Role of the Cerebellum in Externally Paced Rhythmic Finger Movements

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Submitted 11 October 2006; accepted in final form 25 April 2007

Del Olmo MF, Cheeran B, Koch G, Rothwell JC. Role of the cerebellum in externally paced rhythmic finger movements. J Neurophysiol 98: 145–152, 2007. First published April 25, 2007; doi:10.1152/jn.01088.2006. Several studies have suggested that the cerebellum has an important role in timing of subsecond intervals. Previous studies using transcranial magnetic stimulation (TMS) to test this hypothesis directly have produced inconsistent results. Here we used 1-Hz repetitive TMS (rTMS) for 10 min over the right or left cerebellar hemisphere to interfere transiently with cerebellar processing to assess its effect on the performance of a finger-tapping task. Subjects tapped with their right index finger for 1 min (synchronization phase) with an auditory or visual cue at 0.5, 1, or 2 Hz; they continued for a further 1 min at the same rate with no cues (continuation phase). The blocks of trials were performed in a random order. rTMS of the cerebellum ipsilateral to the movement increased the variability of the intertap interval but only for movements at 2 Hz that were made while subjects were synchronizing with an auditory cue. There was no effect on the continuation phase of the task when the cues were no longer present or on synchronization with a visual cue. Similar results were seen after stimulation over the contralateral dorsal premotor cortex but not after rTMS over supplementary motor area. There was no effect after rTMS of the ipsilateral right cervical nerve roots or over the ipsilateral primary motor cortex. The results support the hypothesis of neural network for event-related timing in the subsecond range that involves a cerebellar-premotor network.

INTRODUCTION

Timing is integral to processing sensory information and movement performance, yet our knowledge of the central neural mechanisms involved is still incomplete. Several imaging and clinical studies have suggested a role for cerebellum in the timing of movement and sensation, particularly for short intervals of time in the subsecond range (Rao et al. 2001; Spencer et al. 2003). Patients with lesions of the cerebellum showed increased variability in the intermuscular time relationships during numerous motor tasks (for review see Milak et al. 1997; Thach et al. 1992) and they are impaired on nonmotor tasks that require a precise temporal representation. Similarly there is a wealth of imaging studies that show involvement of cerebellum in motor and nonmotor timing (Lewis and Miall 2003; Macar et al. 2002; Penhune et al. 1998).

More recently Spencer et al. (2003) have made a distinction between the role of the cerebellum in event-based and emergent timing. The former involves tasks that require formulation of an explicit temporal goal that can be evaluated for success or failure and then used to update the timing of the next movement in a longer sequence. In contrast, emergent timing refers to timing that is the result of dynamic processes that interact to cause regular behaviors. Tapping in time to an external cue is an example of event-based timing, whereas repeatedly drawing circles on paper or in the air produces regularity through emergent properties of the neuromuscular system such as stiffness and muscle force that interact to give rhythm to movement.

Although clinical and imaging approaches give important information about the possible sites of timing-related activity, neither allow definite conclusions about mechanism: for example, imaging studies only show correlations with metabolic activity that is itself gathered over a period of seconds, whereas clinical/lesion studies are complicated by the possible reorganization of brain activity that occurs in chronic disease or follows a lesion. Because of this, several groups have begun to supplement these methods with transcranial magnetic stimulation. They have made use of the fact that single-pulse TMS can disrupt function in stimulated areas for short periods of ~200 ms, whereas repeated TMS leads to changes in the excitability of the stimulated area that outlast the period of stimulation by 30–60 min (Huang et al. 2005). In several cortical areas, these changes in physiology are linked to behavioral changes in movement performance (Stenroos et al. 2003). The implication is that TMS can be used to probe the role of brain regions in particular tasks.

In the field of timing studies, rTMS has been applied over the right dorsolateral prefrontal cortex (Jones et al. 2004; Koch et al. 2003) where it leads to underestimation of time perception and reproduction. Recent studies have reported that rTMS over the primary motor (M1) or premotor cortex makes subjects tap closer in time to a regular auditory pacing cue but has no effect on how well subjects adjust their tapping to changes in timing of cues (Doumas et al. 2005). In contrast, single pulses of TMS over M1 have been shown to increase variability of intertap intervals in the continuation phase of a fingertapping task when an auditory pacing cue has been removed (Verysten et al. 2006). This increase in variability was thought to reflect disruption of response implementation processes rather than addition of noise to an integral timing mechanism (Verysten et al. 2006; Wing and Kristofferson 1973). However, when the TMS is applied to the cerebellum, the effect on timing is less clear. Theoret et al. (2001) found that rTMS over medial cerebellum increased variability of timing in a paced fingertapping task, whereas Jancke et al. (2004) found no effect if rTMS was given over lateral cerebellum.

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bellum. The aim of the present study was to test whether rTMS can be used to examine the role of the cerebellum in motor timing, and if so, whether it can identify the postulated cerebellar role in timing short rather than long intervals, particularly in tasks requiring event-based timing. We also tested whether rTMS could be used to study the role of dorsal premotor cortex in such tasks given its strong connections with cerebellum and its postulated role in an explicit timing circuit centered on the cerebellum.

METHODS

Subjects and general procedure

A total of 14 healthy right-handed subjects participated in this study [mean age: 28.2 ± 4.6 (SD) yr; 10 males and 4 females]. Some subjects took part in more than one experiment. Written informed consent was obtained from all subjects. Experimental procedures conformed to the declaration of Helsinki and were approved by the local ethics committee.

The main intention in the series of experiments was to examine performance of a tapping task with the right index finger following application of rTMS over different cortical and cerebellar sites. In all experiments performance was recorded before rTMS (pre-rTMS), immediately after the rTMS (post-rTMS) and 15 min after the rTMS (+15 min).

Experiment 1: effect of rTMS over ipsilateral M1, left or right cerebellar hemisphere on auditory paced-no paced finger tapping (synchronization-continuation task)

Nine subjects tapped on the surface of a force transducer with their right index finger. The force of the tap was not specified; subjects were simply told to tap comfortably. Force was recorded with a sampling frequency of 1 kHz. The subjects were instructed on the operation of the strain gauge device and given practice to familiarize themselves with it. No visual feedback or information about their performance was given to the subjects. Subjects completed three conditions in which they tapped in synchrony to a series of 50-s duration tones for 1 min (synchronization), after which the tone stopped, and they continued to tap at the same pace for 1 min (continuation phase). Three blocks of trials were performed in random order in which the tones were separated by 2,000 ms (0.5 Hz), 1,000 ms (1 Hz), or 500 ms (2 Hz). The time of the pacing tone was not recorded in these experiments.

TMS PROCEDURE. Subjects were seated comfortably in a reclining dentist’s chair with their hands resting on a pillow and the head on a U-shaped adjustable head support. We recorded test motor-evoked potentials (MEPs) from first dorsal interosseus muscle (FDI) with Ag/AgCl electrodes (diameter: 9 mm each) using a tendon-belly montage with an interelectrode distance of ~3 cm. Electromyographic (EMG) signals were amplified and filtered with Digitimer D360 amplifiers Digitimer, Welwyn Garden City, Herts, UK) and then passed through a CED 1401 laboratory interface (Cambridge Electronic Design, Cambridge, UK). The EMG signals were band-pass filtered (low-pass filter: 5 kHz; high-pass filter: 20 Hz) and sampled at 5 kHz with the gain usually adjusted to be 2,000 times. We evoked responses in the target muscle with single pulse TMS. Magnetic stimuli were delivered by a Magstim 200 stimulator connected to a figure of eight-shaped coil with wing diameters of 90 mm (The Magstim Company, Whitland, Dyfed, UK). The coil was placed tangentially to the scalp with the handle pointing backward and rotated away from the midline by 45°. The coil was moved over the hand area of the motor cortex to define point in the scalp (hot spot) where stimulation elicited the largest MEPs in the FDI. After the position of the hot spot was established, the stimulation intensity was decreased in steps of 1% to find the resting motor threshold (RMT). RMT was defined as the intensity where MEPs of ≥50 μV were observed in ≥50% of 10 consecutive stimulations.

rTMS was delivered in three sessions separated by an interval time of ≥1 wk. In each session at random, rTMS was applied to right cerebellar hemisphere (rCH), left cerebellar hemisphere (lCH), or right motor area (ipsilateral M1); all the subjects received all three rTMS treatments. The ipsilateral M1 was chosen as a control site to test for nonspecific effects of the auditory and somatosensory sensations produced by TMS pulses. rTMS consisted of a 10-min train at 1 Hz and 90% of RMT. rTMS over the lateral (left or right) CB was applied 1 cm under and 3 cm left/right to the inion following the same scalp coordinates as Theroret et al. (2001). The coil was positioned tangentially to the scalp, with the handle pointing superiorly. The current in the coil was directed upward, which induced downward current in the cerebellar cortex. For the right M1, the coil position was located as for determination of the hot spot on the left M1 (above).

In two subjects, MRI-guided frameless stereotaxy (Brainsight Frameless, Rogue Research) was used to determine the approximate site of stimulation in the cerebellum. In addition, we could measure the distance of the cerebellum from the coil and compare that with the distance of the coil from M1 when stimulating the motor area (Fig. 1A). This allowed us to calculate the approximate intensity of stimulation at the cerebellum relative to that used to activate M1 using the method of Stokes et al. (2005). This equation indicates that a simple linear correction can be applied to the commonly used MT-based expression of stimulator output to account for the effects of distance: AdjMT% = MT + m × (Dscip − Daim), where AdjMT% is the adjusted MT in percentage stimulator output, MT is the unadjusted MT in percentage stimulator output, Dscip is the distance between the scalp and M1, Daim is the distance between the scalp and a second cortical region (SiteX), and m is the spatial gradient relating MT to distance. In cases where the spatial gradient is unknown, an approximate derivation of distance-adjusted MT can be obtained by replacing m with the average gradient obtained in the Stokes’s study (m = 3).

FIG. 1. A, top left: site of stimulation in 1 subject with the transcranial magnetic stimulation (TMS) coil co-registered to the subject’s magnetic resonance image (MRI) usingBrainsight. The coil was positioned 3 cm to the right and 1 cm under the inion. Top right: distance between the scalp and the cerebellum, calculated withBrainsight, for the same coil position, in the same subject. B: example of the performance of 1 subject before rTMS (thick continuous line) and after repetitive TMS (rTMS, thin lines) for the 2-Hz auditory paced finger-tapping task. The vertical axis indicates the intertap interval (0.50 ms is the reference interval) and the horizontal axis indicates the tap number. Note the higher dispersion in the subject’s response after rTMS.
Experiment 2: ipsilateral cervical motor root stimulation

Six subjects that participated in experiment 1 were asked to perform a synchronization-continuation task at 2 Hz. We investigated the effect of 1-Hz rTMS over the ipsilateral cervical motor root. A standard figure-8 coil was placed over the right neck area lateral to the C7 vertebra at an intensity sufficient to evoke a small twitch in neck and shoulder muscles equivalent to that seen when the stimulus was over the cerebellum (Gerschlager et al. 2002).

Experiment 3: effect of sensory modality

Six of the nine subjects that participated in experiment 1 were asked to perform a synchronization task in the presence of a visual cue for comparison with performance in the cued auditory task. In this case, the visual stimuli were delivered by an LED positioned in front of the subject. The duration of the visual stimulus was the same (50 ms) as for the auditory condition. We examined tapping only at 2 Hz with rTMS over the right lateral cerebellum.

Experiment 4: rTMS over dorsal premotor cortex or SMA

In other seven subjects (2 of them already participated in the previous experiments), we investigated the effect of 1-Hz rTMS (90% RMT) over the dorsal premotor cortex (PMd) or supplementary motor area (SMA) on the auditory paced synchronization-continuation task at 2 Hz. The coil position for left PMd was defined relative to the position of the motor hot spot for the right FDI. A positron emission tomographic (PET) study showed that the PMd is located ~2 cm anterior to the motor cortex hand area (Fink et al. 1997). To minimize motor cortex activation during TMS, we calculated for each subject 8% of the distance between the nasion and inion (~3 cm) and defined the premotor area as this distance from the hot spot of the motor cortex hand area (Munchau et al. 2002). The coil was held with the handle pointing laterally so to induce a medially directed current in the stimulated cortex. According to previous studies (Pascual-Leone and Hallet 1994) stimulation of the SMA employed a figure-8 coil positioned 3 cm anterior to C3 of the 10–20 EEG system in the sagittal midline. The coil was held with the handle pointing posterior, so as to induce in the underlying brain tissue a current flowing with a posterior–anterior direction.

Data analysis

Intertap intervals (ITI) were defined as the time between two consecutive peaks of force. ITIs with a value larger than the mean plus 2 SD were omitted from the analysis. For each condition (pre-rTMS, post-rTMS, and +15 min), mean ITIs and their coefficient of variation (CV) were computed. CV (%) is an indicator of temporal variability, where CV (%) = (SD/mean)/100. The mean force during each trial was also computed. In each trial, the first four taps were excluded from the analysis. A more complex analysis on the force-pulses to determine the style of tapping was not performed due to the limitations of the dataset.

In experiment 1, a four-way repeated-measures ANOVA was performed with main factors of site (rCH, ICH, and M1), cue (synchronization and continuation), time (before, after, 15 min), and frequency (0.5, 1, 2 Hz). In the following experiments, a two-way ANOVA was used to compare the effect of cervical root stimulation [main factors of time (before, after, 15 min) and cue (synchronization, continuation)] or different sensory modalities [main factors of modality (auditory, visual) and time (before, after, 15 min)]. A three-way ANOVA [site: PMd, SMA; cue: synchronization, continuation; time (before, after, 15 min)] was used to compare the effect of rTMS to PMd and SMA. Post hoc t-test were computed using a Bonferroni correction. None of the data violated the normality assumption necessary to conduct parametric statistical tests.

RESULTS

No subjects found the rTMS uncomfortable or experienced any adverse side effects. In some of them, cerebellar stimulation produced a small twitch of posterior neck muscle but this was usually minimal. In experiments 1 and 2, the mean RMT (± SD) was 55 ± 4% of maximum stimulator output with no significant differences between sessions. In experiment 3, the mean RMT was 52 ± 7%.

We calculated the equivalent intensity that we used for stimulating the cerebellum using the model of Stokes et al. (2005). In two subjects, we measured the distance of the TMS coil from the surface of the cerebellum and compared it with the distance to the surface of the motor cortex when placed over M1 using an MRI guided frameless stereotaxy system (Brainsight frameless, Rogue research; Fig. 1A). The distance between the scalp and M1 was 17 mm, similar to the values quoted in Stokes’s study (Stokes et al. 2005), whereas that from scalp to cerebellum the distance was 23 mm. To calculate the TMS intensity that would be needed to produce stimulation at the cerebellum equivalent to RMT at the motor cortex, we used the equation, $\text{RMT}_{\text{CEREB}} = \text{RMT}_{\text{M1}} + m(D_{\text{CEREB}} - D_{\text{M1}})$ where $D_{\text{CEREB}}$ and $D_{\text{M1}}$ are the scalp-brain distances for cerebellum and M1, RMTM1 is the resting motor threshold for M1, RMTCEREB is the “equivalent” resting threshold for cerebellum, and $m$ is a scaling factor that Stokes et al. (2005) estimated at $m = 3$. Thus $\text{RMT}_{\text{CEREB}} = 55 + 3(23 - 17) = 73\%$ of stimulator output (SO).

The actual stimulus intensity used for rTMS over cerebellum was 90% RMTM1 = 49.5% SO. Thus rTMS over the cerebellum was applied at 68% of the estimated RMTCEREB. It is interesting to note that if this calculation is valid, then rTMS over the cerebellum was applied at intensities that have little effect if given at 1 Hz over M1.

Experiment 1, rTMS over ipsilateral M1, left or right cerebellar hemisphere during auditory paced-no paced finger tapping

We first analyzed whether the ITI in the synchronization and continuation phases was affected by rTMS. A four-way ANOVA (site * time * cue * frequency) showed a significant effect of frequency ($F = 4895.77 \ P < 0.001$), consistent with the three different tapping rates but no other main or interaction effects. Thus there was no tendency for subjects to drift ITIs is during the continuation phase, and no effect of rTMS. Indeed all subjects were remarkably accurate. The pre-rTMS ITI values for the synchronization phase were 1.99 ± 0.006 ms at 0.5 Hz, 0.99 ± 0.002 ms at 1 Hz, 0.49 ± 0.0005 ms at 2 Hz. In the continuation phase, the values were 1.9 ± 0.19 ms at 0.5 Hz, 0.96 ± 0.02 ms at 1 Hz, 0.49 ± 0.01 ms at 2 Hz. Although the mean ITIs were accurate, their variability, measured as coefficient of variation (CV) from tap to tap was affected by rTMS. A four-way ANOVA (site * time * cue * frequency) showed a significant interaction between the factors ($F = 2.4 \ P = 0.02$). Thus two three-way ANOVAs (site * time * frequency) were conducted separately for the synchronization and continuation phase. Figure 2 shows that the mean CV for the group in each block of trials was very reproducible apart from a substantial (~50%) increase seen in tapping variability during synchronization at 2 Hz after rTMS over the right cerebellum. This was confirmed in the three-way ANOVA for...
the synchronization phase, indicating a significant site * time * frequency interaction ($F = 2.72 \, P = 0.012$) that was due to the fact that the CV in the 2-Hz task increased immediately after rTMS over the right cerebellum ($t = 3.38 \, P = 0.029$), but then returned to baseline 15 min later. There were no other main or interaction effects. An example of the raw data from one subject before and after right cerebellar rTMS is shown in Fig. 1B. The effect of right cerebellar rTMS was only evident when subjects had to keep in time with the external auditory pacing cue (synchronization phase); there was no effect when subjects continued to tap at the same rate from memory (continuation phase).

Although subjects were given no specific instructions about the force of the tap, all of them tended to tap more strongly at the end of the task than at the start. This was borne out in the four-way ANOVA, which indicated a significant main effect of time ($F = 10.71 \, P < 0.01$) and frequency ($F = 16.63 \, P < 0.01$) but no effect of site and no significant interactions. This was due to the increase in the force exerted across successive trials regardless the site of stimulation and also an increase in the force at lower frequencies of tapping (Fig. 3).

The remaining two experiments investigated the nature of the effect at 2 Hz in more detail.

**Experiment 2: ipsilateral cervical motor root stimulation**

To test whether the effect of rTMS was due to a nonspecific effect of the small muscle twitches in the neck evoked during stimulation, we conducted an experiment in which rTMS was applied over the cervical nerve roots to mimic the sensation experienced when stimulating over the cerebellum. Subjects tapped at 2 Hz only. A two-way ANOVA showed a significant effect of cue ($F = 17.92 \, P < 0.01$) but no main or interaction effects involving TIME. Figure 4 shows the CV for the synchronization and continuation phase separately; there is a higher variability in the continuation phase.

**Experiment 3: auditory versus visual pacing**

Figure 5A plots the CV for 2 Hz tapping before and after rTMS to the right cerebellar hemisphere when subjects had to tap in time with an auditory or a visual cue. Cerebellar
stimulation only has an effect when subjects try to tap in time to an auditory cue. A two-way ANOVA revealed a significant modality * time interaction ($F = 5.31 \, P < 0.05$) that was due to the fact that there was a significant increase in CV after rTMS only in the auditory task (comparison of pre- v. immediately post-rTMS: $t = 2.97 \, P = 0.04$). There were no other significant effects.

**Experiment 4: premotor versus SMA**

Figure 5B plots compare the effect on 2-Hz tapping of rTMS to PMd and SMA. A three-way ANOVA showed a significant site * time * cue interaction ($F = 4.7 \, P = 0.03$) that post hoc analysis revealed was due to a significant increase in the CV immediately after rTMS over PM in the synchronization phase of the task ($t = 3.4 \, P = 0.01$). There were no other significant effects.

**DISCUSSION**

The present data confirm that rTMS over the cerebellum can increase the variability in timing of finger-tapping movements for several minutes after the end of stimulation. In addition, they show that the effects are limited to the hand ipsilateral to the side of rTMS and are more prominent in high-frequency (2 Hz) tapping that is paced by an auditory rather than a visual cue. Similar effects after rTMS over the PMd contralateral to the tapping hand are consistent with the idea that this behavior depends on cerebello-premotor circuit as proposed by Goldberg (1985).

**Stimulation of the cerebellum**

We stimulated the cerebellum at an intensity equal to 90% of the RMT of the ipsilateral M1. However, because the cerebellum is further from the scalp surface than M1, the effective intensity is less than this. When we corrected for the difference in distances according to the method of Stokes et al. (2005) the intensity of cerebellar stimulation was equivalent to 68% RMT over M1. In M1, stimulation at this intensity is below the threshold for activating corticospinal output but is within the range of intensities that are conventionally used to activate cortico-cortical circuits when testing short interval intracortical inhibition and facilitation (SICI/ICF) (Chen et al. 1998; Kujirai et al. 1993). Thus we believe that rTMS was capable of activating at least some elements in the cerebellar hemispheres.

There have been several previous studies in which single-pulse TMS has been applied over the lateral cerebellum to condition the response of motor cortex to a subsequent test stimulus (Ugawa et al. 1995; Werhahn et al. 1996). Thus a single stimulus to the right cerebellum suppresses the amplitude of motor evoked potentials (MEPs) in right hand muscles by TMS over the left M1 if the interval between the stimuli is...
5–6 ms (Ugawa et al. 1995; Werhahn et al. 1996). However, in these reports, the intensity of the TMS pulse was much higher than those employed in the present experiments. Unfortunately, precise comparisons are not possible because a larger coil was used in single pulse designs, and no data are given for M1 threshold using the same coil. Nevertheless, it would not be unreasonable to assume that the intensity needed to produce a significant output from the cerebellum with a single TMS pulse is likely to be much higher than that needed to induce changes in the operation of intrinsic cerebellar circuits. In the TMS literature, the nearest parallel might be to compare the intensity of a TMS pulse capable of evoking a visible muscle twitch from M1 with the intensity necessary to activate intracortical circuits involved in SICI. The former is $\sim 110\%$ RMT, whereas the latter is 70% active motor threshold (AMT). Because AMT is $\sim 80\%$ RMT, this puts the threshold for SICI at 56% RMT or just over one half of the intensity needed to produce a visible movement. On this basis, we would predict that if we had stimulated the cerebellum at twice the intensity used during rTMS ($\sim 100\%$ stimulator output), then a single pulse would have been able to suppress excitability in M1.

**Specificity of cerebellar rTMS**

Because of the auditory and somatosensory sensations that are produced, subjects cannot readily be blinded to application of rTMS. In the present experiments, after effects on movement could have occurred because of persisting discomfort caused by mild neck muscle contraction during rTMS; alternatively, subjects may have become familiarized with the regular 1-Hz timing of the stimulus pulses so that they were distracted when having to tap at different rates (Penton-Voak 1996). However, we believe that these effects were negligible because the effect of rTMS over the cerebellum was specific to the hand ipsilateral to the site of stimulation and was not seen after rTMS to the control site over ipsilateral M1. An additional control in which rTMS was applied over the cervical nerve roots ipsilateral to the tapping hand to produce small contractions of neck and shoulder muscles also failed to show any effect on the tapping task. Thus we think the effects observed were due to cerebellar stimulation. If so, then an ipsilateral effect on performance is expected given the anatomical projections to and from the cerebellar hemispheres (Allen and Tsukahara 1974) and the common finding of ipsilateral activation of cerebellum during simple hand movement tasks in functional imaging studies (Desmond et al. 1997; Fox et al. 1985). Furthermore, others authors have found increased tapping variability from lateral cerebellar lesions when tapping with an effector (finger or foot) ipsilateral to the lesion (Ivry et al. 1988).

**Why was the effect of rTMS specific for tapping rate, cue modality, and synchronization?**

The data showed that rTMS had an effect only when subjects were asked to tap in time to an auditory cue at 2 Hz. There was no effect on lower frequency tapping or on visually cued taps; neither was there any effect during the continuation phase of tapping after removal of the pacing cue. One possible explanation is that although the cerebellum is involved in all types of movement, the very low intensity of stimulation that we used limited us to the most sensitive circuits in the cerebellum and that by chance these are involved in synchronizing taps to fast auditory cues. Alternatively this type of processing might be the most sensitive to external disruption.

Another explanation of the results is that the cerebellum has a more prominent role in rapid, auditory cued tapping than in other movements, and this accounts for the ease with which this particular task was disrupted. It has been hypothesized by several authors that the cerebellum has a particular role in subsecond timing (Ivry 1996; Spencer et al. 2003) as opposed to the seconds timing that may occur in basal ganglia and frontal cortex (Gibbson et al. 1997; Lewis et al. 2003). Indeed, Sadato et al. (1996) found rather slight ipsilateral cerebellar activation in response to slow (0.25–1 Hz) and very fast (3–4 Hz) sequential excursions of the index finger. In contrast, intermediate rates (2 and 2.5 Hz) yielded considerably enhanced rCBF. This would be consistent with our own findings that 2-Hz tapping was particularly responsive to rTMS, whereas 1- and 0.5-Hz taps were unaffected.

If any of these possibilities was the case, then if we had stimulated at a higher intensity then we should have had more widespread effects. It is difficult to address this possibility at present because higher intensities of rTMS inevitably cause more contraction of neck muscles and hence discomfort to subjects. In addition, the higher the intensity, the more likely the stimulus is to spread to noncerebellar structures, limiting the specificity of the conclusions that can be drawn. In the future, more focal stimulators may be able to circumvent these problems. The fact that the stimulus was relatively mild in this study probably also accounts for the apparent discrepancy between our data and previous reports on patients with cerebellar lesions, where increased tapping variability in the continuation phase is a prominent feature.

The sensitivity of auditory cued rather than continuation movements to disruption by rTMS may also be consistent with the idea that the cerebellum plays an important role in controlling tasks that require event-related timing (Gibbson et al. 1997). This involves evaluation of the accuracy of an explicit temporal goal (the time of finger contact) with an external signal (the auditory cue). As Spencer et al. (2003) have pointed out, the cerebellum has been postulated to have a similar role in blink reflex conditioning. Here after a period of training, a conditioning prepulse elicits a blink that is timed to occur just prior to the unconditioned blink stimulus (Thompson 1990). In such a situation, the system must calculate the expected time of the unconditioned stimulus and then produce a blink that is appropriate to anticipate its arrival. If this approach is used in finger tapping, then there can be continuous and rapid updating of the time of the next tap that would reduce the variance of the rhythm. rTMS may disrupt this calculation leading to an increase in the variability of tapping.

The fact that rTMS affected performance in the synchronization but not the continuation phase of the task suggests that these parts of the task recruit different mechanisms that are differentially sensitive to rTMS. In the synchronization phase, the time of motor outputs can be explicitly compared with that of an external event such as the auditory cue. However, in the continuation phase, subjects must mentally extend the rhythm and it may be that motor outputs are then compared with an internal representation of an intended event. If so, then it may be that internal comparisons are performed in a different part of...
the cerebellum or that they are less sensitive to interruption with rTMS. Whatever the mechanism, there is good evidence that the two phases of the task do involve different patterns of brain activity. Thus in an imaging study, Rao et al. (1997) found that during the synchronization phase, sensorimotor cortex, cerebellum and superior temporal gyrus were activated, whereas in the continuation phase, the supplementary motor area, putamen, ventrolateral thalamus, and inferior frontal gyrus were also activated. Thus it is possible that in the continuation phase the contribution of the cerebellum is less important than in the synchronization phase and the impairment by rTMS would not be significant enough to affect timing variability. Finally it should be noted that many authors have previously used the Wing and Kristofferson (1973) model of “clock” and “motor” aspects of timing variability to analyze cerebellar contributions to timing. However, because the mathematical analysis of their model is specific for the continuation phase of a tapping phase, it is not appropriate in the present experiments because this phase was unaffected by our rTMS protocols.

It is less clear why rTMS should have affected the auditory but not visually cued task, although it should be noted that Jancke et al. (2004) also found no effect of 1-Hz rTMS over lateral cerebellum on a similar visually cued tapping task, although the site of stimulation was ~1 cm dorsal to the site studied here. Unlike some other reports, we found the variability of tapping in time with each type of cue was equal, so that initial task performance was equal. Thus we speculate that processing of the visual cue may have involved activation of different circuits in the cerebellum to those involved in the auditory task. Imaging studies suggest that paced finger tapping in the context of auditory pacing stimuli relies more on brain structures subserving internal motor control, whereas paced finger-tapping in the context of visual pacing stimuli relies on brain structures subserving processing or imagination of visual pacing stimuli (Jancke et al. 2000). Furthermore visual cued tapping may engage more activation in the cerebellar vermis than the lateral hemispheres (Jancke et al. 2000).

Consistent with this, Theoret et al. (2001) found that rTMS over the midline cerebellum could increase variability of finger tapping in a task in which subjects had to reproduce the time intervals between a series of visual stimuli that had been presented immediately before on a computer screen.

Changes in tapping force

Although we gave no specific instruction about tap force, subjects gradually increased their tapping force throughout the experiments in all versions of the task; they also tapped harder at 0.5 Hz than at 2 Hz. The lower tap force at higher frequencies is likely to be a mechanical effect that results from the need to rapidly reverse the direction of finger movement at the end of each tap. However, the general increase in force over time was unexpected. It may represent a learning effect akin to that described by Muellbacher et al. (2002) in a paced pinching movement. However, in that experiment, subjects were explicitly required to pinch a transducer between thumb and forefinger as hard as possible, whereas in the present experiments we asked subjects only to tap as closely as possible in time with the cues. Whatever the mechanism, it was unaffected by rTMS over cerebellum and hence involves a mechanism quite separate from the involved in timing movement.

Effects of rTMS over PMd and SMA

The fact that rTMS over PMd affected the synchronization phase of the 2-Hz tapping in the same way as stimulation over the lateral cerebellum is compatible with the strong anatomical projections from lateral cerebellum to PMd. It is also consistent with the suggestion that both structures are part of a network involved in control of externally guided tasks (Goldberg 1985). The same theory may explain why rTMS over SMA failed to have any effect on tapping variability because on this account, it is more likely to be involved in self-generated movements. However, we cannot exclude the possibility that because SMA is located further from the surface of the scalp than PMd, we did not use the correct stimulus intensity to activate neurons in SMA. This would require further experiments with a range of stimulus intensities for rTMS. It is also interesting to note that there was a (nonsignificant) tendency for rTMS over PMd, but not SMA, to reduce the usual increase in tapping force seen during the experiment. It is possible that this indicates a more prominent role of PMd in regulating force of contraction, but again this cannot be resolved from the present data.

Conclusion

The experiments confirm that rTMS over the posterior scalp can interfere with the contribution of cerebellum to control of hand movement. Calculations suggest that the intensities applied are approximately equivalent to those used to activate intracortical circuits in the motor cortex and considerably below those that produce direct activation of cerebellar output pathways. Thus we think that stimulation transiently changed excitability of neural networks in a relatively localized region of cerebellum. These networks appear to have an important role in event-related timing of movements paced by external, particularly auditory, cues.

Acknowledgments

We thank P. Asselman for constant and helpful technical support.

Grants

This work was supported by the Medical Research Council, UK. M. F. del Olmo was supported by the Xunta de Galicia (PGIDIT06PXIB160333PR), Spain.

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