A study using transcranial magnetic stimulation to investigate motor mechanisms in psychomotor retardation in depression

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Abstract

The pathophysiological basis of psychomotor retardation in depression is unclear. In this study, transcranial magnetic stimulation (TMS) was used to examine the functioning of the motor cortical system in 19 depressed patients and 10 healthy control subjects. Motor-evoked potentials were measured in the biceps brachii muscle during a series of tests with the muscle at rest and during voluntary elbow flexion contractions. Maximal voluntary force, as well as force and electromyographic responses to TMS were also measured during fatiguing maximal contractions. Depressed psychomotor-retarded subjects were less able to produce output from the motor cortex than non-psychomotor-retarded, depressed subjects and healthy controls during maximal exertion and fatigue. This finding was independent of depression severity. In contrast, responses to TMS elicited during relaxation or weak contractions did not differ between healthy and psychomotor-retarded subjects. Our study suggests that although the motor pathway from the motor cortex to the muscle is unimpaired, psychomotor retardation in depression is characterized by a reduced ability to drive the motor cortex.

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Key words: Depression, motor cortex, psychomotor retardation, transcranial magnetic stimulation.

Introduction

Psychomotor retardation

Psychomotor retardation is an important facet of depressive illness (Rush and Weissenburger, 1994). It refers to an observable slowing in movement and speech, the latter presumably reflecting slowed thought processes. It can lead to severe functional impairment and in its most disabling form, a patient can be mute and immobile (‘depressive stupor’). It is well established as a diagnostic feature in depression and is arguably a core feature of depression (Parker et al., 1994; Widlöcher, 1983). Its presence has therapeutic implications, for example, predicting response to tricyclic antidepressant treatment (Bielski and Friedel, 1976) and electroconvulsive therapy (Hickie et al., 1996). However, understanding of its pathophysiological basis remains limited and most studies thus far have been descriptive.

The slowness of a retarded, depressed person in interacting with the environment may be accounted for by impairment in one or more of the following processes: attention to and perception of the surroundings, cognitive processing of this input (including decision-making), and/or formulation and execution of a (motor) response. The site(s) of the primary
disturbance that leads to psychomotor retardation is as yet unidentified. In particular, the relative contributions of central cognitive processing and motor dysfunction are unclear. Studies so far have attempted to differentiate the different levels of cognitive processing involved. Cornell et al. (1984) and Rogers et al. (1987) administered tasks of varying cognitive complexity but equal motor difficulty to retarded depressed patients and healthy controls. Their results suggested that both cognitive and motor slowing contribute to retarded function. Brand and Jolles (1987) used memory tasks to discriminate between deficits in encoding information, processing information and executing a motor response. They concluded that aspects of information processing were responsible for the overall delay.

Other researchers have used electrophysiological means to evaluate the processing of stimuli. Giedke et al. (1981) found that although depressives did not differ from healthy controls with respect to auditory-evoked potential latencies, they still took longer to respond to an auditory stimulus. This suggests that perceptual processes are intact and that the perceived delay occurs in subsequent stages of the response. Combining the above approaches in a sophisticated experimental paradigm, Knott and Lapierre (1987) measured both cortical-evoked responses and peripheral electromyographic activity during subjects’ performance of a complex reaction task. Their results confirmed that cortical perception of stimuli was not delayed. However, both central and peripheral mechanisms were implicated in response delay. These approaches have been useful in excluding perceptual delay as a cause of patients’ general slowness in interaction. However, they are limited in their ability to discriminate subsequent stages of processing, in particular, abnormalities in central ‘information processing’ and those at the level of the motor cortex and peripheral motor system.

Another approach has explored the similarities in motor dysfunction in retarded depression and Parkinson’s disease, and it is likely that dopaminergic processes play a key role in this dysfunction (Malhi and Berk, 2007). Flint et al. (1993) found common speech articulation abnormalities which were not present in healthy controls. Sachdev and Aniss (1994) reported similar abnormalities in the execution of simple and complex motor movements in these two disorders, suggesting basal ganglia dysfunction. Although useful comparisons, these provide indirect arguments for the mechanisms involved in psychomotor retardation.

Transcranial magnetic stimulation (TMS)

TMS is a non-invasive means of stimulating brain cortex and has proved a useful tool in investigating aspects of brain function (George et al., 1999). It can activate the primary motor cortex to produce a peripheral motor response, the features of which can be recorded by surface electromyography (EMG), yielding a motor-evoked potential (MEP). Several features of the EMG are described and reflect aspects of motor system functioning. Motor threshold refers to the lowest intensity of stimulation required to elicit a MEP. A stimulus of subthreshold intensity delivered several milliseconds (ms) prior to a suprathreshold stimulus can affect the MEP evoked by the second stimulus (paired pulse TMS). Different timing of the two stimuli tests intra-cortical facilitatory and inhibitory processes (Kujirai et al., 1991). The duration of the period of EMG silence (silent period) after a MEP evoked during a voluntary contraction is thought to reflect cortical inhibitory processes (Chen et al., 1999; Di Lazzaro et al., 2002).

Thus TMS provides a way to test motor function without voluntary cooperation and confers several advantages in studying psychomotor retardation. Other methodological approaches have largely been forced to assume that measures of cognitive and motor functioning reflect patients’ optimal effort despite their depression, i.e. slowed functioning reflects pathophysiological, not motivational, abnormalities. TMS allows elements of the motor system to be assessed independently of voluntary effort. The ability to directly elicit a motor response without antecedent cognitive processing also renders redundant any assumptions that cognitive and motor processes occur sequentially, in parallel or with some overlap, in attributing delay to these different components.

In addition to direct tests of the motor pathway, measurement of the increment in force evoked by TMS during a maximal voluntary muscle contraction can determine whether the muscle was driven maximally by voluntary effort. This may inform on motivation as well as the patient’s ability to fully use his motor cortex capacity. The presence of an ‘upstream’ factor responsible for driving the motor cortex has also been proposed to explain experimental observations in healthy subjects (Gandevia et al., 1996). The ratio of the increment in force evoked by TMS to voluntary force increases with fatiguing exercise, which suggests that a subject’s ability to drive the motor cortex decreases under some conditions. Thus, stressing the motor system with exercise can reveal deficits that are not otherwise seen. For example, Sheean et al. (1997)
demonstrated that subjects with multiple sclerosis who complained of fatigue became progressively unable to drive their muscle fully with fatiguing exercise. This was attributed to an inability to maintain sufficient central drive to the motoneuron pool. Whether slowness in motor functioning is accounted for by deficits within the motor system or upstream of the motor cortex has not been investigated in depressed (and in particular, psychomotor-retarded) subjects and is a question addressed in this study.

In recent years, a few studies have used TMS to assess the motor system in depressed subjects. Samii et al. (1996) demonstrated that MEPs were not facilitated (i.e. increased in amplitude) after exercise of the muscle in non-medicated subjects with depression or chronic fatigue, to the same extent as in healthy controls. The same phenomenon was demonstrated by others (Chroni et al., 2002; Reid et al., 2002; Shajahan et al., 1999, Steele et al., 2000) in medicated depressed subjects compared with healthy controls, suggesting that in depression there is an alteration in facilitatory and possibly, inhibitory, processes at the cortical level. In addition to reduced post-exercise facilitation, Steele et al. (2000) also found longer silent periods (i.e. reflecting cortical inhibitory processes) in depressed (medicated) subjects compared with healthy controls. Others have reported reduced intra-cortical inhibition (tested with the TMS paired-pulse paradigm) and shorter silent periods in unmedicated depressed patients compared to healthy subjects (Bajbouj et al., 2006). Thus the evidence suggests some abnormality in functioning at the motor cortical level in depressed subjects.

The aims of the present study were to explore abnormalities in motor functioning in depressed, psychomotor-retarded subjects and to assess the origin of any deficits found. In particular, the contribution of higher cortical centres responsible for driving the motor cortex (such as the supplementary motor area and premotor areas) was of interest. We hypothesized that psychomotor-retarded, depressed patients would have impaired drive to the motor cortex and that this could be demonstrated during fatiguing exercise in which maximal effort was required. Whereas previous studies did not differentiate subtypes of depression, we tested for differences between depressed subjects with and without psychomotor retardation, comparing their results also with healthy controls. Motor functioning was tested while subjects voluntarily contracted an arm muscle at maximum strength, a demanding experimental condition which tests the ability to drive the motor cortex maximally.

Methods
The study was approved by the institutional review boards overseeing research involving human subjects – Human Research Ethics Committees of the University of New South Wales and the South Eastern Sydney Area Health Service.

Subjects
Nineteen depressed patients and 10 healthy controls were recruited for the study according to the following criteria: age 18–70 yr; able to give informed consent; no neurological or musculoskeletal disorder, or general medical disease likely to affect neuromuscular functioning; no drug or alcohol abuse in the past 12 months; not on benzodiazepines or antipsychotic medication; and no electroconvulsive therapy in the preceding 3 months.

Depressed subjects were recruited from subjects referred to the Black Dog Institute and were clinically assessed by a study psychiatrist to have a DSM-IV diagnosis of major depressive episode (with or without psychomotor retardation, but without psychomotor agitation, the latter also confirmed by CORE agitation scores ≤ 5), no other Axis I diagnosis and a score of ≥ 25 on the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). Depressed subjects were stratified into psychomotor-retarded or non-retarded groups according to total CORE scores of ≥ 8 or < 8 respectively (Parker et al., 1994). As far as possible, subjects were matched for gender and age (± 5 yr) between the three groups, but it was not possible to recruit equal numbers of subjects in each group (i.e. matching was incomplete). Three of eight subjects in the retarded group were on medications (two on mirtzapine, one on tricyclic antidepressant) and seven of 11 subjects in the non-retarded group were on medications (one on mirtazapine, one on tricyclic antidepressant, three on venlafaxine, two on selective serotonin reuptake inhibitor, one on lithium, one on carbamazepine, one on valproate). Healthy subjects had no prior history of depression, were not on any medications and were recruited from staff and relatives of subjects. All subjects participated after giving written informed consent for the study.

Depression ratings
Depression and psychomotor functioning were rated independently by two psychiatrists using the MADRS and CORE scales. Rating interviews and TMS tests were conducted on the same day.
TMS tests

Subjects sat with the right arm held in an arm bar which measured the force of isometric elbow flexion. Visual feedback of this force was provided to the subject by an LED display. Electromyographic activity (EMG) was recorded from the right biceps brachii through surface electrodes in a belly-tendon configuration. EMG was amplified and filtered (16–1000 Hz; CED 1902; Cambridge Electronic Designs, Cambridge, UK). Force and EMG signals were recorded to computer through a laboratory interface (CED 1401, Signal software, Cambridge Electronic Designs). TMS of the motor cortex was carried out using a round coil (90 mm diameter) positioned over the vertex and oriented to stimulate the left hemisphere preferentially (Magstim 200 stimulator; Magstim Co., Whitland, Dyfed, UK). Use of the round coil is standard for the measurement of voluntary activation of the elbow flexors during fatigue. All stimulation was carried out with the stimulator connected through a Bistim module. A series of tests were performed.

Resting threshold. The stimulus intensity needed to elicit a short latency excitatory response (MEP) in biceps brachii when the muscle was resting was measured. Threshold was taken as the intensity needed to elicit a MEP of $>20 \mu V$ with 3 of 5 consecutive stimuli.

Active threshold during weak contractions. Threshold intensity to elicit MEPs was measured while subjects performed a weak voluntary elbow flexion [3.5 Newton metres (Nm) for women, 6 Nm for men] estimated as 10% of expected maximum force. Standard target forces were used rather than forces set as a proportion of subjects’ measured maximum because psychomotor-retarded subjects were predicted to have poor voluntary activation so that their measured maximal voluntary force would be likely to consistently underestimate their muscle strength. Threshold was taken as the intensity needed to elicit an MEP with an amplitude more than background activity with 3 of 5 consecutive stimuli.

Silent period duration during weak contractions. TMS with an intensity of 1.4 times resting threshold was delivered during a weak voluntary elbow flexion (10% of expected force) to elicit a period of EMG silence following the MEP. This was repeated five times. Subjects were instructed to return to the target force as quickly as possible after TMS. The duration of the silent period was taken as the time from the stimulus to the resumption of voluntary EMG.

Paired-pulse inhibition and facilitation. Subthreshold TMS delivered shortly before suprathreshold TMS can inhibit or facilitate the MEP produced by the second test stimulus (Kujirai et al., 1991). Single test stimuli and pairs of stimuli with an interstimulus interval of 2 ms or 12 ms were given randomly at 5-s intervals while the subject remained relaxed. Ten trials of each condition were recorded. The intensity of the conditioning stimulus was set at 0.8 times active threshold and the test stimulus at 1.4 times resting threshold. The area of each MEP was measured between cursors set to encompass the potential. For each subject, the area of MEPs following paired stimuli was expressed as a percentage of the area of MEPs following single stimuli.

Fatiguing maximal voluntary contractions. TMS was delivered before and during four 15-s maximal voluntary contractions (MVCs) separated by 15-s breaks. Stimulus intensity was set at 1.4 times resting threshold. Baseline MEPs ($n = 5$) were recorded at rest. During the contractions, subjects were strongly urged to pull as hard as possible. The force produced at the start of the initial MVC was recorded as the subject’s MVC force, expressed as a percentage of predicted MVC to control for gender differences, i.e. 35 Nm for women, 60 Nm for men. TMS was delivered just after the start and before the end of each contraction. A number of measurements were made at the beginning and end of each MVC. These included voluntary force, any increment in force evoked by TMS, the size of the MEP and the duration of the silent period (see Figure 1).

Perceived effort. At the end of testing, subjects rated the effort that it took to produce MVCs. Effort was rated on a modified Borg scale (0–10 numerical scale with descriptors).

Analysis

Inter-rater reliability was assessed for the MADRS and CORE ratings using Pearson’s correlation (two-tailed). As correlations between the two psychiatrist raters for the MADRS and CORE rating scales were 0.96 ($p < 0.001$) and 0.82 ($p < 0.001$) respectively, MADRS and CORE scores were averaged across the two raters to form a single score for further analyses.

The three experimental groups (depressed retarded, depressed non-retarded and healthy controls) were
compared for differences in age (ANOVA) and gender ($\chi^2$). The two depressed groups were compared for differences in clinical variables (duration of current and lifetime depression, total length of depressive illness, MADRS, CORE) using independent-samples $t$ tests.

Differences in TMS test results between the three comparison groups – depressed retarded, depressed non-retarded and healthy controls – were analysed by one-way ANOVAs. Where ANOVAs were significant, post-hoc tests were done to further test for differences between groups. To show changes over the fatiguing MVCs, paired $t$ tests compared the initial and final values of voluntary force, the increment in force evoked by TMS, the area of the MEP and the duration of the silent period. As concurrent medications may have had an effect on results, the above analyses were repeated in unmedicated subjects and healthy controls only.

In an exploratory post-hoc analysis, Pearson’s correlation (two-tailed) was used to examine the relationship between the test outcomes during fatiguing
MVCs (MVC force as percentage of expected, TMS-evoked increments in force during first and fourth MVCs, change in silent period and MEP area during fourth MVC) and MADRS and CORE scores for all depressed subjects. To test for the relationship between test outcomes during fatiguing MVCs, a separate correlational analysis of these measures was performed in all subjects. Holm’s procedure was used to control for Type I error arising from multiple comparisons.

Results

Psychiatric and demographic variables

The three groups did not differ in age and gender. The two depressed groups did not differ in depression variables or MADRS scores, but differed significantly in CORE scores (see Table 1).

TMS tests

The groups did not differ in the threshold stimulus intensity required to evoke MEPs in the resting biceps brachii, the size or latency of MEPs evoked at rest, the duration of the silent period, or the size or latency of the MEPs evoked during weak contractions, nor were there differences in intra-cortical inhibition as tested with a paired pulse at a 2 ms interstimulus interval (see Table 2). However, thresholds measured during a weak contraction were on average higher for the depressed group (50.9 ± 6.2% maximum machine output) than for the psychomotor-retarded patients (44 ± 8.2%) or the healthy subjects (42.4 ± 5.8%). In addition, intra-cortical facilitation tested with paired TMS at a 12 ms interstimulus interval was greater for the depressed patients (168 ± 40%) than for the psychomotor-retarded patients (119 ± 35%) or the healthy subjects (99 ± 24%).

At the start of the first maximal voluntary contraction, the groups differed significantly in the force generated compared to expected levels, with depressed retarded subjects producing less force than subjects in the other two groups (Table 3, Figure 2). In contrast, the responses to the initial cortical stimulus did not differ. These responses included the increments in force evoked by TMS, as well as the size of the MEPs and the duration of the silent periods, Overall force declined over the four MVCs showing that the contractions produced fatigue (Figure 2a; paired t test \(p < 0.001\)), but there was no difference between the groups (Table 3). The extra force evoked by TMS increased from the beginning to the end of the MVCs (\(p < 0.001\)). When compared in the last contraction (fourth MVC) of the fatiguing protocol, TMS tended to evoke larger force increments in the psychomotor-retarded patients than the healthy or the depressed groups (\(p = 0.056\); Table 3, Figure 2b). In addition, the psychomotor-retarded group showed significantly less increase in the silent period during the last MVC than the other two groups, and less increase in MEP area during the last MVC than the healthy group (Figure 2c, d). The three groups differed significantly in the perceived effort made during MVCs with the psychomotor-retarded subjects reporting lower effort than the controls (see Table 3).
Table 2. Results of TMS measures for all groups

<table>
<thead>
<tr>
<th></th>
<th>Mean (s.d.)</th>
<th>Depressed</th>
<th>Depressed-retarded</th>
<th>Group effects&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Post-hoc SNK&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Meds (n=7)</td>
<td>No meds (n=4)</td>
<td>Meds (n=3)</td>
<td>No meds (n=5)</td>
</tr>
<tr>
<td>Resting threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(% stimulator output)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEP in resting muscle (1.4 T)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td></td>
<td>0.8 (0.5)</td>
<td>0.3 (0.1)</td>
<td>0.9 (1.0)</td>
<td>1.8 (1.9)</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td></td>
<td>13.6 (0.8)</td>
<td>13.5 (0.4)</td>
<td>13.8 (0.8)</td>
<td>13.7 (1.2)</td>
</tr>
<tr>
<td>Active threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% stimulator output)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MEP in active muscle (1.4 T)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td></td>
<td>3.7 (2.2)</td>
<td>2.4 (1.1)</td>
<td>2.4 (1.1)</td>
<td>9.9 (5.5)</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td></td>
<td>11.4 (0.9)</td>
<td>10.9 (0.9)</td>
<td>10.7 (0.3)</td>
<td>11.6 (1.2)</td>
</tr>
<tr>
<td>Silent period in active muscle (ms)</td>
<td></td>
<td>135.2 (29.9)</td>
<td>126.9 (18.0)</td>
<td>114.1 (37.7)</td>
<td>137.1 (30.8)</td>
</tr>
<tr>
<td>Intra-cortical inhibition tested with 2 ms ISI (conditioned MEP as % control)</td>
<td></td>
<td>60 (30)</td>
<td>90 (20)</td>
<td>50 (30)</td>
<td>70 (60)</td>
</tr>
<tr>
<td>Intra-cortical facilitation tested with 12 ms ISI (conditioned MEP as % control)</td>
<td></td>
<td>160 (30)</td>
<td>170 (60)</td>
<td>100 (10)</td>
<td>130 (40)</td>
</tr>
</tbody>
</table>

Meds, Subjects on medications; No meds, unmedicated subjects; MEP, motor-evoked potential; SNK, Student–Newman–Keuls test; 1.4 T, 1.4 times resting threshold; ISI, interstimulus interval; dep, Depressed group; dep-ret, Depressed-Retarded group; H, Kruskal–Wallis H test.

<sup>a</sup>One-way ANOVA was used to compare between depressed, depressed-retarded and control groups. Results are for whole sample unless otherwise indicated.

<sup>b</sup>Results in italics are significant in the subsample of unmedicated subjects only.

<sup>*</sup>No longer significant in analysis of unmedicated subsample.

<sup>f</sup>Significant in analysis of unmedicated subsample (p = 0.019).
Table 3. Results of TMS measures during fatigue for all groups

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>F</th>
<th>p</th>
<th>Post-hoc SNKb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Depressed</td>
<td>Depressed-retarded</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meds (n=7)</td>
<td>No meds (n=4)</td>
<td>Meds (n=3)</td>
<td>No meds (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVC force (% expected)</td>
<td>114.3 (37.5)</td>
<td>127.8 (28.5)</td>
<td>92.6 (9.7)</td>
<td>80.4 (34.8)</td>
<td>111.6 (14.0)</td>
<td>4.17</td>
<td>0.027</td>
</tr>
<tr>
<td>Force at end of fourth MVC (% initial MVC)</td>
<td>73.5 (11.5)</td>
<td>74.0 (13.0)</td>
<td>78.2 (10.8)</td>
<td>76.5 (13.7)</td>
<td>69.3 (10.7)</td>
<td>1.15</td>
<td>0.333</td>
</tr>
<tr>
<td>Force increment evoked by TMS in first MVC (% ongoing MVC)</td>
<td>5.7 (4.3)</td>
<td>4.7 (3.6)</td>
<td>6.6 (2.6)</td>
<td>12.8 (15.6)</td>
<td>3.5 (2.5)</td>
<td>2.46</td>
<td>0.105</td>
</tr>
<tr>
<td>Force increment evoked by TMS in fourth MVC (% ongoing MVC)</td>
<td>8.0 (3.8)</td>
<td>6.4 (5.4)</td>
<td>10.7 (5.2)</td>
<td>14.9 (13.4)</td>
<td>6.3 (2.9)</td>
<td>3.20</td>
<td>0.056</td>
</tr>
<tr>
<td>Change in silent period in fourth MVC (ms)</td>
<td>40.6 (25.7)</td>
<td>37.9 (24.2)</td>
<td>3.7 (9.4)</td>
<td>12.1 (31.2)</td>
<td>43 (25)</td>
<td>5.27</td>
<td>0.012*</td>
</tr>
<tr>
<td>Growth in MEP in fourth MVC (% baseline MEP)</td>
<td>32.9 (31.8)</td>
<td>20.0 (16.4)</td>
<td>7.1 (16.6)</td>
<td>7.5 (13.6)</td>
<td>45.7 (30.9)</td>
<td>5.06</td>
<td>0.014</td>
</tr>
<tr>
<td>Perception of effort – MVC</td>
<td>8.6 (2.3)</td>
<td>8.8 (1.4)</td>
<td>9.2 (0.8)</td>
<td>6.8 (2.8)</td>
<td>9.9 (0.5)</td>
<td>8.74H</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Meds, Subjects on medications; No meds, unmedicated subjects; MVC, maximal voluntary contraction; MEP, motor-evoked potential; SNK, Student–Newman–Keuls test; H, Kruskal–Wallis H test.

a One-way ANOVA was used to compare between depressed, depressed-retarded and control groups.
b Results are for whole sample unless otherwise indicated.

* No longer significant in analysis of unmedicated subsample.
and Figure 2). The above results were not substantially different in a subanalysis of unmedicated subjects and healthy controls only (see Tables 2 and 3).

**Correlations between test outcomes during fatiguing MVCs and MADRS and CORE rating, and between individual test outcomes during fatiguing MVCs**

Of the outcome measures during fatiguing MVCs, CORE scores correlated significantly with MVC force as a percentage of expected force ($r = -0.7$, $p < 0.001$) and change in silent period during the fourth MVC ($r = -0.56$, $p < 0.05$). There were no significant correlations between MADRS scores and force or TMS measures.

As expected, there were strong correlations between individual test outcomes during fatiguing contractions: MVC force vs. TMS-evoked increments in force ($r = -0.62$ and $r = -0.61$, $p < 0.0005$ for the first and fourth MVCs respectively) and change in silent period ($r = 0.45$, $p < 0.05$), TMS-evoked force increments in the first MVC vs. change in silent period ($r = -0.56$, $p < 0.005$), change in MEP area ($r = -0.42$, $p < 0.05$); TMS-evoked force increments in the fourth MVC vs. change in silent period ($r = -0.58$, $p < 0.001$), change in MEP area ($r = -0.49$, $p < 0.01$), change in silent period vs. change in MEP area ($r = 0.39$, $p < 0.05$).

**Discussion**

This study compared responses in the biceps brachii muscle evoked by magnetic cortical stimulation in depressed and psychomotor-retarded subjects. This muscle was specifically selected to allow testing during strong contractions and fatigue. The main finding of this study was that depressed subjects with psychomotor retardation were less able to activate their motor cortex than depressed and healthy controls,
particularly under conditions when maximal exertion was required.

Compared with expected levels for males and females, retarded subjects produced significantly less motor force than the non-retarded depressive and healthy control groups when asked to maximally contract their elbow flexor muscles. In addition, the extra force evoked by TMS during the maximal effort tended to be larger in the retarded patients, although there was considerable variability between subjects. Previous studies have not found differences in the maximal force generated by depressed subjects and healthy controls, but did not test psychomotor-retarded subjects (Chroni et al., 2002; Samii et al., 1996).

Subjects in all groups developed fatigue over the MVC protocol, as evidenced by a decline in the maximal voluntary force. There was also an increased failure of voluntary drive shown by an increase in the increments in force evoked by TMS despite the subjects’ continued maximal efforts. That is, subjects’ voluntary output from the motor cortex became less able to drive the muscle fully (Gandevia et al., 1996; Hunter et al., 2006; Taylor et al., 2006). Although TMS is a non-physiological way of eliciting motor cortical output, a linear inverse relationship between the extra force evoked by TMS and voluntary contraction strength for strong contractions indicates that responses to TMS reflect unused voluntary output (Todd et al., 2003). Thus here, the inadequate voluntary drive was not because the motor cortex was unable to produce more output, but because TMS could evoke extra motor cortical output that was not employed by voluntary effort. This suggests that some fatigue was due to changes within the nervous system upstream of motor cortical output, which resulted in failure of drive to the output cells of the motor cortex. When compared in the last contraction (fourth MVC) of the fatiguing protocol, TMS tended to evoke larger force increments in the psychomotor-retarded patients than the healthy or the depressed groups. Thus, these patients were less able to produce adequate output from the motor cortex when fatigued, compared to the control groups.

As seen in the control groups in this experiment, activation of the motor cortex during sustained maximal contractions typically results in induction of facilitatory (e.g. increase in MEP size) and inhibitory (e.g. increase in silent period) processes (Hunter et al., 2006; Taylor et al., 1996). However, during sustained submaximal contractions, the MEP increases less than during maximal efforts, and the silent period does not increase until subjects become so fatigued that near-maximal efforts are needed to maintain force output (Ljubisavljevic et al., 1996; Taylor et al., 1996). Thus, the smaller increases in the MEP and silent period during the fatiguing protocol in the depressed retarded group compared to the control groups suggest that the depressed retarded patients’ efforts were submaximal and supports the observation that these subjects failed to activate their motor cortex as well as control subjects. The intrinsic relationship between the measures during MVCs (MVC force, TMS-evoked increments in force, change in MEP area, change in silent period) is confirmed by the strong correlations found between them.

The above findings were independent of depression severity. The two depressed groups did not differ in the severity of their current or past depressive illness, as measured by MADRS scores, length of the current or past episodes and total length of illness. There was no correlation between MADRS scores and test outcome measures. On the other hand, correlations were found between CORE scores and test measures, suggesting that impaired drive from the motor cortex is a feature of psychomotor retardation rather than depression per se. The lack of correlation with depression severity argues indirectly that the impaired drive found on TMS testing was not a function of poor motivation (which should be more marked in the more severely depressed, i.e. those with higher MADRS scores).

All subjects were strongly urged to make a maximal effort during testing. When asked to rate the degree of effort made immediately afterwards, the responses of retarded subjects compared to controls suggests that they were aware that they had not utilized their full strength. Others have found that the degree of perceived effort required for a set task did not differ between depressed and healthy subjects, even though EMG outcomes were abnormal in the depressed group (Shajahan et al., 1999; Steele et al., 2000). However, retarded and non-retarded depressed subjects were not assessed separately in these studies. A possible interpretation of our results is that psychomotor-retarded subjects are uniquely unable to produce adequate motor cortical output and are aware of this limitation.

Apart from testing during fatiguing MVCs, a number of other parameters were also measured with the muscle at rest and during weak contractions. Direct activation of the motor pathway by TMS did not show differences between healthy and depressed subjects when subjects were relaxed. There were no differences in the threshold intensity to evoke a motor response, or the size or latency of responses with a
standard stimulus intensity. These results concur with those of previous studies, which have not shown consistent differences in these measures in depressed subjects (Bajbouj et al., 2006; Chroni et al., 2002; Maeda et al., 2000; Reid et al., 2002), although it has been suggested that abnormalities may be hemisphere specific (Bajbouj et al., 2006) or involve hemispheric asymmetries (Maeda et al., 2000).

Threshold intensity was higher in depressed than healthy subjects during weak voluntary contraction. Surprisingly, the thresholds for the psychomotor-retarded subjects were not different from the healthy subjects. Similarly, facilitation of the response to TMS by a preceding subthreshold pulse was increased in depressed subjects but not in retarded subjects. Neither paired-pulse intra-cortical inhibition nor the duration of the silent period differed between groups.

These results differ from those of previous studies which did not find any difference in paired-pulse (12 ms) intra-cortical facilitation (Bajbouj et al., 2006; Maeda et al., 2000), but found differences in paired-pulse intra-cortical inhibition (Bajbouj et al., 2006) in depressed compared to healthy subjects. It is possible that our findings differed because we specifically tested depressed subjects who were psychomotor retarded and non-retarded separately, unlike earlier studies. That is, our results could be accounted for by the involvement of different pathophysiological processes in depression and psychomotor retardation. For example, studies have suggested γ-aminobutyric acid (GABA) and glutamatergic mechanisms affect outcomes with paired-pulse TMS tests (e.g. Ziemann et al., 1998). However, further discussion on this would be premature until the preliminary observations reported here are replicated in larger unmedicated patient samples.

Limitations of this study include the small sample size, although this is in keeping with samples used in comparable studies (e.g. Reid et al., 2002; Samii et al., 1996; Shajahan et al., 1999). Recruitment of subjects with significant psychomotor retardation who met all criteria and were able to comply with study procedures was difficult, and the sample was recruited over several years. Some subjects in both depressed groups were on medications. This was unavoidable as patients presenting to the depression clinic from which the sample was recruited were unwell and could not ethically be withdrawn from medications for the study. Furthermore, results from the additional analysis of TMS test outcomes in the subsample of unmedicated subjects and healthy controls support the findings reported for the whole sample, suggesting that our findings cannot be wholly accounted for by the presence of psychotropic medications.

This is the first study to assess the motor system functioning of psychomotor-retarded depressed subjects compared with depressed and healthy controls, using a battery of TMS measures. It is also the first study to assess in depressed subjects the contribution of factors upstream of the motor cortex, by measurement of the increment in force evoked by a TMS pulse, superimposed on a MVC, testing also whether deficits are further exacerbated by fatigue. We found that deficits in motor functioning in depressed subjects arose from impaired drive to and activation of, the motor cortex, and that these deficits were not a function of depression per se, but were limited to the subgroup of patients who were significantly psychomotor retarded. These findings have implications for our understanding of the mechanisms involved in psychomotor retardation, and the importance of assessing psychomotor disturbance in future studies of the pathophysiology of depression.

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Statement of Interest

None.

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