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Neuroscience Letters 371 (2004) 185–189
Neuroscience Letters
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The effect of rTMS over the cerebellum in normal human volunteers on peg-board movement performance

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Received 15 June 2004; received in revised form 20 August 2004; accepted 28 August 2004

Abstract

Low frequency rTMS over the paramedian part of the right cerebellum was used to test the effects of TMS-induced disruption of the cerebellum on performance of the 10-hole pegboard task. A test group (n = 14) showed significantly increased movement times lasting about 3 min after the 5-min 1 Hz rTMS train, compared to a control group who received no rTMS (n = 14), tested in a parallel group design. The increase was greatest for the hand ipsilateral to the stimulation, but the difference between the two hands was not statistically significant. These results suggest that the rTMS affects cerebellar excitability and cause a short-lasting bilateral change in sensory-motor performance.

Keywords: Cerebellum; Transcranial magnetic stimulation; Sensorimotor control

Transcranial magnetic stimulation (TMS) of the human brain is providing a powerful tool for the study of the motor system [9,19,21]. There are two distinct stimulation modes commonly used for research. First, direct stimulation, in which TMS is applied in a single pulse or as a short train of rapid pulses, can induce a brief "virtual lesion" by temporarily disrupting normal neural processing. This technique has been shown to affect movement preparation and execution in many different experiments, with effects reported for stimulation over several different areas of the cortical motor system (review: [21]). Second, stimulation using long trains of low frequency pulses can modify the excitability of the stimulated area for some time after the end of the stimulation train. Typically, a repetitive stimulation (rTMS) train of pulses at 1 Hz may last 5 or 10 min, and cause an effect that lasts about half as long as the stimulation period [2,5,13,17], although the effects appear to last disproportionately longer for long stimulus trains [20,25].

Despite the clear change in cortical excitability demonstrated with this latter protocol, there have been very few reports of functional changes in motor performance. For example, motor cortical excitability is depressed following an rTMS train over the primary motor cortex at 1 Hz for 30 min [14], but these authors could find no significant performance changes in a set of simple behavioural tasks. They suggest that this may be because plastic changes outside the stimulated area can compensate for the change in excitability of the stimulated tissue, and effective connectivity analysis of functional imaging data was used to show change in the connection between the stimulated left motor cortex and the contralateral dorsal premotor cortex, that might subserve this compensatory function [14].

There is consistent evidence that the cerebellum is strongly implicated in plasticity and adaptation of the motor circuit, both in terms of motor learning [8,23], but also in recovery from cerebral dysfunction [11,22,27]. One might then expect that there would be changes in cerebellar activity during the compensation for motor cortical rTMS, and Lee et al. [14] did report significant change in cerebellar activation after the motor cortical stimulation, measured with functional MR imaging. This is supported by recent experiments using PET scanning [3] showing that, after rTMS over primary motor cortex, the brain areas that showed positive

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doi:10.1016/j.neulet.2004.08.067

correlation between functional activation and the reduction in TMS-evoked MEP amplitudes included the cerebellum. One might further suppose that if the cerebellum was a site involved in active compensation for cortical changes in processing, then rTMS of the cerebellum itself might block this functional compensation. It is therefore important to note that the one report that has shown an effect of rTMS on human motor performance used a stimulation site over the medial cerebellum [24]. In that report, there was a small but significant increase in variability of tapping intervals that followed 5 min of 1 Hz stimulation. There was no effect on mean tapping rate or any effect of rTMS over other control sites.

In this paper, we therefore test the effect of rTMS over the cerebellum on a pegboard task that is sensitive to damage to the cerebellum [6,12,15,16]. We show a significant performance deficit that suggests the rTMS stimulation does affect the normal function of the cerebellum.

Thirty right handed subjects took part, after providing informed consent with research ethics committee approval of the experiments. Subjects were first trained in performing the 10-hole pegboard task [1], using left and right hand in alternate trials. For each trial, the subject began with the hand resting beside the peg-board, which was held steady on the table with the other hand. The experimenter started the trial with a verbal ready-steady-go command, and timed the trial with a digital stopwatch. Trials started every 30 s; because completion times were typically under 10 s, subjects were easily able to turn the pegboard around and rest briefly in the 20 s interval between trials. On rare occasions the subject dropped one or more pegs; those trials were discarded and replaced with the average of the two adjacent trials.

After 10 training trials (5 for each hand, in alternation), we recorded the baseline performance for each subject in another 10 trials, 5 for each hand. For the test group ($n = 14$), the hand used first was controlled, with seven subjects starting with left hand and seven with the right hand. Of the control subjects ($n = 14$), eight started with their right hand and six with their left. As no differences were found between these subgroups, for either test or control groups, the data was combined. The test subjects then were exposed to 300 rTMS stimulation pulses, at 1 Hz, using a flat figure of eight coil and Magstim Rapid 200. Stimulation level was set at between 50 and 70% (mean 58%, median 60%), choosing a level approximately 120% of each subject's resting motor threshold as measured over the left primary motor cortex. The coil was positioned by hand over the right cerebellum, with coil centre 2 cm lateral and 1 cm below the inion, with the current direction upwards in the brain [24,26].

Immediately after the 5-min stimulation period, a further set of 10 pegboard trials was timed. The time between the last rTMS stimulation and the start of the first trial was approximately 1 min for all subjects. Each subject then rested for a further 5 min, before the final set of 10 trials.

For the control group, $n = 14$, the procedure was identical except no stimulation was performed, and subjects rested for 5 min. In addition, two subjects (the two authors) were tested in the rTMS condition more than once (five for RCM, four for LODC), over a period of 8 weeks, and with at least 24 h between each stimulation session.

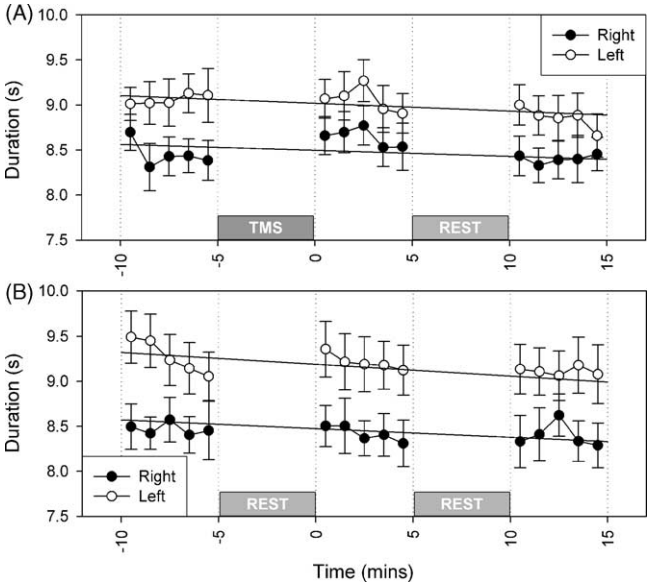

Fig. 1. Average times to complete the 10-hole pegboard task for the TMS test group (A) and the control group (B). Error bars are standard errors, $n = 14$. The movement times are shorter for the preferred right hand. The solid lines are linear regressions to the group data.

The recorded movement times displayed a clear trend toward increasing speed across the trials, regardless of TMS conditions (Fig. 1). We therefore removed this trend by fitting linear regressions to the mean data for each group across the 15 trials, and adjusting the data per subject to correct for the slope of the line. Repeated measures ANOVAs were performed using a mixed model, with group (test or control) as a between-subject factor, and hand (left or right), block (pre-, post-TMS and recovery) and trial (five per block) as within-subject factors. Statistical significance was taken as $p < 0.05$; unless stated otherwise, all non-significant results mentioned in the results have $p > 0.1$.

As the two subjects tested repeatedly, we (R.C.M. and L.O.D.C.) were not blind to the experiment; our data sets were excluded from the main analysis. As with the main experiment, data from these repeated sessions were de-trended using the within-subject group regression line and the repeated sessions were treated as a random factor in this analysis.

There were only 9 trials out of 1110 in which one or more pegs were dropped. The frequency of these trials did not differ across the test and control groups, nor across the pre-TMS, TMS or recovery blocks (chi-squared, $p > 0.5$).

Group mean times to complete the 10-hole pegboard test are shown in Fig. 1 for the test and control groups, shown separately for left and right hand. As is typical for the pegboard task, there was considerable variance between subjects. However, a $2 \times 2 \times 3 \times 5$ repeated measures analysis of variance (rmANOVA) of the raw data, taking factors of group (test or control), hand (left or right), block (pre-, post-

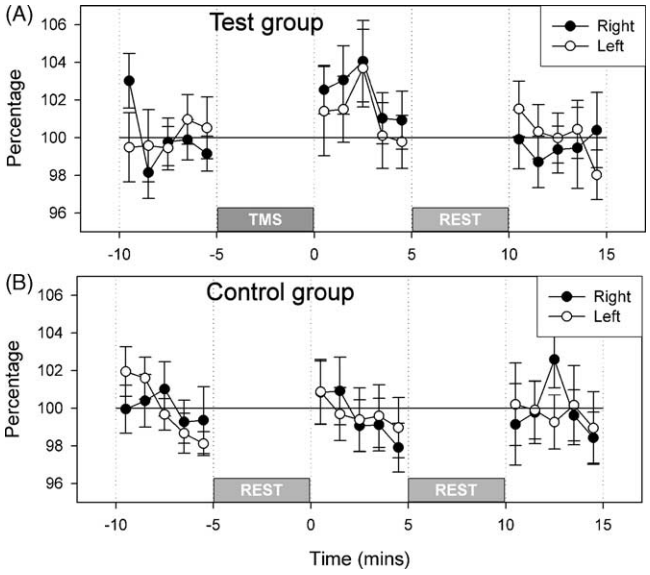

Fig. 2. Average movement times for test (A) and control groups (B), after removing the linear trends shown in Fig. 1 and expression of the data as a percentage of the mean pre-TMS block data, calculated subject by subject. The effect of the TMS stimulation is seen most clearly as an increase in movement time in the three post-TMS trials.

TMS and recovery) and trial number (five trials per block), showed a highly significant effect of hand ($F_{(1,26)}$ =79.3, $p < 0.0001$). Thus there was a clear handedness bias, with subjects performing significantly faster with their preferred right hand [1]. There was also an improvement in performance across the three blocks ($F_{(2,52)}$ = 7.25, p = 0.002), and a trend towards increasing speed across the trials within blocks ($F_{(4,104)}$ = 2.452, p = 0.051). However, there were no significant interactions between the block and trial factors with factors of group or hand. This suggests that there were no TMS-dependent differences in performance improvement with time. We therefore fitted linear regression lines to the group data (Fig. 1, solid lines) and Fig. 2 shows the same data after the linear trend was removed. For display purposes only, the results have been expressed as a percentage of the mean of the five pre-TMS trials, calculated subject by subject.

A 2 × 2 × 3 × 5 (group × hand × block × trial) repeated measures analysis of variance of the de-trended movement times, showed the difference between blocks was statistically significant ($F_{(2,52)}$ = 5.402, p = 0.007), with a significant interaction between group and block ($F_{(2,52)}$ = 3.288, p = 0.042). Analysing the data separately for the right and left hands (2 × 3 × 5: group, block and trial) confirmed a main effect of block and an interaction between block and group for the right hand, but no significant effects for the left hand. For neither hand was there a significant main effect of trial number, nor a significant interaction between block and trial. Hence we collapsed the data across the five trials per block (Fig. 3).

To test more fully for a difference in response to the TMS between the two hands, the mean movement times per block were analysed with a 2 × 2 × 3 rmANOVA (group, hand

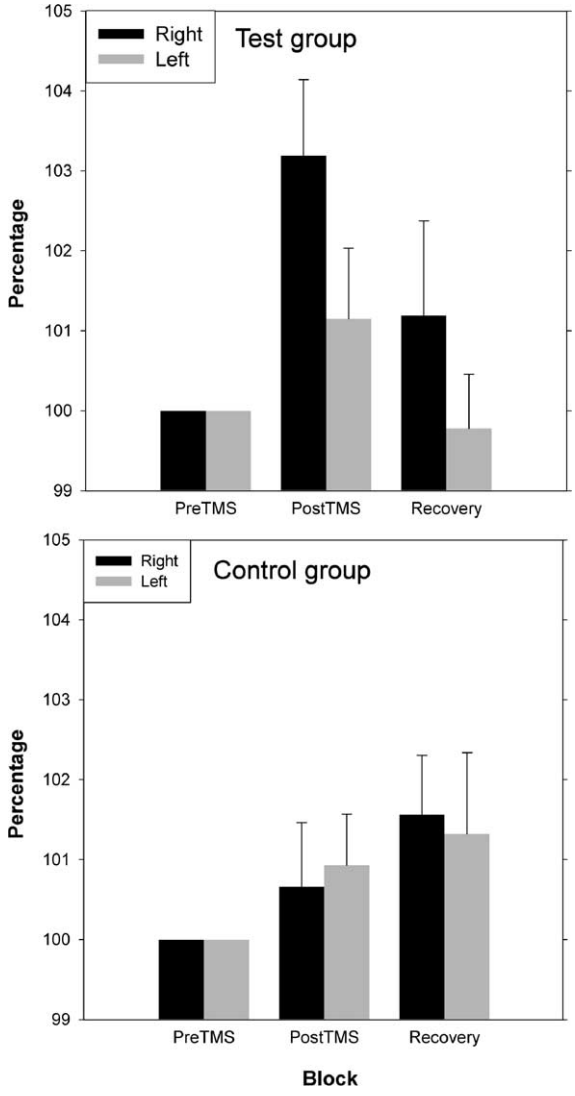

Fig. 3. Mean percentage movement times for the test (A) and control groups (B). The data shown are those plotted in Fig. 2 after collapsing the results to the average of the five trials per block; error bars are 1 S.E.M. (n = 14).

and block). However, there was no significant interaction between hand and block, or hand, block and group; of course, the interaction between group and block, mentioned above, remained significant (p = 0.042). Post hoc pair-wise comparisons between the three blocks showed that the durations for the post-rTMS block were significantly higher than for either the preTMS or the recovery blocks (one-tailed t-tests, $t > 2.308$, $p < 0.029$, d.f. = 27, Bonferroni adjusted for two comparisons).

In additional tests, the two authors, R.C.M. and L.O.D.C., were tested repeatedly with rTMS over five and four separate sessions. Although we were not blind to the experiment, we report these results to provide anecdotal evidence of the repeatability of the effect. There was a significant interaction between block and hand ($F_{(2,2)}$ = 68.9, p = 0.014), with higher completion times in the right hand in the post-TMS block of trials. Post hoc one-tailed t-test comparisons for the

right-hand data, performed separately for each of these two subjects, confirmed that the movement durations in the post-rTMS block were significantly higher than in the pre-TMS block ($p < 0.034$, Bonferroni corrected for two comparisons). There were no significant differences between blocks for the left hand for either subject.

In this paper we show that there is a short-lasting localised reduction in performance of the 10-hole pegboard test, with significantly elevated movement durations for about 3 min immediately following a 5-min period of 1 Hz rTMS over the cerebellum. The effect was quite subtle (less than 5%) and this small effect size may be attributed to the fact that the peg-board task tests a highly over-learned behaviour, and that many cortical and subcortical areas may also contribute to performance. The effect was greater for the ipsilateral hand although the difference between hands was not significant. A control group showed no significant changes in movement duration during trials undertaken in the same schedule, but in which no rTMS was used. Thus, the effect of the rTMS train was to reduce sensory-motor performance for several minutes after the cessation of the rTMS simulation, and we argue that this effect is likely to be due to the temporary disruption of the cerebellum.

This argument is supported by the known relationship between performance at the pegboard task and cerebellar function [6,12,15,16]. Thus, the performance deficit is consistent with perturbed cerebellar function. Also consistent with a cerebellar disruption is the larger effect on the ipsilateral hand, albeit not statistically different from the contralateral hand. We cannot offer a clear reason for why there should have been any contralateral effect, except to point out that the laterality of cerebellar involvement with skilled hand actions is not absolute.

In a similar experiment, Theoret et al. [24] demonstrated increased variability in the timing of finger tapping after medial cerebellar rTMS, but reported no change in tapping rates, and no effect of stimulation over either motor cortex or lateral cerebellar stimulation. They argue that disruption of medial cerebellar function is expected to lead to a performance deficit in timing tasks.

What is the evidence to suggest that TMS can disrupt the cerebellum? This is pertinent because the cerebellar cortex is relatively deep below the scalp, and since TMS also activates the neck muscles, it is difficult to be confident that stimulation levels that are comfortable are sufficient to affect the cerebellar cortical tissue. A recent study using similar protocol and coil positions as used here [10] did not see any effect on tapping speed, but used somewhat less stimulus strength (90% of resting motor threshold). High stimulation levels may reach peripheral nerves and even the brainstem. Single TMS pulses over the medial cerebellum can directly affect motor performance, but the only published reports demonstrate effects on oculomotor control, with brief disruption of saccades, smooth pursuit eye movements and eye head gaze shifts [7,18,29]. The oculomotor vermis is closest to the TMS stimulation coil. More commonly reported has been the influence of conditioning pulses over the cerebellum on the excitability of the finger area of the motor cortex, with a short reduction in cortical excitation 5–6 ms after the cerebellar pulse [26,28]. This is consistent with TMS excitation of cerebellar cortical output (Purkinje cells) that induces a brief silencing of the cerebellar nuclei, disfacilitating the motor cortex. Thus, one potential route for cerebellar TMS to affect sensorimotor control would be via this cerebellar–cortical interaction, with the main effect resulting from the changes cortical excitation. One might then expect that rTMS of cerebral motor structures, including sensorimotor cortex, would also affect sensorimotor performance, and this has not been often reported [14] (but see [10]). Thus, the effects we see may either be due to a direct cerebellar influence action, or an indirect influence via the cerebellar effect on motor cortical function.

TMS over the posterior fossa might also influence sensory-motor performance through its effects on the peripheral nervous system. Werhahn et al. [28] argue that using the same flat figure of eight coil, at stimulation levels higher than those used here (mean 80%), the effects of the posterior fossa conditioning pulses on primary motor cortex were likely to be induced by stimulation of nerves in the brachial plexus, rather than in the cerebellum. However, they positioned their coil 8 cm lateral to the inion, well outside the stimulation area we—and Theoret et al. [24]—targeted. Effective conditioning is known to be restricted to a small area over the cerebellum [26]. Werhahn et al. also oriented their coil at 90° to the position we used, and one wing of the figure of eight was thus over the neck, with a higher likelihood of stimulating the peripheral nerves. Hence it seems unlikely that stimulation of the brachial plexus would have contributed greatly to the effects we observed.

TMS could also influence sensory-motor performance through its effects on the spinal system. Gerschlager et al. [4] propose that TMS of the neck influences spinal excitability, measured by recording the H-reflex, via stimulation of peripheral, ascending sensory tracts rather than by cerebellar activation. We suggest that it is unlikely that such changes in corticospinal excitability could be responsible for the brief change in pegboard performance that we have seen, because Gerschlager et al. [4] reported increased corticospinal excitability and increased spinal H-reflexes that grew larger throughout 30 min following cervical or cerebellar rTMS, and they were not able to measure a recovery of normal excitation levels. Although Theoret et al. [24] did not monitor the time course of their effect of cerebellar TMS on tapping variability, it appears to have been brief, because its behavioural effects were seen using a counterbalanced design with only 10 min rest between sessions of cerebellar and control site stimulation. Hence we would predict their effect to have been brief, as we have found; longer effects would have been lost due to the counterbalanced order of conditions.

In summary, we show an effect of rTMS over the human cerebellum on performance of a rapid skilled visuo-motor movement task that is consistent with short-lasting distur-

bance of cerebellar function. This result is at odds with most previous reports showing no effect of cerebral rTMS on motor performance, although one study has been reported in which rTMS of primary motor cortex did slow the fastest rates of finger tapping [10]. We suggest that difference may be because the cerebellum is a critical part of the central circuit controlling rapid movements, and that the cerebellum may be particularly important in compensating for experimental or pathological changes in cerebral excitation.

Acknowledgements

This work was funded by the James S McDonnell Foundation. RCM is supported by the Wellcome Trust, LODC by the Alfred Benzon Foundation.

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