Available online at www.sciencedirect.com

SCIENCE DIRECT®

Neuroscience Letters 376 (2005) 87–92

Neuroscience Letters

www.elsevier.com/locate/neulet

Contextual influence of TMS on the latency of saccades and vergence

Zoï Kapoula[a,*], Qing Yang[a], Olivier Coubard[a], Gintautas Daunys[b], Christophe Orssaud[c]

[a] *Laboratoire de Physiologie de la Perception et de l'Action (LPPA), UMR7124 CNRS-Collège de France, 11 place Marcelin Berthelot, 75005 Paris, France*

[b] *Department of Radioengineering, Siauliai University, Vilniaus str. 141., 5400 Siauliai, Lithuania*

[c] *Service d'Ophtalmologie, Hôpital Européen Georges Pompidou, 75015 Paris, France*

Received 24 May 2004; received in revised form 8 November 2004; accepted 11 November 2004

Abstract

This study examines the effects of TMS of the right PPC on the latency of saccades and vergence alone or combined and the role of experimental design. Two designs were used: pure blocks with exclusively no-TMS or TMS trials; mixed blocks in which no-TMS and TMS trials were interleaved; a control study with TMS of the primary motor cortex (pure blocks) was also conducted and showed no effects on latencies. In contrast, in the experiment with TMS of the PPC latencies for TMS trials increased relative to no-TMS trials for almost all eye movements (isolated saccades, convergence, divergence, and for saccade and divergence components of combined eye movements). However, such increase was significant for pure blocks only. In mixed blocks no difference between TMS and no-TMS was found mainly because the latency of no-TMS trials increased relative to corresponding latencies in pure blocks. A second study centered on isolated convergence and divergence confirmed the interaction between block-design and TMS effects, and showed significant TMS/no-TMS differences only for the pure design and for a design in which the rate of TMS trials was high (75%). Again, the absence of difference was due to increase of latency for no-TMS trials in mixed blocks with low rates of TMS trials (50% or 25%), but also to decreased effects for the TMS trials themselves. We conclude that latency of all eye movements, saccades and vergence is highly influenced by the context. Such a contextual factor is the number of TMS versus no-TMS trials within a block; low numbers of TMS trials (50% or less) increases baseline latencies. The design of mixed blocks with 50% or less of TMS trials should not be recommended as it underestimates the direct effects of TMS on cortical processing. In fact, the majority of TMS studies on eye movements do use paradigms with high rates of TMS trials (75% or more). Our study confirms the validity of such paradigms.

Keywords: TMS; rPPC; Eye movements; Experimental design; Contextual influence

Transcranial magnetic stimulation is a powerful tool of cognitive neuroscience allowing to examine the involvement of different cortical areas in the preparation of different types of movements. In the field of oculomotor physiology it has been used to study cerebral control of various types of saccades, visually guided or memory-guided. Several studies have shown that TMS of the right PPC increases the latency of visually guided saccades by about 20–30 ms [1,3]. Similar effects have been found for memory-guided saccades [5]. Vergence eye movements allow to adjust the angle of visual axis to the distance of the object in space; they are essential for single binocular vision and also important for depth vision and stereopsis. Kapoula and coworkers [3,4] reported latency increases due to TMS over the right PPC for saccades, vergence and for both components of combined saccade-vergence movements; combined movements being the most frequent movements we make in natural conditions. Thus, the right parietal cortex is instrumental for the initiation of all types of eye movements in 3D space. The mechanism underlying this latency prolongation could be related to the connection between parietal cortex and superior colliculus (SC). The TMS could interfere with excitatory signal the PPC should relay on the SC thereby lengthening the latency

* Corresponding author. Tel.: +33 1 442 716 35; fax: +33 1 442 713 82.
E-mail address: zoi.kapoula@college-de-france.fr (Z. Kapoula).

0304-3940/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2004.11.027

of eye movements. Such signal could be related to fixation disengagement [13].

In most studies [1,3,5] trials with TMS and trials without TMS were done in separate blocks (pure blocks) or in blocks with high rates of TMS (>80%). Another experimental design, widely used in other fields of human physiology is the mixed block design, in which stimulus trials (whatever the stimulus is) and control trials are interleaved. The goal of the present study is to verify whether an experimental design in which TMS and no-TMS trials are interleaved within the same block could provide different results relative to design where the two types of trials are run in separate blocks. The first study showed significant effects of TMS but also significant interaction between TMS and block design. The TMS/no-TMS differences were significant in the pure block design only. A second experiment examines further the effect of experimental design only for convergence and divergence movements. In this experiment, in different blocks the probability of TMS varied from 0% (no-TMS), to 25%, 50%, 75% or 100%.

Nine healthy adult subjects participated in the experiments. Five subjects performed the experiment 1, their ages ranged from 26 to 46 years (mean 36.6 ± 5.7). Other four subjects performed experiment 2, their ages ranged from 29 to 48 years (mean 37.5 ± 9.0). All subjects had normal or corrected-to-normal vision. Binocular vision was assessed with the TNO test of stereoacuity; all individual scores were normal, 60 s of arc or better. Each subject gave informed consent to participate in the study. This investigation was approved by the local ethics committee and consistent with the Declaration of Helsinki.

A single-pulse TMS was applied by a MagStim 200 magnetic stimulator with a figure-of-eight coil (each wing 70 mm diameter) allowing focal stimulation [2]. The right PPC was stimulated by placing the coil 3 cm posteriorly and 3 cm laterally to the vertex. This criterion was also used in prior studies [3,5]. The coil was placed down to the scalp with its handle oriented backward and 45° rightward relative to the midline [9]. The rPPC was stimulated at 60–80% of total stimulator output i.e. well above motor threshold; such capacity has been used by other studiers [8]. The occurrence of blinks was monitored online by observing eye movement traces; the capacity of the stimulator was thus adjusted for individual subjects to avoid blinks. The rising time of the TMS pulse was 5 μs, the decay lasting 160 μs, and a click occurred simultaneously with the stimulation discharge.

For the trials without TMS in mixed blocks, a sound simulating the click of the TMS was produced by a speaker located behind the subject in his median plane 30 cm over the top of his head. For pure blocks without TMS the TMS stimulator was switched on but the coil was placed 30 cm over the head of the subject and oriented towards the ceiling. Thus, acoustic events were similar for all trials, TMS or no-TMS in pure or in mixed blocks.

In experiment 1, the visual display consisted of three LEDs placed at an isovergence circle at 20 cm, and other three LEDs placed at a circle at a distance of 150 cm; the three LEDs at each circle were placed at the center and at ±20°. The required mean vergence angle for fixating any of the far LEDs was 2.3° and 17° for the LEDs at the near circle.

In experiment 2, we used three LEDs along the median plane, for the initial fixation the LED at 70 cm, for convergence the LED at 40 cm, and for divergence the LED at 150 cm.

In a dark room, the subject was seated in an adapted chair with chin rest and forehead. The subject viewed binocularly and faced the display of the LEDs. The display was placed at eye level to avoid vertical eye movements; all LEDs were highly visible as only one LED was illuminated at a time.

In order to elicit short-latency reflexive eye movements, we used the gap paradigm described below. Each trial started by lighting a fixation LED at the center of one of the circles (at 150 cm or 20 cm in experiment 1, and at 70 cm in experiment 2). After a 2.5-s fixation period the central LED was turned off; following a gap of 200 ms a target-LED was turned on for 2 s. TMS was delivered at 90 ms after target onset; for no-TMS trials the acoustic click was also delivered at 90 ms after target onset. When the target-LED was on the center of the other circle it called for a pure vergence eye movement, along the median plane. When it was at the same circle it called for a pure saccade, and when it was lateral and on the other circle the required eye movement was a combined saccade and vergence eye movement.

In experiment 1, all target LEDs for saccades were at 20°. All targets along the median plane required a change in ocular vergence of 15°; similarly, combined movements required a saccade of 20° and a vergence of 15°. In one block, 20 trials for each type of eye movement (saccade, vergence and combined movements) were interleaved randomly, i.e. a total of 60 trials. Two pure blocks without TMS, two blocks with TMS, and 4 mixed blocks (TMS trials at 50%) were performed.

A control study was performed for four of the subjects: one pure TMS block of 60 trials was run in which TMS was delivered 90 ms after target onset on the primary motor cortex; the coil was placed on the vertex with the handle oriented backward.

In experiment 2, fixation point was at 70 cm and targets along the median plane were at 150 cm or 40 cm, and required a change in ocular divergence (2.7°) and convergence (3.6°). In a block of 64 trials, 32 trials of convergence and 32 trials of divergence were interleaved randomly. One pure block without TMS and one block with TMS were run; mixed blocks were also performed with TMS probability of 25% (condition TMS25, 4 blocks), of 50% (TMS50, 2 blocks), of 75% (TMS75, 4 blocks). In the conditions pure blocks and TMS50, there were in total 64 trials with TMS and 64 trials without TMS (32 for convergence and 32 for divergence). In condition TMS25, there were 64 TMS trials and 192 no-TMS trials; in condition TMS75 there were 192 TMS trials and 64 no-TMS trials. Thus, in all conditions there was a minimum of 64 TMS trials.

For both experiments at the beginning and the end a series of calibration trials were performed in which subjects made saccades to an LED target at ±10°, ±20° at various distances (far, close).

Horizontal movements from both eyes were recorded simultaneously with the IRIS, SKALAR device. A medical collar stabilized the head. Eye position signals were low-pass filtered with a cutoff frequency of 200 Hz and digitized with a 12-bit analogue-to-digital converter and each channel was sampled at 500 Hz.

Calibration factors for each eye were extracted from the calibration trials; a linear function was used to fit the calibration data. From the two individual calibrated eye position signals we derived the average of the two eyes, i.e. the conjugate signal (saccade or saccade component), and the difference between the left and right eye, i.e. the disconjugate signal (vergence or vergence component). The onset of a pure saccade or of the saccadic component of the combined movements was defined as the time when eye velocity exceeded 5% of saccadic peak velocity. The onset of the vergence (for pure vergence movement and for the vergence component of the combined movements) was defined as the time point when the eye velocity exceeded 5°/s as vergence is slow type movement. These criteria are standard [3,7,12]. The placement of the markers by the computer was verified by one of the investigators scrutinizing saccade and vergence components on the screen. From these markers, we measured the latency of eye movements, e.g. the difference between target onset and eye movement initiation. Eye movements in the wrong direction, anticipatory movements (latency shorter than 80 ms), slow movements (latencies longer than 600 ms), or movements contaminated by blinks were rejected. About eight percent of trials had to be rejected (range of individual rates 2–13%). Blinks and anticipations were the most frequent causes of rejection.

The results for the control study (TMS of the primary motor cortex versus no-TMS shown in Fig. 1A) were submitted to two-way ANOVA, with as main factors the TMS/no-TMS, and the types of eye movement (saccades, convergence, divergence, saccade, convergence and divergence components of combined movements). There was no effect of TMS over vertex on latencies ($F(1,3) = 0.38$, $P = 0.50$), nor interaction between type of eye movement and TMS ($F(5,15) = 0.24$, $P = 0.44$). Thus the effects of TMS of the PPC on latencies to be presented next are area specific.

The group mean latency for no-TMS trials in pure and in mixed blocks are shown in Fig. 1B for isolated or pure movements, and in Fig. 1C for components of combined eye movements. After testing homogeneity, three-way ANOVA was performed on individual mean latencies with as main factors the type of eye movements (saccades, convergence, divergence, and saccade, convergence, divergence components

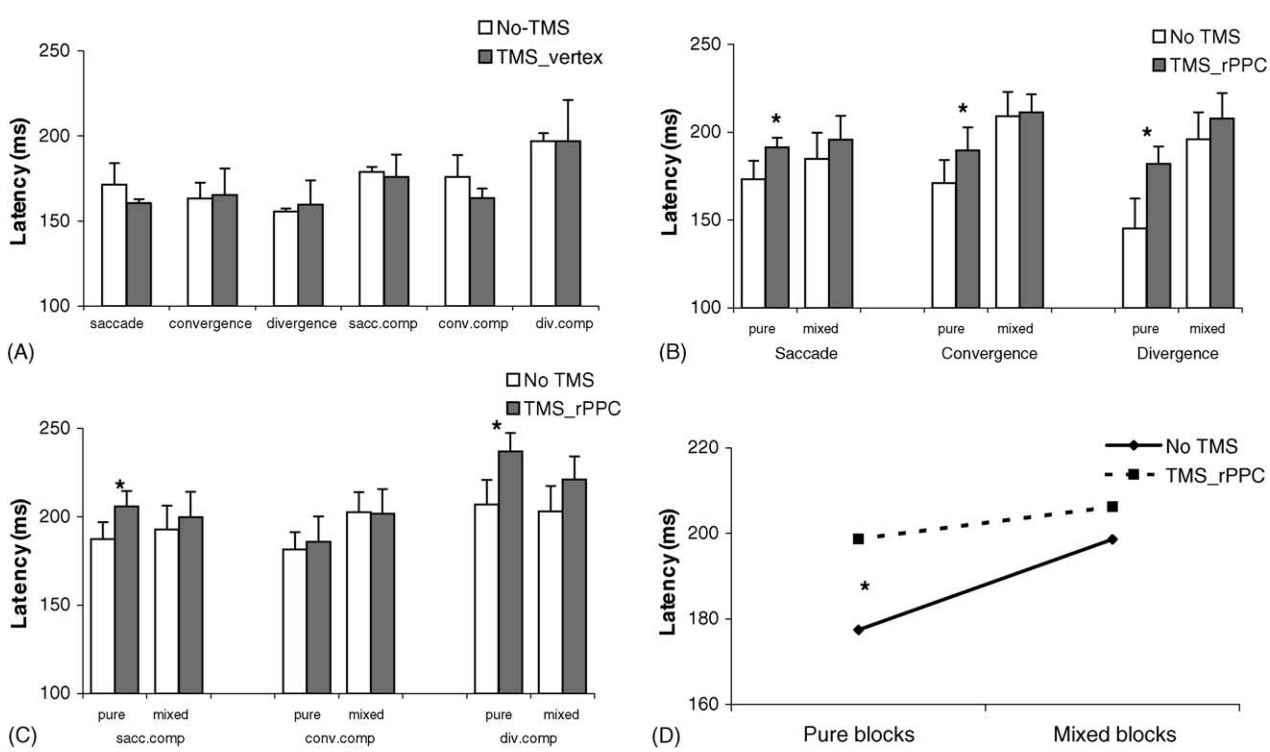

Fig. 1. (A) Group mean latency and standard error of saccades, convergence and divergence for components of combined saccade-vergence movements in pure block from four subjects under conditions of no-TMS and TMS of vertex; data from four subjects. (B and C) Group mean latency and standard error for saccades, convergence and divergence, for components of combined saccade-vergence movements in pure and mixed blocks under conditions of no-TMS and TMS of the right PPC. Asterisks indicate statistically significant latency prolongation by TMS relative to no-TMS. (D) Interaction between the experimental design (pure or mixed blocks) and TMS/no-TMS latency differences; asterisk indicates significant difference for the pure blocks only.

of combined eye movements), the TMS (with/without), and the experimental design (pure, mixed). Post hoc comparisons were done with the Least Significant Differences test. There was a significant main effect of the type of movement ($F(1,4) = 2.78$, $P < 0.05$), and a highly significant main effect of TMS ($F(1,4) = 50.6$, $P < 0.002$). Most important, there was significant interaction between TMS and the design ($F(1,4) = 11.6$, $P < 0.02$). Asterisks in Fig. 1 indicate significant differences between TMS and no-TMS trials occurring for pure blocks only (LSD test, for saccades, $P < 0.04$; convergence, $P < 0.034$; divergence, $P < 0.0001$; for saccade components $P < 0.034$, and for divergence components $P < 0.001$). Fig. 1C summarizes the interaction between TMS and experimental design. As indicated by the asterisk, the TMS/ no-TMS difference is significant for pure blocks only (LSD test, $P < 0.002$). The lack of significant difference between TMS and no-TMS trials in mixed blocks is due to increased latencies for no-TMS trials. Indeed, further post hoc test showed that the no-TMS trials were of significantly longer latency in the mixed blocks than in pure blocks ($P < 0.002$; Fig. 1D), while latency of TMS trials did not differ significantly between the two types of blocks.

In summary, this first experiment shows no-TMS effects on latency when stimulating the primary motor cortex but significant latency increase after stimulation of the right PPC. Latency prolongation occurred for saccades and divergence, either isolated or combined and for convergence latency along the median plane. Importantly, significant latency differences between TMS and no-TMS trials occurred for the pure-blocks design only due to latency increase for no-TMS in the mixed blocks.

Fig. 2 shows the results from experiment 2. It presents the mean latency of convergence (Fig. 2A) and of divergence (Fig. 2B). Three-way ANOVA was performed on individual mean latencies with three main factors: type of eye movement (convergence, divergence), TMS (with/without), and experimental design (four rates of TMS, 25%, 50%, 75%, 100%). There was a significant main effect of the type of eye movement ($F(1,3) = 87.87$, $P < 0.003$, latencies of divergence were shorter than those of convergence), and of TMS ($F(1,3) = 66.63$, $P < 0.004$). Importantly, there was an interaction between TMS and block design ($F(3,9) = 18.87$, $P < 0.001$). For both convergence and divergence the TMS effect was significant only for the pure block design, and for the TMS75 (LSD test, significant at $P < 0.002$, $P < 0.006$ for convergence, and at $P < 0.0004$, $P < 0.002$ for divergence). This interaction is further summarized in Fig. 2C showing significant latency increase only for the pure blocks and for TMS75 (LSD test, $P < 0.00002$, and $P < 0.00001$, respectively). As in the first experiment, latencies for no-TMS trials are found to increase dramatically in mixed blocks particularly for the TMS50 and TMS25 blocks. All comparisons of latencies of no-TMS trials between the TMS25 or TMS50 and the TMS75 or the pure blocks were significant (at $P < 0.05$). Interestingly, in this experiment latencies of TMS trials in the pure blocks or TMS75 were significantly longer than TMS trials in the TMS25 condition (all significant at $P < 0.01$).

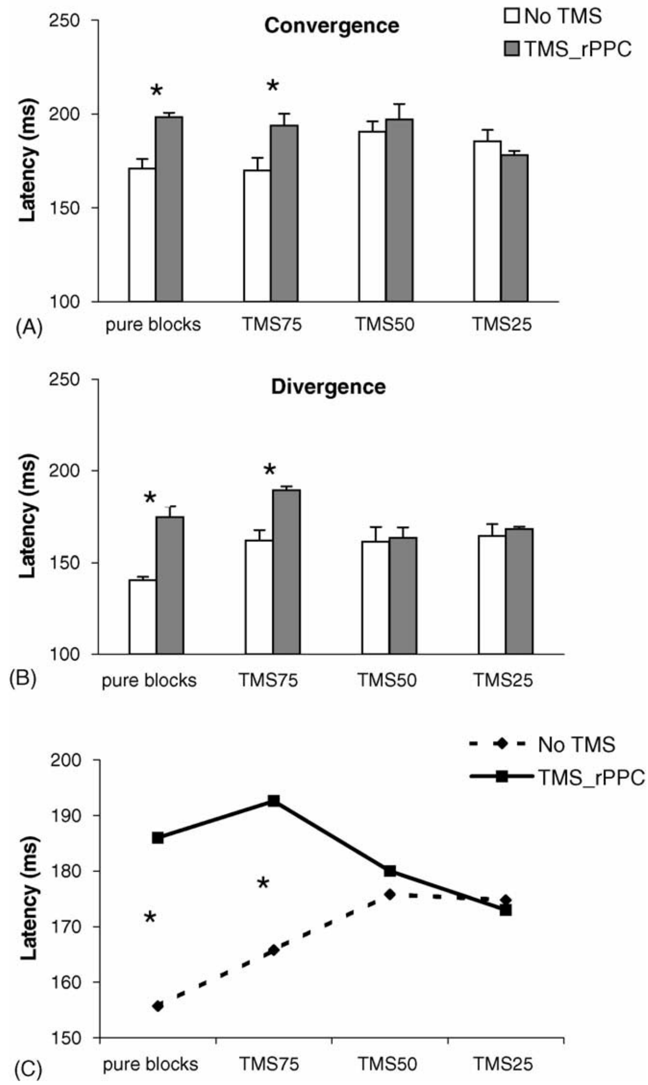

Fig. 2. Group mean latency and standard error for convergence (A) and divergence (B) for blocks in which the probability of TMS trials varied (pure blocks, TMS75, TMS50, TMS25). Asterisks indicate statistically significant latency differences between TMS and no-TMS trials. (C) Interaction between the experimental design and TMS/no-TMS latency differences; asterisks indicate significant differences.

In summary, this second study confirmed the interaction between TMS and experimental design. Mixed block designs with low rates of TMS trials (TMS25, TMS50) produce weak TMS/no-TMS differences due to increase of the latencies even for no-TMS trials; also the efficacy of TMS on TMS trials was decreased at low rates of TMS occurrence (TMS25). Latency is shorter for divergence than for convergence. Next we will discuss these findings.

In the present study, we use a gap paradigm to elicit short-latency eye movements; it is believed that the PPC plays an important role in the initiation of eye movements in such paradigm [6]. At first, this study shows that TMS of the right PPC increases the latency of eye movements used to explore the 3D space, i.e. saccades, convergence, divergence and saccade and divergence components of combined eye movements. The control study in which TMS was applied on the primary motor cortex produced no effects on latency. Thus, the effects of PPC are area specific. All these findings are confirmatory and in agreement with prior studies [3,4]. Recall that patients with lesions of the right PPC showed increased latencies in both directions [6]. Thus our findings of bilateral increase of saccade latency of the TMS of the right PPC is compatible with patients' results and prior TMS studies [3,4]. These results contrast those of TMS of the left PPC producing latency increase for rightward saccades only, i.e. contralateral to the stimulated site, and for convergence [13]. The present data indicate that the right PPC has a common function for the initiation of any type of saccades and vergence. Most likely it is involved in the initiation of eye movements by providing a signal e.g. related to fixation disengagement which is a prerequisite for any movement to occur. TMS interference with this signal could be at the origin of latency increase. The new findings of the present study concern the contextual influence of the TMS on the evaluation of baseline latency. The interest of this influence is twofold: (i) methodological; (ii) theoretical, for better understanding the specific mechanisms of the initiation of different types of eye movements.

The major new finding of the first experiment is that TMS occurrence in the mixed blocks increases the latency also for the no-TMS trials. The second experiment centered on convergence and divergence confirmed this observation and showed substantial latency increase for no-TMS trials particularly when TMS trials occurred at low rate (25% or 50%).

The first attempt to explain this contextual influence could be in terms of events associated to TMS delivery; for instance the accompanying acoustic click could cause "re-engagement of attention" thereby lengthening the latency. Recall, however, that this aspect was controlled, as there was always an acoustic click in pure or mixed blocks for TMS and no-TMS trials.

Another possibility to be considered is that TMS itself could have long-lasting interference effects, but the perturbation effects of TMS known last only 200–250 ms [2]. In our study, the interval separating two successive TMS trials within the mixed blocks was at least 1.5 s. Thus, interference from the prior TMS trial is very unlike. Furthermore if such was the case the increase of the latency for trials without TMS in mixed blocks relative to pure blocks should be correlated with the probability of TMS occurrence. This was not the case as shown by experiment 2, in which latency increases by the same amount regardless of the probability of the TMS occurrence (see Fig. 2C, TMS50, TMS25).

The reason for similar contextual influence of TMS in mixed blocks with 25% and 50% TMS trials is unclear as well as the reason why there is no consistent contextual influence in the 75% condition (i.e. only divergence exhibits such influence). Most likely it is the number of TMS versus no-TMS trials within a block which influences the latencies but in a complex and non-linear way. Whatever the mechanism is the methodological output of this study is that mixed blocks with low rates of TMS trials (50% or less) cannot provide a good baseline for estimating subsequently the effects of TMS itself.

For saccades there is evidence that the latency can be influenced by contextual factors (such as stimulus probability) [10,11]; to our knowledge this is the first time that contextual influences are demonstrated for convergence and divergence.

Experiment 2, in addition to contextual influence discussed above provides some evidence for the sensitivity of TMS direct effects on the rate of TMS trials within the block. Indeed latency for TMS trials is significantly higher for the pure blocks or the TMS75 condition than for the TMS25 condition (see Fig. 2C). The exact mechanism for such higher sensitivity to TMS is not known and needs further investigation. Yet, this is another aspect of the results that argues in favour of the use of pure block paradigms, or at least of blocks with rates of TMS trials >50%. In fact, the majority of TMS studies do use such rates [1,3–5,8,12]. The present study confirms that this is the best protocol to use at least for eye movements, whose latency is known to be highly influenced by several factors; here we show that such influence occurs for both saccades and vergence.

Divergence latency is shorter than convergence latency; in pure blocks for no-TMS trials mean latency value is remarkably short, below 150 ms (see Fig. 1A and Fig. 2B). It is possible that the process of fixation disengagement preceding any eye movement occurs more or less readily for different types of eye movements. Recall that divergence is the transition from close to far and starts from a convergent position of the eyes. We suggest that for divergence, the need to relax from the effort of tonic sustained convergence of the eyes and/or the need to search in the far personal space information of interest accelerate the fixation disengagement process. The TMS effects are more systematic for divergence affecting both pure and combined divergence (see experiment 1).

In conclusion, this study shows that TMS of the right PPC but not of the vertex increases the latency of isolated saccades, convergence, divergence and of saccades and divergence components of combined eye movements. This indicates TMS interference with cortical processing. Most important, it shows, for the first time, that mixed block designs in which TMS occurs at low rates (25% or 50%) has a contextual influence increasing the latency of no-TMS trials and such design should not be recommended. On the other hand, TMS efficacy in interfering with cortical processing can be higher when TMS trials are the most frequent within a block. The results call for methodological precautions and favour the use of designs with rates of TMS trials of 75% or higher in order to demonstrate the direct effects of TMS on cortical processing. The results also uncover, that latencies of all eye movements, saccades and vergence are influenced by contextual factors such as the number of TMS versus no-TMS trials within a block.

Acknowledgements

Qing Yang was supported by a Contract of the European Union QLK6-CT-2002-00151: 'Eurokinesis'. Olivier Coubard was supported by a 'Cognitique' fellowship. Gintautas Daunys, visiting scientist in Paris, was supported by the CNRS/DRI, PECO programs (QLRT-2000, 00442, FP5PRTD). We thank the reviewer for his insightful comments.

References

[1] P.T. Elkington, G.K. Kerr, J.S. Stein, The effect of electromagnetic stimulation of the posterior parietal cortex on eye movements, Eye 6 (1992) 510–514.
[2] M. Jahanshahi, J. Rothwell, Transcranial magnetic stimulation studies of cognition: an emerging field, Exp. Brain Res. 131 (2000) 1–9.
[3] Z. Kapoula, E. Isotalo, R.M. Müri, M.P. Bucci, S. Rivaud-Péchoux, Effects of transcranial magnetic stimulation of the posterior parietal cortex on saccades and vergence, Neuroreport 12 (2001) 4041–4046.
[4] Z. Kapoula, Q. Yang, O. Coubard, G. Daunys, C. Orssaud, Transcranial magnetic stimulation of the posterior parietal cortex delays the latency of both isolated and combined vergence-saccade movements in humans, Neurosci. Lett. 360 (2004) 95–99.
[5] R.M. Müri, A.L. Vermersch, S. Rivaud, B. Gaymard, C.J. Pierrot-Deseilligny, Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortex during memory-guided saccades in humans, J. Neurophysiol. 76 (1996) 2102–2106.
[6] C.J. Pierrot-Deseilligny, S. Rivaud, B. Gaymard, R. Muri, A.L. Vermersch, Cortical control of saccades, Ann. Neurol. 37 (1995) 557–567.
[7] M. Takagi, E.M. Frohman, D.S. Zee, Gap-overlap effects on latencies of saccades, vergence and combined vergence-saccades in humans, Vis. Res. 35 (1995) 3373–3383.
[8] P.N. Tobler, R.M. Müri, Role of human frontal and supplementary eye fields in double step saccades, Neuroreport 13 (2002) 253–255.
[9] P. Van Donkelaar, J.H. Lee, A.S. Drew, Transcranial magnetic stimulation disrupts eye-hand interactions in the posterior parietal cortex, J. Neurophysiol. 84 (2000) 1677–1680.
[10] L. Wang, J.A. Stern, Saccade initiation and accuracy in gaze shifts are affected by visual stimulus significance, Psychophysiology 38 (2001) 64–75.
[11] H. Weber, M. Biscaldi, B. Fischer, Intertrial effects of randomization on saccadic reaction times in human observers, Vis. Res. 35 (1995) 2615–2642.
[12] Q. Yang, M.P. Bucci, Z. Kapoula, The latency of saccades, vergence, and combined eye movements in children and in adults, Invest. Ophthalmol. Vis. Sci. 43 (2002) 2939–2949.
[13] Q. Yang, Z. Kapoula, TMS over the left PPC prolongs latency of contralateral saccades and convergence, Invest. Ophthalmol. Vis. Sci. 45 (2004) 2231–2239.