"Task-related variation in corticospinal output evoked by transcranial magnetic stimulation in the macaque monkey."

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Abstract
1. A volley evoked by transcranial magnetic stimulation (TMS) over the motor cortex was recorded from the medullary pyramid in an awake monkey performing a precision grip task. It was identified as corticospinal using a collision test. 2. The volley latency was 0.50 ms, indicating that it was produced by direct activation of corticospinal neurones. 3. A mean modulation of 13% in the amplitude of this volley was seen during task performance, with the largest volley occurring during the hold phase of the task. A similar pattern of modulation was seen in the EMG responses of hand and forearm muscles to TMS. 4. No comparable modulation was observed in a volley evoked by electrical stimulation of the corticospinal fibres via chronically implanted electrodes in the cerebral peduncle. 5. The results are compatible with direct activation of the corticospinal neurones by TMS at a site close to the soma, with the probability of activation by TMS depending on the current level of cortical excit...
Task-related variation in corticospinal output evoked by transcranial magnetic stimulation in the macaque monkey

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4. No comparable modulation was observed in a volley evoked by electrical stimulation of the corticospinal fibres via chronically implanted electrodes in the cerebral peduncle.

5. The results are compatible with direct activation of the corticospinal neurones by TMS at a site close to the soma, with the probability of activation by TMS depending on the current level of cortical excitability.

Transcranial magnetic stimulation (TMS) has become widely accepted as a means of non-invasively activating the corticospinal tract since its initial demonstration some 10 years ago (Barker, Jalinous & Freeston, 1985). However, accurate interpretation of the results obtained, both in normal subjects and in patients with movement disorders, is still hampered by lack of knowledge concerning the mechanism of activation of corticospinal cells.

Initial studies compared the latencies of responses of single upper limb motor units in humans to TMS and transcranial electrical stimulation (Day, Thompson, Dick, Nakashima & Marsden, 1987). These seemed to show that whilst electrical stimulation produced both direct ('D') and multiple indirect ('T', trans-synaptic) descending volleys, TMS failed to produce the initial, direct excitation of the cortical cells contributing to the corticospinal pathway. Later evidence, however, has shown that TMS does produce a substantial D wave, in both the anaeasthetized and conscious monkey (Edgley, Eyre, Lemon & Miller, 1990, 1992; Baker, Olivier & Lemon, 1994), and in the anaesthetized human (Burke, Hicks, Gandevia, Stephen, Woodforth & Crawford, 1993). It has also been shown that responses to TMS in lower limb muscles are probably due to direct activation of the corticospinal system (Nielsen, Petersen & Ballegaard, 1995). It has been hypothesized that this D wave is generated at the initial segment of the corticospinal neurone, and therefore that the susceptibility of a cell to TMS is dependent on its membrane potential (Edgley et al. 1990). Many reports have suggested that the descending volley evoked by TMS is altered by changes in cortical excitability (Hess, Mills & Murray, 1987; Day, Riescher, Strupppler, Rothwell & Marsden, 1991; Flament, Goldsmith, Buckley & Lemon, 1992; Burke et al. 1993; Nielsen, Petersen, Deuschl & Ballegaard, 1993; Johansson, Lemon & Westling, 1994). However, all such reports in the conscious state have relied on necessarily indirect deductions made from the amplitude of muscle responses evoked by TMS. Here we report recordings of the D wave from the bulbar pyramid in a conscious monkey performing a behavioural task, and demonstrate that, at least in the monkey, there is a significant task-related modulation in the amplitude of this volley. Since most of the large fibres of the pyramidal tract project to the spinal cord, it is a good site to record corticospinal activity (Humphrey & Corrie, 1978).

METHODS

The experiments were performed on a female Macaca fascicularis monkey trained to do a precision grip task (Lemon, Mantel & Muir, 1986) with the right hand. Additional data from another monkey used in an earlier study (Baker et al. 1994) and trained on a different, lever-pull task confirmed the main findings here (see Results). Briefly, the precision grip task requires that the monkey displace two levers into independently defined position windows using a precision grip between finger and thumb. The levers must

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then be held in position for at least 0.8 s (the ‘hold period’), before being released to earn the animal a food reward. After training was complete, the animal was implanted under full surgical anaesthesia (3% isoflurane in 50:50 N2O:O2) and aseptic conditions with a stainless-steel headpiece for head fixation. In the same surgery, two epoxide insulated 150 µm shank diameter tungsten electrodes (impedance at 1 kHz, 10–20 kΩ) were chronically implanted in the left pyramid under stereotaxic control at Horsley–Clarke co-ordinates AP0 and P4 mm and two in the left cerebral peduncles at A7 and A10 mm. These locations were confirmed histologically: the tip of the rostral peduncle electrode was found in the dorsal third of the peduncle at the level of the rostral pole of the lateral geniculate nucleus, and the caudal electrode was located in corticofugal fibres as they entered the tip of the pyramid at A7 and A10 mm. These locations were confirmed histologically: the tip of the rostral peduncle electrode was found in the dorsal third of the peduncle at the level of the rostral pole of the lateral geniculate nucleus, and the caudal electrode was located in corticofugal fibres as they entered the pons at a level just rostral to the posterior commissure. The rostral and caudal pyramidal electrodes were located in the pyramidal tract at levels just caudal to the trapezoid body, and at the caudal end of inferior olive, respectively. A full program of postoperative analgesia and antibiotics was administered. All experiments were performed under licence from the United Kingdom Home Office.

After recovery from surgery, multi-unit activity was recorded from the pyramid electrodes using a specially constructed amplifier which could be ‘muted’ to reduce the stimulus artifact (see Baker et al. 1994). The posterior electrode was connected to the non-inverting input of the amplifier. The head was restrained by bars fixed to the experimental cage. The animal performed the task whilst magnetic stimuli were delivered using a Magstim 200 stimulator (Magstim Ltd, Dyfed, UK) and 7 cm outer diameter figure-of-eight coil (2.2 T maximum magnetic field). The coil was positioned with the handle orientated mediolaterally, and the induced current flowing away from the mid-line. The coil position was chosen to optimize the amplitude of the short-latency EMG response evoked in a subset of up to four hand and forearm muscles. Stimuli were given at a constant rate of 0.3–0.5 Hz whilst the animal performed the task in a self-paced fashion.

Once the optimal coil position was found, the coil was clamped to the experimental cage, fixing it relative to the head. The position of the lead connecting the pyramid electrodes to the amplifier was then adjusted, particularly where it ran close to the coil, until the size of the stimulus artifact became acceptable. This was the single most important factor in obtaining an artifact-free recording. The amplified volley was digitized on-line at 80 kHz by a personal computer with a 1401 interface (Cambridge Electronic Design, Cambridge, UK). EMG, task position signals and stimulus trigger pulses were recorded on an FM tape recorder (bandpass 200 Hz to 10 kHz for EMG, DC–100 Hz for position) and digitized off-line.

The volley evoked by TMS could be identified as corticospinal in origin by collision with an appropriately timed volley excited by stimulation of the cerebral peduncle through the chronically implanted electrodes (Baker et al. 1994).

Trial-by-trial variation in task performance made it likely that any modulation in the size of the volley evoked by TMS would be obscured by intertrial averaging. The position signals for finger and thumb levers were therefore examined on a single trial basis using an interactive computer program. This allowed the experimenter to select a trial, and place cursors at the start and end of the movement. A normalization procedure was then used in which the cursor marking the movement start was designated ‘relative time’ 0. The interval between this and the cursor marking the movement end defined a time unit in the relative time scale for that trial. Analysis extended from relative time −1 to relative time +2. A similar normalization approach has been used in the study of locomotion (Drew & Doucet, 1991) to correct for differences in the duration of individual step cycles.

The amplitude of the volley evoked by each stimulus was then measured as the peak-to-peak height of the initial positive–negative wave (see Fig. 2), and listed with the relative time of stimulus delivery during the task. These were then sorted in ascending order in relative time, and a 30 point moving window used to compile a mean and standard error for the volley amplitude. This smoothed volley height was then plotted versus the mean relative time of each set of 30 points.

EMG responses to TMS were treated similarly. An average of rectified EMG was compiled, triggered by all available stimuli. This was used to define the response onset latency and duration.

Figure 1. Identification of the volley evoked by TMS using a collision test.

The top trace shows the volley produced by TMS alone, recorded from the electrodes in the medullary pyramid. Subsequent traces show the effect of preceding the TMS with an electrical stimulus to the electrodes chronically implanted in the cerebral peduncle at the intervals shown (600 μA, 0.2 ms pulse width, caudal electrode negative). Substantial collision occurred at the interval of 0.4 ms, but almost none was seen at the interstimulus interval of 1.8 ms. M, time of magnetic stimulus; G, end of the gate period during which the amplifier was ‘muted’. Single sweeps. TMS, 30%.
As above, stimuli were sorted according to relative time of occurrence, and a moving average compiled of EMG sweeps with respect to sets of thirty stimuli. The average height of the previously defined response region above the background level of EMG (assessed over the 25 ms period before the stimulus) was measured from these averages, and again plotted versus mean relative time of stimulus occurrence. The response size was not normalized by dividing by the background, as other studies have done (e.g. Flament et al. 1992), due to the presence of periods of near-zero background EMG, which would have produced an artifactually high response amplitude.

RESULTS

The onset latency of the volley evoked by TMS was 0-50 ms. During the implant surgery, the latency of the antidromic field potential recorded from the surface of the motor cortex following stimulation through the anterior pyramidal electrode was 0-55 ms. These values are consistent with our previous observations (Baker et al. 1994). The TMS volley latency is too short to have been produced by trans-synaptic activation; it is a 'D wave' response. Later 'I waves' were not seen in single sweeps of the recording (see Discussion).

Figure 1 shows a collision test between the volley produced by TMS and that produced by electrical stimulation of the chronically implanted peduncle electrodes. The amplitude of the TMS volley was reduced by more than half when a peduncle stimulus preceded TMS by 0-4 ms. The failure of the collision test to abolish the volley completely can be explained if the peduncle stimulus (600 μA, duration 0-2 ms) did not excite all of the corticospinal axons recruited by the TMS. It seems likely that the activity which was not collided was also corticospinal, since it had the same latency and time course. When the interstimulus interval was increased to 1-8 ms there was little evidence of collision, as previously documented (Baker et al. 1994).

Figure 2B–D illustrates the appearance of the volley at three different relative times during the trial, marked by the dashed lines in Fig. 2A. There was a clear modulation during the task, which was 12% of the minimum size of the volley, considerably larger than the standard error limits shown as bars on the right of Fig. 2A. From its 'baseline' amplitude (point B in Fig. 2) the volley began to increase just before lever movement began. It reached a maximum just after the initial rapid change in thumb lever position (point C), remained high during the hold phase of the task, and then rapidly decreased just before the thumb lever was released (point D).

In this session, the hold period (relative time 0 to +1) had a mean actual duration of 2-53 s (range, 0-90–5-71 s). A further analysis was carried out separately on those trials with durations 0-9–2 s, 2–3 s and 3–5-71 s. In each case, a similar modulation in volley amplitude to that of Fig. 2 was seen, confirming that the modulation is not merely an artifact of the relative time method used here.

Figure 2

A, modulation in corticospinal volley amplitude during the task. The horizontal axis plots the ‘relative time’ of events during the task (see Methods). A 30 point moving window was used to smooth the values of volley height. The bars to the right of these plots indicate the maximum and minimum standard error of the mean calculated from the 30 point moving window. Beneath the volley amplitude plot is shown the averaged finger and thumb position signal. B–D, the appearance of the corticospinal volley recording at the phases of the task marked by the dashed lines in A. M marks the time of magnetic stimulus delivery. The peak-to-peak amplitude of the volley is marked 'h'. Averages of 30 sweeps.
Figure 3
A, modulation in the mean EMG response peak amplitude above background (P - B) and background (B) level of EMG for 3 muscles during task performance, during the same experimental session illustrated in Fig. 2. Plots were produced in the same way as in Fig. 2, and also smoothed using a 30 point moving window. Background (B) was measured over the 25 ms period preceding the stimulus, mean peak height (P) was measured over the time corresponding to the response peak as assessed from an average triggered by all available stimuli. 1DI, first dorsal interosseous; FDS, flexor digitorum superficialis; EDC, extensor digitorum communis. B–D, the appearance of the EMG responses at the phases of the task marked by the dashed lines in A. M marks the time of magnetic stimulus delivery. Averages of 30 sweeps. TMS intensity 30% throughout.

Figure 4
A, single sweep recorded through the pyramid electrodes of the volley produced by electrical stimulation of the cerebral peduncle electrodes (during the time marked by the schematic pulse). The amplifier was muted until the time of the stimulus offset. Pulse width (P), 0.1 ms; intensity, 100 μA; caudal electrode negative. 'h' marks the amplitude used to quantify the volley. B, lack of variation in the size of the volley elicited by electrical stimulation of the peduncle with task phase. Data processed as in Fig. 2, and similarly smoothed with a 30 point moving window. The bars to the right of the figure indicate the maximum and minimum s.e.m. calculated from this window.
A clear modulation of the volley following TMS was seen during the task in each of five recording sessions, varying between 8:2 and 21 % (mean, 13%). In all sessions the volley was largest during the hold period (relative time 0 to +1). This was the case even though the TMS intensity was altered (range, 17–30% of maximum stimulator output), producing a volley whose mean amplitude varied from 370 to 1620 μV; no consistent change in the pattern or level of modulation was seen with different mean volley amplitudes.

Figure 3 shows a plot of the EMG background level (B) and the mean response above background (P – B) for three muscles, recorded in the same session as the data in Fig. 2. Points B, C and D are placed at the same relative times as in Fig. 2, to allow comparison with the volley data. From point B (the 'baseline' level) to point C, the measure P – B changed by 560, 970 and 480 % for the first dorsal interosseous (1DI), flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) muscles, respectively. A pattern of modulation broadly similar to that seen in the volley recording was observed. Both volley data and the EMG show an increase just before movement onset, then a decrease, then an increase which is sustained until the end of movement. The main difference is in the relative size of the initial peak before movement onset compared with that seen during the hold period. In the volley data and in the P – B plot for EDC, the hold period response is larger; in the P – B plots for the other two muscles, the initial, pre-movement response is larger. This is probably a result of the non-linear nature of the spinal response to a corticospinal input, especially when the response is superimposed on a widely changing background level.

In addition, data from another animal which have previously been published (Baker et al. 1994) were analysed using the 'relative time' procedure described under Methods. Significant task-dependent changes in the volley were also seen in this case, although they were less pronounced, possibly due to the highly phasic and less precise nature of the lever pull task performed by this animal.

In a control experiment, electrical stimuli were delivered to the cerebral peduncle via the chronically implanted electrodes at a rate of 2 Hz, whilst the monkey performed the task. The volley recorded from the pyramid following this stimulation was then processed in exactly the same way as the TMS volley data to investigate whether it would show any task-dependent modulation. The results of this experiment are given in Fig. 4. This volley (shown in Fig. 4A) had a similar time course and waveform to that elicited by TMS, as expected if both stimuli excite a similar population of fibres. Figure 4B presents the variation of this volley throughout the task. The scale of this figure has been chosen so that height of the maximal standard error is the same as in Fig. 2A. Unlike the volley evoked by TMS, there was no consistent change with task phase.

**DISCUSSION**

The results reported here demonstrate that the size of the D wave volley excited by TMS changes during the course of a voluntary movement. This is not likely to be due to a change in the stimulation parameters (e.g. a change in precise coil position), even during the long experiments recorded here. Firstly, the coil was firmly clamped above the head, which was itself rigidly fixed. Secondly, the stimuli were delivered at a constant rate whilst the animal worked in a self-paced manner; stimuli were thus effectively given at random with respect to task phase. Any changes in stimulation parameters over the course of the experimental session would be cancelled by the post hoc selection procedure used here, as the sweeps comprising each average plotted in Fig. 2 were drawn equally from the beginning, middle and end of the recording session.

The modulation observed is most likely, therefore, to result from changes in the level of cortical activity accompanying task performance. Such a modulation was not seen in the volley produced by direct electrical stimulation of corticospinal fibres at the cerebral peduncle. These findings support the hypothesis of Edgley et al. (1990) that the D wave following TMS is produced by excitation of corticospinal neurones at a point close to their cell body, although we have used a different stimulating coil and orientation from that study. The amplitude of the corticospinal volley presented here should be related to the number of corticospinal neurones excited by the magnetic stimulus, and hence a more reliable indicator of changes dependent on cortical excitability than muscle responses. Such a modulation in cortical excitability would also be expected to alter the synchrony of neuronal response to TMS, and hence reduce cancellation of individual action potentials in the recording. The contribution of this effect to the amplitude changes in the corticospinal volley is unknown.

The modulation of only 12% shown in Fig. 2A on a much expanded scale might seem on initial examination to be disappointingly small, especially given the much larger task-related modulation in EMG responses shown in Fig. 3 (up to tenfold). This is likely to reflect the heterogeneous nature of the cells contributing to the recorded volley, many of which will not modulate their activity with performance of this task. By contrast, evidence from single cell recording in the motor cortex during performance of the precision grip task suggests that almost all the fast corticospinal cells projecting to hand and forearm motoneurones modulate their activity in a task-dependent way (Lemon et al. 1986). It is therefore likely that the task-related modulation in recruitment of this subpopulation by TMS will be greater than that in the global activity measured from the entire tract. In addition, the modulation in EMG response will reflect changes in spinal excitability.
compounded with the changes in the size of the descending volley.

At present we have little information as to how the currents induced by TMS will interact with the natural firing history of a corticospinal cell. The present data seem to show that corticospinal cells are more susceptible to TMS during the hold period of the task than during the initial movement, in which the monkey positions its digits on the two levers. Corticospinal cell activity is largest during this initial phase (Bennett & Lemon, 1994). This implies that the period of maximum corticospinal susceptibility to TMS may not coincide with the time of maximum corticospinal cell activity; possible mechanisms include after-hyperpolarization and refractory period when the cells fire at high rates.

I waves were not visible in single sweeps of the recordings presented here. In averages over all stimulus presentations for one session (i.e. around 2000 sweeps), small later deflections could be seen. However, they were of the order of only 3% of the size of the initial, D wave, rendering detailed analysis of their variability impossible. This is initially a surprising finding, since indirect activation might be expected to be more important in the conscious state than under anaesthesia, where I waves have previously been seen (Amassian, Stewart, Quirk & Rosenthal, 1987; Edgley et al. 1990; Burke et al. 1993).

There are two possible explanations. Firstly, the lack of I waves may reflect the recording arrangement. The pyramid recording electrodes were spaced only 4 mm apart, so that the duration of the recorded triphasic volley was very brief at approximately 0.5 ms. The jitter in the response latency of a single corticospinal axon responding indirectly can be as much as 1 ms (S. A. Edgley, J. A. Eyre, S. Miller & R. N. Lemon, unpublished observations), which would cause substantial cancellation of positive and negative phases of I waves. In reports where I waves have been recorded, electrodes were placed at the spinal level with presumably larger spacings, for the duration of the D wave is often as much as 1 ms; less cancellation would then occur. The greater sensitivity of I waves to the recording arrangement has been noted by Inghilleri, Berardelli, Crucucci, Priori & Manfredi (1989) when using transcranial electrical stimulation in humans.

Alternatively, it may be that indirect activation is relatively unimportant with a mediolateral coil orientation (Amassian, Quirk & Stewart, 1990). With this orientation, Werhahn et al. (1994) showed that single 1DI motor units in man respond to TMS with a single sub-peak. Preliminary observations in the monkey have also shown that single motor units responded to TMS delivered as described above with a single subpeak, at a latency consistent with direct activation (S. N. Baker, E. Olivier & R. N. Lemon, unpublished observations). Thus direct corticospinal excitation may be more important than indirect under the stimulation conditions used in this experiment.

This report provides direct evidence that changes in cortical excitability associated with the performance of the precision grip task are reflected in significant variation in the amplitude of the corticospinal volley evoked by TMS. It further shows that the time course of the EMG responses follows these changes, suggesting that modulation in the amplitude of short-latency EMG responses to TMS is due, at least in part, to changes in the size of the descending corticospinal volley.


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