Effects of magnetic stimulation over supplementary motor area on movement in Parkinson's disease

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Summary
Movement execution can be delayed by transcranial magnetic stimulation delivered over primary motor cortical areas, resulting in transient inhibition of cortico-motor output. Inhibition or disruption of higher-order motor planning and preparatory processes, such as are thought to occur in the supplementary motor area (SMA), would allow an examination of processes at other stages of the motor control system. In this study, six subjects with Parkinson’s disease and six healthy control subjects performed a non-cued sequential finger movement task. At various times relative to movement, high-intensity single-pulse magnetic stimulation was delivered over the region of the SMA, with minimal current spread to primary motor areas. When magnetic stimulation was given at early stages during the movement for parkinsonian subjects, movement times were significantly increased, indicating disrupted movements. Supplementary motor area stimulation had no effect when delivered during later stages of the movement or immediately prior to movement onset, and had no apparent effect on control subjects at any time. It is therefore suggested that the SMA is important in motor planning and preparatory processes, since SMA stimulation has no effect on movements in their later stages when planning may be complete, but may disrupt movements in their early stages, when preparation for later stages may still be in progress. Further, possible instability of motor planning/preparation processes in Parkinson’s disease is suggested, since these processes appeared more susceptible to disruption by magnetic stimulation in parkinsonian subjects than controls.

Keywords: magnetic stimulation; supplementary motor area; movement time; Parkinson’s disease

Abbreviations: MEP = motor evoked potential; SMA = supplementary motor area

Introduction
Transcranial magnetic stimulation delivered over motor cortical areas can influence movements in humans. Supra-threshold stimulation over primary motor cortex can elicit motor evoked potentials (MEPs), involving involuntary muscular contractions in contralateral limbs (Barker et al., 1985), followed by a silent period during which muscular activity is suppressed. The silent period appears to be caused by inhibition at the cortical level (Fuhr et al., 1991; Inghilleri et al., 1993; Roick et al., 1993; Wilson et al., 1993a). It most likely results from inhibition within primary motor cortex, possibly due to excitation of inhibitory interneurons following magnetic stimulation (Wilson et al., 1993b; Schnitzler and Benecke, 1994; von Giesen et al., 1994).

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In simple reaction time studies, supra-threshold magnetic stimulation over motor cortex (which elicits MEPs) can delay movement onset, resulting in prolonged reaction times (Day et al., 1989; Pascual-Leone et al., 1992a, b; Berardelli et al., 1994). It is suggested that such high-intensity stimulation transiently inhibits neurons (probably within primary motor cortex) which are responsible for the initiation of movements (Day et al., 1989; Pascual-Leone et al., 1992a).

Using magnetic stimulation it may be possible to influence processes at other stages in the motor control system. The SMA is shown to be active during movement preparation (Roland et al., 1980), particularly prior to sequential movements (Benecke et al., 1985). It is therefore thought to
be involved in motor planning and preparation for movement (Orgogozo and Larsen, 1979; Goldberg, 1985), although its actions are not fully understood. If high-intensity magnetic stimulation were given over SMA, with minimal current spread to primary motor areas, the effect of disrupting only SMA processes could be examined. Further, if magnetic stimulation were delivered at various times relative to movement, the temporal characteristics of SMA function may be investigated. Results of some preliminary studies have indicated that magnetic stimulation given over the SMA can delay subsequent movements in a sequential finger-movement task (Amassian et al., 1990), and can disrupt bimanual coordination (Pascual-Leone et al., 1994a); however, the effects of SMA stimulation at different stages of motor control processes have not been reported. This was the purpose of the present study.

Parkinson’s disease involves mainly a loss of dopaminergic neurons in nigrostriatal pathways, severely disrupting basal ganglia function (Marsden, 1990). Since SMA input arises largely from the basal ganglia (Tokuno et al., 1992; Hoover and Strick, 1993), SMA function is also impaired in Parkinson’s disease. Electrophysiological studies show that pre-movement SMA activity, associated with motor preparation, is disturbed in Parkinson’s disease subjects (Deecke et al., 1977; Shibasaki et al., 1978; Simpson and Khuraibet, 1987; Dick et al., 1989; Cunnington et al., 1995). Further, Parkinson’s disease subjects show the greatest motor deficit in the performance of non-cued (Jones et al., 1992; Georgiou et al., 1993) and sequential movements (Benecke et al., 1987) for which basal ganglia/SMA motor pathways are most involved (Cunnington et al., 1996). Magnetic stimulation over the SMA in Parkinson’s disease subjects would therefore be of interest, since stimulation of this already disturbed motor system may show different effects to that of the normally functioning motor system of healthy control subjects. By comparing these differences, the nature of impairments in SMA function associated with Parkinson’s disease may be investigated.

Therefore, in this study, Parkinson’s disease and control subjects performed a non-cued sequential finger movement task, and high-intensity single-pulse magnetic stimulation was delivered over the region of the SMA at various times relative to movement. The aim was to examine the effect of SMA stimulation on Parkinson’s disease and control subjects’ movement times, and thereby to investigate the nature of functions of the SMA and deficits associated with Parkinson’s disease.

**Method**

**Subjects**

Six subjects with Parkinson’s disease (mean age 67.3 years) and six healthy control subjects (mean age 57.7 years) participated in the main study. A further four subjects with Parkinson’s disease (mean age 59.3 years) participated, receiving electric stimulation of the supraorbital nerve in place of magnetic stimulation. Clinical details of parkinsonian subjects are shown in Table 1. All subjects were without previous history of stroke, serious head injury, or other neurological disturbance. All Parkinson’s disease subjects remained on their normal medication throughout the study. Informed consent was obtained from each subject in accordance with the declaration of Helsinki, and all experimental work was carried out under the approval of local ethical committees.

**Procedure**

**Magnetic stimulation**

Single-pulse magnetic stimulation was delivered by a Magstim 200 at maximum intensity (100%). It was necessary to use the same high-intensity stimulation for all subjects since, as yet, no overt motor responses have been elicited by single-pulse magnetic stimulation over the SMA; therefore, individual threshold levels for single-pulse SMA stimulation cannot be determined. In any case, no difference has been found between parkinsonian and control subjects in threshold levels to elicit MEPs over primary motor cortex (Valls-Solé et al., 1994); it is therefore most unlikely that results would be affected by threshold differences for SMA stimulation between parkinsonian and control subjects.

Magnetic stimulation was delivered through a 50 mm diameter figure-8 coil. The coil was positioned tangentially to the skull, with the handle parallel to the sagittal axis (pointing occipitally), and with the centre of the figure-8 over the site to be stimulated. Current flow at the centre of the figure-8 was towards the coil handle. This type of coil provides the most focal stimulation, with a maximal field generated at the centre of the figure-8 (Cohen et al., 1990). Further, with the above orientation, current spread is greatest along the sagittal plane, and lateral current spread is minimized (Roth et al., 1991). This coil orientation is likely to be most effective for stimulating the SMA since it is the best orientation for stimulating the adjacent leg area of primary motor cortex which has a similar midline structure and orientation (mostly perpendicular to the scalp surface) as the SMA.

To determine the site for stimulating SMA, magnetic stimulation was given at points 2–4 cm anterior to the vertex (position Cz), in the sagittal midline. This range was estimated to lie close to the SMA, and with the fronto-occipital orientation of current flow associated with the midline sagittal coil orientation, the SMA should be optimally stimulated over these sites.

For each subject, the precise position to stimulate was selected to be sufficiently anterior so that current spread to the primary motor cortex would be insufficient to elicit MEPs. Motor evoked potentials were monitored in the right leg by observing EMG responses in tibialis anterior, and in the right arm by feeling for muscle twitch in deltoid and
Magnetic stimulation over SMA

Table 1 Clinical data for Parkinson's disease subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Disease duration (years)</th>
<th>Webster score*</th>
<th>Medication†</th>
<th>Dose (mg day⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>M</td>
<td>5</td>
<td>9</td>
<td>Sinemet M</td>
<td>300/30</td>
</tr>
<tr>
<td>74</td>
<td>M</td>
<td>9</td>
<td>12</td>
<td>Eldepryl</td>
<td>10 mg</td>
</tr>
<tr>
<td>74</td>
<td>F</td>
<td>14</td>
<td>10</td>
<td>Madopar M</td>
<td>500/125</td>
</tr>
<tr>
<td>67</td>
<td>M</td>
<td>7</td>
<td>11</td>
<td>Sinemet M</td>
<td>300/30</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>6</td>
<td>16</td>
<td>Eldepryl</td>
<td>10 mg</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>3</td>
<td>12</td>
<td>Madopar Q</td>
<td>250/62.5</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>17</td>
<td>16</td>
<td>Madopar M</td>
<td>600/150</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>2</td>
<td>7</td>
<td>Sinemet CR</td>
<td>200/50</td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>7</td>
<td>13</td>
<td>Eldepryl</td>
<td>5 mg</td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>19</td>
<td>21</td>
<td>Sinemet CR</td>
<td>350/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sinemet</td>
<td>1000/250</td>
</tr>
</tbody>
</table>

*Rating of parkinsonian symptoms using Webster (1968) scale; †generic names for medication: Madopar = levodopa/benserazide; Sinemet = levodopa/carbidopa; Eldepryl = selegeline hydrochloride; Parlodel = bromocryptine mesylate.

biceps brachii muscles during facilitation (subjects fully supported the limb and performed sequenced finger-to-thumb opposition). With the coil orientation used, any current spread to primary motor cortex would predominantly affect the leg area, rather than more lateral arm and hand areas. Therefore, a lack of arm activation could be reasonably assumed from the absence of lower-limb MEPs.

The first point at which no MEPs were elicited in right-side lower limbs, nor muscle contractions elicited in right-side upper limbs, for at least three consecutive trials was selected as the site for SMA stimulation. In two parkinsonian subjects it was necessary to stimulate 1 cm lateral to the midline on the right side (ipsilateral to the responding limb) in order to prevent current flow to left primary motor cortex. At this site, significant current spread across the midline would still be expected to cause bilateral SMA stimulation; however, the stimulation may be laterally biased. Therefore, lateralized stimulating sites were carefully matched between parkinsonian and control subjects such that any difference between subject groups would not be influenced by any possible unilateral bias in stimulation.

The precise positions for SMA stimulation in each subject, measured relative to the centre of the figure-8 coil, were (i) 2 cm anterior to Cz, in the sagittal midline (one parkinsonian subject, two control subjects), (ii) 4 cm anterior to Cz, in the midline (three parkinsonian subjects, two controls), and (iii) 4 cm anterior to Cz, 1 cm lateral to the midline on the ipsilateral (right) side (two parkinsonian subjects, two controls).

Sequential movement task
Subjects performed a sequential button-pressing task on a tapping board which consisted of two parallel rows of 10 buttons with two vertically centred start buttons and one centred end button (Mattingley et al., 1992). Subjects pressed buttons from right to left along a simple zig-zag pathway consisting of alternate top and bottom row buttons (10 buttons in all). Precise movement times (the time from the release of one button until depression of the next button) were recorded by computer.

Two practice conditions were first performed. For an initial 16 trials, the zig-zag pathway was fully illuminated by light-emitting diodes underneath each button, and subjects were required to press each illuminated button, moving progressively from right to left as quickly as possible. The lights were then extinguished and for a further 16 trials, subjects were required to perform the same sequential movement remembering the correct pathway. This second condition, with no external cues, was then used throughout the experiment. Trials in which subjects made errors were repeated and only error-free trials were analysed.

Experimental conditions were performed in two blocks (each consisting of 48 trials) in which (i) magnetic stimulation was given at the previously determined site (SMA stimulation), and (ii) the magnetic coil was held above the head, providing no cortical stimulation (sound only), to control for non-specific effects of the stimulator discharge. The order of these blocks were counter-balanced between subjects.

The magnetic stimulator discharge was externally triggered by depression of one selected button in the pathway. The button to trigger was pseudo-randomly selected from buttons 2–7, and varied between trials. Each block also contained 12 trials in which the stimulator was not triggered. Subjects therefore could not anticipate the response for which the magnetic stimulator would discharge.
A variable delay between the button-press and triggering of the stimulator was used so that the time at which the stimulator discharged, relative to the subject's movement onset, could be manipulated. Three levels of delay were individually selected for each subject (based on movement times during practice trials) (Kritikos et al., 1995), and subjects performed 16 trials at each of the levels of delay (12 trials with stimulator discharge, and four without).

**Supraorbital nerve stimulation**

The effect of electric stimulation of the supraorbital nerve was also examined in parkinsonian subjects to control for possible non-specific effects, such as blink responses and scalp sensation, which were sometimes associated with the high-intensity magnetic stimulation. Supraorbital nerve stimulation was delivered via a Caldwell electric stimulator with electrodes placed ~2 cm apart over medial and lateral sides of the right supraorbital margin, on either side of the supraorbital nerve.

Stimulation was given during the movement task in a manner identical to that for magnetic stimulation, i.e. for one pseudo-randomly selected button in each sequence over 48 trials, and at one of three levels of delay with 16 trials at each level. Electrooculography responses were monitored from electrodes placed over the lateral canthus of the right eye and on the right-side inferior margin of the nose. Only trials for which the electrooculography response showed a clear blink reflex were accepted.

**Data analysis**

For both magnetic and electric stimulation, the precise time (relative to movement) at which the stimulator discharged was calculated for each trial. Results were grouped according to whether the stimulator discharge occurred (i) during button press, (ii) during early movement (between 0 and 50% of the inter-button movement time), and (iii) during late movement (between 50 and 100% of the inter-button movement time). Mean movement times were calculated from at least six trials per subject for each condition, for cued responses (i.e. responses during which the stimulator discharged), as well as for two responses immediately before, and two immediately after cued responses.

Movement times were corrected for sequential slowing effects which have been previously reported for Parkinson's disease subjects in similar sequential tapping-tasks (Georgiou et al., 1994). For each subject, the mean gradient of movement times throughout the sequence for non-stimulated trials (representing the level of sequential slowing) was calculated by linear regression and subtracted from movement times in the experimental trials. Final mean movement times therefore reflected only differences due to stimulator discharge, and not any progressive slowing of movements throughout the sequence.

Results were analysed by four-way repeated-measures ANOVA, with a between-subjects factor of group (Parkinson's disease versus control), and within-subjects factors of cue type (SMA stimulation versus sound only), cue period (during button press, during early movement, during late movement), and button number (−2 to +2, where 0 represents the cued response).

**Results**

Mean movement times for Parkinson's disease subjects and controls in each condition are shown in Fig. 1. As can be seen, Parkinson's disease patients were consistently slower (greater movement times) than controls in all conditions. Overall, this difference was found to be significant \[ F(1,10) = 18.43, P < 0.01 \]. However, a significant four-way interaction was also found \[ F(8,80) = 2.40, P < 0.05 \]. Movement times for control and Parkinson's disease subjects were therefore analysed separately.

As shown in Fig. 1, movement times for control subjects did not appear to be influenced by SMA stimulation or by the sound only at any of the cue positions. Accordingly, ANOVA showed no significant main effects or interactions of cue type, cue period, or button number for control subjects.

Parkinson's disease subjects, however, appear to show a greatly increased movement time for the cued response when magnetic stimulation was given during early movement, but not during late movement or during button press, or by the sound only at all cue positions. Similarly, movement times of Parkinson's disease subjects appear to vary little as a result of supraorbital nerve stimulation at all cue positions. ANOVA showed a significant three-way interaction between cue type, cue period and button number for Parkinson's disease subjects \[ F(8,40) = 2.33, P < 0.05 \]; therefore the effect of button number was analysed separately for each condition.

For Parkinson's disease subjects, a significant difference between movement times for consecutive buttons was found only when SMA stimulation was given during early movement \[ F(4,20) = 3.88, P < 0.05 \]. Simple comparisons of this effect showed that the movement time for the cued response (button 0; mean = 414 ms) was significantly greater than that for the non-cued response immediately prior (button −1; mean = 264 ms) \[ F(1,5) = 7.28, P < 0.05 \], but there was no significant difference between the non-cued responses immediately before (button −1) and immediately after (button +1; mean = 310 ms) the cued response \[ F(1,5) = 3.56, P > 0.05 \].

The effect of age on the response to SMA stimulation given during early movement was also examined. The degree of slowing associated with magnetic stimulation was calculated as the difference in movement time from non-cued (button −1) to cued responses (button 0). This degree of slowing was not significantly correlated with age for either control subjects \[ r(5) = 0.38, P > 0.05 \], nor Parkinsonian subjects \[ r(5) = 0.26, P > 0.05 \]. Further, the three control subjects below age 60 years (mean age 49.3 years) showed...
Fig. 1 Mean movement times and standard errors for Parkinson's disease subjects (filled symbols) and control subjects (open symbols) for conditions in which magnetic stimulation was given over the SMA (SMA stimulation), in which the coil was held off the head (sound only), and for electric stimulation of the supraorbital nerve, when stimulator discharge occurred during button press (immediately before movement onset), during early stages of movement, or during later stages of movement. Movement times are shown from two responses before to two responses after the cued response (i.e. the response during which stimulator discharge occurred).

very little difference in the mean degree of slowing than those above 60 years (mean age 66.0 years; mean slowing 6.2 ms and 8.2 ms, respectively), especially when compared with the mean slowing of parkinsonian subjects (mean 150.3 ms).

All parkinsonian subjects showed slowing of movement times when SMA stimulation was given during early movement; however, the extent of slowing varied considerably, from 23.7 s to 418.1 s. This slowing was not significantly correlated with age (as above), severity of symptoms as measured on the Webster (1968) scale \( r(5) = 0.17, P > 0.05 \), nor the duration of disease \( r(5) = -0.06, P > 0.05 \).
Discussion

Results clearly indicate that movements of Parkinson's disease subjects, but not controls, were disrupted (much greater movement times) when magnetic stimulation was given over the SMA during early stages of the movement. Stimulation had no effect on movement time if it was given at later stages of the movement, nor immediately prior to movement onset (during button press). Similarly, the sound of the stimulator discharge and supraorbital nerve stimulation had no significant effect on movement time, no matter when they occurred. Further, disruption of movements was specific to Parkinson's disease subjects—magnetic stimulation over the SMA and the sound of the stimulator discharge alone had no effect on movements of control subjects, and response was not affected by age.

Such disruption of movements in Parkinson's disease subjects was unlikely to result from non-specific effects of the stimulator discharge. Movement performance was largely unaffected by simple distraction or startle due to unexpected stimulator discharge, or due to blink responses and scalp contraction elicited by supraorbital nerve stimulation. Therefore, disruption of movements for Parkinson's disease subjects is most likely to be directly related to the effects of magnetic stimulation over the SMA.

Previous studies have shown that reaction times are delayed by supra-threshold stimulation over contralateral motor cortex (Pascual-Leone et al., 1992a, b) and over the vertex (Day et al., 1989; Berardelli et al., 1994) which elicits MEPs and consequent cortical silent periods. Such delays in reaction time are said to be due to cortical inhibition within primary motor pathways which temporarily halts movement execution.

In the current study, however, disruption of movement appears to be mediated by mechanisms at a different locus. The site for stimulation was sufficiently anterior to minimize current flow to the primary motor cortex, and consequently no MEPs were elicited. If magnetic stimulation had acted directly on primary motor cortex, resulting in cortical inhibition within primary motor pathways, movements could have been disrupted at any point during their execution; however, movements were only disrupted at early stages and not at later stages towards their completion. Therefore, disrupted movements observed were unlikely to result from direct effects of magnetic stimulation on primary motor areas.

Further, previous studies in which stimulation was aimed directly over primary motor cortex, have shown no difference in thresholds to elicit MEPs between Parkinson's disease and control subjects (Valls-Solé et al., 1994), and delayed reaction times following supra-threshold stimulation have been reported in both Parkinson's disease and control subjects (Pascual-Leone et al., 1994b). In the current study therefore, if delayed movement times resulted from similar direct effects of magnetic stimulation on primary motor areas, both Parkinson's disease subjects and controls would be expected to show increased movement times; however, this was not observed—movements were only disrupted for Parkinson's disease subjects.

It is therefore concluded that disruption of movements was most likely to have resulted directly from effects of supra-threshold stimulation on premotor areas, including the SMA which was targeted, rather than the spread of activation to primary motor areas.

Disruption of movements in their early but not later stages by magnetic stimulation over the SMA suggests disruption of motor planning. Motor plans (or motor programmes) are considered here as simply a set of motor commands which specify the forthcoming movement, and are prepared prior to movement execution (for review, see Morris et al., 1994). Premotor cortical areas, including the SMA, are thought to be involved in motor planning and preparation (Orgogozo and Larsen, 1979; Goldberg, 1985); therefore, high-intensity SMA stimulation may disrupt such motor planning processes.

In this study, it is most unlikely that subjects were able to plan the entire 10 button sequence before execution, since the total duration of each sequence was quite long (2–5 s), and subjects were not extensively practised to be able to perform the entire 10 button-press sequence automatically, without external feedback. It is more likely that the entire task was performed as a sequence of simple ballistic movements, with each targeted button-press movement planned at some point in advance, during performance of earlier stages of the task.

As observed, magnetic stimulation over the SMA did not affect individual movements in their late stages, when motor planning for that movement may be complete; however, movements were disrupted by SMA stimulation at early stages of the movement, when preparation for later stages may still be in progress. Supplementary motor area stimulation may therefore prolong movement times by disrupting motor planning during early stages of movement, when later stages are still being prepared.

Disruption of movements in Parkinson's disease subjects and not controls must be due to some aspect of the motor deficit associated with Parkinson's disease. Parkinson's disease subjects show particular deficits for non-cued sequential movements, and basal ganglia/SMA motor pathways which are most involved in these types of movements (Cunnington et al., 1996) appear to be disturbed in Parkinson's disease subjects, although they do necessarily still operate (Simpson and Khuraimet, 1987; Dick et al., 1989; Cunningham et al., 1995). Supplementary motor area activity appears to be prolonged following movement in Parkinson's disease subjects (Cunnington et al., 1995). This may be due to disrupted phasic discharge from the basal ganglia, which is unable to terminate preparatory activity in the SMA sufficiently quickly following movement onset to enable submovements within a movement sequence to be properly organized in a temporal sense (Lans et al., 1995).

In Parkinson's disease subjects, this disturbed motor planning/preparation system, involving the SMA and other premotor areas, may therefore be more susceptible to
disruption by magnetic stimulation than the more robust, normally functioning motor system of control subjects. As observed in this study, magnetic stimulation over the SMA may therefore disrupt movements of Parkinson’s disease subjects but not controls. These results are not incompatible with the hypothesis that hypokinesia in Parkinson’s disease may be due to a delay in the termination of preparatory activity within the SMA as a consequence of defective internal cue production by the basal ganglia (Iansek et al., 1995).

In conclusion, magnetic stimulation over the SMA may disrupt motor planning/preparation processes, with no direct effect on execution via primary motor areas. Results further suggest instability of motor planning/preparation processes in Parkinson’s disease, since these processes may be more susceptible to disruption by magnetic stimulation in Parkinson’s disease subjects than controls.

References


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