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Research report

The functional role of the ventral premotor cortex in a visually paced finger tapping task: A TMS study

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Abstract

The accurate control of timed actions is a fundamental aspect of our daily activities. Repetitive movements can be either self-paced or synchronized with an external stimulus. Finger tapping (FT) is a suitable task to study the mechanisms of motor timing in both conditions. The neuronal network supporting motor timing in FT tasks comprises the lateral cerebellum, the lateral and mesial premotor areas as well as parietal sites. It has been suggested that lateral premotor cortices (PMC) are involved in time representation and sensorimotor transformations needed for synchronization. Most studies have focused on the dorsal aspect of PMC (dPMC) whereas the ventral PMC (vPMC) function has been poorly investigated. Here we used an online transcranial magnetic stimulation (TMS) protocol to probe the role of vPMC in an FT task, as compared to a functionally relevant site (dPMC) and an unrelated one. According to the synchronization-continuation paradigm, subjects had to synchronize their tapping to a periodic continuous visual stimulus, and then continue without the external pacer. Two different visual pacers were used: a tapping finger and a hinged tilting bar. We show that TMS reduced the synchronization error when delivered to the vPMC. This effect was larger when the more abstract hinged tilting bar was used as a pacer instead of the finger. No effects were observed in the continuation phase. We hereby offer the first online-TMS evidence of the involvement of vPMC in visually cued FT tasks.

1. Introduction

All our actions involve the effective timing and control of coordinated movements which rely on seamless sensory and motor integration. In repetitive movements, such as locomotion or chewing, humans show outstanding abilities to keep a precise rhythm and accurately synchronize their action to an external pacer (e.g., when dancing). These skills have been typically studied by means of a finger-tapping (FT) task performed according to a synchronization-continuation paradigm [1]. In this task, subjects are first required to tap in synchrony with an external pacing stimulus, and then continue at the same rate when the pacer is switched off. Typically, inter-tap intervals (ITI) and synchronization errors (SE), i.e., the relative phase between the tap and the pacer, are critical dependent measures. The influence of the pacing stimuli on the motor performance [2] may depend on their physical features, such as sensory modality (auditory, visual, etc.), complexity (e.g., visual flashing light or a complex visual pattern), or intermittent or continuous presentation (e.g., visual flashes or a sinusoidal regime of dimming/brightening light).

The core neuronal network supporting motor timing in FT tasks – across different task conditions and at the sub-second scale – has been explored via neuroimaging techniques and lesion studies showing the involvement of the sensorimotor cortex, lateral cerebellum (Cb), basal ganglia (BG), mesial and lateral premotor areas as well as parietal sites [3–6]. According to current viewpoints, timing is grounded on sensorimotor processes [7–9], and mediated by a distributed network [7], which is modulated by task constraints and the way temporal information is presented [10,11]. Furthermore, transcranial magnetic stimulation (TMS) has proven to be an effective tool for revealing the functional role of specific areas belonging in this network. Single-pulse TMS studies have elucidated the role played by the primary motor cortex (M1) in the FT task, in both the synchronization [12] and the continuation phase [13], showing that movement kinematics was altered although participants were not aware of that. Similarly, the offline interference of a repetitive TMS (rTMS) protocol (1-Hz) on M1 showed either a reduction of SE [14] or a decrease in maximal tapping speed [15].
Pollok et al. [16] tested the different roles of left and right dorsal premotor cortices (dPMC), and concluded that only the stimulation on the left side disturbs synchronization accuracy. Malcom et al. [17] applied rTMS over left vPMC during a stylus-tapping task with an audiotoriometer synchronization paradigm and reported that SE was marginally increased. Moreover, it has been observed that rTMS is ineffective on the lateral Cb [15], but increases ITI variability when applied on the medial Cb [18]. Del Olmo et al. [19] have recently expanded these findings in a series of experiments where rTMS was applied to the right and left Cb, dPMC, the supplementary motor area and M1 in a synchronization–continuation task, at different frequencies using both auditory and visual pacers. These authors observed altered ITI variability when stimulating ipsilateral Cb and contralateral dPMC.

Summing up, there exists a complex network of areas supporting motor timing where each node has a partially specific function. In fact, TMS applied to M1 seems to disrupt response implementation rather than timing processes [12–15]. On the other hand, lateral premotor areas and Cb contribute to event-related timing [4,16,19]. In particular, PMC has been suggested to be involved in time representation, also in the absence of movement [8,20], and in sensorimotor functions [21–24].

In this context, the functional difference between ventral and dorsal premotor cortices is still rather unclear. As an example, neuroimaging studies on synchronization FT tasks suggest that visual stimuli may preferentially activate vPMC, and auditory stimuli mainly engage the dPMC [25], but others have shown that vPMC is more active with auditory cueing and dPMC is active regardless cue modality [6]. So far, TMS research on FT tasks has yielded contradictory results about the effects of stimulation on dPMC [14,16,19], and has devoted poor attention to vPMC [17].

Taken together, these results show an incomplete picture regarding the role of vPMC in FT tasks, which in some cases may diverge from the function of dPMC.

The purpose of the present study is to investigate the involvement of vPMC in a synchronization–continuation FT task, as compared to a functionally relevant site, i.e., dPMC and an unrelated control site.

We administered an online TMS protocol to interfere with the activity of vPMC during the task. Specifically, we applied short trains of stimulation to grant the necessary spatio-temporal resolution that offline protocols cannot provide, for long-lasting repetitive stimulations are more prone to deeply affect unwanted target-adjacent areas and offer no temporal precision. Since vPMC is involved in online sensorimotor timing and motor control [6,26,27], as well as in time representation [8,20], we used periodic and continuous visual pacers in the synchronization phase. To magnify possible differences in TMS effects, we used a salient tapping finger (“Finger”) and an abstract hitting bar (“Bar”) as pacers. The stimuli shared analogous spatio-temporal characteristics, and called for a continuous visuomotor matching. However, the tapping finger is salient for the well-known visual sensitivity to human movement [28] and a higher stimulus–response similarity [29] with respect to the bar. In fact, the finger condition, as compared to Bar, may elicit a representation of the target interval that can be implemented at the motor level with a more direct, less demanding process. We indeed hypothesize that vPMC is engaged in the continuous sensorimotor matching, and that TMS interference is more evident when Bar is used.

2. Materials and methods

2.1. Subjects

Twelve right-handed subjects (10 males; age: mean 26, range 23–32) participated in the study. Handedness was assessed by using the Oldfield questionnaire [30]. The subjects had no musical training or performing experience since this is known to have an influence on FT performance [2]. A preliminary behavioral test evaluated the tapping performance: two subjects were excluded because they produced values falling outside ±2* standard deviation (SD) of the group mean. Participants signed their written informed consent before the experiment. The study, approved by the Ethics Committee of Helsinki University Central Hospital, was in compliance with the Declaration of Helsinki.

2.2. Task, stimuli, experimental design

The subjects performed the FT task according to the synchronization–continuation paradigm pressing the space bar of a computer keyboard with their right index finger. First, they had to synchronize their tap to a periodic continuous visual stimulus. When the stimulus was turned off, the subjects had to go on tapping at the same rate without interruption. The subject’s hand was out of sight and the tap was masked by white noise delivered through earphones, so that visual and acoustic feedbacks were not available for on-line correction.

The visual stimuli consisted in two sequences of images: a hinged bar hitting a horizontal line and a lateral view of a finger tapping on a pad (size: 720 × 500 pixels, Fig. 1a). The stimuli were presented against a black background on a 19 in. PC monitor at a distance of about 70 cm from the subject (resolution: 1024 × 600 pixels, size: 21 cm × 28 cm; visual angle: 33 × 44°). The sequences were presented at 25 frames per second so that movement of both Bar and Finger appeared continuous. The movement of both the Bar and Finger was presented 63 times in the synchronization phase. The 800-ms inter-stimulus interval was chosen on the basis of evidence that lateral PMC is active in the sub-second timing processes [31]. During the continuation phase the monitor was black, and participants were explicitly asked to press the space bar in correspondence with either the Bar or the Finger hitting ground. In a behavioral study [32] we observed that Bar and Finger pacers yielded similar SE values in a synchronization FT task.

Each subject underwent 6 measurements according to a randomized design of 2 (stimuli) × 3 (stimulation sites). Under each experimental condition, the subjects performed 63 taps in the synchronization phase (50.4 s) and 60 taps in the continuation phase (nominally 48 s). The first 3 taps in the synchronization phase were discarded from successive analysis to avoid the initial transitional effects. The subjects were given a rest period of 5 min between the measurements.

An ad hoc script was developed using the Presentation software application (version 11.3, Neurobehavioral Systems Inc.) to present the pacing stimuli, trigger the TMS pulses and collect the behavioral data.

2.3. TMS stimulation

Magnetic stimulation was delivered through a Nexstim eXima stimulator (Nexstim Ltd, Helsinki, Finland) and its biphasic figure-of-8 focal coil (loop average diameter 50 mm). An individual MRI-guided navigation system Nexstim eXima NBS was used to target the motor cortex hand area (for rMT assessment) and the stimulation sites.

The rMT of the right first dorsal interosseus (FDI) served as a reference for stimulation intensity. Single TMS pulses were delivered over the hand representation in the motor cortex and the corresponding motor evoked potentials (MEPs) were measured. A plastic foam attenuating the vibrations of the coil against the head was placed between coil and scalp. rMT was defined as the intensity that produced MEPs of less than 50 μV in 5 out of 10 consecutive stimulations. The motor evoked potentials were measured with a ME6000 EMG recorder and MegaWin software (version 3.0 b6, Mega Electronics Ltd., Kuopio, Finland).

A triple pulse at 900% of the resting motor threshold (rMT) of the FDI muscle was administered before every fourth pacing stimulus (15 times in all) at a frequency of 5 Hz, during the synchronization phase (Fig. 1b). More specifically, the three pulses were given 100, 300, and 500 ms after the third pacing stimulus onset. During the task, the subjects were comfortably seated on a reclining chair. TMS–click sound was masked by auditory white noise, and bone conduction was reduced thanks to a thin piece of plastic foam placed between the coil and the head.

The stimulation was delivered to three cortical sites: two premotor areas (ventral and dorsal) and a Control site (Fig. 1c). Ventral and dorsal premotor cortices were respectively defined as those portions of PMC inferior and superior to the virtual continuation of the inferior frontal sulcus [33]. The coil was positioned in such a way as to induce a maximal current flow (black arrows in Fig. 1c) oriented perpendicular to the precentral sulcus. As control, TMS was delivered along the midline at the intersection with the central sulcus, inducing a maximal palmar–anterior flow.

2.4. Data analysis

The parameters of interest were: (i) synchronization error (SE) in the synchronization phase: calculated as the difference between the onset of a tap and the onset of the stimulus; (ii) intertap interval (ITI) in the continuation phase: calculated as the time elapsed between the onsets of two successive taps; (iii) contact time (CT): calculated as the time elapsed between tap onset and offset. CT was evaluated both in the synchronization phase (CT-S) and in the continuation phase (CT-C). For all these parameters both mean values and within-trial variability, as
Fig. 1. Methods. Panel A: samples from the two visual sequences used as pacers, the Bar and the Finger. Panel B: experimental design. Panel C: surface view of the stimulation sites, vPMC, dPMC, and Control site.

assessed by SD, were calculated. In the synchronization phase, SE and CT data of the 4-tap cycles were grouped in Early ($T_0$ and $T_1$) and Late taps ($T_2$ and $T_3$). This grouping was based on the assumption that online TMS temporally excerpts local effects on stimulated tissues and the taps that are closer to magnetic pulses are more affected by our experimental manipulation. Mean SE and CT were averaged in each group, whereas the corresponding SD values were evaluated accounting for the propagation of measurement error according to the following equations:

$$SD_{Early}^2 = \frac{1}{2} SD_{T_0}^2 + \frac{1}{2} SD_{T_1}^2$$
$$SD_{Late}^2 = \frac{1}{2} SD_{T_2}^2 + \frac{1}{2} SD_{T_3}^2$$

A three-way RM-ANOVA with factors SITE (dPMC, vPMC, Control), PACER (Bar, Finger) and TIME (Early, Late) was used to analyze the mean values and variability of synchronization phase measures (SE and CT). Two-way RM-ANOVA with factors SITE (dPMC, vPMC, Control) and PACER (Bar, Finger) was used to analyze mean values and variability of Continuation phase measures (ITI, CT-C). Two-way and one-way RM-ANOVAs and Tukey’s honestly significant difference (HSD) post hoc tests were further used to analyze simple effects. Repeated measure analyses of variance (RM-ANOVAs) were run after having verified the required statistical assumptions. Normality was verified by means of the Kolmogorov–Smirnov test with Lilliefors’ correction. Sphericity assumption was evaluated with the Mauchly’s test and, in case of violation, the Greenhouse–Geisser correction was applied to recalculate the $F$-value. The effect sizes were measured using (1) partial eta squared for the three-way ANOVA and for the follow-up two-way ANOVAs, and (2) Cohen’s $d$ for correlated samples for simple effects. All statistical analyses were run by using custom made MatLab (Mathworks, Inc.) scripts or SPSS (SPSS, Inc.).

3. Results

3.1. The synchronization error

SE mean values were normally distributed in all conditions. Sphericity was violated only for the two-way interaction SITE $\times$ PACER ($W = 0.313, p = 0.01$) and the Greenhouse–Geisser correction ($\varepsilon = 0.593$) was used in this contrast.

The analyses on SE showed, under all conditions, the well-known phenomenon of negative asynchrony [2,34], i.e., the tendency of a tap to precede the pacing stimulus. The omnibus SITE $\times$ PACER $\times$ TIME three-way RM-ANOVA revealed a significant interaction between factors ($F(2,18)=6.28, p<0.01; \eta^2_p = 0.41$) (Fig. 2). In addition, the analysis showed significant main effects of TIME ($F(1,9)=9.0, p<0.02; \eta^2_p = 0.08$) and SITE ($F(2,18)=4.7,$
The three-way interaction was further investigated using two-way ANOVA follow-up tests with factors SITE and TIME separately for each pacer. In the Bar condition, the stimulation on each site affected SE differently, depending on the temporal distance from the TMS train ($F(2,18) = 9.8$, $p < 0.01$; $\eta^2_g = 0.52$). Indeed, post hoc analyses on factor TIME at each level of SITE showed that the stimulation of vPMC reduced tap anticipation (SE) in Early taps ($t(9) = 3.25$, $p < 0.01; d = 0.37$). Stimulation on dPMC and Control did not yield any significant effect on SE over time (dPMC: $t(9) = 0.30$, $p > 0.77$; d = 0.02; Control: $t(9) = 1.02$, $p > 0.33$; $d = 0.11$). Furthermore, in the proximity of the TMS train (Early) the stimulation of vPMC produced a significantly smaller tap anticipation than the stimulation of dPMC ($t(9) = 2.76$, $p < 0.02$; $d = 0.43$) or Control site ($t(9) = 3.35$, $p < 0.01$; $d = 0.63$). SE during the stimulation over dPMC showed intermediate values between those related to vPMC and Control site perturbations, but did not significantly differ from the latter ($p > 0.4$). Far from the stimulation pulses (Late) SE differences among sites were not significant ($p > 0.74$). SITE x TIME follow-up test on level Finger yielded no significant simple effects ($F(2,18) = 1.57$, $p > 0.23$). Taken together, these observations suggest that TMS has an early, site-specific (vPMC) effect when the Bar pacer is presented.

Within-trial SD of SE was normally distributed in all conditions. The sphericity assumption was not violated. SE variability was evaluated through a three-way RM-ANOVA with the same factors as for SE mean values. Only the main effect of TIME was significant ($SD_{Early} > SD_{Late}$: $F(1,9) = 18.2$, $p < 0.01$; $\eta^2_g = 0.90$), entailing that the TMS induced an increase in variability, regardless of site of stimulation or type of visual cue.

### 3.2. ITI in the continuation phase

ITI mean and SD values were normally distributed in all conditions. The sphericity assumption was not violated. ITI mean values and variability were analyzed by means of a two-way RM-ANOVA with factors SITE and PACER; there was no significant main effect or interaction. This suggests that TMS during the synchronization phase did not affect ITI in the continuation phase, a result in agreement with the observation in the SE analysis, showing that the TMS stimulation effect seems to decay soon after the first two taps.

### 3.3. Contact time

CT mean and SD values were normally distributed in all conditions. The sphericity assumption was not violated. The three-way RM-ANOVA (SITE x PACER x TIME) applied to mean values and variability of CT in the synchronization phase (CT-S) revealed neither interactions nor main effects. Two-way RM-ANOVAs (SITE x PACER) were used to evaluate CT mean values and variability in the continuation phase (CT-C); in both cases interaction and main effects were not significant. Therefore, in neither phase (synchronization or continuation) did our stimulation protocol have any effect on finger contact time during tapping (Table 1).

### 4. Discussion

Most TMS studies on FT tasks have focused on the dorsal aspect of the precentral gyrus [14,16,19]. One study investigating the role of vPMC evidenced only weak effects in an audiomotor synchronization task [17]. Here we show that TMS stimulation on vPMC, but not on dPMC, was effective in disturbing timed movements.

The perturbation was revealed by the alteration of SE values: taps were delayed, i.e., executed closer to the pacing stimulus, which resulted in a reduction of the negative asynchrony. Negative asynchrony is a well-documented manifestation of feed-forward control and event anticipation in FT synchronization tasks [2,34]. Our TMS protocol likely disturbed this anticipatory process. Indeed, it has been recently suggested that vPMC is involved in the representation of sequentially structured events, and is crucial for anticipation of external changes for a prompt and appropriate motor response [35].

Interestingly, the stimulation effects faded after the first two taps following the TMS pulses. This result informs us on the very short-term effects of this online TMS stimulation protocol on motor performance. A direct consequence was that the tapping performance in the continuation phase was not altered in terms of ITI size or variability. This observation implies that, on the whole, a solid representation of ITI could be set during the synchronization phase notwithstanding the stimulation, and the target interval was effectively reproduced in the successive phase. Another relevant observation is that the kinematic parameter of CT in the synchronization phase was not altered by TMS on premotor cortices. Our result is complementary to previous data showing altered tap durations when the stimulation is delivered on M1 [12]. This suggests that our TMS protocol interfered with a specific phase of the tapping cycle (tap anticipation), and, on a functional level, that premotor areas behave differently from M1 in FT tasks. Indeed, M1 is supposed to be more involved in the actual implementation of the motor plan rather than in timing control, whereas premotor areas are likely to be engaged in more cognitive functions.

The higher susceptibility to stimulation of vPMC, as compared to dPMC, may be explained in different ways. At a pure motor level,
Table 1

<table>
<thead>
<tr>
<th>Synchronization phase</th>
<th>SE</th>
<th>Finger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>-28 ± 13 (46 ± 4)</td>
<td>-44 ± 14 (38 ± 3)</td>
</tr>
<tr>
<td>Late</td>
<td>-39 ± 13 (59 ± 7)</td>
<td>-42 ± 12 (47 ± 5)</td>
</tr>
<tr>
<td>dPMC</td>
<td>-47 ± 15 (46 ± 5)</td>
<td>-46 ± 15 (45 ± 6)</td>
</tr>
<tr>
<td>Control</td>
<td>-57 ± 16 (47 ± 9)</td>
<td>-51 ± 14 (44 ± 6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuation phase</th>
<th>ITI</th>
<th>Finger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>140 ± 11 (18 ± 2)</td>
<td>136 ± 9 (17 ± 2)</td>
</tr>
<tr>
<td>Late</td>
<td>139 ± 9 (20 ± 2)</td>
<td>137 ± 6 (20 ± 2)</td>
</tr>
<tr>
<td>CT-S</td>
<td>136 ± 6 (19 ± 1)</td>
<td>145 ± 7 (20 ± 1)</td>
</tr>
</tbody>
</table>

vPMC has been observed to be preferentially involved in the control of distal movements, as finger tapping is; dPMC is essential for proximal movements [36]. With respect to sensorimotor functions in a triggered FT task, vPMC could be specifically involved when visual cues are presented, whereas dPMC might be more engaged by audioimotor transformations [25], but this issue is still under debate [6,37,38]. An intriguing explanation comes from neurophysiological studies on macaques. vPMC would be involved in matching action-associated visual information into a motor representation for guiding execution [39]. dPMC, instead, seems to play a key role in motor preparation [40], and its activity reflects the motor significance of the instructional cue irrespective of its modality [41]. In our experiment, on the one hand, activity perturbation in vPMC is likely to reflect its engagement in the fundamental visuomotor matching process needed for proper synchronization at each tap. On the other hand, TMS is less effective on dPMC as a consequence of its possible involvement in the less-demanding motor preparation of a simple, repetitive cued movement [42].

From a methodological point of view, it is argued that, besides interfering with local brain activity, TMS also induces unwanted effects, such as physical discomfort. Indeed, ventral stimulations may be perceived as more disturbing than dorsal ones, because temporal and face muscles can be activated as a secondary effect. Here we observed specific site-related effects only in the Bar condition, but not in the Finger condition. Therefore, the effect on vPMC is related to the type of pacer used in the synchronization task.

We explicitly used a salient pacer (tapping finger) and an abstract pacer (hitting bar). They both provide continuous guidance for finger tapping, but they are likely to elicit different representations of the target interval that, accordingly, requires diverse sensorimotor transformations. In fact, we hypothesized that a tapping finger would have fostered a more salient representation of the target ITI, thus requiring a more direct visuomotor transformation. It is well documented, indeed, that body-related information, such as hand and facial gestures, are recognized and imitated by newborns [43], and processed by specialized brain networks in adults [44]. Human biological motion has also been shown to be a salient type of visual stimulus [45] that activates sensorimotor and premotor regions [46–48]. Also, cortico-spinal excitability exhibits a similar modulation during the observation and execution of actions [49], and behavioral studies have shown that finger tapping is facilitated by the observation of congruent actions because of a high stimulus–response similarity [29]. All these data suggest that hand action observation not only activates sensorimotor areas, but also that such activation is site-specific and may prime actual motor execution. For the above-mentioned reasons, the Finger pacer might have provided a particularly salient stimulus to trigger synchronized actions. This saliency may facilitate the visuomotor transformation required for the task, by means of faster or simpler computations. In agreement with this idea, TMS affected the synchronization with the Bar pacer, but not with the Finger pacer. The action-salient tapping finger might have required less effort and/or recruit a more extended bilateral temporo-parieto-frontal neuronal network of areas. On the other hand, the action-abstract hitting bar might require more complex visuomotor matching, and induce a less stable interval representation, thus amplifying TMS interference effects on subjects’ performance.

In conclusion, to our knowledge, this is the first TMS study investigating the specific role of vPMC in visually guided FT tasks. Our novel online TMS protocol provided better spatial and temporal accuracy than classical offline rTMS protocols. We provide further evidence that vPMC, as part of a distributed network subserving motor timing, is likely to be involved in time representation and sensorimotor synchronization.

References


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