Transcranial magnetic stimulation of the posterior parietal cortex delays the latency of both isolated and combined vergence–saccade movements in humans

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Abstract

To explore the 3D visual environment most frequently we make combined saccade–vergence eye movements. We studied the effect of transcranial magnetic stimulation (TMS) of the right posterior parietal cortex (rPPC) on such combined eye movements versus isolated saccade and vergence. In the main experiment, TMS was applied on the rPPC 80, 90 or 100 ms after target onset. In a control experiment, TMS was applied over the primary motor cortex at 90 ms after the target presentation. TMS trials were compared with no-TMS trials. TMS of the motor cortex had no effect at all on eye movements. TMS of the rPPC had no effect on the accuracy of eye movements, but it caused a latency increase: the increase was similar for the two components of the combined saccade–vergence movements, and it did not alter the naturally existing tight relationship of latency between the two components. Furthermore, the amount of latency prolongation was similar to that of isolated vergence, and of saccades in either direction (ipsilateral or contralateral relative to the stimulated site). Latency prolongation was time-specific but in a different way for different types of eye movements: for combined and convergence eye movements, the critical time window was ≥130 ms or more prior to the onset of eye movement, while for saccades and divergence TMS was disruptive later, ≥110 ms or more prior to the onset of eye movements. The latency increase is attributed to the interference by the TMS with the fixation disengagement process, for which the rPPC is believed to be instrumental. These results suggest that fixation disengagement occurs earlier for convergence and combined eye movements than for saccades and divergence.

Keywords: Humans; Eye movement latency; Fixation disengagement; Saccade–vergence common triggering; Transcranial magnetic stimulation time specificity

Transcranial magnetic stimulation (TMS) is an interference technique used in healthy humans to produce a temporary functional deficit [8]. In the oculomotor field, it allowed rapid progress of knowledge on the cortical control of eye movements. TMS of the right posterior parietal cortex (rPPC) produces latency prolongation for saccades bilaterally [9,13]. These results are consistent with studies of patients with lesions of the rPPC and indicate that this region is involved in visuo-spatial orientation for both sides, namely in the process of fixation disengagement, which is a critical step for any eye movement to occur [12]. The role of the rPPC in the initiation of vergence was first examined by Kapoula et al. [9]. It was found that TMS interferes with both saccades and vergence.

Most frequently we perform combined saccade–vergence eye movements to fixate objects that differ both in direction and in depth. Yarbus [18] was the first to study the initiation of such movements and pointed out that vergence starts before the saccade. Yang et al. [17] reported a high rate of mild asynchrony (10–20 ms) of the latency of the two components. Thus, combined eye movements involve the initiation of a complex motor program, and the two components may not be perfectly synchronized. Nevertheless, Tagaki et al. [15] reported that the latencies of the two components are highly correlated, and that both components are influenced similarly by the fixation task.
These authors suggested a common decision mechanism for both components: small latency discrepancies between the two components could be due to different delays in triggering subsequently the distinct saccade and vergence brainstem generators. Thus, the fact that the rPPC is involved in the triggering of isolated saccades or vergence does not necessarily imply that the initiation of the combined movement is also controlled by the same structure. The main goal of this study is to test whether TMS of the rPPC interferes with the triggering of combined movements and if the relationship between the two components is altered by TMS. Other novelties of this study relative to our prior study [9] are: the use of a focal stimulator and of multiple time windows for delivering the TMS.

Five healthy adult subjects, three females and two males, participated in the present experiment. Their ages ranged from 26 to 46 years (mean 36.6 ± 5.7). All subjects had normal or corrected-to-normal vision. Binocular vision was assessed with the TNO (The Netherlands Organization) test of stereoaucity; all individual scores were normal, 60° 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 a more focal stimulation [8]. In the prior study [11] the coil used was afoveal (90 mm diameter), and the area stimulated was maximally in an annulus of the same size under the coil. Figure-of-eight coils are wound so that the current induced under the midregion is over twice that under each of the edges [1]. Even so, in many coils this midregion is up to 4 cm long, potentially activating a similar area within the brain. Regardless of the coil shape the depth of effective stimulation is limited to approximately 2 cm [5]. The rPPC was stimulated by placing the coil 3 cm posteriorly and 3 cm laterally to the vertex, also used in some previous studies [11]. Eighty percent of total stimulator output well above motor threshold was used, similarly to the study of Tobler and Muri [16]. For the control experiment, we stimulated the vertex. For reference trials without TMS, the stimulator was switched on but the coil was placed 30 cm over the head of the subject and oriented towards the ceiling.

Three light-emitting diodes (LEDs) were placed at two isovergence circles (20 cm and 150 cm from the subject): one at the center and the others at ± 20°. The required mean vergence angle was 17° for the close LEDs and 2.3° for the far LEDs. In a dark room, the subject was seated in an adapted chair with a medical collar to avoid head movements.

Each trial was started by illuminating a fixation LED at the center of one of the circles (far or close). After a 2.5 s fixational period the central LED was turned off; following a gap of 200 ms a target LED was turned on for 2 s. In each block, the three types of eye movements were interleaved randomly. TMS of the rPPC could occur 80, 90 or 100 ms after the onset of the target (with equal probability). Two subjects performed six blocks of 60 trials with TMS of the rPPC and four blocks of 60 trials without TMS. Three subjects performed two blocks of 60 trials with TMS of the rPPC and two blocks of 60 trials without TMS. Four subjects performed one block of 60 trials with TMS over the vertex; this test was confirmatory and was limited to the time interval of 90 ms as it has been shown in the past that TMS of the vertex at 80 ms has no effect on the eye movements [9].

Horizontal movements from both eyes were recorded simultaneously with the IRIS, SKALAR device (Delft, The Netherlands). This system has an optimal resolution of 2° of arc, a range of 30° for lateral excursion and is linear within 3% for excursion up to 25° [14]. Eye position signals were low-pass filtered with a cut-off 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 saccades to ± 10°, ± 20° recorded in a calibration task. From the two individual calibrated eye position signals we derived the conjugate (saccade or saccade component) signal from the mean of both eyes and the disconjugate signal (vergence or vergence component) from the difference between the two eyes (Fig. 1). The onset and the offset of eye movements were defined the same as in our previous studies [9,17]. We measured the latency, the time difference between target onset and eye movement initiation. The gain is the ratio of eye movement amplitude to target amplitude. Eye movements in the wrong direction, anticipatory (latency < 80 ms) or slow (latency > 400 ms) movements, or movements with blinks were rejected.

The non-parametric Friedmann test was used to test the existence of an overall difference between TMS and no-TMS conditions; the Wilcoxon signed rank test was used for paired comparisons between the two conditions. Comparison of percentages between the TMS and no-TMS conditions was done with the $\chi^2$ test.

Saccade latencies are known to deviate from unimodal distribution. At least three classes of latencies have been described: express latencies, fast regular latencies and slow regular latencies [5,6]. According to the studies of Fischer et al. [4] and Gezeck et al. [6], after inspection of the distribution of the latencies in the present study, we regrouped them into three classes, corresponding to express-type, fast regular-type and slow regular-type of latencies (see Table 1).

In the no-TMS condition, the highest rate of express latencies (80–120 ms) was observed for divergence, and to a lesser extent for saccades or saccade components of combined movements. TMS had no significant effect on the percentage of express-type of latencies except a diminution for saccade components of combined eye movements when TMS was delivered at 80 ms after target onset (Table 1a).
Overall, TMS had no effect on the mean express-type of latency.

The fast regular-type of latency (121–150 ms) was, in general, more frequent than the express type (Table 1b). There was a significant modification of the rates of such latencies in only three of the 24 cases (indicated by asterisks next to the percentage values), and the change could be in either direction (decrease or increase). Again, there was no significant modification of the mean latencies when comparing TMS and no-TMS conditions.

The slow regular-type of latencies (151–400 ms) represented the larger majority for all types of eye movements (Table 1c). There was no significant change in their rates between no-TMS and TMS conditions except an increase from 51% to 81% for divergence with TMS at 80 ms. When TMS was delivered at 80 ms after target onset there was significant latency prolongation only for divergence ($P < 0.01$). In contrast, there was significant latency prolongation for all types of eye movements when TMS occurred at 90 ms after target onset (all $P < 0.01$, except for convergence components of combined movements where the prolongation tended towards significance, $P = 0.06$). Statistical analysis applied on all three types of latencies grouped together (express-type, fast regular and slow regular) relative to no-TMS conditions gave very similar results, i.e. significant latency prolongation for all movements when TMS occurred at 90 ms, and for divergence only when TMS occurred at 80 ms.

To better understand the time specificity of TMS effects for different types of eye movements, we regrouped the latencies on the basis of when TMS occurred relative to the onset of the eye movements; this was obtained by subtracting from the eye movement latency the time (80, 90 or 100 ms) after target onset at which TMS was delivered. To give an example, if TMS occurs at 80 ms after the target onset but the latency of the eye movement is 220 ms in one trial and 160 ms in another trial, TMS could interfere with different hypothetical subprocesses in one case (e.g. fixation disengagement, movement metrics specification), or it could even not interfere at all in the latter case. Only trials with slow regular-type of latencies were analyzed (>150 ms) for both TMS and no-TMS conditions (Fig. 2). For saccades and divergence latency delays significantly if the TMS occurs earlier than −110 ms prior to the onset of the movement ($P < 0.05$). In contrast, for convergence and combined movements latency delays significantly when TMS occurs even earlier, −130 ms or more prior to the onset of the movement ($P < 0.05$).

TMS of the motor cortex delivered at 90 ms after target onset caused no significant latency prolongation relative to

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**Fig. 1.** (Scheme top right) Different types of eye movements elicited: isolated or pure horizontal saccades, pure convergence, or divergence along the median plane, and combined convergent or divergent movements. Typical recordings of the three types of eye movements, isolated saccades (a) and convergence (b), combined convergent movements (c), and combined divergent movements (d). The conjugate signal (saccade or saccade component) is obtained by averaging the position signal of the two eyes (LE + RE)/2; the disconjugate signal (convergence, convergence or divergence component) is the difference between the two signals LE − RE. The arrows at ‘i’ and at ‘e’ indicate the onset and the end of each movement, respectively.

**Fig. 2.** Mean latency and standard deviation in the no-TMS and TMS conditions. In the TMS conditions latencies (time interval from target onset to eye movements onset) are regrouped according to the time point at which TMS occurred relative to the eye movement onset; to create these groups we subtracted from the latency the time of TMS delivery relative to target onset (80, 90 or 100 ms). Asterisks indicate a statistically significant prolongation relative to no-TMS trials. The TMS effect is time-specific, and time specificity is different for pure and combined movements.
no-TMS (all $P > 0.05$ for different types of eye movements).

The accuracy of eye movements was examined in no-TMS and both TMS experiments. There was no effect of TMS in either experiment (all $P > 0.05$).

Latency prolongation induced by the TMS cannot be due to unspecific overall perturbation, e.g. interference of the sensory treatment of the target. There are several arguments against such interpretation: (i) latency prolongation occurred after TMS of the rPPC, not of the motor cortex; (ii) latency prolongation was time-specific; (iii) the accuracy of eye movements remained unchanged, thus target localization was unaffected. As in the prior study [9] we attribute latency prolongation to the interference of the triggering signal that the rPPC should deliver to the superior colliculus (SC), thereby lengthening the latency of all eye movements in 3D space, either isolated or combined.

Indeed, some evidence that the parietal cortex is activated prior to vergence movements exists in humans [10] and more so in monkeys [7]. The signal provided by the rPPC is probably related to the fixation disengagement process which is a prerequisite for any eye movement to occur [3]. This is compatible with the study of a patient with lesions of the rPPC who showed marked bilateral increase of saccade latency [12]. As suggested by patient studies [12], the left PPC might be involved in the initiation of eye movements via a different mechanism, and we recently provided some evidence for this with a TMS study of normals (Yang and Kapoula, unpublished data).

Takagi et al. [15] proposed a conceptual model for the initiation of combined movements according to which the decision to move most likely is common for the direction and the depth component; the common decision would then be transmitted to the distinct but interactive brainstem saccade and vergence generators. In line with this, Chaturvedi and Van Gisbergen [2] provided evidence for a common target selection and amplitude computation process of stimuli in direction and in depth. Our observation of TMS induced latency increase for both components of combined eye movements without alternation of their tight correlation is compatible with models of a common triggering mechanism and with physiological data.

TMS of rPPC had no effect on eye movements with express-type or fast-regular type of latencies, and this is compatible with previous observations [13]. Given that in our study TMS occurred 80, 90 or 100 ms after target onset and express or fast-type of latencies are of the order of 80–150 ms, TMS occurred too late to disrupt the fixation disengagement subprocess. Our additional analysis of the TMS effect relative to the onset of eye movement strengthens this conclusion. In line with physiological knowledge and models of the saccade system [3] we suggest that fixation disengagement occurs relatively early, perhaps in the first 100 ms and this for all movements with latencies below 150 ms. A final point is that for combined movements and convergence TMS prolonged the latency when it occurred at $\geq 130$ ms or more prior to the eye movement, while for saccades and divergence TMS lengthened the latency even if it occurred later ($\geq 110$ ms). Perhaps fixation disengagement occurs earlier for all combined eye movements and for convergence than for saccades and divergence. This is compatible with an EEG study showing different patterns and different time courses of parietal activation for saccades, vergence and combined movements [10].

In conclusion, this study shows that TMS of the rPPC

Table 1

<p>| Group mean latency (ms) together with standard deviation (SD) in the no-TMS and TMS conditions |
|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>(a) Express eye movements (80–120 ms)</th>
<th>Saccades</th>
<th>Convergence</th>
<th>Divergence</th>
<th>Saccade components</th>
<th>Convergence components</th>
<th>Divergence components</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-TMS</td>
<td>106 ± 13 (7)</td>
<td>99 ± 17 (6)</td>
<td>103 ± 13 (20)</td>
<td>102 ± 11 (9)</td>
<td>105 ± 13 (6)</td>
<td>112 ± 8 (7)</td>
</tr>
<tr>
<td>TMS-80</td>
<td>112 ± 6 (4)</td>
<td>94 ± 20 (13)</td>
<td>102 ± 14 (2*)</td>
<td>114 ± 8 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMS-90</td>
<td>100 ± 10 (2)</td>
<td>105 ± 21 (16)</td>
<td>105 ± 14 (4)</td>
<td>100 ± 10 (3)</td>
<td>116 ± 12 (2)</td>
<td></td>
</tr>
<tr>
<td>TMS-100</td>
<td>108 ± 17 (9)</td>
<td>94 ± 8 (13)</td>
<td>107 ± 7 (10)</td>
<td>110 ± 8 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Fast regular eye movements (121–150 ms)</td>
<td>No-TMS</td>
<td>141 ± 8 (13)</td>
<td>140 ± 8 (24)</td>
<td>139 ± 8 (29)</td>
<td>140 ± 7 (17)</td>
<td>140 ± 7 (23)</td>
</tr>
<tr>
<td>TMS-80</td>
<td>138 ± 7 (33*)</td>
<td>135 ± 10 (23)</td>
<td>128 (6*)</td>
<td>136 ± 7 (16)</td>
<td>132 ± 9 (24)</td>
<td>137 ± 10 (16)</td>
</tr>
<tr>
<td>TMS-90</td>
<td>139 ± 5 (19)</td>
<td>139 ± 9 (24)</td>
<td>129 ± 9 (16)</td>
<td>138 ± 6 (18)</td>
<td>141 ± 5 (29)</td>
<td>137 ± 9 (7)</td>
</tr>
<tr>
<td>TMS-100</td>
<td>139 ± 7 (26*)</td>
<td>148 ± 0 (8)</td>
<td>137 ± 8 (17)</td>
<td>142 ± 7 (13)</td>
<td>145 ± 9 (5)</td>
<td>141 ± 6 (19)</td>
</tr>
<tr>
<td>(c) Slow regular eye movements (151–400 ms)</td>
<td>No-TMS</td>
<td>192 ± 3 (80)</td>
<td>194 ± 5 (70)</td>
<td>182 ± 4 (51)</td>
<td>195 ± 2 (74)</td>
<td>193 ± 3 (71)</td>
</tr>
<tr>
<td>TMS-80</td>
<td>193 ± 7 (63)</td>
<td>201 ± 8 (77)</td>
<td>204 ± 7* (81*)</td>
<td>203 ± 6 (82)</td>
<td>205 ± 7 (71)</td>
<td>230 ± 12 (84)</td>
</tr>
<tr>
<td>TMS-90</td>
<td>211 ± 7* (79)</td>
<td>214 ± 10* (76)</td>
<td>208 ± 7* (68)</td>
<td>220 ± 8* (78)</td>
<td>210 ± 10 (68)</td>
<td>244 ± 14* (91)</td>
</tr>
<tr>
<td>TMS-100</td>
<td>185 ± 5 (65)</td>
<td>186 ± 5 (92)</td>
<td>197 ± 44 (70)</td>
<td>193 ± 5 (77)</td>
<td>187 ± 8 (88)</td>
<td>204 ± 7 (81)</td>
</tr>
</tbody>
</table>

Means are shown according to the TMS delivery relative to target onset (80, 90 or 100 ms). Latencies are arbitrarily regrouped into three types and their respective rates (%) are shown in parentheses: (a) express-type of latency (80–120 ms); (b) fast regular-type of latency (121–150 ms); (c) slow regular-type of latency (151–400 ms).
delays the initiation of the naturally made combined saccade–vergence movements and it does so in a similar way for the two components without altering the naturally existing tight relationship between the latency of the two components.

Latency increase is attributed to interference by TMS with the fixation disengagement subprocess, for which the rPPC is believed to be instrumental. Most importantly, the study also shows that TMS is disruptive earlier for some eye movements; perhaps fixation disengagement occurs earlier for convergence and combined eye movements.

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