Muscle responses to transcranial stimulation in man depend on background oscillatory activity

W. Kyle Mitchell, Mark R. Baker and Stuart N. Baker

J. Physiol. 2007;583;567-579; originally published online Jul 12, 2007;

DOI: 10.1113/jphysiol.2007.134031

Muscle responses to transcranial stimulation in man depend on background oscillatory activity

W. Kyle Mitchell[1], Mark R. Baker[2] and Stuart N. Baker[2]

[1]*Department of Anatomy, Cambridge University, Cambridge CB2 3DY, UK*
[2]*Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK*

Muscle responses to transcranial stimulation show high sweep-to-sweep variability, which may reflect an underlying noise process in the motor system. We examined whether response amplitude correlated with the level of prestimulus background EMG, and network oscillations. Transcranial magnetic or electrical stimulation was delivered to primary motor cortex whilst human subjects performed a precision grip task known to promote beta-band (∼20 Hz) cortical oscillations. Responses were recorded from two intrinsic hand muscles. Response magnitude correlated significantly with the level of background EMG (mean $r^2 = 0.20$). Using a novel wavelet method, we quantified the amplitude and phase of oscillations in prestimulus sensorimotor EEG. Surprisingly, response magnitude showed no significant correlation with EEG oscillations at any frequency. However, oscillations in the prestimulus EMG were significantly correlated with response size; the correlation coefficient had peaks around 20 Hz. When oscillations in one muscle were used to predict response amplitude in a different muscle, correlations were substantially smaller. Finally, for each recording, we calculated the best possible prediction of response size obtainable from up to 20 measures of prestimulus EEG and EMG oscillations. Such optimal predictions had low correlation coefficients (mean $r^2 = 0.2$; 76% were below 0.3). We conclude that prestimulus oscillations, mainly in the beta-band, do explain some of the variability in responses to transcranial stimulation. Oscillations may likewise increase the noise of natural motor processing, explaining why this form of network activity is usually suppressed prior to dynamic movements. However, the majority of the variation is determined by other factors, which are not accessible by noninvasive recordings.

(Received 5 April 2007; accepted after revision 22 June 2007; first published online 12 July 2007)
Corresponding author S. N. Baker: Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK. Email: stuart.baker@ncl.ac.uk

The technique of transcranial magnetic brain stimulation (TMS) has found many diverse applications since its introduction by Barker *et al.* (1987). The means by which a magnetic stimulus delivered over the motor cortex stimulates neural tissue and evokes a contralateral twitch has been extensively studied. The stimulus produces both direct (D) and indirect (I) activation of corticospinal neurones (Day *et al.* 1987; Edgley *et al.* 1990), which in turn activate spinal motoneurones monosynaptically. The relative extent of D and I activation can be changed by the orientation of current induced by the magnetic coil (Werhahn *et al.* 1994; Olivier *et al.* 2001; Di Lazzaro *et al.* 2001). However, one puzzling feature of TMS is the high variability of the peripheral response to a constant stimulus. In contrast to the stereotyped response of a muscle following an electrical stimulus to the nerve innervating it, responses following TMS have a high coefficient of variation (Amassian *et al.* 1989; Kiers *et al.* 1993; van der Kamp *et al.* 1996; Ellaway *et al.* 1998).

The source of TMS response variability appears to be common across motoneurone pools, since response amplitudes from stimulus-to-stimulus are correlated between different muscles (Ellaway *et al.* 1998). Previous work has excluded a number of possible explanations. One hypothesis was that the variability could result from slight alterations in the position of the brain within the skull produced by the cardiac pulse pressure wave. However, there was no reduction in variability when stimuli were triggered at fixed points in either the cardiac or respiratory cycle (Amassian *et al.* 1989; Ellaway *et al.* 1998).

The neural circuits of primary motor cortex can show spontaneous oscillatory activity in frequency bands around 10 and 20 Hz; these manifest as peaks in the power spectrum of sensorimotor electroencephalogram (EEG) or magnetoencephalogram (MEG) (Salmelin & Hari, 1994; Pfurtscheller *et al.* 1996). Whilst the oscillations around 20–30 Hz are coherent with the EMG of contracting muscles (Conway *et al.* 1995; Baker *et al.* 1997; Salenius

 DOI: 10.1113/jphysiol.2007.134031

et al. 1997), those at 10 Hz show weak or absent coherence (see Baker *et al.* 2003 for discussion). Corticospinal neurones form part of the cortical oscillatory network (Jackson *et al.* 2002), and their firing is partially phase-locked to the oscillations (Baker *et al.* 2003). This presumably indicates a cyclical modulation in the excitability of the corticospinal cells. It is known that the extent of both direct and indirect corticospinal activation by TMS depends on the ongoing level of excitability of the cortex (Baker *et al.* 1994, 1995; Di Lazzaro *et al.* 1998*b*). TMS is usually given during either steady contractions, or at rest, both of which conditions potentiate cortical oscillations (Pfurtscheller *et al.* 1996; Baker *et al.* 1997; Kilner *et al.* 2000). It is therefore reasonable to hypothesize that TMS response variability is partly due to spontaneous modulation in cortical excitability during oscillations.

An alternative means of stimulating the motor cortex non-invasively is transcranial electrical stimulation (TES). At low intensities, this appears to activate corticospinal axons directly (Edgley *et al.* 1990, 1997; Di Lazzaro *et al.* 1998*a*), and the amplitude of the descending volley is little effected by cortical excitability (Di Lazzaro *et al.* 1999). D wave volleys elicited by TES show little variability (Burke *et al.* 1995), supporting the hypothesis that response variability to TMS may arise from fluctuations in cortical excitability.

TMS response variability is of some experimental interest *per se*, as it influences the reliability of magnitude measurements made from a given number of stimuli. However, it may also provide a window on an important physiological process. It is reasonable to expect that whatever causes a variable response to TMS will also add variability to natural motor output. The presence of noise in the motor system is known to be a key constraint on performance (Harris & Wolpert, 1998). Determining the source of this noise is important to understand how the brain optimizes movement control.

In this paper, we present evidence that TMS response amplitude does indeed depend on oscillations present just prior to the stimulus. However, although this dependence was statistically significant, it was weak. In addition, variations in TES response were also weakly correlated to the level of prestimulus oscillations. We suggest that other fluctuations in cortical and spinal excitability, uncorrelated to overt oscillatory activity, may contribute the major part of the measured response variation, and by implication the major part of system noise during natural motor tasks.

Methods

Electrophysiological recording and behavioural task

Experiments were performed in 20 normal human subjects, all of whom gave written informed consent. Each stimulus type (TES, or TMS with two directions of induced current) was tested on seven to eight subjects; two people participated in experiments on both variants of TMS. Procedures were approved by the Local Research Ethics Committee and conformed to the *Declaration of Helsinki*.

Subjects gripped two levers between finger and thumb in a precision grip. For some experiments, lever displacement was measured by potentiometers, and springs opposed lever movement. In other experiments, lever displacement was measured by optical encoders and force was generated by torque motors controlled by a computer to simulate a spring-like load. In both cases, a force of 1 N was required initially to move the lever from its end stop; thereafter, force increased at a rate of 0.025 N mm^{-1} lever displacement. Visual feedback of lever position was provided to the subject via two cursors on a computer video monitor. At the start of a trial, two target boxes appeared on the screen at a location corresponding to 12 mm lever displacement, and the subject was required to move the cursors rapidly into target. After a 3 s hold period, the targets moved linearly from 12 mm to 24 mm displacement over 2 s, followed by a further 3 s hold phase at 24 mm displacement. The subjects were then required to release the levers; the next trial began 1.5 s later. This task corresponds to the 'Aux1' Hold–Ramp–Hold task of Kilner *et al.* (2000), and has been used in much of our previous work (Riddle & Baker, 2005, 2006).

Recordings were made of electromyogram (EMG) activity from the first dorsal interosseous (1DI) and abductor digiti minimi (AbDM) muscles of the right hand using adhesive surface electrodes (Biotrace 0713C, MSB Ltd, Marlbrough, UK). Bipolar EEG was recorded from left sensorimotor cortex with electrodes (Neuroline 720 00-S, Medicotest, St Ives, UK) placed 20 mm lateral and 30 mm anterior and posterior to the vertex; the anterior electrode was connected to the non-inverting input of the amplifier. Signals were amplified (gain 500–5K, bandpass 30 Hz to 2 kHz for EMG; gain 50K, bandpass 3 Hz to 2 kHz for EEG) and digitized at 5 kHz sampling rate by a Power1401 interface (CED Ltd, Cambridge, UK) running Spike2 software, together with signals indicating lever position, stimulus intensity and the time of trial onset and stimulus delivery.

Transcranial stimulation

Transcranial magnetic brain stimulation was delivered using a Magstim 2000 stimulator (The Magstim Co. Ltd, Whitland, UK) and 7 cm outside diameter figure-of-eight coil. The coil was orientated at an angle of approximately 45 deg to the midline over the left hemisphere, at the scalp location which produced the lowest threshold response

in the right 1DI muscle. The coil was then fixed rigidly in place by attachment to a modified motorcycle helmet, which fitted tightly on the head. The weight of the combined helmet and coil assembly was taken by vertical support straps to improve subject comfort. The induced current in the brain flowed anteromedially; this form of stimulation is referred to as AM TMS here, and probably produces D and early I wave activation of corticospinal neurones (Werhahn *et al.* 1994; Sakai *et al.* 1997; Di Lazzaro *et al.* 1998*a*; Di Lazzaro *et al.* 2001). By connecting an additional cable, interposed between stimulator and coil, the current direction could be reversed; this PL TMS probably produces later I wave activation of corticospinal neurones.

The threshold for 1DI muscle activation was determined whilst the subject made a gentle abduction of the index finger. Threshold was defined as the intensity which produced visible responses at appropriate latency in half of the sweeps. Stimulus intensities of 1.1×, 1.3× and 1.5× threshold were then used. The intensity was randomly chosen from these values for each stimulus by a computer which controlled the stimulator via a parallel port interface.

For experiments using transcranial electrical stimulation (TES), stimulating electrodes were placed at the vertex (cathode) and 60 mm lateral (anode). Electrical stimuli were given using a Digitimer D180 stimulator (Digitimer Ltd, Welwyn Garden City, UK). The threshold for 1DI activation during finger abduction was determined; experiments used an intensity 1.3× threshold.

One stimulus was delivered per trial of the behavioural task. With 1/9 probability, the stimulus was delivered between 3.95 and 4.078 s after the trial start, corresponding to the Ramp phase of the task. With 8/9 probability, the stimulus was delivered between 5.95 and 6.078 s after the trial start, corresponding to the second hold phase. The exact time of stimulus delivery within these ranges was determined randomly (uniform distribution) from trial to trial. In this report, only the stimuli from the second hold phase are considered; it has previously been shown that cortical oscillatory activity is maximal during this part of the task (Kilner *et al.* 2000). Recordings were made from approximately 100 trials of the task for each stimulus intensity tested.

Analysis

The first stage of analysis separated out stimulus times according to intensity; stimuli of different intensity were then analysed separately. A stimulus-triggered average of rectified EMG was compiled, and the experimenter determined the onset and offset latencies (t_1 and t_2, respectively) of the response by placing interactive cursors. The amplitude R_j of the response to the jth stimulus was then taken as the mean over this period:

$$R_j = \frac{1}{(t_2 - t_1)} \int_{t_1}^{t_2} E_j(t)\mathrm{d}t \qquad (1)$$

where $E_j(t)$ denotes the rectified EMG at time t post-stimulus. Response amplitude is often measured in other studies as the area under the response. Since the response duration $t_2 - t_1$ was fixed for a given subject, the mean amplitude used here differs only from the response area by the scale factor $1/(t_2 - t_1)$. Identical modulations will therefore be seen using either measure.

The level of background muscle activity B_j was assessed by finding the mean rectified EMG over a period immediately preceding the stimulus. The effects of different background durations was systematically investigated in the initial part of this study (see Fig. 3*C*); for the remainder of the analysis, a background length of 500 ms was used.

The dependence of response amplitude on the background EMG was determined by fitting the linear regression model:

$$R_j = mB_j + c + \varepsilon_j \qquad (2)$$

where m and c are the slope and intercept parameters of the model, and ε_j are the residuals, being the part of the variation in R_j which could not be explained by correlation with B_j.

In order to investigate whether the presence of spontaneous oscillatory activity could explain the remaining variation, we needed to measure the amplitude and phase of oscillations in the prestimulus EEG or EMG. Standard Fourier methods are poorly suited to this task. To avoid spectral leakage, Fourier approaches require the use of a window, which tapers the signal amplitude to zero at the edges of the analysed data section (Press *et al.* 1989). This accordingly emphasizes the signal in the middle of the section, rather than that at its edges. However, the signal immediately prior to the stimulus is most likely to influence response amplitude. Conventional symmetric wavelet analysis is no better – for example, as noted by Baker & Baker (2003), Gabor wavelets are equivalent to using Fourier transforms with a Gaussian window, and again emphasize the data in the middle of the analysis window.

In this paper, we used a novel wavelet which was asymmetric, and which had its largest amplitude concentrated at one end of the analysis window. The wavelet at frequency f was defined as:

$$W^f(t) = -\frac{5ft}{4} \mathrm{e}^{\left(1+\frac{5ft}{4}\right)2\pi f t i} \qquad (3)$$

This is the product of an alpha function having a peak $0.8/f$ before the stimulus, with a complex sinusoid; the real and complex parts of W are illustrated in Fig. 1*A* for $f = 20$ Hz.

The stages of the analysis are illustrated by the remainder of Fig. 1. For a given frequency of interest (20 Hz in this example), a section of EEG or rectified EMG was extracted lasting seven oscillation periods prior to the stimulus (here 350 ms; Fig. 1*B*). This duration was chosen because W has negligible amplitude at this lag. The dot-product of the signal S with the wavelet W was found, thereby estimating the amplitude of oscillations at this frequency for trial j:

$$A_j^f = \int_{t=-7/f}^{0} W^f(t) S_j(t) \mathrm{d}t \qquad (4)$$

A multiple linear regression was then carried out between the response residuals after background correction ε_j, and the oscillation amplitudes, using the regression model

$$\varepsilon_j^f = m_1 \,\mathrm{Re}\left(A_j^f\right) + m_2 \,\mathrm{Im}\left(A_j^f\right) + c \qquad (5)$$

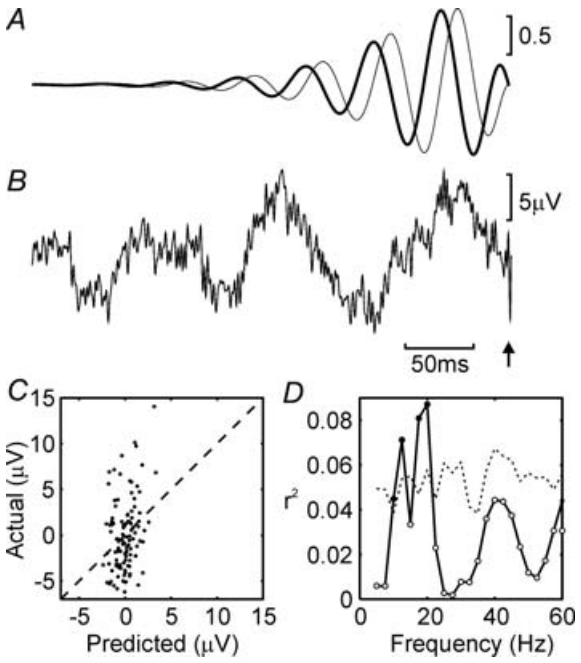

Figure 1. Method used to estimate correlation of response with prestimulus oscillations
A, novel asymmetric wavelet developed for this analysis; real (thick line) and imaginary (thin line) components are shown. *B*, example section of prestimulus EEG. Arrow marks time of stimulus delivery. *C*, correlation of actual response size with response predicted based on 20 Hz oscillations for a single subject, stimulus type and muscle. Dashed line shows identity. *D*, variation of correlation coefficient with frequency of EEG oscillation used for prediction. Dotted line indicates significance limit ($P < 0.05$); filled symbols indicate bins above significance.

where ε_j^f are the best-fit predicted values of ε_j from this regression using amplitudes of frequency f, and $\mathrm{Re}(A_j^f)$, $\mathrm{Im}(A_j^f)$ indicate the real and imaginary parts.

Figure 1*C* shows a scatter plot of the actual responses ε_j *versus* the best-fit prediction from the oscillation amplitudes at 20 Hz, $\varepsilon_j^{20\mathrm{Hz}}$, for an example dataset (PL TMS, 1.3× threshold in a single subject). There is considerable scatter here; however, the regression gave an r^2 value of 0.087. The regression model was then refitted to the data after the response size values had been randomly shuffled. This was repeated 100 times, and the r^2 values so obtained ordered. The 95th largest value was 0.058; since the actual (unshuffled) correlation was larger than this, it denoted a significant correlation ($P < 0.05$).

Finally, the entire procedure was repeated for frequencies between 5 and 60 Hz, in 2.5 Hz steps, yielding the plot of r^2 *versus* frequency shown in Fig. 1*D* (continuous line); also shown is the $P < 0.05$ significance level determined by the Monte-Carlo shuffling procedure (dotted line). In this example, prestimulus oscillations in the EEG between 12.5 and 20 Hz predicted some of the response variability. However, in this plot results for 23 different frequency bins are presented, leading implicitly to multiple statistical comparisons. A significant correlation was not assumed to be present unless at least four bins were above significance – this number was chosen from a binomial distribution with $P(\mathrm{hit}) = 0.05$, to yield an overall significance level of $P < 0.05$. In Fig. 1*D*, exactly four frequencies crossed the significance limit, indicating a significant correlation with prestimulus EEG oscillations in this case.

A separate analysis aimed to determine the best possible prediction which prestimulus oscillations combined with background EMG could make of response amplitude. For this purpose, a different regression model was used:

$$R_j^N = m_o B_j + \sum_{n=1}^{N} m_n V_j^n + c \qquad (6)$$

Here, R_j^N is the prediction of the response amplitude to the jth trial using N variables V in addition to the EMG background B. There were available 92 possible variables, being the real and imaginary parts of A_j^f, which could be calculated from either prestimulus EEG or EMG. The frequency f ranged from 5 to 60 Hz in 2.5 Hz steps. The variables V were chosen from these possibilities to maximize the regression coefficient r^2 using that number of variables.

To avoid overfitting the data when using large numbers of variables, a cross-validation approach was employed. V_1 was initially chosen as the first of the possible 92 variables. Linear regression obtained the best estimate of coefficients c and m_n, using all available responses *except the first*. These coefficients were then used to form a prediction of the first response's size, R_1^1. This was then repeated for the

second response, and so on, building up a complete set of predicted responses R_j^1. The regression coefficient r^2 was then calculated as:

$$r^2 = 1 - \frac{\mathrm{Var}(R_j - R_j^1)}{\mathrm{Var}(R_j)} \quad (7)$$

The entire procedure was repeated choosing each of the 92 possible variables as V_1 in turn; the choice which gave the largest associated r^2 was accepted.

A similar approach found the optimal variable V_2 for the model using two variables, and so on up to $N = 20$ variables. Examination of the r^2 coefficient then showed the fraction of the response variance which could be explained using an optimal linear combination of prestimulus oscillation parameters.

Results

Figure 2 presents an example of raw data gathered from a single subject, showing lever position signals from the precision grip task, EEG and EMG (Fig. 2*A*). The transcranial stimulus (here TMS) was delivered during the second hold phase of the task. The stimulus caused a long-lasting artefact on the EEG, as the TMS coil was in close proximity to the recording electrodes; however, this was of no consequence as the analysis used only EEG data immediately prior to the stimulus.

Responses to TMS showed considerable variability from one stimulus to the next; 10 successive responses to the same intensity in each muscle are illustrated in Fig. 2*B*. Whilst several trials produced large responses, in others the response was barely noticeable above the baseline. Even in these raw data, it is clear that the response amplitude covaried between the two hand muscles.

In this study, we used three types of stimulation: TES, and TMS with two current directions. Previous work has shown that altering the current orientation changes the mode of activation of corticospinal neurones (Werhahn *et al.* 1994). Figure 2*C* presents the onset latencies of responses measured from each muscle and subject, divided according to the stimulus type and intensity expressed relative to active motor threshold. Because different subjects were used for the different stimulus types, direct intrasubject comparisons of latencies are not possible. However, a clear pattern does emerge from Fig. 2*C*, which is broadly consistent with the literature. TES produced short onset latencies, compatible with D wave activation. AM TMS generated responses with latencies similar to TES in some subjects, but in others they were around 2 ms later, indicating probable I1 activation of corticospinal cells. PL TMS had exclusively later responses, presumably corresponding to I waves from I1 to I3.

Figure 3 presents some population data on the responses to different types of stimuli. In Fig. 3*A*, *B*, *D* and *E*, results from each subject in muscles 1DI and AbDM are shown as points, with the boxes showing the median and interquartile range. The response sizes which we studied were comparable between the two different current orientations of TMS used for different intensities relative to threshold (Fig. 3*A*). Responses at the single intensity of TES investigated were comparable to those at the lowest intensity of TMS tested.

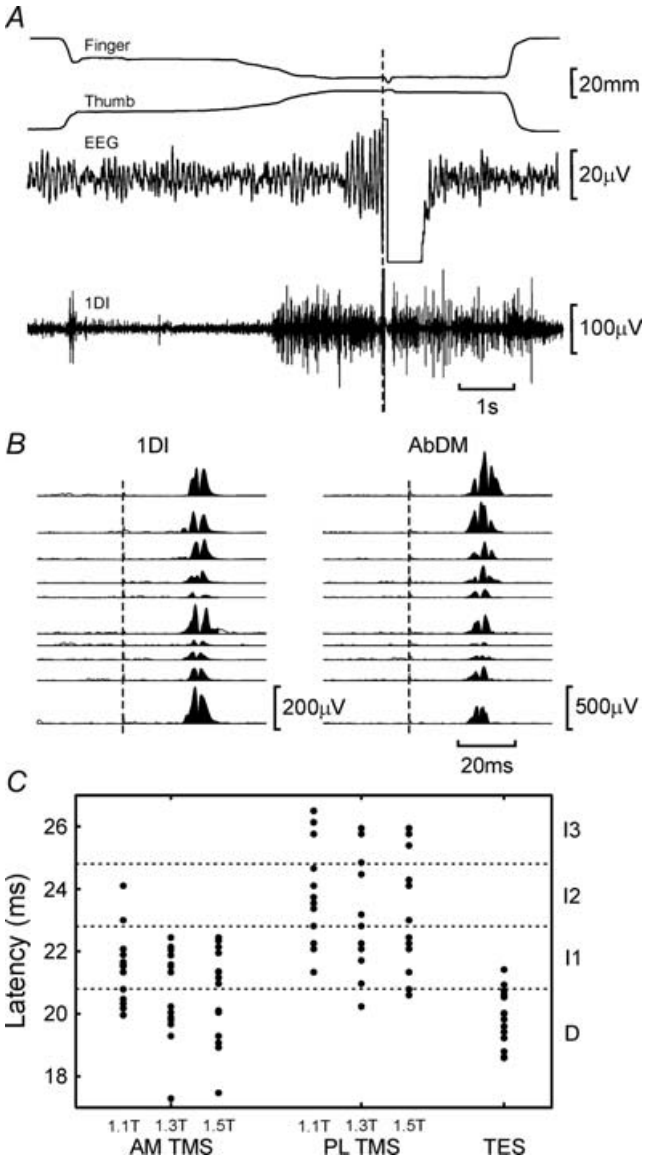

Figure 2. Example data
A, raw records from one subject, showing lever position signals during performance of the precision grip task, sensorimotor EEG and raw EMG from the 1DI muscle. Vertical dashed line indicates time of stimulus delivery (AM TMS, 1.3× threshold). *B*, 10 successive responses in rectified EMG to the same stimulus recorded in the same subject as illustrated in *A*, in muscles 1DI and AbDM. *C*, latency of all responses recorded, grouped by stimulus type and intensity. Dashed lines and labels to right indicate putative earliest corticospinal volley responsible.

It has previously been reported that responses become less variable as the stimulus intensity increases (Kiers *et al.* 1993; van der Kamp *et al.* 1996). Although our results showed a large amount of interindividual variation in the coefficient of variation (CV, Fig. 3*B*), for AM TMS and PL TMS there was a significant effect of intensity on CV (both ANOVA, $P < 0.01$). Whereas for PL TMS there was a monotonic decrease in the median CV with increasing intensity, for AM TMS variability at the middle intensity tested was larger than with either stronger or weaker stimuli. Surprisingly, TES produced responses which were only a little less variable than the similar sized responses elicited by the lowest intensities of TMS (median CV: AM TMS 1.1T, 69%; PL TMS 1.1T, 76%; TES, 58%); the difference between AM TMS and TES just failed to reach significance ($P = 0.053$), whereas there was a significant difference between PL TMS and TES ($P = 0.017$, both Mann–Whitney U-test).

It is well known that TMS responses increase in size with increasing levels of general background contraction (Hess *et al.* 1986); however, it is less clear whether the moment-by-moment fluctuations of background EMG immediately preceding each stimulus influence the response amplitude. Equally, it is unclear what is the optimum duration over which the background EMG should be measured. To address the latter question,

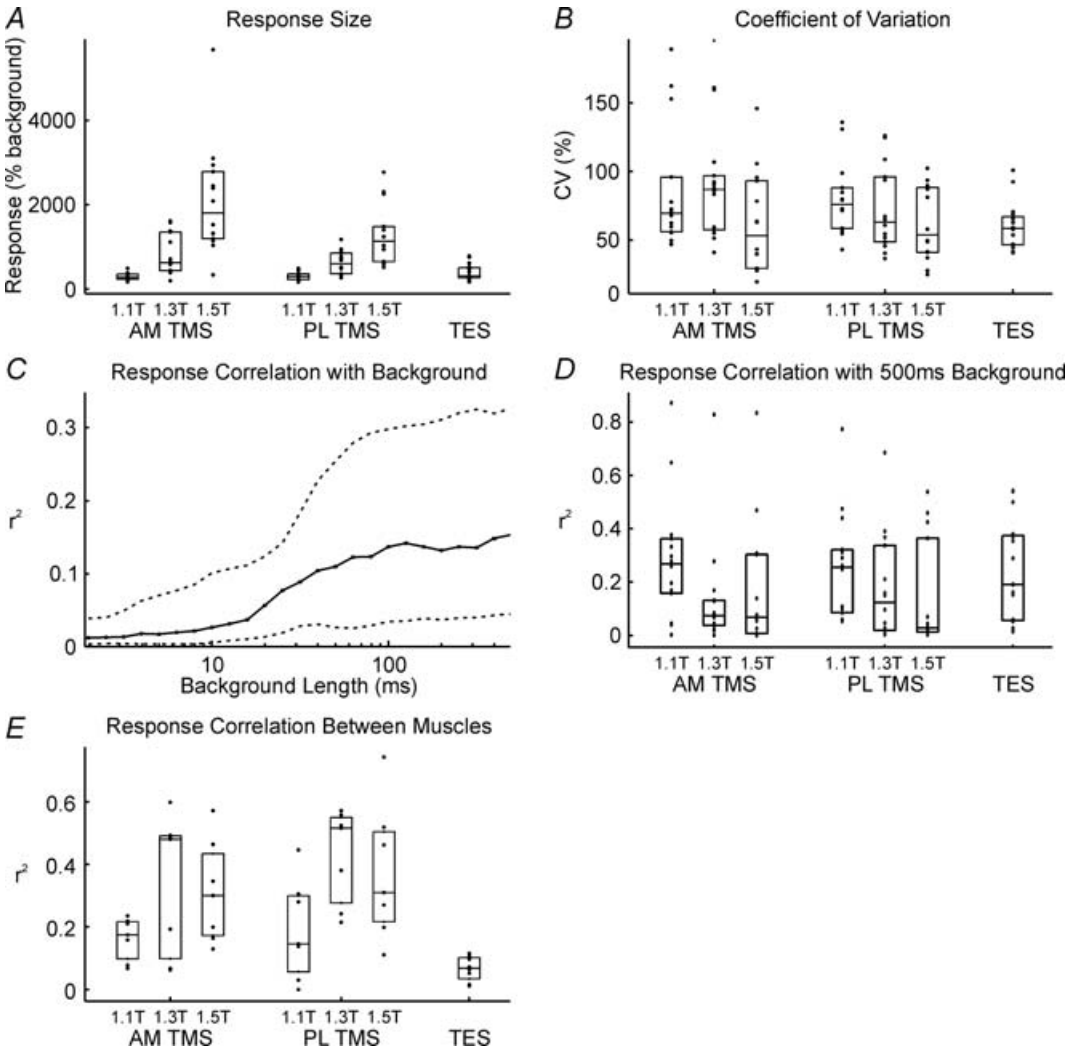

Figure 3. Response measures
A, response size, expressed as a percentage of the mean prestimulus background level of EMG. *B*, coefficient of variation. *C*, response correlation with single trial level of background EMG, for different durations of the prestimulus background region. Continuous line shows median correlation coefficient; dashed lines show interquartile range. Responses to different stimulus types and intensities have been combined. *D*, response correlation with background EMG, for a 500 ms-long background duration, separated by stimulus type. *E*, correlation between responses in the two intrinsic hand muscles recorded. In all panels, dots show individual results; boxes show the median and interquartile ranges. Results are grouped by stimulus type and intensity relative to threshold.

we calculated the correlation of the response amplitude with background; background duration was varied from 2 ms to 500 ms before the stimulus. Figure 3*C* shows the median value of r^2 (continuous line), and the interquartile ranges (dotted); responses to all stimulus types, and at all intensities, have been included in this figure. The background correlation appears to increase sharply for durations around 20 ms, and then to plateau above 100 ms. A background duration of 500 ms was used in all subsequent analysis.

Figure 3*D* shows the correlation of response amplitude with a 500 ms-long background, separately for each response. Overall, 73% of responses were significantly correlated with the background EMG (*t* test on each regression coefficient, $P < 0.05$). For both variants of TMS, this correlation decreased significantly with increasing intensity (ANOVA, $P = 0.0026$ and $P = 0.023$ for AM TMS and PL TMS, respectively). The correlation for TES was not significantly different from that at the lowest intensity of AM TMS or PL TMS ($P > 0.05$, Mann–Whitney *U*-test).

Figure 3*E* presents the correlation between the response amplitudes of the two muscles studied. Whilst the correlation appeared largest at the middle intensity tested (1.3× threshold) for both types of TMS, only for PL TMS did this trend become significant (ANOVA, $P < 0.05$). The median r^2 value for TES was 0.068, compared with 0.18 and 0.15 for the lowest intensities of AM TMS and PL TMS, respectively; TES responses covaried significantly less than responses to AM TMS (Mann–Whitney *U*-test, $P < 0.05$) but not PL TMS ($P > 0.05$).

Whilst Fig. 3*C* and *D* makes it clear that there was often a correlation of response size with the background EMG prior to the stimulus, this usually explained less than 30% of the response variance. Figure 4 shows the results of trying to predict the remaining variability in response size from prestimulus EEG oscillations. Results were averaged across subjects and muscles, for each different type and intensity of stimulus. The significance limits (dotted lines) were determined by averaging r^2 estimates from shuffled data, and taking the 95th percentile. At the two lowest intensities of TMS used, and for TES, there was no significant correlation of response amplitude with EEG oscillations (Fig. 4*A*, *B*, *D*, *E* and *G*, fewer than 4 bins above significance). For PL TMS at the greatest intensity tested (1.5× threshold), seven frequencies from 20 to 35 Hz had significant correlations; however, these r^2 values were very small (< 0.03). For AM TMS, 10 frequencies above 37.5 Hz had significant correlations. We conclude that prestimulus EEG oscillations can explain little or none of the observed variation in response amplitude.

It is known that beta-band oscillations are not confined to the sensorimotor cortex, but also are propagated down to motoneurons and can be observed in the EMG of contracting muscles; this leads to corticomuscular coherence. Following the failure to predict response amplitude from EEG features, we investigated whether oscillations in the background EMG would be a more effective predictor. This was tested by applying exactly the same analysis as described in Fig. 4 to the prestimulus rectified EMG of the muscle whose response was to be predicted. Figure 5 presents regression coefficients for this analysis averaged across subjects and muscles, in a similar format to Fig. 4.

The results using EMG oscillations were quite different from those with EEG oscillations. For all stimulus types and intensities, multiple frequency bins were above significance. In many cases there were peaks close to 20 Hz, although higher frequencies were also capable of significant response prediction – for AM TMS at 1.1× threshold, the peak at 40 Hz was actually larger than that at 17.5 Hz. For both types of TMS, the mean regression coefficients at ∼20 Hz showed some decline

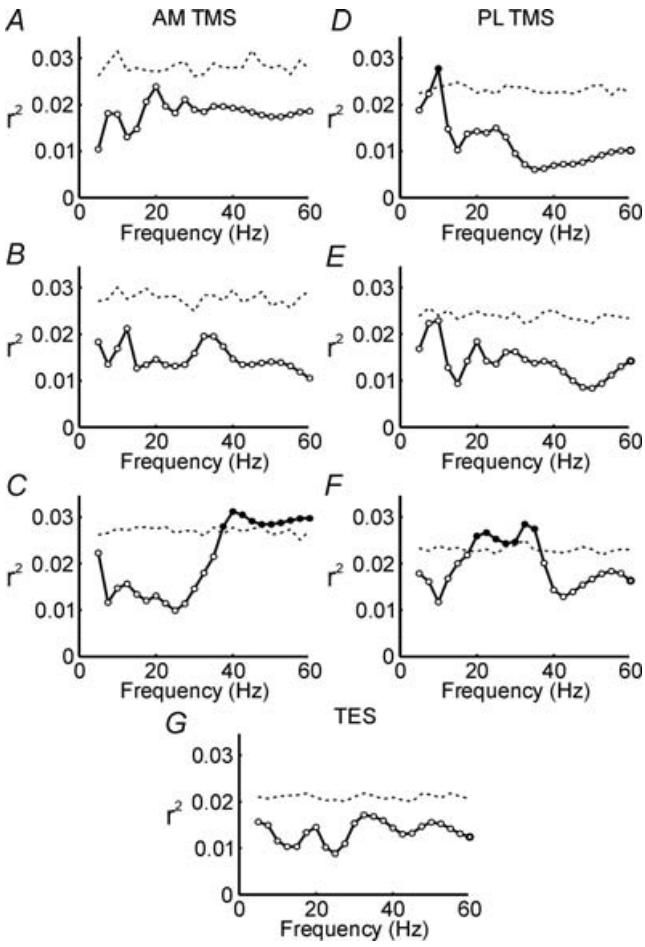

Figure 4. Correlation of response magnitude with EEG oscillations
Each plot shows the correlation coefficient averaged across subjects and muscles, as a function of oscillation frequency. Dashed line shows the significance limit ($P < 0.05$); filled symbols show bins above significance. *A*–*C*, results for AM TMS at 1.1×, 1.3× and 1.5× threshold. *D*–*F*, results for PL TMS at 1.1×, 1.3× and 1.5× threshold. *G*, results for TES.

with increasing stimulus intensity, although r^2 values were comparable between AM TMS and PL TMS. TES showed a clear broad peak around 20 Hz, but this was smaller in size than those for the lowest TMS intensity used. The exact frequency of the peak varied for different stimulus types and intensities. For example, for PL TMS at 1.3× threshold, the peak was at 20 Hz. However, at 1.5× threshold, the averaged r^2 was not significant at this frequency, and the peak was instead at 15 Hz.

The success in predicting response amplitude from prestimulus EMG could result from two distinct contributing factors. The EMG may represent global changes in excitability, or alternatively the analysis could be detecting modulations in the activity of the motoneurone pool which are specific to that muscle. In order to address this, we carried out a further analysis in which the responses in one muscle (1DI or AbDM) were predicted by the prestimulus rectified EMG in the other. Figure 6 shows the results of this analysis, averaged across subjects and muscles and presented in the same format as Figs 4 and 5.

Using a different EMG for prediction from the responding muscle substantially reduced the regression coefficients. For AM TMS, no frequencies yielded significant predictions on average. Only for PL TMS at 1.3× and 1.5× threshold was there a significant prediction (> 4 bins above significant level shown by dotted line); only for the highest intensity used were ~20 Hz frequencies effective at predicting response magnitude.

Figure 5 shows clearly that there was, on average, a significant correlation between response amplitude and prestimulus EMG oscillations. However, only a small fraction of the response variance was explained ($r^2 < 0.09$, Fig. 5) by a single frequency. In many cases, multiple frequency bins rose above significance, but the analysis of Fig. 5 does not distinguish whether these

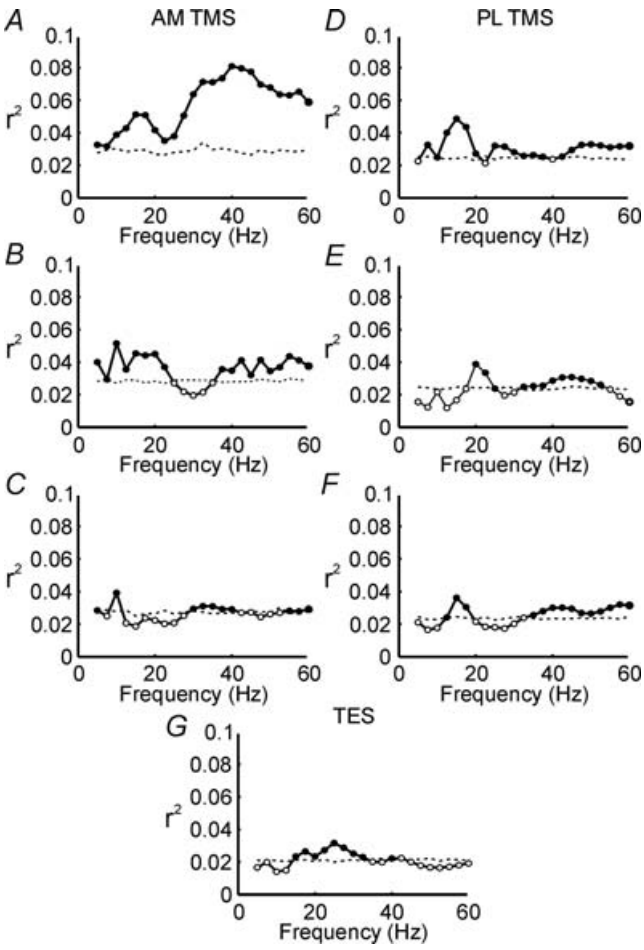

Figure 5. Correlation of response magnitude with EMG oscillations in the responding muscle
Same plotting conventions as Figure 4. *A–C*, results for AM TMS at 1.1×, 1.3× and 1.5× threshold. *D–F*, results for PL TMS at 1.1×, 1.3× and 1.5× threshold. *G*, results for TES.

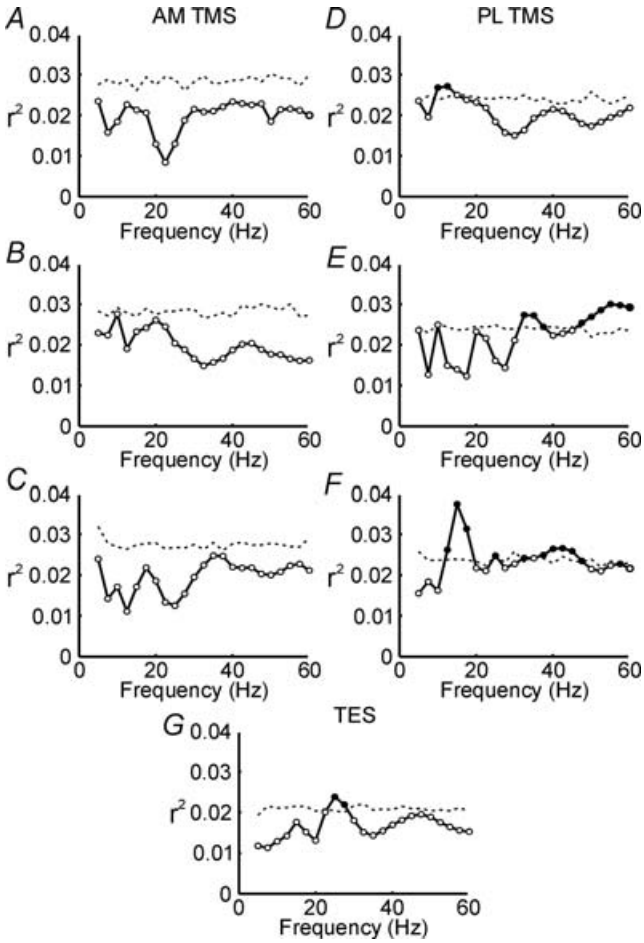

Figure 6. Correlation of response magnitude with EMG oscillations in a different muscle
Prestimulus EMG from the 1DI muscle was used to predict responses in AbDM, and vice versa. Same plotting conventions as Figs 4 and 5. *A–C*, results for AM TMS at 1.1×, 1.3× and 1.5× threshold. *D–F*, results for PL TMS at 1.1×, 1.3× and 1.5× threshold. *G*, results for TES.

different frequencies provided redundant or independent information. If they were partially independent, then using measurements of prestimulus oscillations at multiple frequencies would improve the prediction of response amplitude. By contrast, if the frequencies were redundant, nothing would be gained by considering more than a single frequency.

In order to investigate this further, we carried out a multivariate linear regression, in which the EMG background, and the real and imaginary parts of the amplitude of wavelets at all frequencies measured from both prestimulus EEG and EMG were potential independent variables; the dependent variable was the response amplitude. Initially, regressions were calculated using the EMG background and one other independent variable. All possible choices of this single variable were tested, and the variable with the largest r^2 used. The analysis was repeated with a further independent variable, again with all possible choices of this variable tested and the selection yielding the largest r^2 kept. This procedure was repeated for up to 20 variables in addition to the EMG background. Cross-validation was used throughout to avoid over-fitting the regression model to the data; further details are given in Methods. Figure 7*A* shows an example of r^2 plotted *versus* the number of additional variables included in the model, for responses in the 1DI muscle following PL TMS stimulation at 1.3× threshold in a single subject. Because cross-validation was used, the correlation coefficient did not simply rise monotonically as more variables were included in the model. Instead, there was a rapid rise in r^2 up to seven variables; addition of further variables then impaired the prediction. Figure 7*B* shows a scatter plot of the actual response amplitude *versus* the predicted amplitude, using the best seven variables, which gave the maximum r^2 value (0.27).

Figure 7*C* shows the population distribution of the maximum regression coefficient obtained using up to 20 variables, in addition to the EMG background. Although a small number of points achieved high levels of response prediction, in the majority of cases r^2 was smaller than 0.3. A substantial element of the response variability cannot therefore be predicted by any combination of the analysed variables.

Discussion

In this paper, we have demonstrated that several measures of prestimulus activity correlated with response amplitude. The most effective predictor of response size was the background level of EMG. Many previous studies have shown that response amplitude grows with the strength of a background contraction (e.g. Hess *et al.* 1986). Nielsen (1996) found that response variability could be reduced by providing feedback of contraction strength, allowing the subject to maintain a more constant contraction than in the uncontrolled condition. However, previous work has not resolved whether the moment-by-moment changes in background level are capable of modulating the response.

The data of Fig. 3*C* and *D* shows clearly that instantaneous background does have an effect. However, the r^2 values were modest, indicating that only around 15% of the response variance was explained by the background EMG. This is perhaps understandable, since background EMG is a measure of *activity* immediately before the stimulus. Response amplitude will by contrast be affected by the level of *excitability* at the moment the stimulus is given. Whilst activity and excitability are connected, this is not always a simple linear relationship (Matthews, 1999). For example, a strong contraction just prior to the stimulus would produce a high prestimulus background EMG, but leave the motoneurons in a relatively refractory state as they traversed the early 'scoop' part of their after-hyperpolarization membrane potential trajectory (Schwindt & Crill, 1972).

The difference between activity and excitability may also underlie the modest performance of all other measures

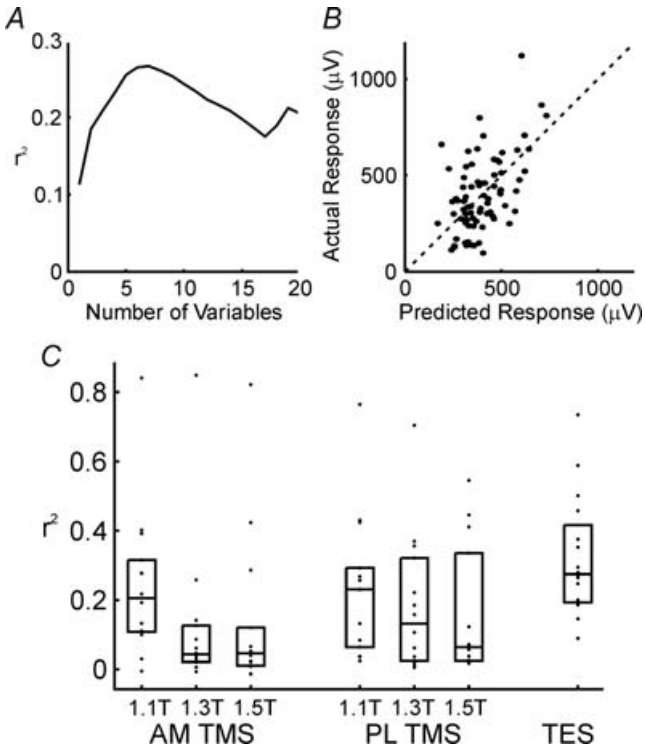

Figure 7. Optimal prediction of response amplitude
A, example dependence – for a single subject and muscle – of correlation coefficient with number of variables included in the regression model. *B*, example scatter plot of the actual *versus* predicted response using the optimal model. *A* and *B* are for PL TMS, 1.3× threshold, muscle 1DI. *C*, distribution of correlation coefficient for optimal model across all subjects and muscles recorded. Dots show single results; boxes indicate median and interquartile range. Responses are grouped by stimulus type and intensity relative to threshold.

which we tested to predict response variability. For example, the D wave cortical response to TMS appears maximal during the hold phase of a precision grip task similar to that used here, and is smaller during active movement of the manipulandum levers (Baker *et al.* 1995). However, pyramidal tract neurones normally show maximal firing rate during movement, and reduced firing in the hold period (Lemon *et al.* 1986; Baker *et al.* 2001; Davies *et al.* 2006). For the cortex, as well as motoneurons, excitability and activity can thus show a complex interrelationship, and prestimulus activity is likely to have only limited predictive power over response amplitude.

The highest correlation coefficients obtained in this study were between response amplitudes from the two different muscles studied (1DI and AbDM, Fig. 3*E*); these were substantially larger than the best amplitude prediction from prestimulus activity of the responding muscle (Fig. 7*C*). The result is surprising, since these muscles are not usually functional synergists. However, there is detectable motor unit synchrony between these muscles (Nadler *et al.* 2000), which may indicate some common input leading to shared excitability fluctuations. If even a part of the excitability fluctuations are shared between the populations controlling each muscle, this will result in the observed correlation. By contrast, past activity is only a limited predictor of current excitability. Oscillations in the EMG of one muscle were an even poorer predictor of response amplitude in the other than when using the responding muscle's own prestimulus EMG (Fig. 6 *versus* Fig. 5), consistent with the expected low correlation between the controlling network for these muscles acting on opposite sides of the hand.

Spontaneous cortical oscillations should modulate cortical excitability in a powerful way. Such oscillations are most likely to be generated and paced by networks of inhibitory interneurones (Wang & Buzsaki, 1996; Traub *et al.* 1999; Pauluis *et al.* 1999; Baker & Baker, 2003), and each oscillation cycle should see the balance of input to a pyramidal neurone switch from predominantly inhibitory to excitatory synapses. Additionally, in monkey motor cortex neurones synchronize to local oscillations in the beta-band around 20 Hz (Baker *et al.* 2003), which is close to the mean firing rate of pyramidal tract cells (Baker *et al.* 2001; Davies *et al.* 2006; Witham & Baker, 2007). A cell which has fired at the peak of one oscillation cycle will be deeply hyperpolarized during the oscillation trough, both by intrinsic conductances causing the after-hyperpolarization and by the inhibitory synaptic input produced by the local interneurone network. This should make it relatively inexcitable. As the oscillation cycle nears its next peak, network inhibition is released, and the after-hyperpolarization in M1 pyramidal tract cells shows a peak, raising the cell towards firing threshold. Neurones will be highly excitable at this time (Wetmore & Baker, 2004; Chen & Fetz, 2005; Witham & Baker, 2007). Synchronized oscillatory activity should therefore reflect oscillatory changes in excitability to a stimulus.

Against these theoretical considerations, it is surprising that EEG oscillations do not correlate with response size (Fig. 4). However, EMG oscillations do show significant correlation (Fig. 5). There are two possible explanations for this finding. Firstly, it could be that only oscillations within the motoneurone pool are of any consequence for response amplitude prediction. In this case, EMG oscillations predict the variable response of motoneurons to the descending corticospinal volley, fluctuations in which could be unrelated to the oscillations. It is of interest that a good correlation of response size with EMG oscillations was seen for responses to TES (Fig. 5*G*). TES probably produces mainly direct activation of corticospinal axons, at a site deep to the cortex. The evoked volley is thus relatively insensitive to changes in cortical excitability (Di Lazzaro *et al.* 1999). The correlation of response size with EMG oscillations in this case may therefore reflect predominantly spinal mechanisms.

Additionally, since it is known that EMG rhythms are synchronized with those in the cortex, EMG oscillations may act as a surrogate measure of the cortical oscillatory network's state. In this case, EMG could be more effective than EEG in predicting response amplitude, as EMG oscillations would relate only to the selected part of the cortical network which projects to the target muscle. By contrast, EEG shows the average activation over a wide, and functionally heterogeneous, area of cortex. In agreement with this, the correlation of response size with EMG oscillations was larger for TMS responses (where the descending corticospinal volley does depend on cortical excitability, Baker *et al.* 1995) than for TES responses of similar size (compare Fig. 5*A* and *D* with Fig. 5*G*). In related work, Gilbertson (2007) also found that a peripheral measure (finger acceleration) was a better measure of central beta oscillations than sensorimotor EEG.

More differences between the findings with AM TMS and PL TMS might have been expected, given the different apparent activation of corticospinal fibres by these stimuli (Werhahn *et al.* 1994; Di Lazzaro *et al.* 2001; present Fig. 2*C*. However, it is known that AM TMS above threshold will evoke both D and I waves (Di Lazzaro *et al.* 2001). Because TMS probably stimulates corticospinal neurones directly close to their initial segment, the extent of D as well as I wave activation can vary with cortical excitability (Baker *et al.* 1995; Di Lazzaro *et al.* 1998*b*). Our data imply that these two forms of TMS produce responses with similar variability (Fig. 3*B*), and similar relations to the level (Fig. 3*C* and *D*) and oscillatory state (Fig. 5) of background EMG.

Aside from the difference between excitability and activity, there are two further potential explanations for the small correlation of oscillation measures with response

amplitude. Firstly, because all of the analysis used here is linear, it is possible that there is a substantial, but non-linear, dependence between response and oscillatory state. The spiking threshold of neurones imposes a nonlinearity which can render interpretation of numerical results from linear analysis tools difficult (see, e.g. Baker *et al.* 2003). Further investigation of this possibility would require the development of novel analytical tools capable of examining nonlinear effects, and is beyond the scope of this paper.

Secondly, it may be that there is a further source of variability in network excitability which is not captured by prestimulus population oscillations. Such variability could not be explained by simple random fluctuations in the excitability of single cells, since at a population level these should average out and produce a relatively invariant response. For fluctuations to have an effect on the population activity, they must be correlated between cells (Shadlen & Newsome, 1998). Jackson *et al.* (2003) demonstrated that cortico-motoneuronal cells with similar muscle projection fields had greater synchronization, indicating correlated input and a tendency to coupled excitability modulation. Synchronous oscillations certainly form one source of this correlated input between neurones. However, Baker *et al.* (2001) showed that more than 40% of synchrony between identified pyramidal tract output neurones was outside the 'beta-band'. Likewise, Kilner *et al.* (2002) found a substantial component of non-beta-band synchrony between EMGs recorded from different muscles, indicating non-oscillatory coupling of motoneurone pools. At both cortical and motoneuronal levels, therefore, correlated fluctuations in excitability may occur which are not optimally analysed by focusing on individual narrow frequency components. It is interesting to note that several of the plots of r^2 *versus* frequency using prestimulus EMG (Fig. 5) show significant effects over a broad range of frequency, not just in the narrow beta-band.

As noted in the Introduction, TMS response variability may be an indicator of motor system noise which would influence a natural movement similarly to this evoked response. Our results indicate that a small, but functionally significant, portion of the system noise is related to spontaneous oscillations. We have previously argued that the oscillatory state entered by motor cortex during a steady contraction may be unsuited to the generation of dynamic movements, which is why this state is abolished shortly prior to movement onset (Kilner *et al.* 1999). Gilbertson *et al.* (2005) reported that movements initiated during periods of high beta-band oscillatory activity had reduced peak acceleration compared to movements triggered at random. If oscillations contribute extra noise to motor processing, the reduced efficiency of movement initiation during oscillatory epochs could be a consequence of this impaired motor function. The small fraction of total noise which is accounted for by oscillations in the present study parallels the small – but significant – effects on peak movement acceleration reported by Gilbertson *et al.* (2005).

In conclusion, we have shown that prestimulus oscillations in the motor system contribute to part of the observed variation in response to transcranial stimulation. However, a substantial part of this variation is not linearly correlated with any measure of prestimulus activity. Almost all studies to date have focused on first-order parameters of transcranial stimulation responses, such as mean amplitude, onset latency and threshold. However, our results imply that response variability is accessing a feature of the motor system which cannot be quantified in any other way. It is possible that response variability could therefore provide extra diagnostic value in clinical situations, or yield further insights into the consequences of experimental manipulations. We therefore suggest that future TMS studies should routinely report response variability as well as more conventional measures.

References

Amassian VE, Cracco RQ & Maccabee PJ (1989). Focal stimulation of human cerebral cortex with the magnetic coil: a comparison with electrical stimulation. *Electroencephalogr Clin Neurophysiol* **74**, 401–416.

Baker MR & Baker SN (2003). The effect of diazepam on motor cortical oscillations and corticomuscular coherence studied in man. *J Physiol* **546**, 931–942.

Baker SN, Olivier E & Lemon RN (1994). Recording an identified pyramidal volley evoked by transcranial magnetic stimulation in a conscious macaque monkey. *Exp Brain Res* **99**, 529–532.

Baker SN, Olivier E & Lemon RN (1995). Task-related modulation in the amplitude of the direct volley evoked by transcranial magnetic stimulation of the motor cortex and recorded from the medullary pyramid in the monkey. *J Physiol* **487.P**, 69*P*.

Baker SN, Olivier E & Lemon RN (1997). Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J Physiol* **501**, 225–241.

Baker SN, Pinches EM & Lemon SN (2003). Synchronisation in monkey motor cortex during a precision grip task. II. Effect of oscillatory activity on corticospinal output. *J Neurophysiol* **89**, 1941–1953.

Baker SN, Spinks R, Jackson A & Lemon RN (2001). Synchronization in monkey motor cortex during a precision grip task. I. Task-dependent modulation in single-unit synchrony. *J Neurophysiol* **85**, 869–885.

Barker AT, Freeston IL, Jalinous R & Jarratt JA (1987). Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery* **20**, 100–109.

Burke D, Hicks R, Stephen J, Woodforth I & Crawford M (1995). Trial-to-trial variability of corticospinal volleys in human subjects. *Electroencephalogr Clin Neurophysiol* **97**, 231–237.

Chen D & Fetz EE (2005). Characteristic membrane potential trajectories in primate sensorimotor cortex neurons recorded in vivo. *J Neurophysiol* **94**, 2713–2725.

Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AL & Rosenberg JR (1995). Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. *J Physiol* **489**, 917–924.

Davies RM, Gerstein GL & Baker SN (2006). Measurement of time-dependent changes in the irregularity of neural spiking. *J Neurophysiol* **96**, 906–918.

Day BL, Rothwell JC, Thompson PD, Dick JPR, Cowan A, Berardelli A & Marsden CD (1987). Motor cortex stimulation in intact man. II. Multiple descending volleys. *Brain* **110**, 1191–1209.

Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P & Rothwell JC (1999). Effects of voluntary contraction on descending volleys evoked by transcranial electrical stimulation over the motor cortex hand area in conscious humans. *Exp Brain Res* **124**, 525–528.

Di Lazzaro V, Oliviero A, Profice P, Saturno E, Pilato F, Insola A, Mazzone P, Tonali P & Rothwell JC (1998*a*). Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. *Electroencephalogr Clin Neurophysiol* **109**, 397–401.

Di Lazzaro V, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, Profice P, Tonali P & Rothwell JC (2001). The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. *Exp Brain Res* **138**, 268–273.

Di Lazzaro V, Restuccia D, Olivero A, Pofice P, Ferrara L, Insola A, Mazzone P, Tonali P & Rothwell JC (1998*b*). Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. *J Physiol* **508**, 625–633.

Edgley SA, Eyre JA, Lemon RN & Miller S (1990). Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *J Physiol* **425**, 301–320.

Edgley SA, Eyre JA, Lemon RN & Miller S (1997). Comparison of activation of corticospinal neurones and spinal motoneurones by magnetic and electrical stimulation in the monkey. *Brain* **129**, 839–853.

Ellaway PH, Davey NJ, Maskill DW, Rawlinson SR, Lewis HS & Anissimova NP (1998). Variability in the amplitude of skeletal muscle responses to magnetic stimulation of the motor cortex in man. *Electroencephalogr Clin Neurophysiol* **109**, 104–113.

Gilbertson T (2007). Oscillatory activity in the human motor system. PhD Thesis, University College London.

Gilbertson T, Lalo E, Doyle L, Di Lazzaro V, Cioni B & Brown P (2005). Existing motor state is favored at the expense of new movement during 13–35 Hz oscillatory synchrony in the human corticospinal system. *J Neurosci* **25**, 7771–7779.

Harris CM & Wolpert DM (1998). Signal-dependent noise determines motor planning. *Nature* **394**, 780–784.

Hess CW, Mills KR & Murray NMF (1986). Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neurosci Letts* **71**, 235–240.

Jackson A, Gee VJ, Baker SN & Lemon RN (2003). Synchrony between neurons with similar muscle fields in monkey motor cortex. *Neuron* **38**, 115–125.

Jackson A, Spinks RL, Freeman TC, Wolpert DM & Lemon RN (2002). Rhythm generation in monkey motor cortex explored using pyramidal tract stimulation. *J Physiol* **541**, 685–699.

Kiers L, Cros D, Chiappa KH & Fang J (1993). Variability of motor potentials evoked by transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* **89**, 415–423.

Kilner JM, Baker SN & Lemon RN (2002). A novel algorithm to remove electrical cross-talk between surface EMG recordings and its application to the measurement of short-term synchronisation in humans. *J Physiol* **538**, 919–930.

Kilner JM, Baker SN, Salenius S, Hari R & Lemon RN (2000). Human cortical muscle coherence is directly related to specific motor parameters. *J Neurosci* **20**, 8838–8845.

Kilner JM, Baker SN, Salenius S, Jousmäki V, Hari R & Lemon RN (1999). Task-dependent modulation of 20–30 Hz coherence between rectified EMGs from human hand and forearm muscles. *J Physiol* **516**, 559–570.

Lemon RN, Mantel GWH & Muir RB (1986). Corticospinal facilitation of hand muscles during voluntary movement in the conscious monkey. *J Physiol* **381**, 497–527.

Matthews PB (1999). The effect of firing on the excitability of a model motoneurone and its implications for cortical stimulation. *J Physiol* **518**, 867–882.

Nadler MA, Harrison LM & Stephens JA (2000). Acquisition of a new motor skill is accompanied by changes in cutaneomuscular reflex responses recorded from finger muscles in man. *Exp Brain Res* **134**, 246–254.

Nielsen JF (1996). Improvement of amplitude variability of motor evoked potentials in multiple sclerosis patients and in healthy subjects. *Electroencephalogr Clin Neurophysiol* **101**, 404–411.

Olivier E, Baker SN, Nakajima K, Brochier T & Lemon RN (2001). Investigation into non-monosynaptic corticospinal excitation of macaque upper limb single motor units. *J Neurophysiol* **86**, 1573–1586.

Pauluis Q, Baker SN & Olivier E (1999). Emergent oscillations in a realistic network: the role of inhibition and the effect of the spatiotemporal distribution of the input. *J Comput Neurosci* **6**, 27–48.

Pfurtscheller G, Stancak A & Neuper C (1996). Post-movement beta synchronization. A correlate of an idling motor area? *Electroencephalogr Clin Neurophysiol* **98**, 281–293.

Press WH, Flannery BP, Teukolsky SA & Vetterling WT (1989). *Numerical Recipes in Pascal. The Art of Scientific Computing*. Cambridge University Press, Cambridge.

Riddle CN & Baker SN (2005). Manipulation of peripheral neural feedback loops alters human corticomuscular coherence. *J Physiol* **566**, 625–639.

Riddle CN & Baker SN (2006). Digit displacement, not object compliance, underlies task dependent modulations in human corticomuscular coherence. *Neuroimage* **33**, 618–627.

Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T & Kanazawa I (1997). Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. *Exp Brain Res* **113**, 24–32.

Salenius S, Portin K, Kajola M, Salmelin R & Hari R (1997). Cortical control of human motoneuron firing during isometric contraction. *J Neurophysiol* **77**, 3401–3405.

Salmelin R & Hari R (1994). Spatiotemporal characteristics of sensorimotor neuromagnetic rythms related to thumb movement. *Neuroscience* **60**, 537–550.

Schwindt PC & Crill WH (1972). Membrane-potential trajectories between spikes underlying motoneuron firing rates. *J Neurophysiol* **35**, 311–325.

Shadlen MN & Newsome WT (1998). The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J Neurosci* **18**, 3870–3896.

Traub RD, Jeffreys JGR & Whittington MA (1999). *Fast Oscillations in Cortical Circuits*. MIT Press, Cambridge, MA, USA.

van der Kamp W, Zwinderman AH, Ferrari MD & van Dijk JG (1996). Cortical excitability and response variability of transcranial magnetic stimulation. *J Clin Neurophysiol* **13**, 164–171.

Wang XJ & Buzsaki G (1996). Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J Neurosci* **16**, 6402–6413.

Werhahn KJ, Fong JKY, Meyer BU, Priori A, Rothwell JC, Day BL & Thompson PD (1994). The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. *Electroencephalogr Clin Neurophysiol* **93**, 138–146.

Wetmore DZ & Baker SN (2004). Post-spike distance-to-threshold trajectories of neurones in monkey motor cortex. *J Physiol* **555**, 831–850.

Witham CL & Baker SN (2007). Network oscillations and intrinsic spiking rhythmicity do not covary in monkey sensorimotor areas. *J Physiol* **580**, 801–814.

Acknowledgements

This work was funded by The Wellcome Trust.