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Application of Wavelet Based Denoising Techniques to rTMS Evoked Potentials

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Abstract— **This paper presents a new method of removing noise from the EEG response signal recorded during repetitive transcranial magnetic stimulation (rTMS). This noise is principally composed of the residual stimulus artifact and mV amplitude compound muscle action potentials recorded from the scalp muscles and precludes analysis of the cortical evoked potentials, especially during the first 15ms post stimulus. The method uses the wavelet transform with a fourth order Daubechies mother wavelet and a novel coefficient reduction algorithm based on cortical amplitude thresholds. The approach has been tested and two methods of coefficient reduction compared using data recorded during a study of cortical sensitivity to rTMS at different scalp locations.**

Index Terms **- evoked potentials, rTMS, muscle artifact, noise reduction**

I. INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is currently being used as a treatment for major depression. It is believed that by stimulating the dorsolateral prefrontal cortex (DLPFC), one can affect deeper regions of the brain responsible for regulating an individual's mood [1]. The current clinical technique obtains an estimate of the stimulus amplitude as a fraction (80-120%) of the motor cortex threshold of the abductor pollicis brevis upper motor neurons, and an estimate of the stimulus position as 5cm anterior to this motor stimulus site measured in a sagittal plane. Neither the stimulus amplitude nor site may be optimal for that patient's DLPFC stimulation, and the low success rate (approximately 30-35%) may in part reflect this. It has been found that cortical sensitivity varies in different regions of the brain [2]. The overall objective of our research is to develop a technique that would use brain evoked potentials to determine the optimum amplitude, stimulus site and frequency to increase the efficacy of rTMS. This requires the ability to record and analyze short to medium latency evoked potentials (within the first 30 ms post stimulus) to determine cortical sensitivity rather than longer latency event related potentials recorded by others e.g. [2] because the latter are determined by both cortical sensitivity and primarily cortical connections. As well the cortical motor thresholds are determined by both cortical sensitivity of the motor cortex not DLPFC and the subliminal excitability of the lower motor neuron pool.

EPs are generated by the synchronous activation of a group of neurons within the cortex — a minimum requirement for stimulating deeper regions within the brain. However, the very large magnetic field during rTMS at clinical amplitudes saturates the EEG input amplifiers unless these are decoupled during the stimulation using techniques such as sample and hold circuitry [3], [4]. Unfortunately the cortical EPs, occurring especially during the first 20ms, are difficult to analyze because they are obscured by the residual magnetic artifact signal and the very large (mV) synchronous compound muscle action potential (CMAP) recorded from the stimulated temporalis and occipitofrontalis scalp muscles. Most researchers, e.g. [3], ignore the first 20-30ms and concentrate on longer latency event related potentials because of this noise. Even previous work that applied digital filtering with a bandwidth of 150Hz-2kHz could only reliably analyze EPs later than 13ms [4]. This paper focuses on the development of a novel method for removing these sources of noise, allowing us to analyze EPs occurring after the first 4ms post stimulus.

II. WAVELETS

A. Wavelet Analysis

EP recordings are typically composed of transient events, which complicates Fourier analysis. Being highly nonstationary signals, EP recordings are ideally suited for wavelet analysis, [5], which has the ability to localize transient events in time and frequency [6], [7]. It is akin to Fourier analysis, however instead of representing a signal by a series of scaled and shifted sine and cosine functions, wavelet analysis uses a series of wavelets which are transient functions that are finite in time and band-limited [7]. They are derived from a *mother wavelet*, ψ, by shifts and dilations, as in (1),

$$\psi_{a,b}(t) = \frac{1}{\sqrt{a}}\psi\left(\frac{t-b}{a}\right) \tag{1}$$

where a is the scaling parameter and b is the shifting parameter.

As shown in (2), wavelet decomposition correlates a signal with a series of wavelets [6]. By applying the wavelet transform (WT) to a signal, it produces a series of detail and approximation coefficients (Dj and Aj respectively, where $j = 1 \ldots J$, represents the resolution level) representing different time and frequency resolutions. The WT can be applied recursively to the approximation coefficients to further decompose the signal into additional resolution levels.

$$W_{\psi}\left\{x\right\}(a,b) = \int_{-\infty}^{\infty} x(t)\psi^{*}_{a,b}(t)\,dt \tag{2}$$

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The wavelet coefficients produced by the continuous wavelet transform (CWT) represent redundant information. The analysis is simplified with the use of the discrete wavelet transform (DWT), which uses an orthonormal basis to represent the signal. An important property of the wavelet transform is that the signal can be reconstructed from its inverse without loss of information.

B. Wavelet Denoising

Very effective wavelet denoising methods exist which apply the wavelet transform, reduce the wavelet coefficients based on a certain threshold using shrinkage functions and then reconstruct the signal with the modified coefficients. Techniques for estimating thresholds (noise estimation) have been well researched. Traditional approaches include VisuShrink, SureShrink and RiskShrink [8], [9]. These methods are very effective when the signal to noise ratio is high. Unfortunately, the signal to noise ratios in our data sets are on the order of -44dB.

Another aspect is the selection of the shrinkage function, $\delta(c)$, which dictates how and which coefficients are modified. Typically only coefficients that exceed the threshold are taken under consideration to be modified, whereas the others are set to 0. Soft thresholding, described by (3), subtracts the magnitude of the threshold from any coefficients that exceed it and sets the others to 0. Hard thresholding, described by (4), zeroes coefficients if they do not exceed the threshold. These shrinkage functions are the two most commonly used and are applied in this paper.

$$\delta_j^{\text{soft}}(c_j) = \begin{cases} sgn(c_j)\left(|c_j| - \lambda_j\right), & |c_j| > \lambda_j \\ 0, & |c_j| \le \lambda_j \end{cases} \tag{3}$$

$$\delta_j^{\text{hard}}(c_j) = \begin{cases} c_j, & |c_j| > \lambda_j \\ 0, & |c_j| \le \lambda_j \end{cases} \tag{4}$$

where λ_j is the threshold at level j and c_j represents the wavelet coefficients at level j.

III. METHODS

A. Data Acquisition

Sixteen normal volunteers, 11 male and 5 female aged 19 to 59 years (mean age 33.2 ± 14.6), with no known neuro-psychological symptoms, gave written consent and participated in the study. The study was approved by the REB of St. Josephs Healthcare, Hamilton, Ontario, Canada. Evoked potentials were recorded at a sampling rate of 5 kHz using a modified EEG system compatible with rTMS [4]. The bandwidth of the system was 0.16Hz to 2kHz. Each subject was instrumented with 16 gold cup notched electrodes (no central electrodes) in the 10-20 configuration with a linked ear reference. rTMS was carried out with a Magstim Super Rapid stimulator (The Magstim Co. Ltd., Carmarthenshire, Wales, UK) and a Magstim figure-of-eight air cooled coil P/N 1640. The rTMS protocol involved right and left sided stimulation at 1Hz and 10Hz, respectively, with a stimulation intensity of 110% of the motor threshold. The resulting responses were epochs of 100ms and 70ms for right and left sided stimulation, respectively. Stimulation was applied at three separate regions of the DLPFC: Brodmann areas 9 (B09), 10 (B10) and 46 (B46). The recorded responses at each Brodmann area were synchronously averaged (60 and 80 responses for left and right stimulation respectively) to remove background instrumentation and EEG noise. As a control, sham stimulation was performed with a passive coil at B46 and an active coil about 1m away with an intensity of 60% of maximum energy. As a result of the sample and hold circuitry and high pass filtering, the averaged EEG recordings exhibited a consistent exponential rise of the baseline throughout the entire response. This exponential component was removed prior to any data processing by fitting a second order function .

B. Proposed Method

The WT is applied to the signal and decomposed into $J = 5$ levels making use of the Daubechies wavelet with 4 vanishing points (db4).

One can apply the techniques of wavelet denoising to the recorded signals by modifying the noise estimation strategy. The averaged EEG is typically composed of a CMAP, cortical evoked responses as well as some residual background EEG activity, with the CMAP being the main problem in studying the cortical response immediately after the stimulus. The difficulty is exacerbated by the broad overlapping bandwidths of all of these components as well as no *a priori* knowledge about the underlying cortical evoked responses during the first 15ms of the response. Since the CMAP is a few orders of magnitude larger than the cortical response, from the perspective of the traditional method of wavelet denoising, our interest is in the "noise" of the signal. Thus after denoising the CMAP, the residual can be recovered, which will contain the signal of interest.

The unconventional characteristics of the noise require a different noise estimation strategy in order to determine the thresholds. The thresholds were established from the maximum absolute values of the wavelet coefficients of sham stimulation responses. In our results, the sham stimulations usually elicited some short duration auditory EPs (from coil clicks) around 20ms. Since short latency EPs probably represent cortical action potentials rather than synaptic field potentials they would most likely be shorter in duration. Therefore, it was assumed that the auditory EPs would be a suitable estimate of any cortical responses occurring earlier in the evoked response. As well several subjects exhibited cortical EPs during true stimulation at B09 without CMAPs which had similar amplitudes and durations.

The sham responses were first inspected visually to ensure they were suitable estimates. From this set of data the detail wavelet coefficients with the maximum absolute values were recorded for the levels D1-D4 of wavelet decomposition. In addition, the thresholds for D5 and A5 were set to 0, so that the residual would not contain the lower frequency components as this frequency band predominantly contains

CMAP components. This set of values, shown in Table I, was then used as the set of thresholds.

TABLE I

THRESHOLDS USED IN THE ANALYSIS

Level	D1	D2	D3	D4	D5	A5
Threshold	0.010271	0.013558	0.01268	0.037645	0	0

C. Summary of proposed method

1) Determine thresholds from sham recordings
2) Apply the WT to decompose the signal (5 levels, Daubechies wavelet with 4 vanishing points)
3) Apply the thresholds using soft or hard thresholding
4) Apply the inverse WT to reconstruct the signal using the modified wavelet coefficients
5) Calculate the residual by subtracting the denoised signal from the original signal

IV. RESULTS

The proposed method was applied to the all the responses for all 16 subjects. Due to space limitations , only a sample response of a patient to 80 pulses with a frequency of 10Hz at the left B10 area is shown in Figure 1. The first 5 ms (stimulus presented at 1ms) is not shown to account for the amplifier lockout. The figure shows the extent to which the CMAP complicates the analysis of EPs in the DLPFC. This response contains a typical example of the CMAP encountered in the recorded signals lasting approximately 30ms. Superimposed cortical responses, however, can be observed in some of the channels in the 23ms area. The CMAP responses from the temporalis muscle are even larger for the B46 results, an area commonly used for treatment of major depressive disorder. Lioumis et al. [10] have avoided analyzing such cortical EPs, elicited at clinical stimulation amplitudes, by rejecting all responses containing signals greater than $50\mu V$ and severely lowpass filtering at 45Hz.

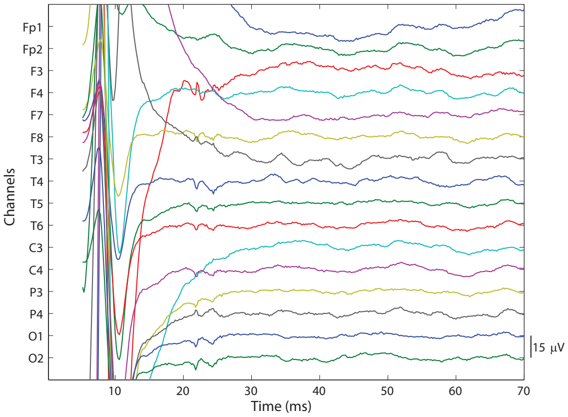

Fig. 1. Response to 80 pulses at 10Hz to left B10 for a 59 year old male subject

The results of the proposed method were compared with the digital filtering performed in [4] which was applied to the entire epoch. Figure 2 shows the response after digital filtering with a zero phase 60^{th} order Chebyshev filter, bandpass 150Hz to 2kHz. Although it was effective in removing baseline fluctuations and limiting the CMAP to the first 15ms, the magnitude of the CMAP was still significantly larger than the rest of the signal making analysis of this region difficult. This figure also shows the channel average which has been subtracted from each channel response to address a non-zero linked ear reference.

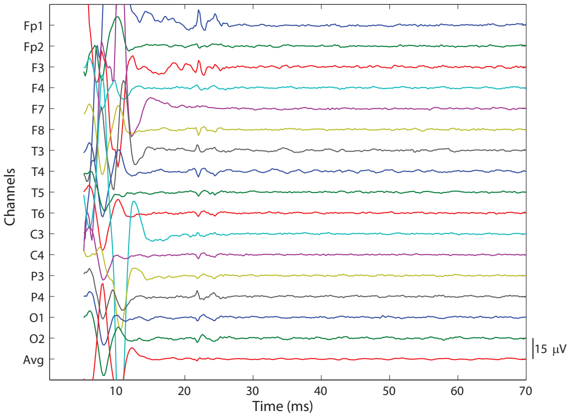

Fig. 2. Response after digital filtering

Figure 3 shows the residual from wavelet denoising of the response using the soft shrinkage function. In comparison to Figure 2, the CMAP is greatly attenuated within the first 15ms. Upon closer inspection, there are some differences in the signal between 15 and 20ms, however the signal beyond 20ms remains unchanged. The residual after applying the hard shrinkage function demonstrated even greater attenuation of certain components of the response, as seen in Figure 4.

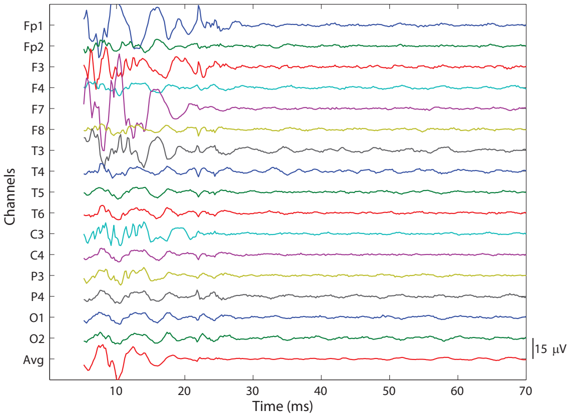

Fig. 3. Residual of wavelet denoising by soft thresholding

V. DISCUSSION

By visual inspection, the residuals of the wavelet denoising results show considerable attenuation of the muscle artifact within the first 15ms of the response in comparison to digital filtering. This result is consistent with the assumption that the large magnitude of the CMAP would produce correspondingly large wavelet coefficients. By thresholding

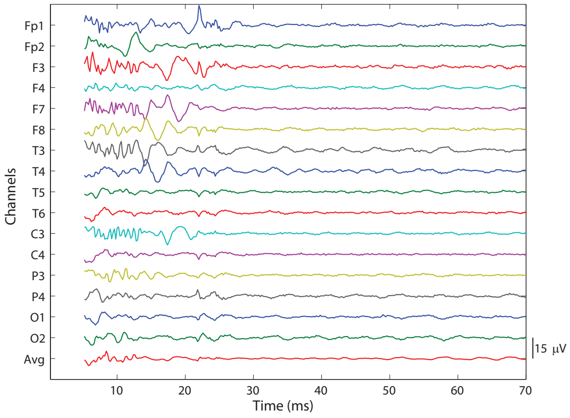

Fig. 4. Residual of wavelet denoising by hard thresholding

these large coefficients, they are scaled or removed from the residual signal. Short duration EPs even in the $15\mu V$ range are readily apparent in the 5 to 30ms time window in contrast to other published results for DLPFC stimulation [10]. Furthermore, in the region from 15ms to 20ms, there is considerably more activity in the residual responses in comparison to digital filtering. This can be attributed to the fact that wavelet analysis retains a broader bandwidth even though we have entirely removed the lowest frequency band of the decomposition. It is important to note that these components do not imply the addition of information, they are attenuated versions of the original wavelet coefficients.

There is a significant difference between the soft and hard thresholding method results. Although both methods successfully attenuate the CMAP, the residual after soft thresholding still retains a component of the large muscle responses in the original signal and simply limits the amplitude of the very large coefficients to be within the threshold. The residual after hard thresholding, on the other hand, completely eliminates any components that exceed the threshold. Although it is true that the large coefficients represent the CMAP, there may be some contribution from any underlying cortical activity. Without any prior information, the magnitude of that contribution is difficult to estimate, unless further research is carried out. However, the large oscillations in Fig. 3, especially in the Fp1 and F7 channels do not resemble EPs because of their amplitude and long durations, and in our estimation are residual CMAP components. Thus, the two thresholding methods supply us with two perspectives. The residual produced by soft thresholding can be considered as simply limiting the large coefficients to the range of the signal of interest, i.e. the estimated cortical response. This is analogous to assuming a worst case contribution from the cortical response. On the other hand, the residual produced by hard thresholding only leaves the coefficients that have a greater probability of being a product of cortical activity, thus eliminating some ambiguity. It represents the view that since we have no information as to the size of the contribution from the cortex we should eliminate the coefficient entirely to avoid including reduced CMAP components in our EPs.

An interesting aspect in Figure 4 is the greater amount of high frequency activity in left sided channels closer to the stimulation location (Fp1, F3 and F7) followed by longer duration EPs. Although we are presenting preliminary results, these may indeed be superimposed cortical action potentials as the initial stimulation spreads to neighboring neurons through short cortical branches. Furthermore, the high frequency activity in C3 is curious because of its distance from the site of stimulation. This result was seen for many subjects and may be due to long fiber tracts connecting the stimulus site to the central cortex.

VI. CONCLUSIONS

Wavelet analysis has been shown to be effective in removing all or most of the noise due to muscle activation from DLPFC rTMS responses, allowing further quantification of these EPs. Both denoising methods were more effective than digital filtering, for the first 15ms of response. The better method seems to be hard thresholding because it limits the possibility of misidentifying CMAP components as cortical EPs.

REFERENCES

[1] A. Pascual-Leone, B. Rubio, F. Pallardó, and M. D. Catalá, "Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression," *The Lancet*, vol. 348, no. 9022, pp. 233–237, Jul. 1996.

[2] S. Kähkönen, J. Wilenius, S. Komssi, and R. J. Ilmoniemi, "Distinct differences in cortical reactivity of motor and prefrontal cortices to magnetic stimulation." *Clin neurophysiol*, vol. 115, no. 3, pp. 583–8, Mar. 2004.

[3] V. Nikouline, J. Ruohonen, and R. J. Ilmoniemi, "The role of the coil click in TMS assessed with simultaneous EEG." *Clin Neurophysiology*, vol. 110, no. 8, pp. 1325–8, Aug. 1999.

[4] H. de Bruin, G. Hasey, and J. Hemily, "Dorsolateral prefrontal cortex sensitivity to rTMS." *Proc. of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, vol. 2011, pp. 1997–2000, Aug. 2011.

[5] V. J. Samar, a. Bopardikar, R. Rao, and K. Swartz, "Wavelet analysis of neuroelectric waveforms: a conceptual tutorial." *Brain and language*, vol. 66, no. 1, pp. 7–60, Jan. 1999.

[6] I. Daubechies, *Ten lectures on wavelets*. SIAM: Society for Industrial and Applied Mathematics, 1992.

[7] S. Mallat, *A wavelet tour of signal processing*. Academic Press, 1999.

[8] D. Donoho and J. Johnstone, "Ideal spatial adaptation by wavelet shrinkage," *Biometrika*, vol. 81, no. 3, pp. 425–455, 1994.

[9] D. Donoho and I. Johnstone, "Adapting to unknown smoothness via wavelet shrinkage," *J. Amer. Statist. Assoc.*, vol. 90, no. 432, pp. 1200–1224, 1995.

[10] P. Lioumis, D. Kicić, P. Savolainen, J. P. Mäkelä, and S. Kähkönen, "Reproducibility of TMS-Evoked EEG responses." *Human brain mapping*, vol. 30, no. 4, pp. 1387–96, Apr. 2009.