Neuropsychologia 50 (2012) 3729–3735

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Research Report

# 1 Hz rTMS of the left posterior parietal cortex (PPC) modifies sensorimotor timing

Vanessa Krause [a,b,c,*,1], Shahid Bashir [c,d,1], Bettina Pollok [a,b], Anuhya Caipa [c], Alfons Schnitzler [a,b], Alvaro Pascual-Leone [c,**]

[a] Heinrich-Heine-University Duesseldorf, Medical Faculty, Institute of Clinical Neuroscience and Medical Psychology, Universitaetsstr. 1, 40225 Duesseldorf, Germany
[b] Heinrich-Heine-University Duesseldorf, Medical Faculty, Department of Neurology, Germany
[c] Berenson-Allen Center for Noninvasive Brain Stimulation and Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA
[d] Autism Research and Treatment Center, Shaik AL-Amodi Autism Research Chair and Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

*Article history:*
Received 7 December 2011
Received in revised form
20 September 2012
Accepted 19 October 2012
Available online 26 October 2012

*Keywords:*
Repetitive transcranial magnetic stimulation (rTMS)
Posterior parietal cortex (PPC)
Sensorimotor timing
Anticipatory motor control
Synchronization

ABSTRACT

In order to investigate the relevance of the left posterior parietal cortex (PPC) for precise sensorimotor timing we applied 1 Hz repetitive transcranial magnetic stimulation (rTMS) over left PPC, right PPC and visual cortex of healthy participants for 10 min, respectively. The impact on sensorimotor timing of the right hand was assessed using a synchronization task that required subjects to synchronize their right index finger taps with respect to constant auditory, visual or auditory–visual pacing. Our results reveal reduced negative tap-to-pacer asynchronies following rTMS of the left PPC in all pacing conditions. This effect lasted for about 5 min after cessation of rTMS. Right PPC and visual cortex stimulation did not yield any significant behavioural effects. Since suppression of left PPC modified right-hand synchronization accuracy independent of the pacing signal's modality, the present data support the significance of left PPC for anticipatory motor control over a primary role in multisensory integration. The present data suggest that 1 Hz rTMS might interrupt a matching process of anticipated and real sensorimotor feedback within PPC. Alternatively, downregulation of left PPC activity may affect M1 excitability via functional connections leading to a delay in motor output and, thus, smaller tap-to-pacer asynchronies.


## 1. Introduction

Precise sensorimotor timing is essential for everyday activities, especially when quick and flexible adjustment of movements with respect to external changes is required. A well-established behavioural paradigm to study sub-second sensorimotor timing is the synchronization task requiring subjects to tap with their index finger in synchrony with a regularly occurring pacing signal. From auditory pacing it is known that subjects usually tap *prior* to the actual pacing signal while having the impression of tapping in exact synchrony, a phenomenon known as *negative asynchrony* (Repp, 2005). For visual pacing, both positive and negative asynchronies have been observed. In general, visually-guided synchronization seems to be closer to the pacing signal as compared to auditory synchronization, although tap-to-tap variability is increased (Krause, Pollok et al., 2010; Pollok, Krause, Butz, & Schnitzler, 2009; Repp, 2005).

The brain network subserving sensorimotor timing comprises primary sensorimotor cortices (S1/M1), premotor and supplementary motor cortices (PMC/SMA) as well as posterior parietal cortex (PPC), thalamus and cerebellum (Jancke, Loose, Lutz, Specht, & Shah, 2000; Krause, Schnitzler et al., 2010; Pollok, Gross, Muller, Aschersleben, & Schnitzler, 2005; Pollok et al., 2009; Schnitzler, Timmermann, & Gross, 2006). A critical role within this cerebello-thalamo-cortical network has been ascribed to the PPC which is assumed to fulfil two main functions: (i) integration of multisensory information; as well as (ii) anticipatory motor control (Andersen & Buneo, 2002; Andersen & Cui, 2009; Blakemore & Sirigu, 2003; Creem-Regehr, 2009; Culham, Cavina-Pratesi, & Singhal, 2006; Culham & Valyear, 2006). Anticipation of external cues as well as feedback of one's own movements is assumed to be due to an internal model located in the cerebellum. The PPC may hold the anticipation until reafferent information from the actual movement is available and matches both information (Blakemore & Sirigu, 2003). Information may then be sent back to the cerebellum in order to update the internal model in favour of subsequent movements. In line with

* Corresponding author at: Heinrich-Heine-University Duesseldorf, Medical Faculty, Institute of Clinical Neuroscience and Medical Psychology, Universitaetsstr. 1, 40225 Duesseldorf, Germany. Tel.: +49 211 81 12161; fax: +49 211 81 13015.
** Corresponding author at: Berenson-Allen Center for Noninvasive Brain Stimulation and Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA.
*E-mail address:* Vanessa.Krause@uni-duesseldorf.de (V. Krause).
[1] Authors contributed equally.

0028-3932/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuropsychologia.2012.10.020

this hypothesis, alterations of the functional interplay between PPC and cerebellum depending on the predictability of the pacing signal were shown (Pollok, Gross et al., 2008). Furthermore, PPC is assumed to be relevant for the integration of multisensory information (Andersen & Buneo, 2003; Creem-Regehr, 2009). Since auditory, visual and tactile-kinaesthetic information converge in parietal regions, PPC has been proposed as sensorimotor interface responsible for both the multisensory conversion and its integration with ongoing movements and movement intentions (Andersen & Buneo, 2002; Buneo & Andersen, 2006).

Application of repetitive transcranial magnetic stimulation (rTMS) with different frequencies and protocols allows the investigation of causal relationships between stimulated brain regions and behavioural outcomes. While there is definite intra- and inter-subject variability in the effects of rTMS (Maeda, Gangitano, Thall, & Pascual-Leone, 2002; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000), in most instances, low-frequency, continuous rTMS with 1 Hz yields a transient suppression of activity in the directly targeted brain region, while high-frequency rTMS results in a transient facilitation (Chen, 2000; Hallett, 2007; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Valero-Cabre, Pascual-Leone, & Rushmore, 2008; Valero-Cabre, Payne, Rushmore, Lomber, & Pascual-Leone, 2005). Thus, downregulation of left PPC using rTMS with 1 Hz offers an opportunity to assess its causal role in sensorimotor timing.

Additionally, it remains elusive to what extent early information processing in primary sensory cortices is involved in sensorimotor timing. Since sensory processing is supposed to be more important for visual synchronization as opposed to auditory synchronization (Jancke et al., 2000; Pollok et al., 2009), it is likely that the visual cortex is involved in sensorimotor synchronization with respect to visual pacing. Contrasting rTMS effects on cortical regions associated with early visual and higher cognitive processing, like PPC, promises insights into the control of sensorimotor timing in modality-specific synchronization tasks.

The aim of the present study was to shed further light on the distinct role of the PPC in precise sensorimotor timing. To this end, activity in left PPC, right PPC and visual cortex was modulated using rTMS and the impact on a synchronization task was assessed. Assuming that PPC is crucial for integration of multisensory information, we hypothesized that sensorimotor timing should be affected by PPC rTMS particularly for auditory–visual pacing. On the contrary, sensorimotor timing should be affected independently of the pacing signal's modality in case PPC is rather relevant for anticipatory motor control. In case sensorimotor timing with respect to visual pacing rather relies on processing in early sensory as compared to higher cognitive cortices, visual cortex rTMS is hypothesized to influence visual synchronization performance.

## 2. Materials and methods

### 2.1. Subjects

We studied 13 healthy, right-handed subjects (9 male, 4 female; age 24.08 $\pm$ .87 years; mean $\pm$ standard error of mean; range 20–31 years) who did not have contraindications to receive TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). All subjects gave their written informed consent prior to the study, which had been approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All subjects had normal or corrected to normal sight and were classified as right-handed ($1.94 \pm .03$) by means of a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971). For right-handedness a minimum score of $+1$ was required (minimum value $-2$ indicating left-handedness, maximum value $+2$ indicating right-handedness). At the time of the study subjects reported not to be taking any medications or drugs that might have affected cortical excitability or altered cognitive function. All subjects had normal physical and neurological exams and had participated in previous TMS sessions tolerating TMS without any side-effects or complications.

### 2.2. TMS equipment

We employed a frameless stereotactic navigation system (Nexstim Ltd, Helsinki, Finland) equipped with a magnetic stimulator (MagPro, MagVenture A/S, Farum, Denmark) and a Nexstim 59 mm mean winding diameter figure-of-eight TMS coil type (201383P) delivering biphasic pulses. Subjects remained silent during the study to avoid speech-induced modulation of cortical excitability. Subjects were asked to keep their eyes open throughout the experiment. Prior to TMS all subjects underwent a high-resolution T1-weighted structural magnetic resonance imaging (MRI) scan (3.0 T GE MRI scanner, GE Healthcare). Imaging data were fed to the navigation software (eXimia 3.1, Nexstim Ltd, Helsinki, Finland) for automatic 3-D brain reconstruction that was used to guide navigation and deliver TMS over the targeted regions (left PPC vs. right PPC vs. visual cortex). At the end of each session, the location of the stimulated sites was plotted using Nexstim stereotactic infrared registration to each subject's structural MRI scan.

### 2.3. Identification of rTMS brain targets

For rTMS of left and right PPC, stimulation was applied over locations corresponding to the anatomical delineation of left and right angular gyrus. Right PPC stimulation served as control condition since subjects performed the task with the right hand only. The stimulation sites were identified on each subject's MRI scan and co-registered with scalp coordinates. Visual cortex was defined as the occipital brain region encompassing the striate cortex from which TMS induced phosphenes in central visual field (Walsh & Pascual-Leone, 2003). Mean Talairach coordinates of stimulation sites were $-40 \pm 1.41$ (mean $\pm$ standard deviation), $-50 \pm 1.28$, $51 \pm 1.79$ (left PPC); $40 \pm 1.15$, $-51 \pm 1.30$, $50 \pm 1.30$ (right PPC) and $18 \pm 1.59$, $-98 \pm 1.24$, $2 \pm .90$ (visual cortex).

Intensity of rTMS was adjusted to 90% of individual phosphene thresholds measured using single pulse TMS and the adaptive staircase method, i.e. stimulation intensity was decreased when subjects reported phosphenes, and was increased when absence of phosphenes was reported. Mean phosphene threshold was $59.38\% \pm 1.48\%$ of stimulator output. Mean stimulation intensity was $57.88\% \pm 1.92\%$ of stimulator output. 1 Hz rTMS was applied for 10 min in three separate sessions targeting right PPC or left PPC or visual cortex. The order of stimulation sessions was counterbalanced across subjects.

### 2.4. Behavioural paradigm

Sensorimotor synchronization performance was assessed using a synchronization task differing with respect to the pacing signals' modalities (auditory (A), visual (V), or auditory–visual (AV)). Subjects performed the synchronization tasks in separate runs with their right index finger. The duration of each run was 35 s resulting in 315 s throughout the experimental session. The pacing signals were presented regularly with a constant inter-stimulus interval of 800 ms. In the A condition, the auditory signal consisted of a binaural click (sine-wave, duration 10 ms). In the V condition, the visual signal was a red circle appearing in the middle of the screen with a diameter of 3 cm corresponding to 3.4° of visual angle and a duration of 10 ms. In the AV condition, the signal comprised both the auditory click and the visual circle presented with the same onset.

### 2.5. Experimental set-up and data collection

Subjects were comfortably seated in the TMS chair with a distance of .5 m to a computer screen. They were asked to fixate a grey cross on a black background in the middle of the screen in order to minimize eye movements. Subjects performed continuous flexions and extensions of the right index finger—thereby pressing the space bar on the computer keyboard as closely synchronized with the pacing signals' onsets as possible. The onset of finger taps was determined as soon as the space bar was pressed. Stimuli were presented and controlled with the help of a Windows laptop using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA).

Prior to task recording, subjects were given the opportunity to get familiarized with the task for one trial of the AV condition. Subsequently, each subject participated in a baseline synchronization trial consisting of three runs (A, V, AV) before rTMS was administered. Immediately after rTMS intervention, subjects were required to perform the three synchronization runs again followed by a rest period of 5 min. Then the three runs were repeated (Fig. 1). The order of synchronization runs was counterbalanced across sessions and subjects, but within one session the order of runs remained constant.

### 2.6. Data analysis

Sensorimotor timing accuracy was determined by the so-called mean negative asynchrony – corresponding to the mean temporal distance between onset of finger taps and pacing signals – and the mean tap-to-tap variability. In each run, the first three taps were discarded from further analysis. Values below and above