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Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans

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Abstract

Imaging and lesion studies suggest that the cerebellum is involved in the self-generation of timed motor responses. Using repetitive transcranial magnetic stimulation (rTMS), we studied the effects of transient disruption of the lateral or medial cerebellum on a paced-finger-tapping task (PFT). Results show greater variability on the PFT task following a 5 min train of 1 Hz rTMS to the medial cerebellum. Magnetic stimulation of the lateral cerebellum or motor cortex, and sham stimulation, had no effect on performance. Expanding the results of neuroimaging studies, these data show the causal link between activity in the medial cerebellum and the production of timed movements. This is the first demonstration of the feasibility of transiently disrupting the cerebellum by rTMS and inducing behavioral effects. This method of 'virtual lesions' can expand the study of the role of the cerebellum in motor control and cognition. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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The cerebellum is believed to be involved in the temporal representation of information. One measure of timing function is the paced finger-tapping (PFT) task in which subjects must replicate with their index finger a sequence of stimuli separated by a constant time interval. Patients with cerebellar lesions have been shown to be less accurate than normal controls on the PFT task and on perceptual judgements requiring precise timing [6]. Using the PFT task, Ivry et al. [5] reported that damage to the lateral cerebellum (LC) causes deficits in central processes (i.e. timing per se) while lesions of the medial cerebellum (MC) impairs the implementation of correctly timed responses [5]. In normal subjects, imaging studies have also provided evidence for cerebellar implication in the production of timed motor responses. Activation of the lateral and vermal regions of the cerebellum was observed during variations of the PFT procedure isolating the timing components of the task [8,18]. Furthermore, timing processes were also found to be located in the superior parts of the vermis and cerebellar hemispheres during a task in which subjects had to estimate time differences between intervals [9] and differences in velocity of somatosensory stimuli [10].

The converging imaging and lesion data thus seem to point to an active role for the cerebellum in timing functions. However, imaging studies only provide a correlational link between brain activation and behavior while data obtained from brain-damaged subjects can be affected by a number of factors including size of the lesion, general cognitive impairments resulting from the brain injury and plastic brain reorganization after the insult. One way to investigate the causal link between brain activity and performance in normal subjects is transcranial magnetic stimulation (TMS), a technique that transiently disrupts the function of a given cortical target [3,17,23]. Repetitive TMS (rTMS) affects the activity of targeted brain areas for several minutes beyond the end of stimulation by modulating cortical excitability. It is believed that slow rTMS at frequencies of ≤ 1 Hz decreases cortical excitability while stimulation at higher frequencies increases excitability [13,14,16]. In turn, this transient disruption can lead to behavioral effects. For example, slow rTMS to the visual cortex has been shown to significantly reduce visual cortex excitability [1] and impair performance on a visual perception and visual imagery task [12]. Although we know of no study detailing the behavioral effects of rTMS applied to

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cerebellar structures, single pulse TMS over the cerebellum has been shown to decrease motor cortex excitability [21,22,24] and modulate visually guided saccades [4] and smooth pursuit eye movements [15]. In the present study, we used slow rTMS to the cerebellum to investigate its role in timing functions using the PFT task in normal subjects.

Seven right-handed healthy subjects (one female) aged 28–38 were used in this experiment. All were familiar with TMS but naive to the aim of the study. Written informed consent was obtained from all subjects. This study was approved by the Institutional Review Board and rTMS was applied under an Investigational Device Exemption from the Food and Drug Administration. TMS was performed with a 70 mm figure-of-eight coil and a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK). Subjects were first fitted with a tight lycra cap to allow marking of stimulation sites and seated in a chair where the motor threshold was assessed. Right hemisphere motor threshold was defined as the minimal intensity of stimulation capable of inducing motor evoked potentials (MEPs) greater than 50 μV peak-to-peak amplitude in at least six out of ten trials. The site of stimulation was the scalp position which induced MEPs of maximal amplitude in the left first dorsal interosseus muscle. Subjects were then placed in front of a computer screen (viewing distance 50 cm) where the task was performed. The participants saw a series of 10 black squares on a white background flashed at a constant interval (475 ms) and attempted to replicate this series by tapping on a keyboard with their left index finger 10 times following presentation. The series was repeated 12 times for each rTMS condition. The task was designed to last approximately 3 min, as studies using 1 Hz rTMS trains to the motor cortex [2] and applying rTMS to non-motor areas during cognitive tasks (see Ref. [12]) have shown that the disruption lasts for approximately half the duration of the rTMS train applied. Performance on the task was evaluated immediately following a 5 min train of 1 Hz rTMS to the stimulation sites (Fig. 1A) at an intensity of 90% of the motor threshold. The coil was placed tangentially to the scalp with the handle of the coil pointing dorsally along the midsagittal axis of the subject's head. The targeted areas were: (1) the site where motor threshold was determined (MT); (2) MC (1 cm below inion); (3) left LC (1 cm below inion and 3 cm lateral to midline); (4) sham at the MC location (coil held at 90° from scalp). Overall, each subject received 300 stimuli per train, per stimulation site, for a total of 1200 (300 were sham). All subjects tolerated well rTMS to the cerebellum, although some reported a mild discomfort due to muscle twitching. Stimulation site order was counterbalanced between subjects and a 10 min rest period was used between conditions. Mean interval between key presses and standard deviations (SD) were calculated for each condition in each subject. SD was used as the measure of variability.

Fig. 1B summarizes the results. The average overall inter-

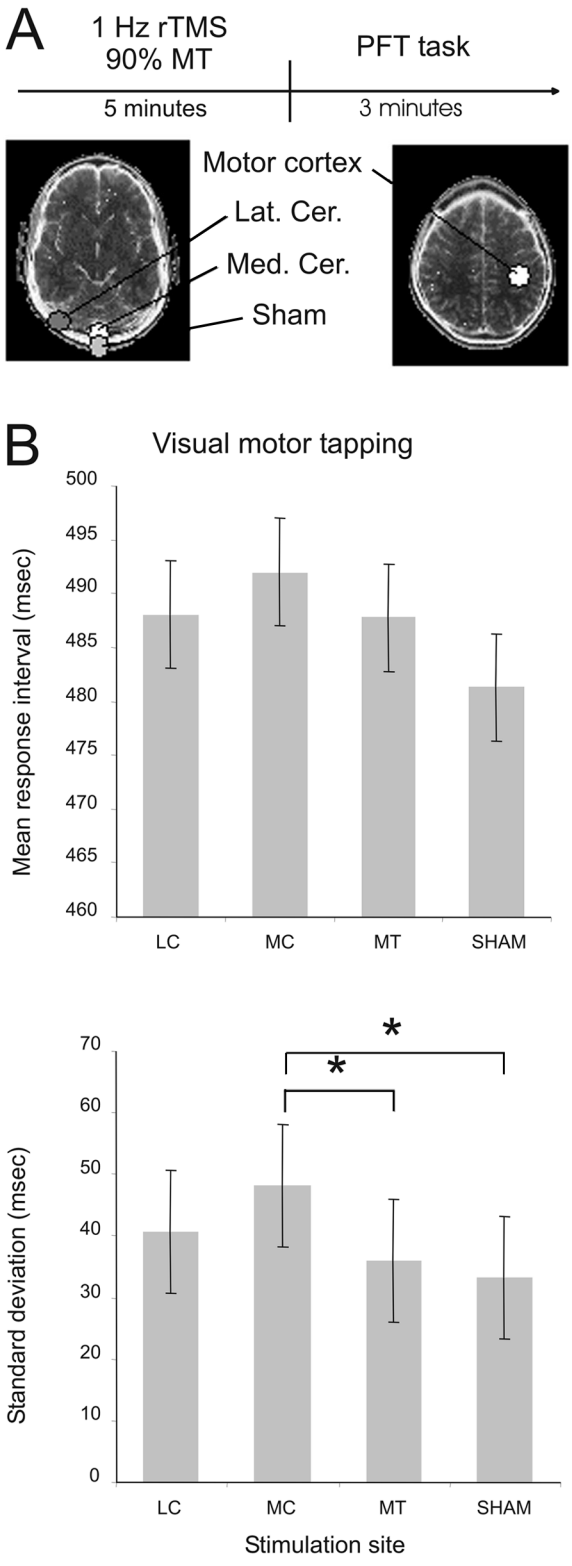

Fig. 1. (A) Experimental design and anatomical MRI showing the rTMS stimulation sites. The sequence is repeated for each stimulation site and is counterbalanced across subjects. (B) Mean inter-response intervals and standard deviations for each rTMS stimulation site. LC, lateral cerebellum; MC, medial cerebellum; MT, site where motor threshold was determined. *significant difference ($P < 0.02$).

response-interval (IRI) across all of the conditions was 487.28 (SD = 39.47) and there were no significant differences across rTMS conditions (repeated measures ANOVA; $F_{3,18} = 0.93$, $P = 0.45$). The average for the individual conditions were as follows: LC rTMS (M = 488.05, SD = 40.74), MC rTMS (M = 491.96, SD = 48.08), MT rTMS (M = 487.78, SD = 35.92), and Sham rTMS (M = 481.31, SD = 33.15). The critical performance measure was the standard deviation of the 108 IRIs produced in each condition. An overall significant difference in variability between the four rTMS conditions was demonstrated by a one way repeated measures ANOVA ($F_{3,18} = 6.34$, $P < 0.01$). Post-hoc direct comparisons of the variances were then made between the groups using Tukey's test. It was found that the MC rTMS condition had a significantly higher variance than the Sham rTMS condition ($P < 0.01$) and the MT rTMS condition ($P < 0.02$). None of the other conditions differed significantly from Sham rTMS or from each other (all P's > 0.05).

The results reveal that rTMS delivered to the medial cerebellum increases the variability in self-paced attempts to replicate an external sequence in normal subjects. This is consistent with data showing activation of the vermis during motor [8,18] and perceptual [9,10] timing and supports the notion that the cerebellum acts as a specialized module for timing [7]. However, rTMS to the lateral part of the cerebellum failed to significantly impair the finger tapping task. This is at odds with the data of Ivry and colleagues [5] in lesioned patients which suggest that the temporal functions of the cerebellum are controlled by the lateral cerebellum as opposed to the vermis, and with imaging data pointing to activity within the cerebellum restricted to the hemispheres in a memory-timed movement task [11]. However, a recent fMRI study showed medial cerebellum activation, rather than lateral cerebellum activation, during a time perception task [20]. As noted by Penhume and collaborators [18], demands on the cerebellar timing system might be greater during visual tasks than during auditory tasks such as the one used in the patient study [5]. This is supported by the fact that behavioral variability during a PFT task is greater in a visual compared to an auditory condition and that the visual task also produces stronger vermal activation [8]. The increased variability following medial cerebellum stimulation in the present study might thus be explained by the additional resources needed to process timing cues in a visual task. This cannot explain, however, the absence of an effect following magnetic stimulation of the lateral cerebellum. The simplest explanation would be that the TMS coil was not directly overlying the cerebellar hemisphere regions involved in timing functions. These areas might also be deeper within the lateral cerebellum, requiring a stronger magnetic output to reach them. For these reasons, the fact that rTMS to the lateral cerebellum does not alter response timing only reflects the fact that at this intensity and location rTMS had no effect on the PFT and in no way rules out a role of the lateral cerebellum in timing functions. Varying both location and intensity of stimulation might therefore yield different results.

The effect demonstrated here shows that repetitive TMS can transiently disrupt activity within the medial cerebellum, possibly by decreasing neuronal excitability. In turn, this inactivation can impact behavioral output. It is important to note that the cerebellum is only a part of a distributed network which is believed to mediate timing functions [19]. Indeed, the supplementary motor area, sensorimotor cortex and prefrontal cortex, among others, have also been implicated in the generation of timed movements [8,10,19]. This suggests that the cerebellum's involvement in timekeeping functions might be secondary to sensorimotor processes, matching temporal information from sensory input with motor systems [18,19]. In addition, activation of the vermis during a time perception task was found to occur later in the course of a trial (before and during movement execution), suggesting cerebellar involvement in sensory integration rather than explicit timing [20]. We cannot rule out the possibility that rTMS to the cerebellum resulted (trans-synaptically) in more widespread effects along the functional network, accounting in part for the behavioral results. One can assume, however, that the rTMS effects should be greatest at the stimulated site. Furthermore, trans-synaptic effects to primary motor cortex or supplementary motor area are unlikely to account for the results presented here since rTMS to M1 did not affect the PFT task. Despite the large network of brain areas contributing to the production of timed movements, our results suggest that disruption of a small part of the medial cerebellum is sufficient to disturb the production of timed movements. This is the first demonstration of rTMS over the cerebellum in a "virtual lesion" setting. This approach makes it possible to evaluate the role of the cerebellum in motor and cognitive tasks and thus provides an interesting tool for the study of cerebellar function in normal subjects.

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