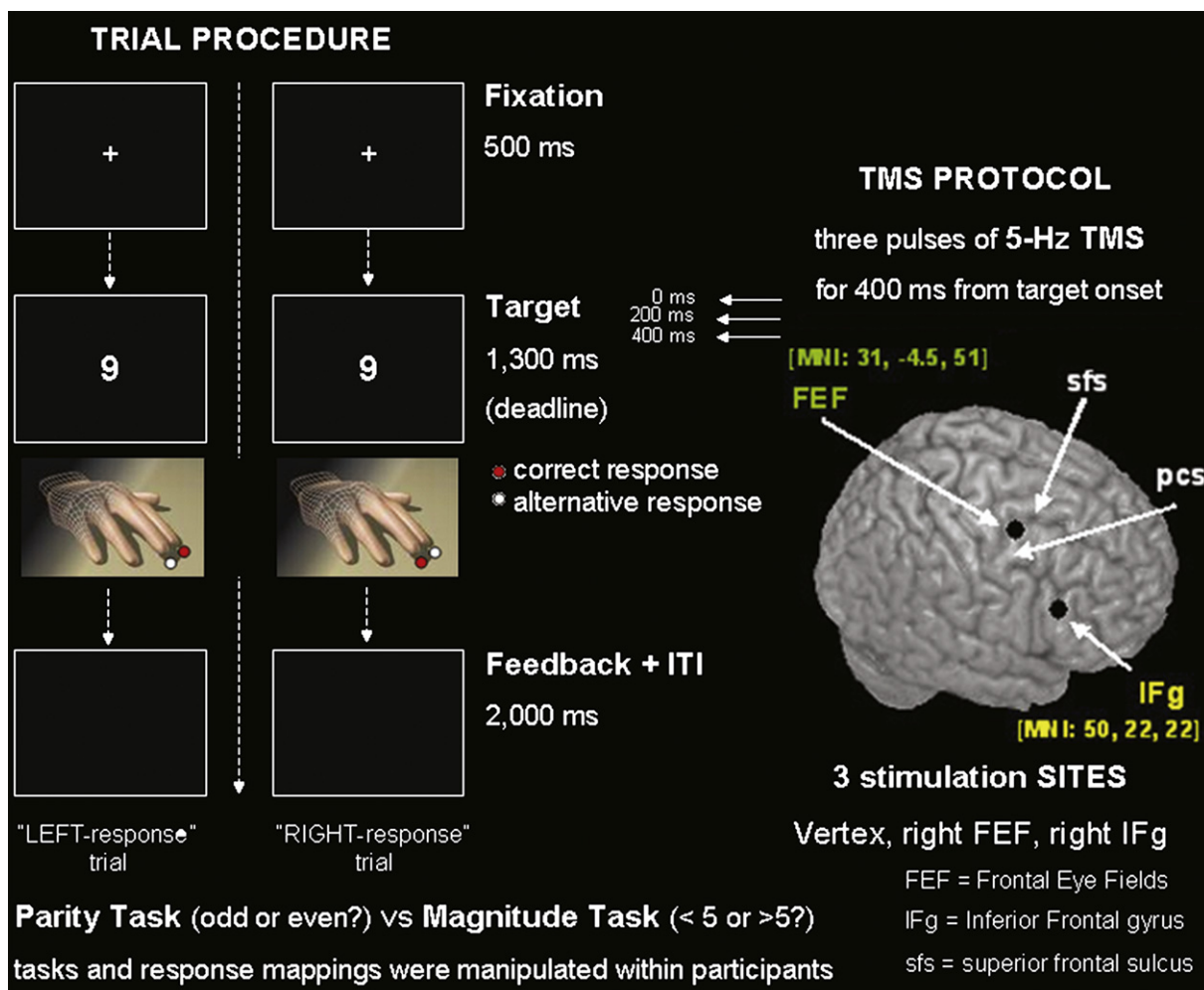


Fig. 2 – On each trial, participants fixated the centre of a display where a digit (1–9, 5 excluded) appeared for 1300 msec. In half the blocks digits were classified as smaller/larger than 5, in the other half as even/odd. Participants responded with their right index and middle finger. Since 9 is large in the experimental range, the right-side key is compatible with a left-to-right representation of the numbers 1–9, and the left-side key is incompatible.

size: Arial 48 Bold) subtending approx. $1.2^\circ \times 1.9^\circ$ of visual angle was shown on black background for 1300 msec (see Fig. 2). In the magnitude task digits were to be classified as smaller/larger than 5, in the parity task digits were classified as even/odd. Participants responded by pressing the left key with their right index finger and the right key with their right middle finger. An 800-msec visual feedback ("Error" in case of incorrect or "Too Slow" in case of missing response) or blank screen (in case of correct response) followed, and was then replaced by another 1200 msec blank screen before the start of a new trial. Since the experimental set comprised numbers ranging from 1 to 9, numbers from 1 to 4 were considered small and numbers from 6 to 9 were considered large in either task (Dehaene et al., 1993). We therefore expected, in the baseline, to find an advantage for left-key responses to 1–4 and for right-key responses to 6–9. A unimanual protocol with right-hand responses only was preferred to the most common bimanual protocol to avoid interference with motor programming and execution, since movements of the right hand are directly controlled by the left hemisphere. In addition, the left but not the right frontal lobe is generally thought

to be involved in bilateral role in the programming of the movements of either limb (see e.g., Rushworth et al., 1998; Rothi and Heilman, 1993; but see Chambers et al., 2007). By adopting an ipsilateral unimanual response mode, therefore, our rTMS effect was unlikely to originate from interference with contralateral response programming and execution. In case of generalised interference with response programming and execution, moreover, rTMS would have affected task performance as a whole rather than the SNARC effect only.

5-Hz rTMS was delivered for 400 msec (from stimulus onset) over rFEF, vertex and rIFG on each trial while participants performed magnitude or parity judgment tasks. Order of blocks (i.e., vertex, rFEF, rIFG) and of tasks (i.e., magnitude and parity judgment) were pseudo-randomized between participants. Order of task for each participant was kept constant in all the blocks. More precisely, the order of stimulation sites was counterbalanced between participants with a Latin square design, and each participant was tested once on each site in the whole session. Since we had three stimulation sites and ten participants, there were three order groups (ABC, BCA and CAB), having 3, 3 and 4 participants respectively. The

order of tasks instead was maintained constant within participants, with a classical ABBA design. Half the participants performed a block of magnitude comparison, followed by two blocks of parity judgment and finally one of magnitude comparison over each stimulation site (ABBA group). The other half had the reverse assignment (i.e., parity judgment, magnitude comparison, magnitude comparison and parity judgment; BAAB group). Task switching therefore was balanced between tasks and for each participant. At the beginning of each of the four mini-blocks, moreover, there were 8 random dummy trials (one for each target number) during which rTMS was not delivered. These were introduced as a short warming up practice and were excluded from analysis. Mapping of responses onto keys was balanced within participants in each task, so that each number was responded to with both the left and the right key by each participant for each task and block. In total, participants were presented with 576 experimental and 192 practice trials and completed the experiment in a single session. Each cell of the design Site (rFEF, vertex, rIFG) \times Task (magnitude, parity) \times Magnitude (small, large) \times Distance (close, far from the reference) \times Response key (left, right) contained 12 observations per individual.

1.5. Data analysis

Response latency and accuracy were determined on a trial-by-trial basis. After having excluded the presence of speed-accuracy trade-offs, median reaction times (RTs) were entered in an exploratory repeated measures analysis of variance (ANOVA) having 5 critical factors: site of stimulation, task, number magnitude, numerical distance of the target from the (explicit or implicit) reference and response side. Because the five-factorial ANOVA showed that rTMS had a different effect in the two tasks, two separate follow-up ANOVAs were performed for the magnitude and the parity task respectively. Finally, planned *t*-tests were performed to check the status of the SNARC effect, regardless of the presence of a significant *F*-value in the Site \times Magnitude \times Response interaction by following a hypothesis-driven approach.

2. Results

Total error rate averaged 4.76% and a positive correlation of RTs and errors was found within subjects over the 48 cells of the design ($R = .26, p < .001$), indicating the absence of speed-accuracy trade-offs. A repeated measures ANOVA $3 \times 2 \times 2 \times 2 \times 2$ having Site (rFEF, vertex, rIFG), Task (magnitude, parity), Magnitude (small, large), Distance (close, far from the reference) and Response key (left, right) as factors was performed on median RTs of correct responses. Order of the tasks (between participants) was not taken into account, since it was not either significant or involved in any interactions. This overall analysis revealed significant main effects of Task [$F_{(1,9)} = 58.16, p < .001$], magnitude comparison being 50 msec faster than parity judgment, Magnitude [$F_{(1,9)} = 15.17, p < .01$], smaller numbers being responded to 6 msec faster than larger numbers (size effect) and Distance [$F_{(1,9)} = 25.73, p < .001$], far numbers being responded to 8 msec faster than close

numbers (distance effect). The significant two-way interactions between Task and Distance [$F_{(1,9)} = 23.89, p < .001$] and between Magnitude and Response [$F_{(1,9)} = 26.60, p < .001$] respectively indicated that the distance effect was significant for the magnitude comparison task only [$T_{(9)} = 7.34, p < .001$ vs $T_{(9)} = -1.45, p > .10$], and that a SNARC effect was present. They were further qualified by a four-way interaction between Task, Magnitude, Distance and Response [$F_{(1,9)} = 8.59, p < .05$], a three-way interaction between Site, Magnitude and Response [$F_{(1,9)} = 4.27, p < .05$] and the crucial four-way interaction between Site, Task, Magnitude and Response [$F_{(1,9)} = 3.75, p < .05$]. The interaction between Magnitude and Response was modulated by Distance in the parity judgment [$F_{(1,9)} = 9.78, p < .05$] but not in the magnitude comparison task ($F < 1$).

To clarify the task-dependent effects of rTMS on the SNARC effect, data for parity and magnitude judgments were then entered separately into a repeated measures ANOVA $2 \times 2 \times 2 \times 2$ having Site, Magnitude, Distance and Response as within-participant factors. The ANOVA for the parity judgment revealed only a significant two-way interaction between Magnitude and Response [$F_{(1,9)} = 38.69, p < .001$] and a significant three-way interaction between Magnitude, Distance and Response [$F_{(1,9)} = 9.78, p < .05$]. The factor Site did not show a significant main effect and was not involved in any interactions, which suggests that rTMS had no site-specific effect during parity judgment. The ANOVA for the magnitude judgment revealed a main effect of Distance [$F_{(1,9)} = 53.87, p < .0001$], and a significant two-way interaction between Magnitude and Response [$F_{(1,9)} = 6.83, p < .05$]. The crucial three-way interaction between Site, Magnitude and Response was significant as well [$F_{(2,18)} = 7.96, p < .01$], indicating that for the magnitude task rTMS had site-specific effects on the SNARC effect. The SNARC effect indeed was fully significant when rTMS was applied over the vertex [$F_{(1,9)} = 10.19, p < .01$] but not when it was applied over rFEF [$F_{(1,9)} = 2.13, p = .17$] or rIFG ($F < 1$).

A series of paired-samples *t*-tests were then performed to investigate the fate of the SNARC effect for small and large numbers (i.e., for the left and the right side of the mental number line respectively) in each relevant condition, by following a hypothesis-driven approach. In the baseline (vertex-rTMS), participants showed a normal SNARC effect in either task, responding faster with the left key to small numbers and with the right key to large numbers (Fig. 3). In magnitude comparison, the difference between right and left responses was significant in the baseline both for small and large numbers [small: 29 msec, $T_{(9)} = 2.61, p < .05$, large: 34 msec, $T_{(9)} = 4.05, p < .01$]. It was eliminated on both sides of the mental number line with rIFG-TMS [small: 2 msec; large: 8 msec; $T_s < 1$], and on the left side only with rFEF-TMS [small: 5 msec, $T < 1$; large: 22 msec, $T_{(9)} = 2.51, p < .05$]. Paired-samples *t*-tests on individual regression slopes (Lorch and Myers, 1990) were performed, showing that both rFEF-TMS and rIFG-TMS reduced the SNARC effect relative to baseline [$T_{(9)} = 1.96, p < .05$, one-tailed; and $T_{(9)} = 2.45, p < .05$, respectively].

In the parity judgment task, the difference between right and left responses was significant in the rIFG block for small numbers [small: 25 msec; $T_{(9)} = 2.29, p < .05$; large: 6 msec,

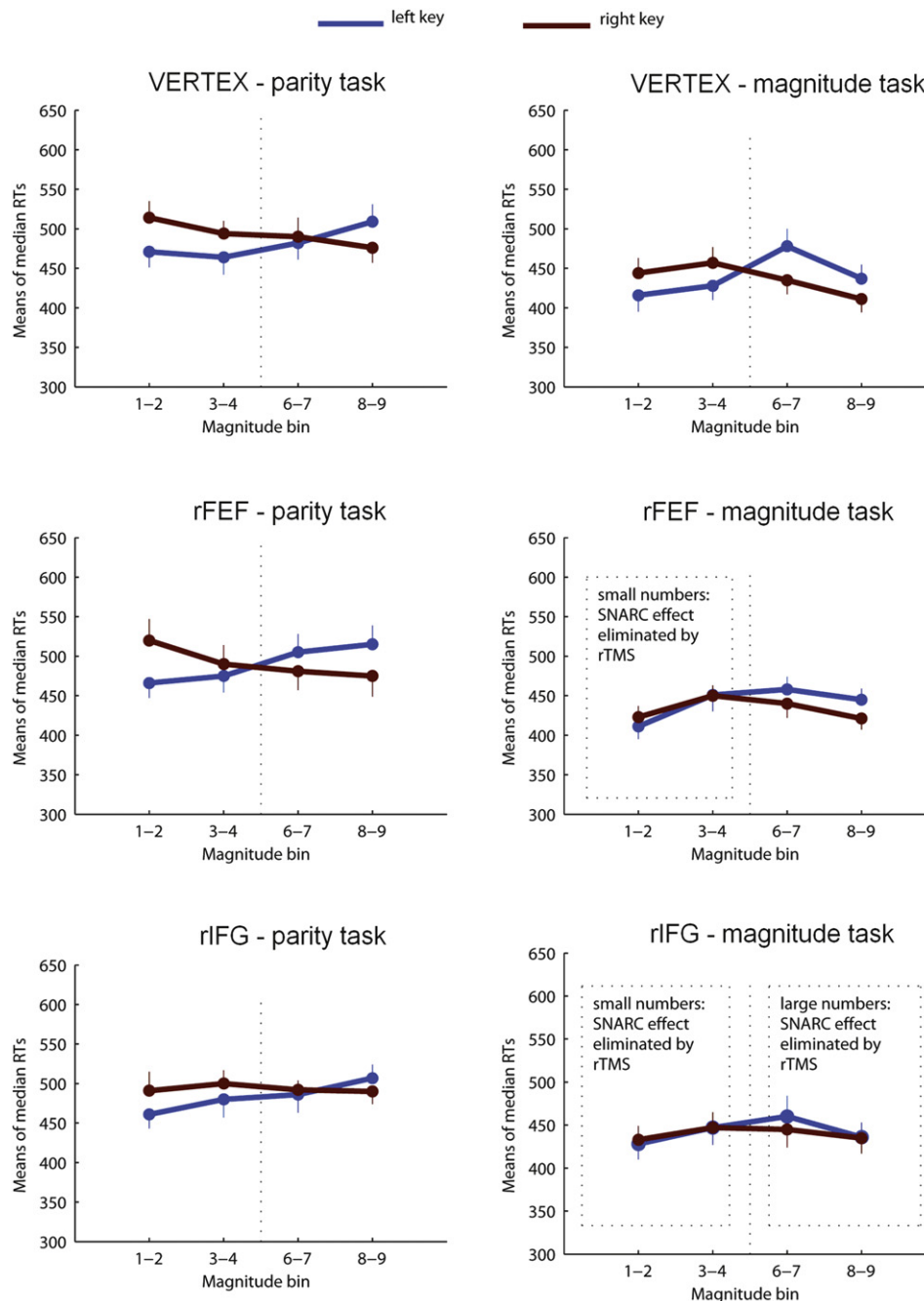


Fig. 3 – Mean of median RTs as a function of magnitude bin (each comprising one even and one odd digit) and stimulation site are shown with standard error bars in the two tasks. rFEF stimulation eliminated the S–R correspondence effect for small numbers and rIFG stimulation eliminated it for both small and large numbers in magnitude judgment. Note that although magnitude judgment was performed on average 50-msec faster than parity judgment, rTMS effects can be assumed to cover all the time from stimulus presentation to response selection in either task (see Wassermann et al., 2008). Previous studies showed that the SNARC effect found in parity judgment can be reduced with bilateral parietal rTMS (Rusconi et al., 2007). The present study shows that it remains unaffected while rTMS is delivered to right frontal cortex. In magnitude judgment, unlike parity judgment, participants are asked to keep a reference number in mind. One logical possibility, then, is that rTMS over rIFG and over rFEF selectively suppressed the correspondence effect by interfering with generic working memory resources. This is ruled out here, however, since RTs were significantly faster for magnitude (i.e., the task with the supposed additional load) than for parity judgments; moreover, generic interference from rTMS on working memory capacity or executive functions should have affected the task as a whole, leading to slower overall RTs in magnitude judgments. Another possibility is that the storage component of spatial working memory selectively disrupted by rTMS. Indeed, in magnitude judgments, the numerical reference might have been kept in mind as a position in mental space. However, visual short term memory can normally retain up to about 4 items and storage capacity depends on the posterior parietal lobe (Xu and Chun, 2006). Moreover, rFEF–rTMS did not suppress the spatial effect in toto but for small numbers only (i.e., those on the left-side of mental space) which is incompatible with such explanation, that should apply to both small and large numbers in the range under consideration. It may instead hold for rIFG–rTMS.

$T < 1$], and the same pattern was observed in the baseline [small: 36 msec, $T_{(9)} = 3.36$, $p < .01$; large: 12 msec, $T_{(9)} = 1.63$, $p < .10$, one-tailed]. In the rFEF block, the difference between right and left responses was significant both for small and large numbers [small: 35 msec, $T_{(9)} = 3.09$, $p < .05$; large: 32 msec, $T_{(9)} = 2.67$, $p < .05$]. Paired-samples *t*-tests on individual regression slopes showed that neither rFEF-TMS nor rIFG-TMS modified the SNARC effect relative to the baseline ($P_s > .20$).¹

As a last step, to further test for the selectivity of rTMS effects in magnitude comparison, Pearson product-moment correlation was calculated on SNARC effects as measured by individual betas. As it is immediately evident on visual inspection (see Fig. 4), the SNARC effect in magnitude comparison and parity judgment was positively correlated in the baseline condition (Vertex: $R = .672$, $p = .033$), whereas such correlation was absent with rFEF and rIFG stimulation (rFEF: $R = .073$, $p = .842$; rIFG: $R = .046$, $p = .900$). Interestingly, the correlation between the rTMS disruptive effects on rFEF and rIFG, as measured by baseline-corrected betas in magnitude comparison, was positive and close to significance (rFEF: $R = .610$, $p = .061$).

3. Discussion and conclusion

In the present study, we tested with rTMS the involvement of two right frontal areas, rFEF and rIFG, which have been respectively indicated as crucial nodes of the anterior dorsal and ventral circuit for spatial attention (e.g., Corbetta and Shulman, 2002), in the SNARC effect, often interpreted as a behavioural marker of access to a mental representation of number akin, in Western cultures, to a left–right oriented line (Dehaene et al., 1993, 2003). It has frequently been claimed that the neural basis for the representation of numbers in space is in the parietal lobe, since areas there mediate both spatial and numerical processing (Hubbard et al., 2005). When space processing is impaired following right-hemisphere injury, some number-related tasks may also be impaired (Zorzi et al., 2002). However, evidence from neurological patients has also indicated a role for the rIFG in the spatial representation of numbers (Doricchi et al., 2005) and the emphasis on the parietal cortex raises the question of what role the FEF, a major node of the “parieto-frontal spatial network” that is mono-synaptically connected to the posterior parietal cortex, may have in space–number interactions. Here we demonstrate that two frontal areas implicated in spatial orienting have a causal

role in number space processing (Corbetta et al., 2005). We therefore reasoned that if spatial attention was involved in the mental representation of number, not only posterior (see Rusconi et al., 2007) but also anterior attentional circuits might contribute to it. In particular, they would be crucial whenever number magnitude is relevant to the participant’s behaviour, as it was in previous studies that suggested a specialized role for prefrontal cortex in numerical tasks (Doricchi et al., 2005; Nieder and Miller, 2003).

Ten right-handed healthy adults received online rTMS over rFEF, rIFG and vertex in a single session while performing number magnitude or parity judgments on foveally presented digits with unimanual key-presses. Stimulation site (rFEF, rIFG, vertex), task (magnitude, parity), distance (close vs far from the numerical midpoint of the range) and response key (left vs right) were manipulated within participants (see Figs. 1 and 2). Speed-accuracy trade-offs were absent and, in general, magnitude judgment was performed 50-msec faster than parity judgment. A distance effect (i.e., slower responses to numbers closer to the reference) was found in magnitude but not in parity judgment, and an average 20.5-msec (se: 4) SNARC effect, consisting of advantage for left responses to numbers 1–4 and right responses to numbers 6–9, was present. However, the SNARC effect met a different fate depending on task and stimulation site. More precisely, it was unaffected by stimulation site in parity judgment, whereas during magnitude judgments it was eliminated for both small numbers (9/10 participants showed decrease in the effect relative to vertex-rTMS; mean overall decrease: 26 msec, se: 7) and large numbers (8/10 participants showed a decrease in RT; mean: 26 msec, se: 10) with rIFG-rTMS, and for small numbers only (8/10 participants showed a decrease in RT; mean: 24 msec, se: 9) with rFEF-rTMS (see Fig. 3). In neither case, however, did rTMS affect average task performance; only the marker of spatial number processing was selectively disrupted. This is also consistent with the fact that visuo-spatial left hemi-neglect can extend to number space while leaving numerical processing and mental calculation largely intact (e.g., Zorzi et al., 2002). While, in the baseline, individual measures of the SNARC effect in magnitude comparison and parity judgment were positively correlated, rTMS over rFEF and rIFG decoupled SNARC in magnitude comparison and SNARC in parity judgment (see Fig. 4). Moreover, in magnitude comparison, rFEF-rTMS disruptive effects on the SNARC resulted positively correlated with rIFG-rTMS effects, thus suggesting action over a common brain mechanism.

When put in a broader context, these results suggest that multiple substrates may account for very similar effects of dimensional overlap (Kornblum et al., 1990) between number magnitude and spatial response codes. Our data suggest that the neural fate of a number stimulus within spatial processing networks is task-dependent such that the spatial coding elicited when magnitude is task-relevant depends crucially on the contribution of right frontal cortex, while that elicited when it is task-irrelevant does not. So far, such explicit-implicit dissociation had been reported with tasks that required different mental operations and response modes, such as a parity judgment on Arabic digits and number interval bisection (Priftis et al., 2006).

¹ In the baseline, for both tasks the interaction between Magnitude and Response signalled the presence of a significant SNARC effect [$F_{(1,9)} = 20.20$, $p < .01$ and $F_{(1,9)} = 21.51$, $p < .01$ for magnitude comparison and parity judgment respectively]. Differential RTs (dRTs) (RTs of right responses minus RTs of left responses) were then computed for each of the four bins of magnitude in the two tasks: if a SNARC effect was present dRT should be captured by a line having negative slope (i.e., faster left responses to smaller numbers and faster right responses for large numbers). Single-sample *t*-tests on individual regression slopes (Lorch and Myers, 1990) showed that slope values were significantly below zero [magnitude comparison: $T_{(9)} = 4.42$, $p < .001$, one-tailed; parity judgment: $T_{(9)} = 4.22$, $p < .001$, one-tailed].

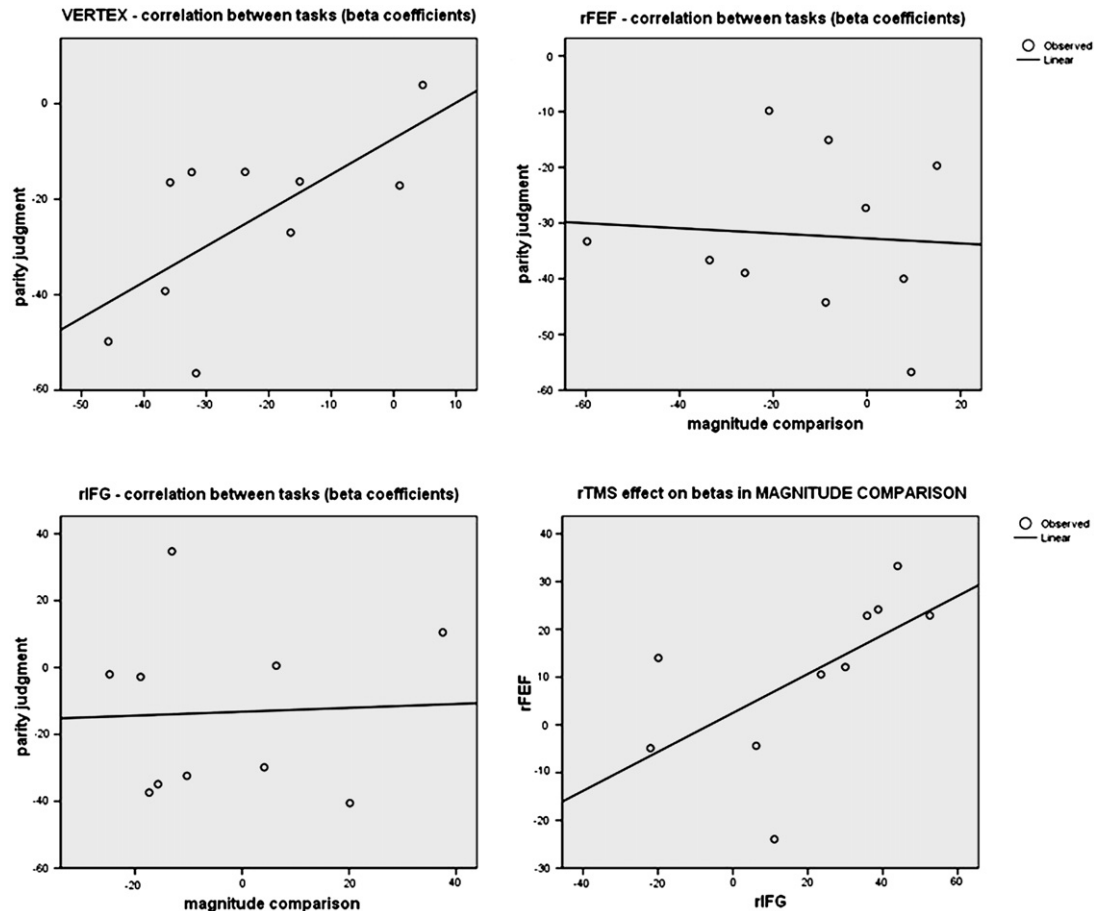


Fig. 4 – Beta coefficients of individual regression functions (a compact measure of the SNARC effect) in two different conditions are shown in each plot with reference to their best linear fit. The upper left panel shows a strong positive correlation between the SNARC effect in parity judgment and the SNARC effect in magnitude comparison with Vertex-rTMS (baseline condition). Such correlation breaks down with rFEF-rTMS (upper right panel) and rIFG-rTMS (lower left panel). The lower right panel, instead, depicts rFEF and rIFG betas in magnitude comparison, after subtraction of their respective baseline beta. It shows that the effects of rTMS over rFEF and rIFG are positively correlated within subjects, which may indicate that these two sites subserve a common cognitive mechanism.

In the present study, the SNARC effect was unaffected by rTMS in the parity judgment task, although it was positively correlated with the SNARC effect in magnitude comparison in the baseline measurement. Rusconi et al. (2007) tested the fate of the SNARC effect in a parity judgment task during stimulation of four parietal sites. More precisely, stimulation was centred either on the posterior portion of posterior parietal cortex or on the anterior portion of posterior parietal cortex of either hemisphere. This was done with lateralized presentation of the stimuli since the experiment was aimed at investigating the functional-anatomical relation between the Simon and SNARC effects. However, the SNARC effect was significantly reduced by stimulation over posterior but not over anterior sites of either hemisphere. When number magnitude – and its related spatial representation – is irrelevant to the task, the SNARC effect seems therefore to rely on posterior parietal circuits which are known to be involved in spatial attention orienting and image retention (Nobre et al., 1997; Xu and Chun, 2006). It is very likely that the same parietal circuits play a role in the spatial coding of numbers

also when number magnitude is relevant, however, the present study does not address that specific point. It does show, instead, that right anterior areas play an important role in numerical space processing during explicit magnitude comparison. In our interpretation, this role does not derive from a putative right-hemisphere specialisation for magnitude judgment and left-hemisphere specialisation for parity judgment, since this would require the additional assumption that hemisphere-specific attentional and response systems mediate orienting towards number space and response priming in the two tasks. Although we do not necessarily believe this latter assumption is unreasonable, we currently give our preference to the most parsimonious interpretation.

In the magnitude judgment task, participants were required to compare a target number with a fixed reference. In other words, unlike in the parity judgment task, they were asked to keep a reference number in mind. Could rTMS over rIFG and over rFEF have selectively suppressed the SNARC effect in the magnitude task only, by interfering

with working memory resources? This is unlikely: first, RTs were significantly faster in the magnitude (i.e., the task with an additional load) than in the parity judgment task, which points against an interpretation of our results in terms of task difficulty; second, generic interference with working memory capacity (or even executive functions) should have affected the task as a whole, leading to slower RTs in magnitude judgments. This was not the case, since the effect of rTMS in magnitude judgment was confined to the suppression of the SNARC effect and did not slow down average performance. Moreover, rIFG–rTMS suppressed the SNARC effect for both small and large numbers, whereas rFEF rTMS did not suppress the SNARC effect *in toto* but for small numbers only. This is in apparent contradiction with Doricchi et al.'s study, in which rIFG lesions produced hemispatial neglect and interfered with the processing of contralateral number space. However, our results could be easily accommodated within the framework of a *distributed injury model* as opposed to a *local injury model* of hemispatial neglect, as proposed, for example by Corbetta et al. (2005; see also Robertson et al., 1998, and Husain and Rorden, 2003). Corbetta et al. (2005) proposed that spatial attention deficits in neglect arise from the combination of structural dysfunction in the ventral attention network (causing deficits in attentional resources and disengaging/reorienting) and the concomitant functional dysfunction of the dorsal attention network (causing deficits in orienting attention towards the contralateral hemisphere). On this ground, the patients of Doricchi et al. (2005) not only had a lesion in the ventral attentional system, that is supposedly in charge for reorienting attention in either hemisphere, they also had secondary functional impairments in the dorsal attentional system, that were mainly responsible for the exacerbation of attentional deficits in the contralesional hemisphere. By interfering transiently and selectively with either system, we were thus able to partial out the bilateral role of a node in the ventral system (rIFG) from the lateralized effects of functional impairments to a node in the dorsal system (rFEF) while participants were exploring internal number space.²

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² Since the IFG is generally closer to the scalp than the FEF, and it has been shown that scalp–cortex distance can be crucial for TMS effects (e.g., Stokes et al., 2005, 2007), the bilateral effect of rIFG–rTMS may be due to greater effective stimulation of this region relative to rFEF. In the absence of data on scalp–cortex distances in our participants, however, it is not possible to directly test the goodness of this alternative hypothesis.

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