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Dorsolateral Prefrontal Cortex Sensitivity to rTMS

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Abstract— **This paper presents the preliminary results of a study to determine dorsolateral prefrontal cortex sensitivity to rTMS stimulation presented at clinically accepted amplitudes, frequencies and locations. A specially developed EEG system with 10-20 electrode locations was used to record the short latency magnetically evoked potentials. Sixteen normal subjects were stimulated using 10 Hz for the left hemisphere and 1 Hz for the right. The evoked potentials recorded for left sided stimulation were significantly larger than for the right sided stimulation. Further, the stimulation energies, though within the range used clinically for the treatment of depression were insufficient to excite evoked potentials in several subjects.**

***Index Terms*—evoked potentials, rTMS, stimulus cortical sensitivity, transcranial magnetic stimulation,**

I. Introduction

Transcranial magnetic stimulation (TMS) has been used during the past two decades to elicit responses in the human brain. There has been considerable interest in the immediate effects of repetitive stimulation (rTMS) on post stimulus EEG and event related potentials (e.g. P300). A summary of a number of such studies can be found in [1]. Recently rTMS has been used to treat neuro-psychiatric disorders such as depression by stimulating the left or right dorsolateral prefrontal cortex (DLPFC) with high (>1Hz) and low (1Hz or less) rates respectively [2],[3]. To determine the patient specific cortical sensitivity and hence stimulation energy, the coil (e.g. "figure of eight") is placed on the scalp over the motor cortex and the underlying cortical tissue excited with single 300 – 400 μs monophasic or biphasic pulses to find the lowest energy capable of inducing a compound action potential (CMAP) from a hand muscle, usually the abductor pollicis brevis. This motor cortex activation threshold energy is termed the motor threshold (MT). Since there are no immediate recordable results such as the CMAP for the DLPFC, 80 to 120% of the MT is chosen as the stimulation energy for this area. For the treatment of depression the stimulus site is chosen by convention (5 cm anterior on a sagittal plane from the location of MT) rather than individual patient responses.

There is very good evidence that the cortical responses are very dependent on the stimulus site with some sites even having no or very limited responses [4]. It has also been found that even the motor threshold varies considerably intra-subject from session to session [5] and prefrontal and motor cortices have different reactivity to TMS [6]. The optimum stimulation current direction can also vary by at least 45^{o} among subjects [7]. Finally the distance between the cortex and coil (scalp surface) has been found to be very important with an increase of ~2.8% in the MT for each additional millimeter [8].

Given this inter-subject variability, a common treatment protocol could be suboptimal or ineffective for many patients who would otherwise benefit from rTMS. To determine successful DLPFC stimulation, immediate brain evoked potentials (EP), or event related potentials (ERP) could potentially have value in "personalizing" treatment site and stimulus energy. However, the very large magnetic field (1 to 2 Tesla) of each rTMS pulse couples into the patient electrodes, cables and input amplifiers resulting in a very large voltage artifact that can saturate the input amplifiers for several 100 ms. Most modern EEG systems are protected from large voltage transients both by input protection diodes and low pass filtering of the EEG signal, typically below 70 Hz. Although this bandwidth is adequate for long latency ERPs [1], it cannot record the much higher frequency content EPs.

This paper presents some of the preliminary results of a study which used EPs to determine the sensitivity of the DLPFC to rTMS, and hence successful stimulation, with energies, frequencies and locations currently used for treatment of depression. The short latency EPs were recorded using a custom system [9] with blocking amplifiers similar to those described by Virtanen et al [10].

II. Materials and Methods

Sixteen normal volunteers, 11 male and 5 female aged 19 to 59 years (mean age 33.2 ± 14.6) gave written consent and participated in the study. The study was approved by the Research Ethics Board of St. Joseph's Healthcare, Hamilton, ON, Canada. Each subject was instrumented with 16 recording gold cup electrodes located in the 10-20 configuration (no central electrodes) with linked ear reference. These electrodes were fully notched ("C" electrodes) to avoid excessive heating by eddy currents induced by the high intensity repetitive magnetic stimuli [11]. MRI images were obtained for each subject and used with a Brainsight stereotactic system (Rogue Research Inc, Montreal, Canada) to locate the cortical stimulation sites and electrode locations. This system also references the stimulating coil position to the selected cortical site.

The thresholds (MT) for the left and right motor cortex were obtained as described above and used to establish the

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stimulation levels. A Magstim Super Rapid (The Magstim Co. Ltd., Carmarthenshire, Wales, UK) stimulator and Magstim figure-of-eight air-cooled coil P/N 1640 (0.93Tesla peak magnetic field) were used to deliver the biphasic stimuli. The primary objective of the study was to determine the relative cortical sensitivities of the three DLPFC areas suggested for treatment of depression, Brodmann areas 09, 10 and 46. These areas were identified on a reconstructed 3 dimensional image of the brain using Brainsite software. Stimulus site was chosen as the middle part of each Brodmann area. As well the effects of stimulus number were investigated for the left Broadmann area 46 (B46), by sequences of 40, 60 and 80 stimuli delivered at 10 Hz at 110% of MT using either true or sham rTMS. The effects of stimulus energy were also investigated for the right B46 area with sequences of 60 pulses delivered at 1 Hz with sham, 90, 100 and 110% of MT. Sham rTMS stimulation used a passive coil held at B46 and an active coil approximately 1 m away set at 60% of maximum energy to give the acoustic clicks.

The responses were recorded by the custom built EEG system, bandwidth .16 Hz to 2 kHz, at 5 kHz sampling rate and the responses ensemble averaged in real time. The system locked out the amplifiers, using sample and hold circuitry, for 3.0 ms during which the magnetic pulse was given (at 1 ms). All stimulation sequences were separated by 1 min of passive EEG recorded at 200 Hz and the subject wore ear plugs throughout.

III. Results

A Data Processing

In this study we are interested in the short latency EPs which would probably represent cortical action potentials rather than the synaptic field potentials recorded for longer latency ERPs and spontaneous EEG. Further, at 10 Hz stimulus rate we could only maximally record 100 ms post stimulus. However, due to the limitations of the Labview based data acquisition system, only the first 70 ms of data could be recorded and averaged for left sided stimulation at 10 Hz. The preliminary EP feature chosen was average channel signal power in selected time windows similar to [4]. The averaged responses were therefore further digitally bandpass filtered using a zero-phase shift Chebyshev filter from 150 Hz to 2 kHz to ensure a 0 baseline and remove some residual stimulus artifact and the very large (mV) muscle evoked M-waves recorded from primarily the temporalis muscle.

The resulting signals are reliably artifact free from 4.4 to 100 ms if no M-wave was elicited, and from 10 – 13 ms on if large M-waves were originally present. Visual inspection of the results for all 16 subjects showed no EPs past 35 ms. Total channel average power was therefore calculated for the 4.4 to 35 ms window in sham stimulations, and the 10 or 13 to 35 ms window in true stimulations to quantify the short latency EPs. Total average power was also calculated for the 35 ms to end of the collection window to quantify the resulting background activity.

B Auditory Evoked Responses

Despite subject earplugs, the coil clicks elicited auditory evoked potentials in the bandwidth of interest for both sham and true stimulation. Figure 1 shows a typical response for left sham stimulation. This pattern most commonly occurred for 10 Hz sham with the dominant spike response occurring at 18-19 ms post stimulus. Although the subject for Fig. 1 had nearly identical sham responses for right sided stimulation at 1 Hz, fewer subjects had auditory responses for right sided stimulation. There was however, considerable variation in left sham auditory responses, both in shape and latency. A more detailed analysis of the auditory responses showed that they tended to be equal in amplitude when grouped in a particular area such as in Fig. 1, where the bilateral frontal lobe channels have the same amplitude. Further these responses are highly correlated, suggesting a common source with volume conduction to the scalp surface.

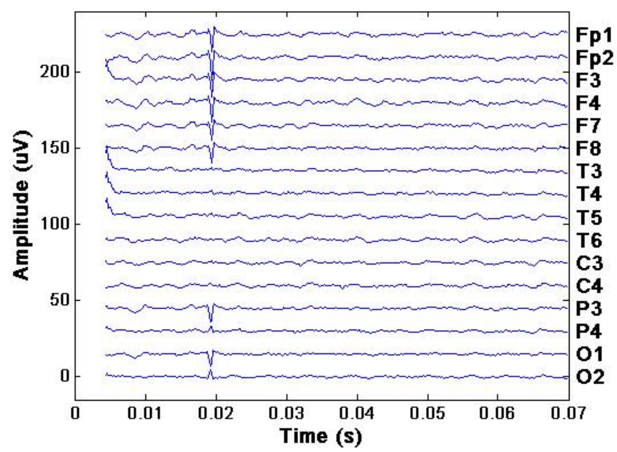

Figure 1: Response of a 53 year old male to 80 pulses of 10 Hz sham stimulation with coil at left B46

C True Responses

Most left and right sided true responses still contained some residual M-wave artifact in the first 10 ms of signal. Figure 2 shows the response for another subject to left sided stimulation of 80 pulses at 110% MT, with very little remaining artifact. The coil centre is located over Broadmann area 46 which is close to the F3 electrode position. It can be seen that all EPs occur in the left hemisphere and there is no short latency conduction to the contralateral side. The channels containing significant responses, Fp1, F3, F7, T3, T5, C3 and P3 are uncorrelated, indicating these signals are not the result of volume conduction from common sources. Although differentially amplitude modulated acoustic responses can be seen at 19 ms, the left sham responses for this subject had no auditory EPs. The true stimulation auditory responses were probably due to the click being louder and exceeding the threshold with the active coil on the skull and the stimulus level higher at 63% than the sham level. For the majority of subjects the auditory responses were present during sham, but these auditory EPs were entirely abolished, delayed or differentially amplitude modulated by the true stimulation.

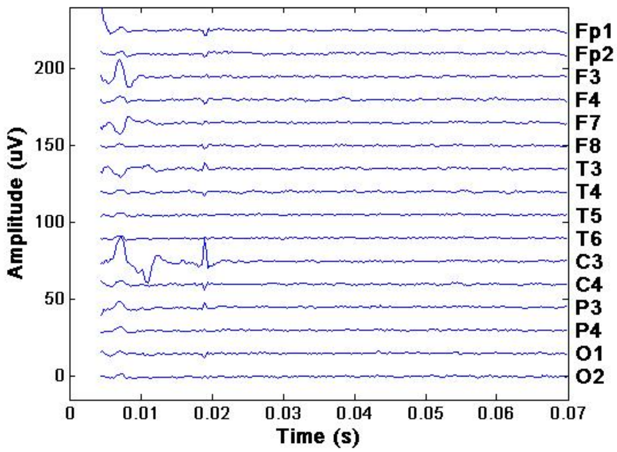

Figure 2: Response of a 19 year old female to 80 pulses at 10 Hz to left B46.

Figure 3 presents the EPs for 60 pulses of right sided stimulation at 110% MT for another subject. There were small auditory EPs during sham in the frontal lobes similar to Fig 1 at 19 ms, and these have been slightly delayed and amplitude modulated. Again there was little evidence of trans-callosal conduction with EPs limited largely to the side of stimulation.

D Study Results

Cortical excitability was determined by dividing the average power in each processing window by the sham evoked average power in the corresponding window. This would also take into account the greater attenuation effect of ensemble averaging on random background EEG with increasing EP responses. The sham patterns could not be subtracted from the true patterns because even if auditory EPs were present in the true response, they were modulated. For the following figures a value greater than 1 shows cortical excitation, while values near 1 or less show little excitation or even cortical inhibition. Our study results showed that there was considerable variation in the individual responses to 110% MT 40, 60 and 80 stimuli delivered at 10 Hz to left B46, with no significant change in cortical responses with increasing number of stimuli. Figure 4 shows the individual subject responses for different amplitudes as a percent of MT of 1 Hz pulses to right B46. Statistical analysis with one-way ANOVA showed no consistent significant increase in EP amplitudes with increasing stimulus amplitudes. However, a paired t-test for 90% and 110% showed a significant ($p < .01$) increase in average amplitudes of 1.95 to 2.82.

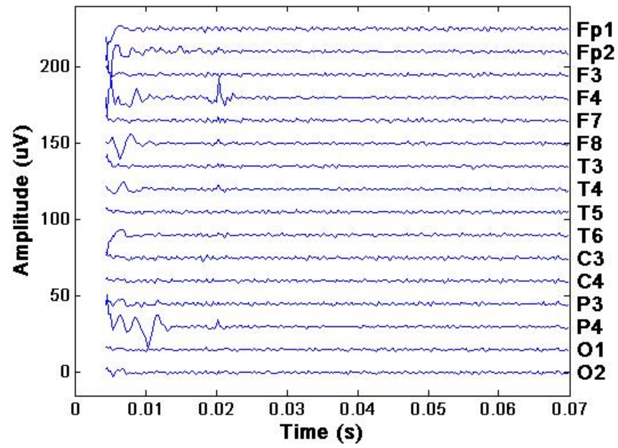

Figure 3: Response of a 21 year old female to 60 pulses at 1 Hz to right B46.

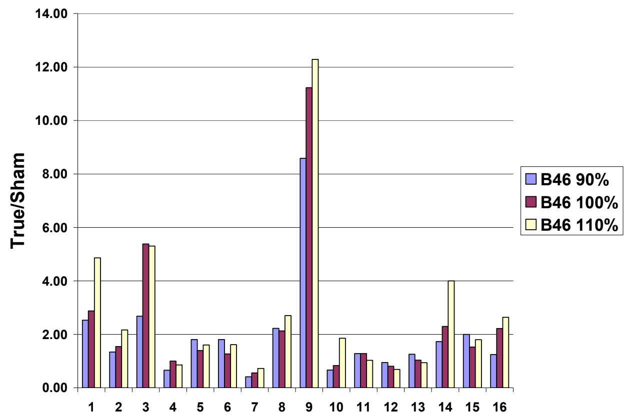

Figure 4: Individual subject response ratios for EP window for different amplitudes of right B46 stimulation pulses

The results of stimulating B46 at 110% MT with 60 pulses at 10 Hz for the left side and 1 Hz for the right showed significant differences in cortical sensitivity and background responses between the two hemispheres. The average ratios for the EP window (10 – 35 ms) for the left and right sides were 3.76 and 2.82 respectively. When two outlier subjects were removed because of very high ratios, 16.2 on the left for one and 12.3 on the right for another, the left median was found to be significantly larger than the right ($p < .05$) using a Wilcoxon matched pairs test. Figure 5 shows a comparison between left and right background window (35 ms to 70 ms left, 100 ms right) response ratios for this stimulation. The results for subject 2 are not included because the high left ratio at 22.6 vs 1.11 right would compress the display. The average ratio for the left side was larger than for the right, 3.34 vs 1.50 and the left median was significantly higher than the right ($p < .05$) again using a Wilcoxon one-tailed matched pairs test. This non parametric test had to be used since the ratio distributions were not Gaussian.

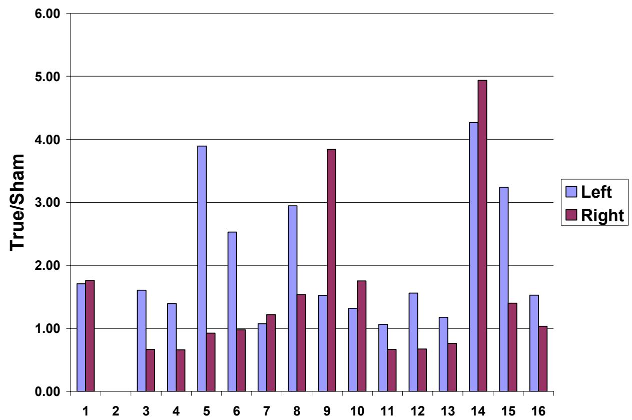

Figure 5: Left and right background window response ratios for 60 pulses at 110% MT, 10 Hz left and 1 Hz right to B46

IV. DISCUSSION AND CONCLUSIONS

We selected the 150 Hz – 2kHz to measure rTMS EPs to eliminate lower frequency M-waves and also auditory ERPs resulting from the coil clicks. Such lower frequency ERPs with the coil touching the scalp have been reported previously in the literature [12] with these concentrated in the temporal and frontal-central brain areas. However, in [12] the signals were collected in the .1-500Hz bandwidth with the first 20 ms ignored, and the averaged responses further filtered using a passband of 1-30 Hz. The bilateral EPs recorded from sham stimulation, with no active coil touching the scalp, but with amplitude levels similar to 110% MT could result from deeper neural structures in the frontal midbrain area. These sharp EPs occurred very frequently for left sham and true 10 Hz rates and less often for right sham and true 1 Hz stimulation. Their shape and duration were not altered by extending the bandwidth to 12 Hz to 2 kHz They remain a problem when quantifying and interpreting rTMS evoked EPs

There are significant differences between left and right stimulation results at 110% MT. However, we cannot conclude that the left B46 cortex is more sensitive than the right in the EP bandwidth used. In all likelihood, since high frequency rTMS is reported to have an excitatory effect on cortical activity, the differences could be attributed to the 10 Hz pulse rate as opposed to 1 Hz. However, a study using 10 Hz for the right and 1 Hz for the left would help answer this question. The overall results of the study for both left and right sided stimulation showed considerable inter-subject variability in cortical responses, e.g. Figs. 4 and 5, despite using an MRI guided system to precisely identify B46, and a marked swim cap to ensure consistent placement. This further suggests that a personalized approach may be required during rTMS therapy. Quantitative EP methods of the type described here may prove useful in this regard.

Despite using the clinically accepted 110% MT stimulus amplitude, several subjects showed no appreciable EPs for left sided stimulation, and 5 subjects in Fig 4 had response ratios less than or near 1. It can be concluded that for a number of subjects the accepted 110% MT amplitude is insufficient for B46 stimulation, especially for right side stimulation at 1 Hz. Figure 5 shows that 10 Hz left rTMS increases background averaged activity, in agreement with the current view. However we found that right sided 1 Hz stimulation decreases such activity (ratio <1) as predicted but only in some subjects, with unexpected increases in cortical activity in others being noted. Finally Figs. 2 and 3 show that short latency EPs can be measured during the first 20 ms post stimulation, a window ignored in most other rTMS studies. There also seems to be no short latency trans-callosal conduction resulting from DLPFC stimulation at these frequencies.

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