Reaching to a target is disrupted by repetitive transcranial magnetic stimulation (rTMS) over the cerebellum:

Empirical support for state-estimation by feed-forward internal models

9,888 Words, ALL inclusive

Abstract

The role of the cerebellum in the control of movement remains to be explicitly defined. Recent theoretical approaches assume the existence of internal models in the cerebellum, which perform both forward and inverse computations in predicting the sensory and motor consequences of movement commands. We hypothesised that repetitive transcranial magnetic stimulation (rTMS) over the right lateral cerebellum would disrupt the end-points of fast reaching movements to a remembered visual target. The task incorporated a steady lateral movement to create start-point uncertainty and irregularity between trials, and a final fast-reaction reaching movement. Application of rTMS immediately before the reaching movement significantly perturbed the distribution of end-points for stimulated versus unstimulated trials. Stimulation over the motor cortex had a smaller effect on movement accuracy, and in the opposite direction to the cerebellar perturbation. These results provide support for the existence of forward models in the cerebellum computing state-estimations of the motor system in the feed-forward control of fast reaching movements.

Introduction

The cerebellum has long been implicated in the 'smooth and effective control of movement' (Eccles *et al*., 1967), but precisely what computations the cerebellar cortical network performs has remained elusive. Recent theories of cerebellar function (Miall *et al*., 1993; Wolpert *et al*., 1998; Wolpert & Ghahramani, 2000) propose that the cerebellum instantiates multiple forward and inverse models of the motor system. Given sensory feedback about the state of the body and a motor copy of ongoing and planned movements, inverse models compute the desired motor commands, while forward models predict the sensory consequences of these commands. The sensory prediction amounts to an estimation of the state of the motor system, given the current commands. This 'state estimation' is output back to motor areas to influence motor planning.

Support for the existence of forward models in the cerebellum comes from experimental paradigms involving saccadic eye movements and/or rapid reaching to a visual target (see Desmurget and Grafton, 2000; Wolpert & Ghahramani, 2000 for excellent reviews). If an unexpected perturbation to the target position or the dynamics of the arm occurs (for example by small trans-saccadic 'jumps' in the target position, or by external forces applied to the arm by a robotic manipulator, Desmurget *et al*., 2001; Krakauer *et al*., 1999), functionally relevant adjustments to the saccade or reaching movement can be made *before* the minimum time necessary for sensory feedback to have an effect (i.e. less than 150 ms for visual, and 80ms for proprioceptive feedback). In the first case, motor outflow from correction saccades following the target jump is used to modulate ongoing reaching to the target. In the second case, after training with the manipulator subjects learn an internal model of the arm's new dynamics, including the external force field, and reaching accuracy improves.

Other supportive evidence has also come from studies on patients with cerebellar lesions. Such patients are able to reach to visual targets, but their movements are slow, the trajectories variable and the end-points inaccurate (Bonnefoi-Kyriacou *et al*., 1998). We hypothesised that stimulating the cerebellum in *healthy* subjects with repetitive transcranial magnetic stimulation during a reaching movement, would temporarily disrupt cerebellar cortical processing, and thus have some measurable effect on reaching accuracy.

Transcranial magnetic stimulation (TMS) has gained prominence in cognitive neuroscience as a 'virtual lesion' tool to study the chronometry and functional involvement of cortical areas in sensory, motor, and cognitive tasks (Pascual-Leone *et al*., 1999, 2000; Walsh & Cowey, 2000).

Several groups have studied the effect of cerebellar stimulation on the excitability of motor cortex, in a paired-pulse paradigm (Ugawa *et al*., 1991; Saito *et al*., 1995; Werhahn *et al*., 1996; Pinto & Chen, 2001). These studies showed an inhibitory effect of a single cerebellar TMS pulse on the excitability of primary motor cortex (M1), as evidenced by a decreased amplitude of muscle evoked potential (MEP) elicited by a second TMS pulse over the M1 'hand' area.

Given that magnetic stimulation over the cerebellum produces demonstrable electrophysiological modulation of the motor cortex, can it also be used to interfere with functionally relevant processing? To date, studies applying TMS over the cerebellum have shown only limited effects on movement tasks, namely disturbance of saccadic and smooth pursuit eye movements (Hashimoto & Ohtsuka, 1995; Ohtsuka & Enoki, 1998), and increased variability in the timing of finger tapping movements (Théoret *et al*., 2001).

Théoret *et al.*'s (2001) study employed repetitive TMS (rTMS), which is more effective in disrupting processing than single stimuli, in an investigation of motor timing. Their task was performed immediately following a five-minute train of stimuli at 1 Hz, thus the effects they demonstrated were probably due to a *general* modulation of cerebellar cortical excitability, rather than due specifically to interference with ongoing processing. There are as yet no published studies showing an effect of cerebellar TMS on movement accuracy.

We devised a task to engage cerebellar processing that involved reaching to a previously-seen target, and found that rTMS over the cerebellum before the final reaching stage of the movement perturbed the movement end-point in nine out of ten subjects. We examined the end-point of movements in particular, since this parameter is ecologically more valid for motor control (as compared to the trajectory or dynamics of the arm, for example), and the optimisation of this parameter is likely to be the goal of the motor control system (Harris & Wolpert, 1998).

Methods

Subjects

Seven male and three female subjects, aged 27 ± 7 years (mean ± standard deviation), including the author and two co-workers (LC and RCM) participated in the experiment. All subjects were right handed and had normal or corrected vision. The experimenter observed the subjects at all times for signs of side effects due to the stimulation. Most subjects experienced slight facial and neck muscle contractions as a result of stimulation. Several potential subjects experienced pain or large muscle contractions with low-intensity cerebellar stimulation, and were withdrawn from further experiments their data are not reported here. All subjects gave their informed consent. The experimental procedures were approved by the local ethical committee, and the intensity and frequency of stimulation used was well within accepted safety limits (Wassermann *et al*., 1998).

Magnetic Stimulation

A Magstim Rapid stimulator (Magstim Company, Cardiff), and two stimulating coils were used. A 'double-cone' coil (outer diameter 14 cm, Magstim Company, Cardiff) was used for right hemisphere lateral cerebellar stimulation in all subjects, and a 'figure-of-eight' coil (outer diameter 9 cm, Magstim Company, Cardiff) was used for left hemisphere motor cortical control stimulation over the 'hand' area in seven subjects. The double cone coil was centred 3 cm lateral and 1 cm caudal to the inion, along a line joining the inion with the auditory meatus (Pinto & Chen, 2001). Coil orientation was such that the induced current flowed caudal to rostral along a sagittal axis. For motor cortical stimulation, the centre of the figure-8 coil was positioned roughly 5 cm lateral and 1.5 cm anterior to the vertex, at the optimal position for eliciting contractions in the right first-dorsal interossus (FDI) muscle. The figure-of-eight coil orientation was roughly perpendicular to the central sulcus, and was such that the induced current flowed from postero-lateral to antero-medial across the motor strip. Coil position was maintained with a sturdy frame.

Pilot studies in several subjects indicated that a train of 3 magnetic stimulations at 20 Hz could modulate the amplitude of motor evoked potentials elicited in the FDI by subsequent motor cortical stimulation ('paired-pulse' paradigm). These parameters were used in the present experiment, with stimulator intensity set at 45% of the maximum stimulator output (100% = 1.5 Tesla).

Behavioural Task and Measurements

Subjects sat upright, their heads held steady by a chin rest, and wore liquid crystal display goggles (Translucent Technologies, Canada), the glass of which switched from being transparent to opaque (white) during the task. Subjects viewed a small (1 x 2 cm) target reflected in a half-silvered mirror. The virtual image of the target was positioned to appear 42 cm from the subject, on the vertical meridian (see Figures 1A and 2).

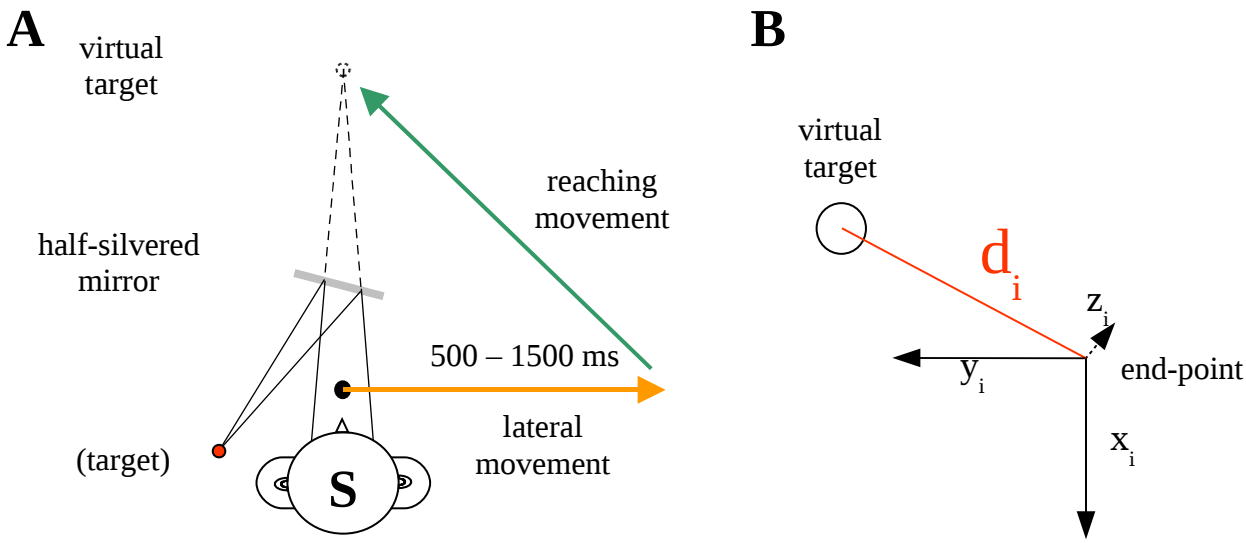

***Figure 1**. **The experimental set-up. A.** Subjects (**S**) sat facing a virtual target (red circle), reflected in a half-silvered mirror (grey rectangle), and pressed a switch (black circle). Three audible tones served as a preparation cue. On the third tone, subjects moved their hand laterally (orange arrow) at about 40 cm/s for a random period of between 500 and 1500 ms. A continuous tone served as the GO signal, which subjects reacted to by reaching straight to the target (green arrow). **B**. The movement end-point was measured in the Cartesian x, y, and z-axes, with the origin located 65 cm infront of the subject. The end-point error, d_i was the magnitude of the vector from end-point to target. Stimulating coils (not shown) were positioned over the subjects' right lateral cerebellum or left primary motor cortex. See also Figure 2.*

Subjects began each trial by holding down a switch on the surface 25 cm infront of them, using their forefinger. One second after the switch was pressed, a train of 3 equally spaced audible tones was presented (total length, 1000 ms), each tone slightly higher in pitch than the last. This was the preparation cue. On the third tone, the subject began moving his hand laterally, away from the body at a steady speed of approximately 40 cm/s. Lifting the forefinger from the switch triggered the glass of the goggles to become opaque, denying subjects further vision of the target and their arm. After a random period of between 500 and 1500 ms, a fourth, higher-pitch and continuous tone was sounded. On this GO signal, subjects made a fast-reaction reaching movement straight to the target, so as to finish 'touching' the virtual target with the tip of their forefinger. Three rTMS pulses were

applied randomly on half the trials beginning 50 ms after the GO signal. This delay ensured that the stimulation train ended just before the reaching movement began (i.e. within the reaction time – see Figure 2, and compare Figure 4). At the end of the reaching movement, subjects kept their hand still until the continuous tone had ceased. At this time, vision of the target was returned, and subjects could note the end-point of their movement. The next trial began when the subject held down the switch. See Figures 1A and 2.

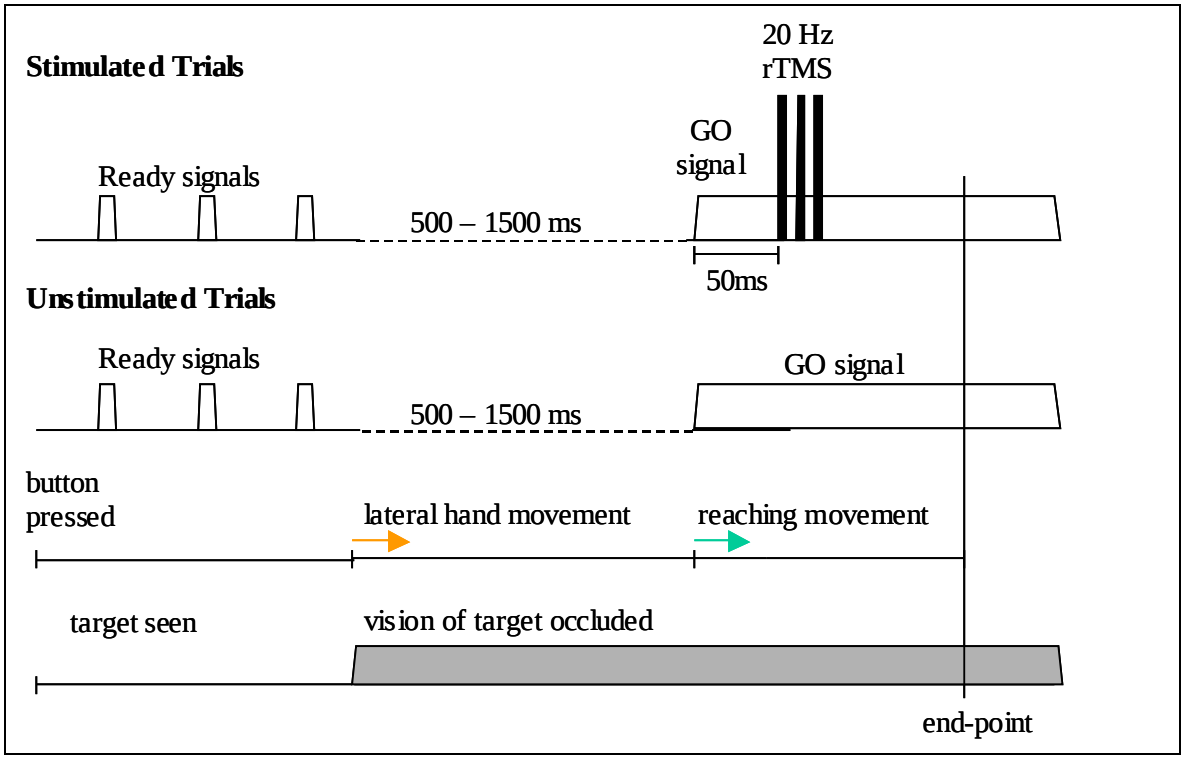

Figure 2. Stimulus conditions and timing. Upper panel: Stimulated Trials*. Cerebellar or motor cortical rTMS (heavy black vertical lines) was applied 50 ms after the GO signal (open trapezium), in 3 pulses at 20 Hz.* ***Middle panel: Unstimulated Trials****. Control trials were identical to stimulated trials except that no rTMS pulses were presented.* ***Lower panels: Arm Movements and Vision of Target****. Button presses started each trial. After the third preparation signal, subjects made a lateral hand movement (orange arrow), then on the GO signal, reached to the target (green arrow). Vision of the target was occluded (grey trapezium) when the lateral hand movement began, and was returned after the end of the trial. The thin black vertical line indicates the end-point of the reaching movement across panels.*

Sixty training trials were given during which some initial feedback was provided to subjects about the speed and direction of the lateral hand movements, and the timing and accuracy of the final reaching movement. Randomly in half the training trials, the double-cone coil, positioned safely away from the head was triggered with three 20 Hz pulses as in the experimental trials.

The subjects' finger positions during the task were monitored with a tracking device (Polhemus 'Fastrak'). The transmitter was positioned on the surface 65cm directly infront of the subject, while the receiver (1.5 x 1.5 x 1.5 cm) was securely attached over the tip of the subject's right forefinger. All apparatus was controlled through a personal computer, operating bespoke software (RC Miall).

Data Analysis

The tracking device sampled at 125 Hz the distance of the receiver from the transmitter in three Cartesian axes (with the origin in the transmitter device) – see Figure 1B. Calibration measurements were taken at the end of each experiment, with the subject holding his or her finger steady at the perceived target location in full vision. Data was exported into Matlab, and analysed as follows. Finger position traces were aligned with respect to the GO signal (the fourth tone), and the end-point of the reaching movement was determined by calculating the first zero-crossing in the derivative of velocity following the maximum velocity (the maximum velocity was roughly at the mid-point of the reaching movement).

Each trial, ***i*** yielded an end point in three coordinates $[x_i, y_i, z_i]$. The end-points were averaged to give the mean end-point for stimulated $[x_s, y_s, z_s]$ and unstimulated $[x_u, y_u, z_u]$ conditions. The target location $[x_t, y_t, z_t]$ was obtained from calibration trials. The magnitude of 3-dimensional vectors was determined, where necessary, by the following: $\mathbf{d} = \sqrt{[x^2 + y^2 + z^2]}$.

In the first analysis, the distance from the target (end-point error) was calculated for each trial:

$$\text{End-point error,} \quad d_i = \sqrt{[(x_i - x_t)^2 + (y_i - y_t)^2 + (z_i - z_t)^2]} \qquad (1)$$

and the mean error calculated for stimulated (d_s) and unstimulated (d_u) trials:

$$\text{Mean error,} \quad d_s = \Sigma\, d_{is} / n_s \qquad (2) \qquad \text{Mean error,} \quad d_u = \Sigma\, d_{iu} / n_u \qquad (3)$$

Where n_s and n_u are the number of trials for stimulated (30) and unstimulated (30) conditions respectively. Mean end-point errors for the cerebellar- stimulated and unstimulated conditions were compared with repeated measures analysis of variance (RM-ANOVA) with factors of subject and stimulation. Control motor cortical versus cerebellar stimulation data was compared in a further RM-ANOVA restricted to only five subjects using RM-ANOVA with factors of subject, location,

and stimulation. Subjects 2 and 3 underwent only 20 (rather than 30) motor cortical stimulation trials, meaning inclusion of their data in the latter RM-ANOVA was not valid.

We also carried out a secondary analysis of the end-point data for the following reasons. Firstly, we had no *a priori* reason to predict consistent stimulation-contingent differences in a particular spatial direction or dimension across subjects. The measurement of absolute end-point error (Equation 1) also gave us no information about the *direction* of this error in a stimulus-dependent manner. It is possible that a subject's mean error for unstimulated trials was of equal amplitude, but in the opposite direction with respect to the target, to the mean error of the stimulated trials, thus cancelling out this difference. Secondly, we could not be certain that in every case subjects attempted to point to exactly the same location during the task as they did during the calibration trial. Thirdly, each subject might miss the target in a consistent way – for example always pointing to the right of, or always below the target. Cerebellar rTMS may have had a disruptive effect that brought the mean end-point of movements *closer* to the target. Thus, although accuracy in this case would seem to *increase* with stimulation, the actual effect of rTMS may have been a perturbation masked by an intrinsic bias. For the above reasons, we conjectured that taking the mean of the unstimulated trials as the origin of measurement would serve as a better reference point. Furthermore, the axis of measurement should be the axis that unites the means of stimulated and unstimulated distributions. To this end, the following secondary analysis was performed.

Each experiment produced two clusters of points in three dimensions, and our experimental question related to the difference in mean end-points for stimulated versus non-stimulated clusters. Therefore, we transformed the end-point coordinates for each trial into a single quantity representing the distance from the mean of the unstimulated trials along the axis joining the means of stimulated and unstimulated distributions (hereafter the 'principal axis'). This was achieved by the following calculations:

Components $[x_p, y_p, z_p]$ of distance along the principal axis between means:

$$[x_p, y_p, z_p] = [(x_i - x_u), (y_i - y_u), (z_i - z_u)] \bullet \{[(x_s - x_u), (y_s - y_u), (z_s - z_u)] / d_{us}\} \qquad (4)$$

Where d_{us} is the length of the vector between unstimulated and stimulated means. Division by this vector normalises the principal axis vector to a length of one, leaving the distribution of the transformed data points constant, whilst rotating the stimulated cluster onto the principal axis.

The distance along the principal axis for each end-point is then the sum of the components x_p, y_p, and z_p. The results of the above formula were confirmed for one subject's data using trigonometry. This calculation is shown in diagrammatic form below (Figure 3).

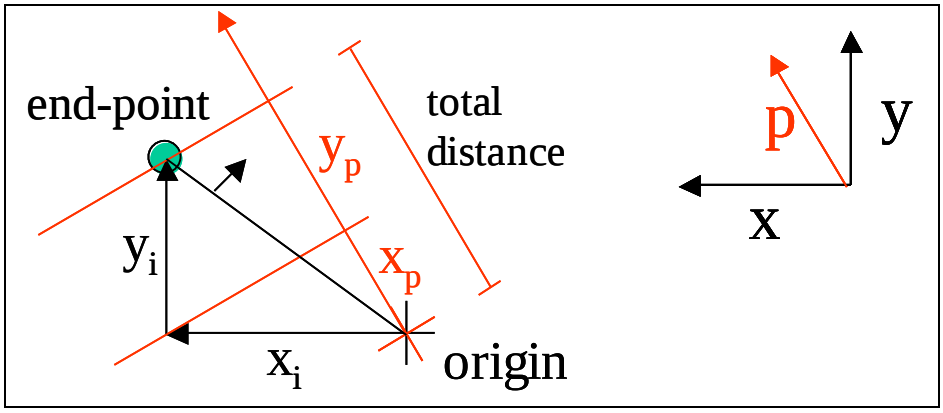

Figure 3. Vectorial rotation of data onto the principal axis between means. *Two dimensions are illustrated for clarity: higher-dimensional calculations are comparable. The Cartesian axes,* **x** *and* **y** *are shown in black lines, the principal axis,* **p** *between the distribution means are in red.* ***Left panel****: The origin is indicated by the intersection of orthogonal axes at the lower right. The end-point for a single trial (green circle) has Cartesian components* $\mathbf{x_i}$ *and* $\mathbf{y_i}$*. Spatial transformation of* $\mathbf{[x_i, y_i]}$ *onto the principal axis,* **p** *gives the components* $\mathbf{[x_p, y_p]}$*. These quantities represent the components of distance along the principal axis, of lines perpendicular to that axis passing through the x- and x-+ y- components of the untransformed co-ordinates. The total distance, then, is the sum of* $\mathbf{x_p}$ ***and*** $\mathbf{y_p}$*.* ***Right panel****:* ***x****,* ***y****, and* ***p****-axes for reference. The overall effect of the transformation was to extract components of variance along the principal axis from the original* $\mathbf{[x_i, y_i]}$ *components, by rotating the Cartesian vector (diagonal black line) onto the principal vector,* **p** *– rotation depicted by oblique black arrow. The mean and variance of the data remain constant.*

In the second analysis, then, the mean distance of end-points along the principal axis was determined separately for stimulated and unstimulated conditions. The results for cerebellar stimulation alone were compared with a RM-ANOVA with factors of subject and stimulation. Control data (cerebellar and motor cortical stimulation together) for five subjects was then compared with a RM-ANOVA with factors of subject, location, and stimulation. All statistical tests were assessed at the 5% level of significance.

Results

Hand trajectory and end-point locations

A representative hand trajectory trace is shown in Figure 4. The x-, y-, and z- axes are plotted as separate traces against time. Although the following variables were not explicitly measured, some general points can be made. Reaching movement reaction time, judged by the deflection in the z-axis following the GO signal, was of the order of 250 – 300 ms. The most part of the movement (also from the z-axis), was completed between 750 and 1000 ms after the GO signal. For most trials, hand-trajectories were comparable, with only a few anomalous traces (for example the single stimulated z-axis trace, and the single unstimulated x-axis trace that are quite separate from the main cluster). Such trials are probably where subjects either reached too early, paused then continued, or reached too late, missing the GO signal. There seems to be greater variation in the reaction times for unstimulated trials (note the increased spread in the z-axis). This probably represents the 'startle effect' of the rTMS. This issue is taken up in the Discussion. The data below are typical for all subjects and all conditions.

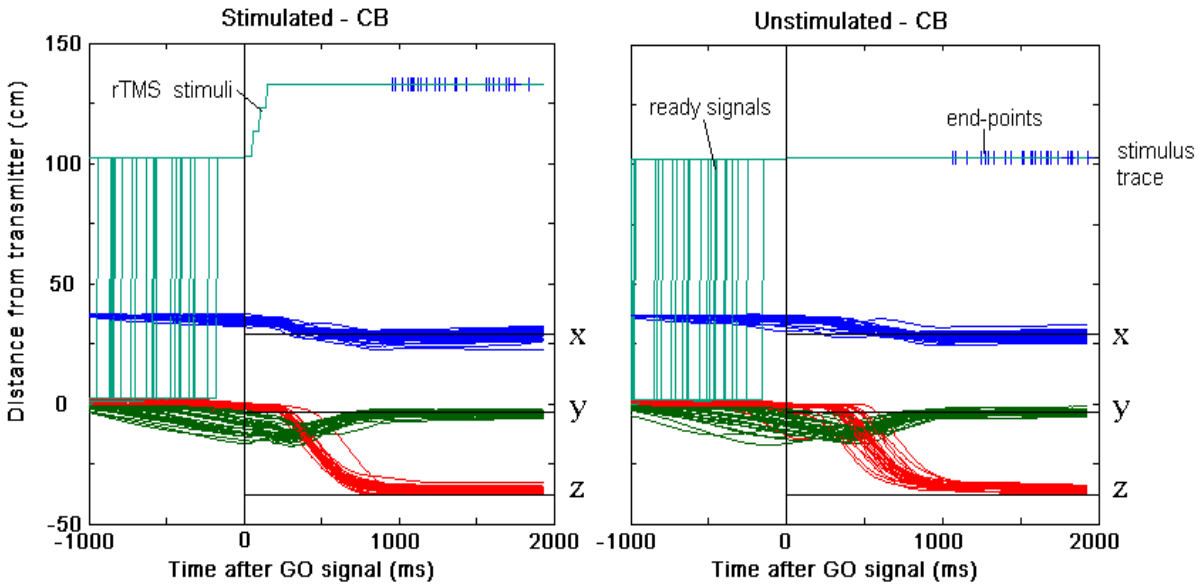

Figure 4 – Typical hand trajectory traces*. x-, y-, and z-axes are plot separately against time for one subject, with 30 traces per axis per panel. All traces are aligned with respect to the GO signal.* ***Left panel****:* ***Stimulated Trials*** *(cerebellum).* ***Right panel****:* ***Unstimulated Trials****. The* ***upper trace*** *(light green) shows stimulus traces, downward deflections show preparation (ready) signals, three upward stepped deflections in the left panel show rTMS stimuli – note their absence in the right panel. Vertical blue lines crossing the stimulus trace show the end-point of movement for each trial. Blue, green, and red traces show x-, y-, and z-axes respectively. The lateral hand movement is notable primarily in the y-axis (dark green). The rapid reaching movement is notable primarily in the z-axis (red), vertical movements. Horizontal black lines (from 0 to 2000 ms) in x-, y-, and z-axes indicate the calibrated target location. CB – cerebellar.*

The same data as in Figure 4 are displayed in Figure 5 as end-points in two dimensions. These graphs plot distance from target (black lines in Figure 4) for each trial. The first graph shows x- versus y-axes, the second y- versus z-axes. These plots show a definite bias to the reaching end-point with respect to the calibrated target location, in that end-points are consistently shifted along one or both axes in a certain direction. For example, in the right panel, there are no negative z-values. This shows perhaps a 'gravitational' effect – negative z-values represent overshooting the target vertically upwards – this is also clearly seen in Figure 4.

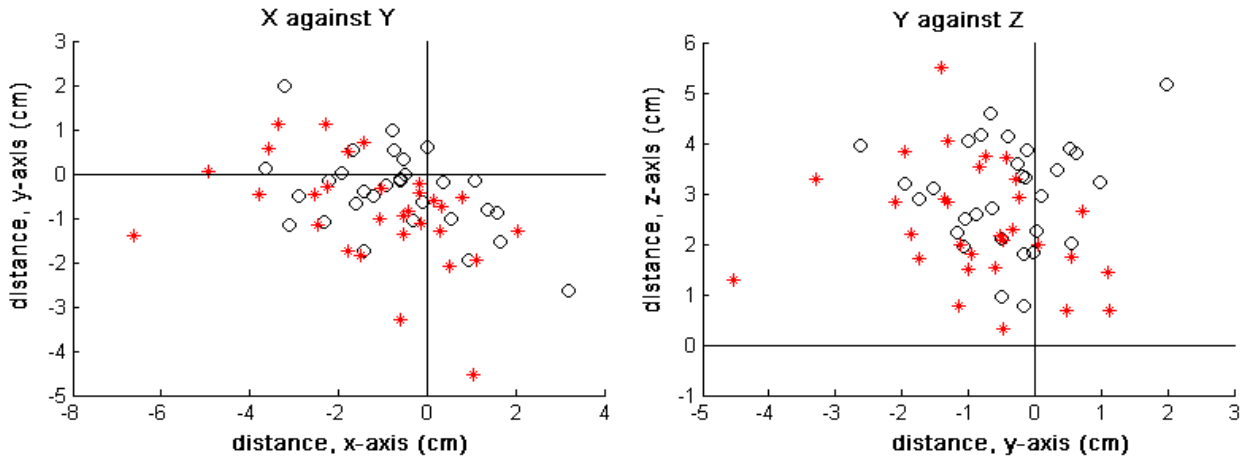

Figure 5. Typical end-point plots in two dimensions*. Stimulated trials are shown as red asterisks, unstimulated trials as open circles. All scales reflect distance in centimetres from the target location (the origin, 0,0).* ***Left panel****: x- against y-axes. Note that no end-points occurred in the upper-right quadrant, and that there is an orientation to the cluster.* ***Right panel****: y- against z-axes. Note that all end-points lie above the line z = 0, and more are to the left of the z-axis. In several subjects, there were clear differences between distributions. The data above are less visually-separable.*

End-point errors

The end-point error (distance from target) of each reaching movement was determined as detailed in the Methods section (Equation 1). The grand mean over all subjects for cerebellar and motor cortical stimulation is shown in Figure 6.

As shown, there was a clear increase in end-point error with cerebellar stimulation (4.72 ± 0.20 cm, mean ± s.e.m.) as compared both to the cerebellar control condition (4.13 ± 0.14 cm) and the motor cortical stimulation (2.96 ± 0.14 cm). The motor cortical control yielded a mean error of 3.15 ± 0.14

cm. Cerebellar conditions, regardless of stimulation, produced much higher errors than did motor cortical conditions. Possible reasons for this finding will be considered in the Discussion.

Figure 7 displays the mean end-point error separately for each subject. In the upper panel showing cerebellar stimulation results, five subjects show increased errors with cerebellar stimulation. This is not evident, or is reversed for subjects 1, 3, 8, 9, and 10. Repeated measures analysis of variance on the cerebellar condition data alone (ten subjects) gave significant main effects of stimulation ($F_1 = 25.86$, $p < 0.001$) and subject ($F_9 = 140.54$, $p < 0.001$), with significant interaction effects of stimulation x subject ($F_9 = 13.05$, $p < 0.001$). Interpretation of these results by visual inspection of Figures 6 and 7 suggests there was a general, significant trend towards increased errors in the cerebellar stimulation, and that the magnitude of difference was significantly different between subjects. The lower panel of Figure 7 presents data for the seven subjects who participated in the control motor cortical stimulation experiment (data pooled in right columns of Figure 6). The stimulated and unstimulated means are much closer together, and in five of the seven subjects, the end-point error in the motor cortical stimulation condition is slightly *lower* than without stimulation. This accounts for the decreased error of the motor cortical grand means (Figure 6).

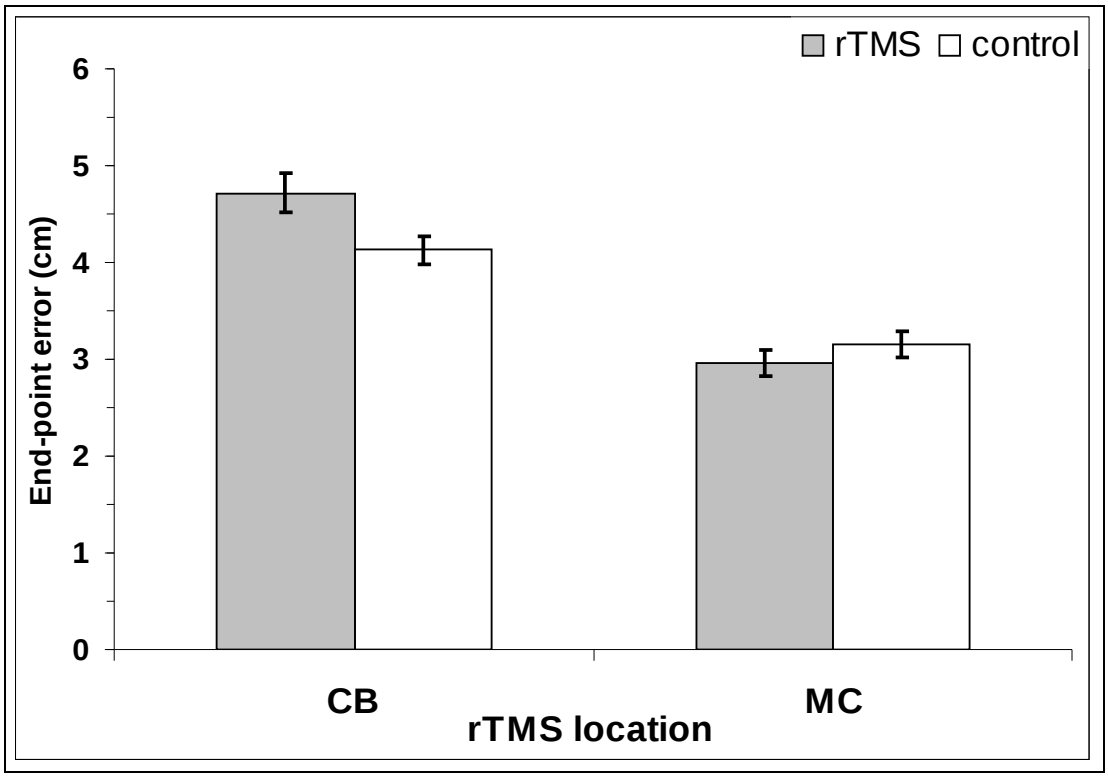

Figure 6. Mean end-point errors for all conditions pooled across subjects. *Data show means ± standard errors. Grey bars – rTMS conditions, open bars – control (no-stimulation) conditions. Errors are clearly higher with cerebellar (CB) stimulation than both without stimulation and with motor cortical (MC) stimulation. There is a slight decrease in end-point error with motor cortical stimulation. The cerebellar difference may represent a disruption of processing, while the small motor cortical difference an increase in functionally useful cortical excitability. N = 300 (CB), 210 (MC).*

To compare the end-point errors for cerebellar versus motor cortical stimulation, a three-way analysis of variance with factors of subject, location, and stimulation was performed for the five subjects (Subjects 6 to 10) who performed equal numbers of trials in both cerebellar and motor cortical conditions (n = 30). This yielded main effects of subject (F_4 = 38.09, $p < 0.001$) and location (F_1 = 88.09, $p < 0.001$) but no main effect of stimulation (F_1 = 2.15, $p = 0.144$). Significant interaction effects of subject x location (F_4 = 66.46, $p < 0.001$) and subject x location x stimulation (F_4 = 4.312, $p = 0.003$) were also found.

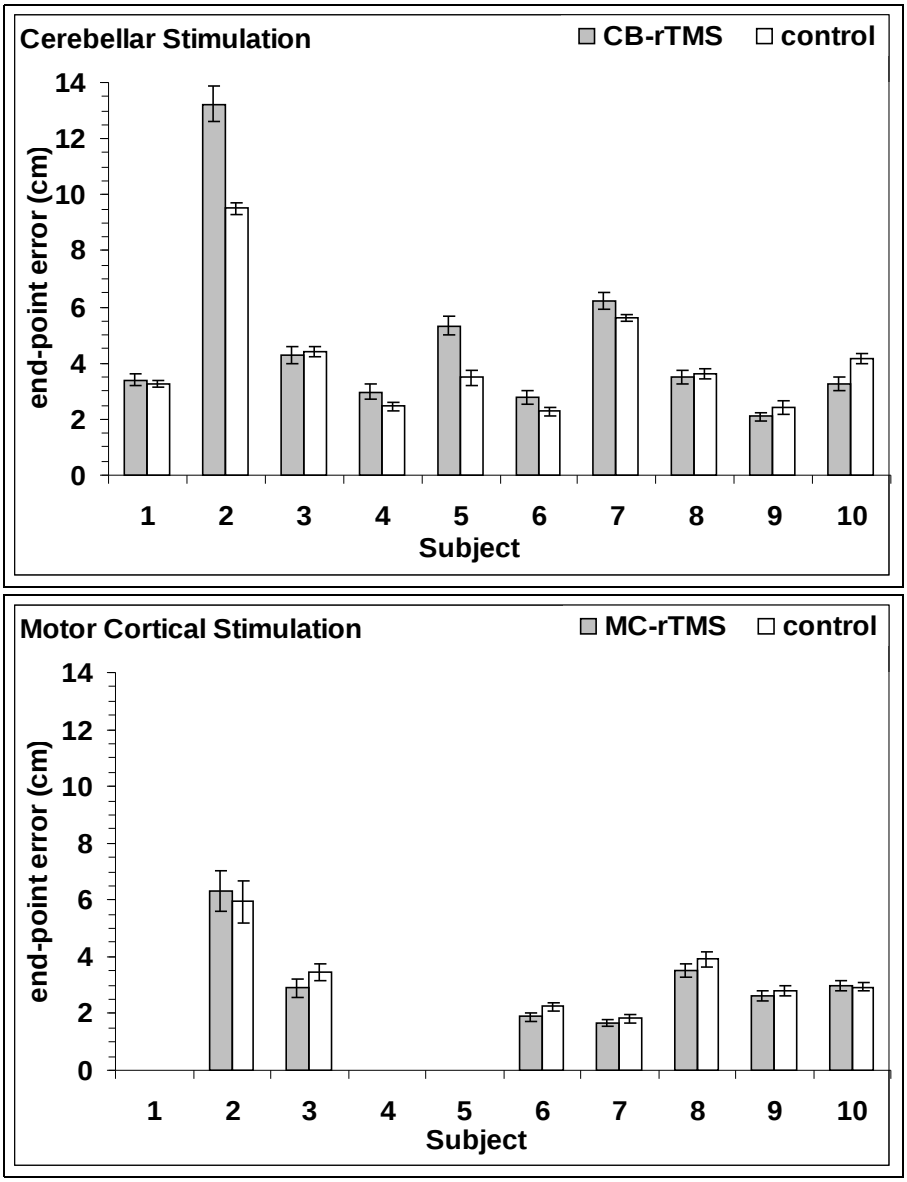

Figure 7. Mean end-point error for cerebellar and motor cortical stimulation conditions. *Data show individual subjects' means ± standard errors in distance between end-points and the target. Filled bars – stimulated trials, open bars – control, unstimulated trials.* ***Upper panel****: Cerebellar (CB) stimulation in 10 subjects.* ***Lower panel****: motor cortical (MC) stimulation in 7 subjects. Numbers in both panels refer to the same subjects. N = 30 (CB), 20-30 (MC).*

Generally speaking, then, cerebellar stimulation increases end-point error, while motor cortical stimulation decreases error to a small extent. The extent to which subjects display stimulus-dependent variation is itself significantly variable (between-subjects main and interaction effects).

Variance along the principal axis

Spatial transformation of data separately for each subject (see Methods, Equation 4) maintained the mean and variance of the distribution, and allowed the distance along the principle axis (the axis between the means of stimulated and unstimulated distributions) of each data point to be calculated (recall Figure 3). Since these data are now independent of both the origin of measurement (the tracking device), and the target, they reflect more accurately the stimulation-dependent variation for each subject. However, we could not determine, with this analysis alone, in which direction *with respect to the target*, any *overall* differences were.

Figure 8 plots the mean distance along the principal axis, with the origin at the mean of the unstimulated distribution, for stimulated and unstimulated conditions separately. Since the data is measured from the unstimulated mean, the latter distribution appears only as a standard error above zero for comparison with the stimulated condition.

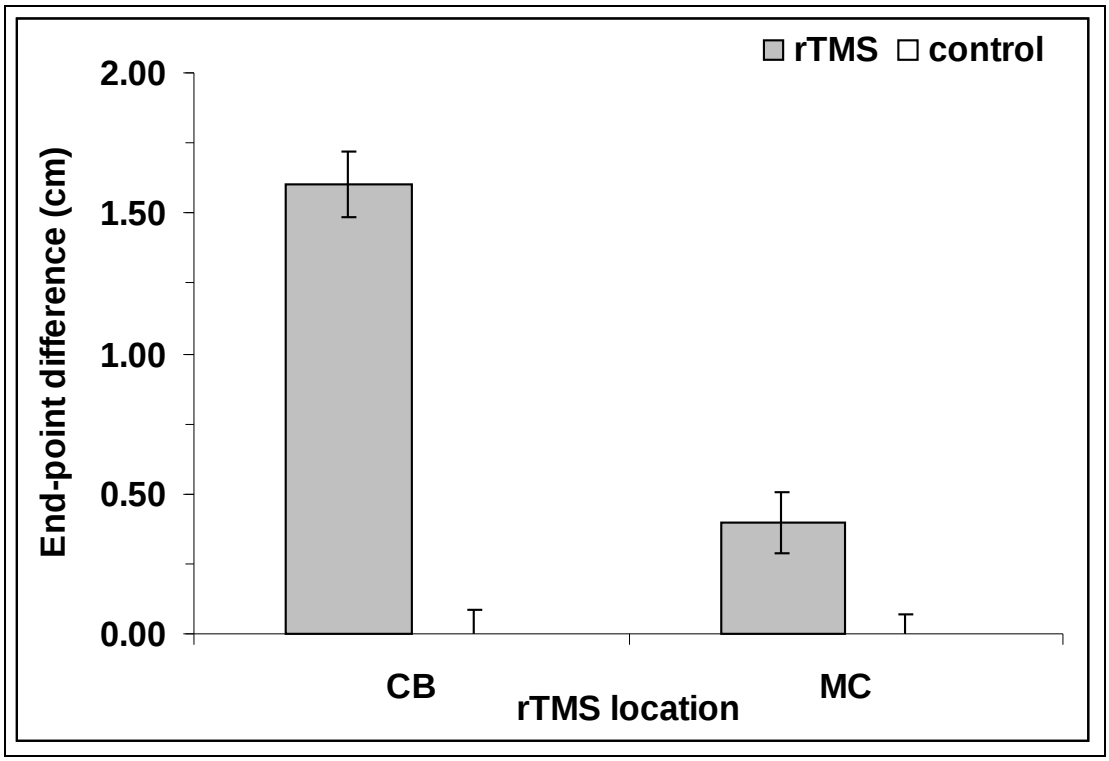

Figure 8. Mean distance along the principal axis for cerebellar and motor cortical conditions, pooled across subjects*. Data are mean, ± standard error, in centimetres. Unstimulated means are by definition zero, with standard error about zero (positive error bars shown for comparison). Filled bars – stimulated trials. Left column – cerebellar (CB) stimulation, right column – motor cortical (MC) stimulation. N = 300 (CB), 210 (MC).*

A clear difference is evident in these data, with the difference between cerebellar stimulated (1.61 ± 0.12 cm) and unstimulated (0 ± 0.08 cm) distributions being much higher than the difference between motor cortical stimulated (0.4 ± 0.11 cm) and unstimulated (0 ± 0.07 cm) conditions.

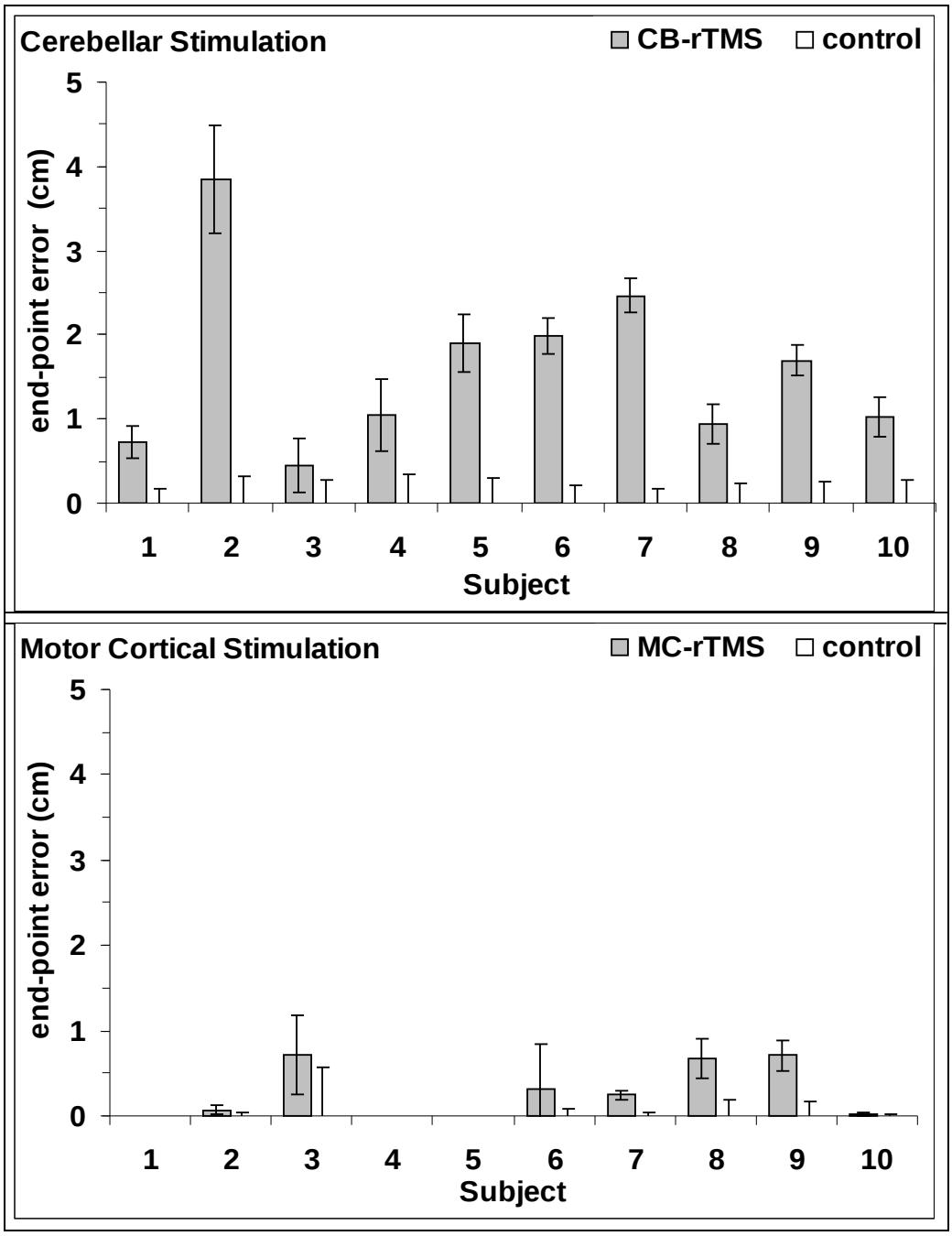

Figure 9. Mean principal axis difference for cerebellar and motor cortical stimulation conditions. *Data shows individual subjects' means ± standard errors in centimetres along the principal axis joining the stimulated and unstimulated distributions. Filled bars – stimulated trials, error bars above zero – control, unstimulated trials.* ***Upper panel****: Cerebellar (CB) stimulation in 10 subjects.* ***Lower panel****: motor cortical (MC) stimulation in 7 subjects. Numbers in both panels refer to the same subjects. N = 30 (CB), 20-30 (MC).*

The data was then plotted separately for each subject (Figure 9). By comparison of the upper (cerebellar stimulation) and lower (motor cortical stimulation) panels, it is clear that the large difference between stimulated and unstimulated distributions is not similar across subjects, while the standard errors of each condition are in most cases similar.

Analysis of variance for the cerebellar stimulation alone showed significant main effects of stimulation ($F_1 = 173.7$, $p < 0.001$) and subject ($F_9 = 4.91$, $p < 0.001$), and a significant interaction effect of stimulation x subject ($F_9 = 6.87$, $p < 0.001$).

Visual inspection of Figure 9 suggests a clear interpretation of these results: subjects differed in the amount to which stimulated versus unstimulated distributions were separable, but overall, there were clear and significant differences. In only one case (Subject 3) were error bars overlapping, and therefore the distributions not statistically different (not explicitly tested). The lower panel of Figure 9 (motor cortical stimulation) shows, for subjects 2, 3, 6 and 10 no significant difference between stimulated and unstimulated means (error bars overlapping), while for subjects 7, 8, and 9, there are larger and significant differences of up to 0.75 cm.

Again, to compare cerebellar and motor cortical stimulation, a three-way analysis of variance with factors of subject, location, and stimulation was performed for five subjects (Subjects 6 to 10). This yielded significant main effects of subject ($F_4 = 2.52$, $p = 0.044$), location ($F_1 = 36.98$, $p < 0.001$) and stimulation ($F_1 = 117.41$, $p < 0.001$). All interaction effects were significant at the 5 % level, however the location x stimulation interaction ($F_1 = 40.92$, $p < 0.001$) remained at much higher significance. These data together suggest that cerebellar stimulation perturbs the end-point of the reaching movement away from the unstimulated mean significantly more than motor cortical stimulation. The magnitude of this difference varies significantly between subjects. Significance tests were not carried out for individual subjects.

Discussion

We aimed to investigate whether the end-point of a two-phase motor task would be perturbed by repetitive transcranial magnetic stimulation (rTMS) immediately before the reaching phase. Our primary analysis showed that, on average, in trials where subjects received stimulation over the cerebellum, they missed the target by 0.6 ± 0.1 cm (mean ± s.e.m.) more than in unstimulated trials (Figure 6). For motor cortical stimulation, this difference was only 0.2 ± 0.1 cm. This analysis was unsatisfactory, however, as detailed in the Methods section. In the secondary analysis, we spatially transformed the data into a single component of magnitude along the principal axis (the axis joining the means of stimulated and unstimulated distributions for each subject). This latter analysis proved to be a more sensitive measure of stimulus-dependent differences in the distributions of end-points. The difference between stimulated and unstimulated means in the secondary analysis was 1.6 cm for cerebellar and 0.4 cm for motor cortical stimulation (Figure 8). The extent to which subjects displayed differences varied significantly between subjects in both analyses (Figures 7 and 9). In short, there was large inter-subject variability.

Taking these results together, rTMS over the cerebellum significantly affects the end-point distribution of our reaching task. To a certain extent, as shown in the mean end-point errors in Figure 6, this difference amounted to a decrease in accuracy of the movement with respect to the target – five out of ten subjects were between 1 and 3.5 cm less accurate with cerebellar rTMS, while the other five showed small differences in either direction. Stimulation over the motor cortex showed no such effect. If anything, motor cortical stimulation *increased* the pointing accuracy slightly (Figure 6). If we assume that motor cortical excitability may have some bearing on functional tasks, then rTMS before a movement begins may facilitate, rather than disrupt functioning. Previous studies have shown that high frequency (over 5 Hz) rTMS over the motor cortex increases cortical excitability as measured by the electromyographic response to a further single motor cortical stimulation (Berardelli *et al*., 1998, whereas low frequency (1 Hz or less) stimulation decreases excitability (Pascual-Leone *et al*., 1994; Modugno *et al*., 2001; Touge *et al*., 2001). There was only a small trend in the present data to support this assertion, however, and the stimulation intensity used was approximately 10-20 % of stimulator output below the threshold for eliciting evoked potentials in the muscles of the hand (unpublished pilot studies). This intensity of stimulation may not sufficiently affect motor cortical excitability with only short trains every ten seconds or so between trials. Furthermore, few task-dependent functional effects of motor cortical TMS have been published, suggesting that this physiological factor may not be functionally relevant in motor tasks (see for example Müllbacher *et al*., 2000). However, this absence of

evidence must not be taken to be evidence of absence, better-controlled experiments and standardised and calibrated methodology will provide adequate answers to these questions.

What effect is repetitive stimulation over the cerebellum having? Is the effect due specifically to a disruption of cerebellar cortical processing? I shall now discuss two possible non-specific or peripheral factors that might explain our findings.

1) Cerebellar TMS is notoriously uncomfortable in that, by necessity, the large stimulating coil must be placed over the sternocleidomastoid and trapezius muscles of the neck, scalp muscles, large blood vessels in the confluence of the sinuses, and most importantly, branches of the facial nerve. Furthermore, the cerebellar cortex is situated several centimetres below the surface of the scalp, necessitating a higher stimulator output to penetrate into the skull and affect the nervous tissue. Cerebellar TMS is uncomfortable and might disrupt movement accuracy in subjects engaged in sensitive movement tasks. This is unlikely for several reasons, however. Firstly, subjects who found the stimulation anxiety producing or painful were excluded from the experiment – the ten subjects whose results are presented here tolerated the stimulation well. Secondly, while the extent to which stimulation-induced neck, shoulder, and facial contractions varied between subjects, this variation did not seem to be associated with reaching accuracy. Subjects 1 (the author) and 3, who showed the least difference between stimulated and unstimulated conditions (Figure 9), had quite large rTMS-evoked contractions, while subjects 5, 6, and 8, who had participated in many TMS studies (and who were therefore more relaxed and less disturbed by the stimulation) showed large and significant differences between conditions. The remaining subjects stood somewhere between these extremes.

2) Another possibility is that peripheral afferent inputs, conveyed by sensory nerves in the scalp, muscles, and other tissues were disrupting motor cortical processing via indirect actions on primary or secondary sensori-motor cortices. Such peripheral stimulation is known to have a facilitatory effect on motor cortex excitability (Lars Christensen, personal communication), and this possibility cannot entirely be ruled out as an explanation for cerebellar disruption. Against this assertion, however, again we saw large differences between subjects in task performance, whereas the amount of peripheral afferent activity induced by the stimulation would have been roughly constant, and at least equally non-specific across subjects. Furthermore, with motor cortical rTMS in the present study we have seen a slight *improvement* in end-point accuracy at a stimulation frequency known to increase cortical excitability. It is hard to explain location-specific differences in task performance by reference to non-specific cortical excitability changes. The effect of both high-frequency motor

cortical TMS *and* peripheral afferent input on motor cortical excitability is facilitatory. Yet the effects of cerebellar and motor cortical stimulation in the present results were in opposite spatial directions with respect to the target location.

Experiments to control for the above non-specific effects would incorporate the following modifications. Using identical apparatus and conditions to stimulate subjects over the neck, but away from the cerebellum, would control for both the physical perturbations and the non-specific peripheral afferent confounds. Such control studies are now being carried out in our laboratory. Alternative control experiments might position the stimulating coil over the left lateral cerebellum, or incorporate movement analyses. By recording directly the rTMS-induced contractions and any perturbations in the arm position (for example with an accelerometer, electromyograph, or through a detailed analysis of the present arm trajectory measurements), the extent of motor perturbation could be determined and correlated with end-point accuracy. Such analyses are vital if we are to rule out these non-specific confounds. Finally, by analysing the distribution of reaching movement start-positions (i.e. the deflection seen in the z-axis of Figure 4), and correlating, trial-by-trial these data with the reaching movement end-points, it will be possible to detect physical perturbations present before the reach began. A single analysis (Subject 6) of this data had been performed at the time of writing, and by visual inspection alone, there seemed to be no marked difference in start-points between the stimulation conditions, whereas significant end-point differences were found.

Several further methodological points are worthy of mention. Firstly rTMS may have had a ‘startle effect’ on subjects, thus shortening their reaction time to the GO signal, or perhaps decreasing the variability in reaction times. This parameter was not explicitly measured, but can be seen as a greater spread in hand-trajectories in the z-axis (Figure 4). This is an almost inevitable confound of magnetic stimulation over the cerebellum for the reasons mentioned above. The rTMS pulses were presented 50 ms after the GO signal, reducing the potential startle effect somewhat. However, the only adequate controls for this confound would be identical stimulation over the left cerebellum or neck, or the incorporation of sham rTMS (three auditory pulses at 20 Hz, and 1 ms duration, for example, along with a non-cerebellar evoked muscle contraction, with the stimulating coil in place). Secondly, in general, subjects showed larger end-point errors with cerebellar conditions regardless of stimulation, than in motor cortical conditions (see Figure 6). There could be several reasons for this. There may be a training effect, since motor cortical conditions were carried out after cerebellar conditions in all subjects. Counterbalancing order of stimulation-location would control for this. There may also be an accumulative effect of rTMS over the motor cortex, such that cortical excitability might increase throughout the duration of the experiment, influencing end-point

accuracy overall, in a stimulation-*in*dependent manner. This was seen in pilot studies in several subjects (unpublished), where 90 paired-pulse stimulations (cerebellar rTMS, followed 6 ms later by motor cortical single pulse TMS) had an increasingly facilitatory effect on right hand first dorsal interossus MEP amplitudes. This latter finding is interesting in its own right, and might be explicable on the grounds of the hypothesis that repetitive TMS has effects that outlast the duration of the pulse-train. Further investigation of this factor is required. The third possibility for explaining decreased errors in motor cortical conditions is that the position of the figure-of-eight coil was less constraining and uncomfortable for the subject than that of the cerebellar double cone coil. The control in this situation would be to have both coils positioned in all experiments, but to have only one active coil connected to the stimulation equipment.

Finally, in the analyses of both end-point error (Figure 7) and distance along principal axes (Figure 9), there was large variability across subjects. This variability was of high significance in all relevant analyses of variance. In particular, subject 2 showed the largest error in both stimulated and unstimulated trials for both cerebellar and motor cortical stimulation. There are several reasons for inter-subject variability, many of which have already been noted. Several more are especially relevant to our purpose. If we assume that cerebellar rTMS does indeed have a disruptive effect on reaching accuracy, and since it is well-documented, though not universally appreciated in published studies, that coil positioning, orientation, and intensity of stimulation are highly sensitive parameters across subjects, then failure accurately to control for these methodological factors may result in just the kind of inter-subject variability that we have observed. Particularly for the cerebellum, situated beneath much non-nervous tissue, and located several centimetres under the scalp, accuracy of coil placement is vital. The disruptive action of TMS is believed to be maximally effective only for populations of neurons directly under the centre of the figure-of-eight and double-cone coils, the focus of stimulation being only 0.5 - 1 cm in diameter (Pascual-Leone *et al*., 1999). Thus, with a 28 cm coil, and large variation in subjects' head-sizes, neuroanatomically-specific coil positions, with respect to a standardised scalp landmark, are unlikely to be achievable, that is in order to activate the same area of cerebellar cortex across subjects. Without the use of brain imaging (structural MRI)-registration technology (for example 'Brainsight' developed by the MagStim Company) along with careful calibration of simulation intensity for each subject, this is likely to be an unresolved confound. Intensity calibration may be possible if replicable effects of cerebellar TMS on motor cortical excitability can be demonstrated. This is unlikely to be the case, as our pilot studies indicated, without the former confound of stimulation location being resolved first.

Such methodological considerations are vital in all magnetic stimulation paradigms, particularly with cerebellar rTMS, yet published cerebellar TMS studies (Hashimoto & Ohtsuka, 1995; Ohtsuka & Enoki, 1998; Théoret *et al*., 2001) neglect to go into any great methodological detail on these issues. Furthermore, sufficient control experiments such as those postulated above, are rarely considered. Having discussed the more obvious potential confounds to the present findings, it is pertinent to discuss what we believe to be the correct explanation.

Does cerebellar rTMS disrupt internal models of the motor system?

If we assume that the stimulation conditions had a neurophysiologically-relevant disruptive effect on cerebellar cortical processing, and that all confounding variables have been discounted, then what are the possible explanations for the observed perturbations in movement end-points? I examine firstly the possibility that the representation of the *target* was disrupted, secondly that the *motor command* was disrupted, and finally, that the *body-state estimation* was disrupted.

Disruption of the target representation

In order to reach to a current or remembered visual target, an accurate representation of the target position must be encoded and stored temporarily ‘somewhere’ in the nervous system. Candidate areas for this kind of processing are usually in the posterior parietal ‘dorsal stream’, for example in the superior parietal sulcus (Sereno *et al*., 2001). In order to be incorporated into a motor program, however, the target representation must be output to areas involved in motor planning and preparation. Miall and colleagues (1993) suggested that target representations are output from posterior parietal cortex to the lateral hemispheres of the cerebellum, which computes the desired motor commands through an inverse dynamics model of the motor system (the shoulder-, elbow-, and hand-joint torque and stiffnesses, for example). This calibrated motor command, which in the cerebellum is integrated with detailed information concerning the state of the body (see below), is then sent back ‘up’ to the motor cortices to influence and calibrate planned and ongoing movements. Later processing by the cerebellum, (when the motor command is on the way ‘down’ to the motor apparatus) predicts the sensory consequences of this motor command, reporting back to the motor cortices in fast, internal feedforward/feedback loops during the movement itself.

In the present experiment, repetitive magnetic stimulation over the lateral hemisphere of the cerebellum might have disrupted the target-representation, such that the subsequent motor plan was based on an inaccurate estimate of target location with respect to the body. This is an intriguing possibility, and one that cannot be ruled out on the present results. Several further experiments may

help to clarify the role of the target representation in cerebellar motor control. Firstly, subjects saw the target only at the beginning of the trial, and not when the target-directed reaching movement was executed. Thus, subjects reached towards a remembered target location, just as Sereno *et al.*'s Macaque monkeys made saccades to a remembered location after a distracting task. The vital question, then, is when does the parietal cortex output the target representation to the cerebellum? If this output only occurs when the target is visible, then it is unlikely that the disruptive effect of rTMS in the present study was due to target disruption – the motor command for the reaching movement was issued at least 500 – 1500 ms (the variable delay in our task) after the occlusion of the visual target. By manipulating the time between visual target offset and the GO signal in the present protocol, this question may be answerable. Alternatively, magnetic stimulation over the posterior parietal cortex at different times before the GO signal may produce a similar disruption in end-point accuracy. A problem with this latter experiment would be in dissociating the effects of parietal stimulation on the *cerebral* motor command from those on the *cerebellar* motor processing. A further problem with both the above experiments is that the differences in timing of critical processing between areas is likely to be of the order of several or at most tens of milliseconds. However, TMS, with pulse durations of less than a millisecond, may be the best methodology for studying this system in humans. Alternatively, both parietal and cerebellar patients could be compared with normal controls, using two different tasks. The first task should be sensitive to parietal TMS, but which both cerebellar patients and normals perform equally well (e.g. a task without rapid, accurate reaching, but which demanded a good target representation). The second task should be sensitive to cerebellar TMS, but which both parietal patients and normals perform equally well (e.g. a fast, smooth, movement that was not directed at an explicit visual target, such as writing one's signature, or a rapid finger-thumb opposition task). Unfortunately, designing such a TMS-sensitive cerebellar task is precisely what the present study is addressing. Progress will be made only when controls both internal and external to the protocol are considered.

If we assume that no such target representation is output to the cerebellum at the critical point within the reaching movement reaction time (when the rTMS is applied), then could the subject use other target-related sources of information? Vision is not available to the subject, but eye-position information may be. Prior to the target's occlusion, subjects fixate on the visual target in preparation for the reaching movement. If subjects maintain their gaze during the period of visual occlusion, then eye-position in the orbits (extra-ocular muscles), and accommodation and vergence (intra-ocular muscles) will serve to provide intrinsic information on target position. Experiments designed to test this hypothesis could require subjects to make a brief saccade away from the target while vision is occluded, but before the stimulation is applied (using saccade-triggered stimulation

and varying the time delay). Thus, any motor or proprioceptive outflow from the oculomotor system, which was able to influence target-directed reaching through cerebellar processing, would be disrupted by stimulation over the cerebellum occurring 100 ms, say, after saccade execution. Finally, the target position could be altered at different stages of the task. Vision of a new target in a different location, but without vision of hand location, could be provided briefly *after* the rTMS pulses. If reaching accuracy improved with vision of the new target, but was not altered when no stimulation was given (comparing rTMS-two-targets with rTMS-one-target, and similarly for unstimulated trials), this would suggest that an accurate target representation is required for reaching movements, and that cerebellar rTMS impairs this representation. If no *relative* improvement in the stimulated condition were found, the disruptive effect of cerebellar rTMS would therefore be due either to effects on the motor command, or the body state estimation.

Disruption of the motor command

The second possible explanation for our results in terms of cerebellar function, is that motor commands were disrupted either prior to the beginning of the reaching movement, or as the movement was evolving towards the end-point. The latter possibility can be excluded for the following reason: the stimulation was complete before the reaching movement began, and no further stimuli were applied. Is it possible that motor commands were disrupted just before being sent to cerebral motor areas, thus altering the dynamics of the movement?

Since, at the time of the rTMS stimuli, subjects were within the reaction time for the reaching movement, the target location, and sensori-motor information is *already* being integrated into an appropriate motor command before the rTMS stimuli are applied. If we consider that the viscosity and inertia of the arm muscles are such that 50-100 ms is required after the muscle cells have depolarised, before the arm starts to move (Desmurget *et al*., 2001), the temporal difference between the onset of stimulation and the motor cortical output commands is further reduced. Considering the ‘internal model’ framework, the cerebellar cortex is hypothesised to integrate the current state of the body with the motor plan expressed in target or desired coordinates, and output this estimated motor command to the motor cortex. If this is the case, and if cerebellar rTMS disrupts the motor command, then it could only do so by disrupting either the state estimation of the body, the target representation, or the integrated result of the two. Separation of these factors empirically may be difficult with human subjects (Miall & Wolpert, 1996). They might be separable, however, if it could be shown that one type of information is processed in the cerebellar cortex, and another type in the deep nuclei. This seems unlikely, given that both mossy fibres and climbing fibres sent collaterals to cerebellar deep nuclei *en route* to the cerebellar cortex – the

information is available at both sites. It is likely that the distinction between sensory (proprioception, state estimation) inflow and motor command outflow serves academic and linguistic rather than functional neurophysiological expediency, however, and may therefore be empirically inseparable, even though our models posit them as separable entities.

In the final discursive section, I consider the putative disruption of the body-state estimation.

Disruption of the body-state estimation

The cerebellum receives feedback from the body via proprioceptors in the muscles, joints, and skin, the target representation from the posterior parietal cortex, and copies of motor commands issued by the motor system. In our task, the state of the body (i.e. the position and velocity of the arm) was varying continuously up to the start of the reaching movement, when a fast, ballistic movement was then required. Since vision was denied, subjects could not use visual information to gauge the position of the arm. They had to rely on proprioceptive feedback, which was then incorporated with the desired state to influence motor commands. Since much of the input to the cerebellum originates in the somatic motor apparatus (the body), conveyed by sensory afferents in ascending spinal columns, and eventually mossy and climbing fibres, to the cerebellar cortex, it perhaps follows that any disruptive effect on cerebellar function will affect primarily this bodily-derived information.

What experiments have been performed to support this assertion? Providing vision of the hand, but not the target may improve reaching accuracy. In a positron emission tomography (PET) study, Inoue and co-workers (1998) showed that in fast-pointing to a visible target, end-point errors when the pointing hand was *not* visible were nearly seven times as large as when vision of the hand was provided (3.3 cm versus 0.5 cm). Similarly, the variability in end-points was nine times higher in the unseen-hand condition. Note that the targets were always visible, on a head-mounted display. The cerebellum was highly activated in both conditions when baseline subtractions were performed, and the subtraction between the two experimental conditions did not show any ipsilateral cerebellar activation. Clearly, in both seen and unseen hand conditions, the cerebellum was involved in task-processing. Stronger support for the importance of hand-position estimation comes from a pointing task in which initial hand position, and the perception thereof, were explicitly measured. Vindras, Desmurget, Prablanc and Viviani (1998) designed a pointing task in which subjects aimed at 24 virtual targets arranged in two concentric circles. These authors showed that subjects produced similar end-point errors both when they moved their right hand to reach a target, and when they used their left hand to position a cursor where they felt their right hand (which did not move) to be. Importantly, the errors in both conditions were in a similar direction and of similar magnitude. They

concluded that both motor and perceptual systems use a common information source to estimate initial hand location. This tallies with the present finding if we assume that rTMS disrupted the proprioception-derived state-estimation of the hand, which had a knock-on effect on motor planning and control, resulting in systematic directional errors (that is, along the principle axis) for each subject.

In an elegant and well-controlled study, Desmurget *et al.* (2001) convincingly demonstrated activation of the cerebellum in reaching to unseen targets. Subjects lay with their heads in a PET scanner, and made saccades and/or reaching movements to one of eight targets in their right visual field. On half the trials, the target jumped from one location to another trans-saccadically and imperceptibly. Trajectories and end-points of both the arm and eyes were measured. Mean hand movement reaction times (270 ms) and movement times (620 ms) were similar to the present study's results. Importantly, hand trajectory analysis demonstrated that subjects began correcting hand movements on jump-trials before the mid-way point, before visual or proprioceptive feedback was able to modulate the rapid, ongoing movements. Very highly significant islands of activation in the ipsilateral cerebellar hemispheres and the vermis were shown for the reaching movements alone. Furthermore, when the activation specific to trials when the subject made corrections in his reaching movement [(Reach with target jump) – (Reach with target stationary)] was analysed, only three significant activations remained: The contralateral sensorimotor cortex, the contralateral intraparietal sulcus, and the ipsilateral parasagittal cerebellum. Given that the reaching movements were of roughly the same velocity and amplitude, and the targets of a similar size and location to the present study, their study provides indirect support for the critical engagement of the cerebellum in our task. Further evidence for the role of state estimation in forward modelling and motor control has been comprehensively reviewed elsewhere (Miall and Wolpert, 1998; Wolpert *et al*., 1998; Desmurget & Grafton, 2000).

Conclusion

We used repetitive transcranial magnetic stimulation over the cerebellum to determine the effect of disruptive stimulation on the end-point distributions of fast, accurate reaching movements. We found a highly significant perturbation in end-point distribution in nine out of ten subjects, however differences between subjects were large.

The evidence in the present report supports the assertion that cerebellar forward models are involved in the smooth and effective control of fast, accurate reaching movements to visual targets. By designing a task that incorporated uncertainty in the starting position, we were able to disrupt the cerebellar estimation of the hand's position and significantly perturb the reaching movement. Our data comports well with similar studies using target or arm perturbations to investigate the learning and dynamics of internal models, and is supported by imaging studies demonstrating significant cerebellar activations in similar reaching tasks. The wealth of suggestions for future research and control conditions in the foregoing discussion attests to the fact that internal modelling is still a fairly new hobby in cognitive neuroscience, but it is one which should keep us busy for many years to come, and which likely will bear much fruit.

Acknowledgements

I would like to thank Lars and Chris at SteinLab HQ, who provided relaxed, friendly, and supportive supervision throughout the duration of the research placement. Somehow I managed to escape a veteran of only three or four cerebellar rTMS experiments, while LC and RCM clocked up a good two dozen between them. Additionally, without Chris's nimble Matlab fingers, I would have been lumbered with learning a programming language along with all the rest of it. This contribution, along with Lars' Viking determination was greatly appreciated. As the rTMS-evoked migraines and phosphenes subside, I shall look back with fondness on this stimulating period of my life.

References

Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Curra A, Gilio F, Modugno N, Manfredi N (1998) Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Experimental Brain Research 122:79-84

Bonnefoi-Kyriacou B, Legallet E, Lee RG (1998) Spatio-temporal and kinematic analysis of pointing movements performed by cerebellar patients with limb ataxia. Experimental Brain Research 119:460-466

Desmurget M, Grafton ST (2000) Forward modeling allows feedback control for fast reaching movements. Trends in Cognitive Sciences 4:423-431

Desmurget M, Gréa H, Grethe JS, Prablanc C, Alexander GE, Grafton ST (2001) Functional anatomy of nonvisual feedback loops during reaching: A positron emission tomography study. Journal of Neuroscience 21:2919-2928

Eccles JC, Ito M, Szentágothai J (1967) *The Cerebellum as a Neuronal Machine*

Grafton ST, Mazziotta JC, Woods RP, Phelps ME (1992) Human functional anatomy of visually guided finger movements. Brain 115:565-587

Harris CM, Wolpert DM (1998) Signal-dependent noise determines motor planning. Nature 397:780-784

Hashimoto M, Ohtsuka KJ (1995) Transcranial magnetic stimulation over the posterior cerebellum during visually guided saccades in man. Brain 118:1185-1193

Inoue K, Kawashima R, Satoh K, Kinomura S, Goto R, Koyama M, Sugiura M, Ito M, Fukuda H (1998) PET study of pointing with visual feedback of moving hands. Journal of Neurophysiology 79:117-125

Krakauer JW, Ghilardi MF, Ghez C (1999) Independent learning of internal models for kinematic and dynamic control of reaching. Nature Neuroscience 2:1026-1031

Miall RC, Wolpert DM (1996) Forward models for physiological motor control. Neural Networks 9:1265-1279

Miall RC, Weir DJ, Wolpert DM, Stein JF (1993) Is the cerebellum a Smith Predictor? Journal of Motor Behaviour 25:203-216

Miall RC, Reckess GZ, Imamizu H (2001) The cerebellum coordinates eye and hand tracking movements Nature Neuroscience 4:638-644

Modugno N, Nakamara Y, MacKinnon CD, Filopovic SR, Bestmann S, Berardelli A, Rothwell JC (2001) Motor cortex excitability following short trains of repetitive magnetic stimuli. Experimental Brain Research 140:453-459

Müllbacher W, Ziemann U, Boroojerdi B, Hallett M (2000) Effects of low frequency transcranial magnetic stimulation on motor excitability and basic motor behaviour. Clinical neurophysiology 111:1002-1007

Ohtsuka KJ, Enoki T (1998) Transcranial magnetic stimulation over the posterior cerebellum during smooth pursuit eye movements in man. Brain 121:429-435

Pascual-Leone A, Valls-Sollé J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117:847-858

Pascual-Leone A, Bartrez-Faz D, Keenan JP (1999) Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. Philosophical Transactions of the Royal Society of London, B 354:1229-1238

Pascual-Leone A, Walsh V, Rothwell JC (2000) Transcranial magnetic stimulation in cognitive neuroscience - virtual lesion, chronometry, and functional connectivity. Current Opinion in Neurobiology 10:232-237

Pinto AD, Chen R (2001) Suppression of the motor cortex by magnetic stimulation of the cerebellum. Experimental Brain Research 140:505-510

Saito Y, Yokota T, Yuasa T (1995) Suppression of motor cortical excitability by magnetic stimulation of the cerebellum. Brain Research 694:200-206

Sereno MI, Pitzalis S, Martinez A (2001) Mapping of contralateral space in retinotopic coordinates by a parietal cortical area in humans. Science 294:1350-1354

Theoret H, Haque J, Pascual-Leone A (2001) Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans. Neuroscience Letters 306:29-32

Touge T, Gerschlager W, Brown P, Rothwell JC (2001) Are the after-effects of low-frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses?. Clinical neurophysiology 112:2138-2145

Ugawa Y, Day BL, Rothwell JC, Thompson PD, Merton PA, Marsden CD (1991) Modulation of motor cortical excitability by electrical stimulation over the cerebellum in man. Journal of Physiology 441:57-72

Vindras P, Desmurget M, Prablanc C, Viviani P (1998) Pointing errors reflect biases in the perception of the initial hand position. Journal of Neurophysiology 79:3290-3294

Walsh V, Cowey A (2000) Transcranial magnetic stimulation and cognitive neuroscience. Nature Reviews Neuroscience 1:73-79

Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogragphy and Clinical

Neurophysiology 108:1-16

Werhahn KJ, Taylor JL, Ridding MC, Meyer B, Rothwell JC (1996) Effect of transcranial magnetic stimulation over the cerebellum on the excitability of motor cortex. Electroencephalography and Clinical Neurophysiology 101:58-66

Wolpert DM, Ghahramani Z (2000) Computational principles of movement neuroscience. Nature Neuroscience 3:1212-1217

Wolpert DM, Kawato MI (1998) Multiple paired forward and inverse models for motor control. Neural Networks 11:1317-1329

Wolpert DM, Miall RC, Kawato MI (1998) Internal models in the cerebellum. Trends in Cognitive Sciences 2:338-347