

A Simple Wavelet-Based Test for Evoked Responses

Authors

Norton, Jonathan D.^a; Eswaran, Hari^b; Lowery, Curtis L.^b; Wilson, James D.^c; Murphy, Pamela^b; Preissl, Hubert^b

Affiliations

a. Div. of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

b. Dept. of Obstetrics and Gynecology, UAMS, Little Rock, AR, USA.

c. Graduate Inst. of Technology, University of Arkansas at Little Rock, Little Rock, AR, USA.

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Abstract

Statistically valid detection of evoked responses from magnetoencephalographic (MEG) sensors is complicated by temporal autocorrelation. By decorrelating time series and transforming them toward normality, the discrete wavelet transform (DWT) allows the analyst to test for an association between stimulus and sensor time series with appropriate degrees of freedom.

Eswaran et al (2002a) used a 151-channel fetal MEG system to obtain serial recordings from ten pregnant subjects. There were three to eight recordings per subject. In each recording session, the fetus was stimulated by 500Hz and 1 KHz tones with a relative frequency of 80% to 20%, respectively.

In this new analysis of the same data, the fetal MEG signals were compared to two different stimulus waveforms: the Frequent tone and the Novel stimulus, defined as a change in pitch. WaveDetect was developed to determine whether there was a significant association between the stimuli and the MEG traces. This test is performed by taking the DWT of each series, and then computing the Spearman correlation between the wavelet coefficients for an appropriate scale.

A significant response (*i.e.*, correlated stimulus-sensor pair) was detected from each patient. This result suggests that the combination of serial recordings and WaveDetect may ensure reliable detection of auditory evoked responses.

Keywords: Evoked response, fetal, magnetoencephalography, wavelets

Introduction

Magnetoencephalography (MEG), a noninvasive technique for detecting brain activity, can be used to assess the neurological health of the human fetus (Blum et al, 1985). SARA (SQUID Array for Reproductive Assessment) is a specialized MEG system that has been developed to study fetal brain activity, as well as other aspects of fetal and maternal physiology. An important feature of the SARA system is that it allows the investigator to assess the functional development of the fetal brain by testing for sensory evoked responses. Favorable results have been achieved with both auditory (Eswaran et al, 2002a) and visual (Eswaran et al, 2002b) stimulation. This study focuses on auditory stimulation.

The problem of testing for an evoked response in an MEG signal, fetal or otherwise, is a difficult one. Because of the high resolution of the MEG time series, traditional hypothesis testing methods are invalidated by high temporal autocorrelation. Autocorrelation represents statistical dependency between nearby time points, making the actual number of degrees of freedom effectively unknown. The WaveDetect test, which is described in the Analysis section, capitalizes on certain properties of the discrete wavelet transform (DWT) to resolve this problem.

In adult MEG or EEG, it is typical to carry out a detailed study of the spectral content of the signal, examining multiple frequency bands. Fetal MEG is a less mature field, so we have started with the more modest goal of detecting a correlation between the fetal brain waves and the stimulus. The risk of detecting a spurious or artifactual correlation has been minimized by developing a valid statistical test and by concentrating on sensors in the vicinity of the fetal head.

Materials and Methods

Experimental Design

The experimental protocol is described in detail in Eswaran et al (2002a). Ten subjects were recruited with normal pregnancies ranging in gestational age from 30-35 weeks. The subjects were asked to participate in the study on three to five different days in one week of gestation, and asked to return for a second phase between 36 and 40 weeks of gestation. Each subject participated in three to eight sessions.

Multiple recordings were performed to reduce the probability of a false positive, *i.e.*, no response recorded from a healthy fetus. The fetal auditory evoked response is dependent on the position and sleep state of the fetus, so the probability of detection can be increased by performing multiple recordings on different days. No incidents of abnormal hearing were reported to us after birth.

Fetal MEG recordings were performed using the SARA device (CTF Systems, Inc., Port Coquitlam, Canada). The system consists of 151 primary magnetic sensors (first order gradiometers) arranged in a concave array covering the maternal abdomen from the pubic symphysis to the uterine fundus. To attenuate the influence of external magnetic fields, it was installed in a magnetically sealed room (Vakuumschmelze, Germany).

The auditory stimulus system consisted of a speaker that was situated outside the shielded room and attached to 12 feet of Tygon tubing. This tubing was connected to an air-filled bag, which was secured over the apex of the maternal abdomen. The sound stimulus was a 100ms tone burst with a combination of 500 Hz (frequent tone - 80%) and 1 KHz (rare tone - 20%) frequency with rise and fall times of 10 ms. The tones had an

intensity of 120 dB (SPL), as measured in the air at the end of the tube. The mean interstimulus interval was 1 s, with a randomization of 100 ms. A constant 10 ms delay was introduced by the tubing. Each session lasted for six or eight minutes, depending on patient comfort.

The recordings were made with a sampling rate of 312.5 Hz and with a passband of DC to 100 Hz. Interfering maternal and fetal heart signal components were removed by the combination of Woody filtering and the orthogonal projection method (Vrba et al, 2003). This method was applied to the raw signal in order to remove maternal magnetocardiographic (MCG) artifact and then reapplied to the resulting data set to remove fetal MCG artifact.

Analysis

WaveDetect is based on the wavelet transform (Daubechies, 1992). Like the Fourier transform, the wavelet transform brings out harmonic properties of a time series, but unlike the classic Fourier transform it is sensitive to local changes in frequency. It is also superior in the sense that, in the case of the discrete transform described below, higher frequency phenomena are appropriately examined at a higher temporal resolution.

The wavelet transform comes in several variations, all of which are rooted in the continuous wavelet transform (CWT). To compute the CWT, a function $\mathbf{f}(\mathbf{t})$ (often a time series) is convolved with dilations and translations of another function, $\Psi(\mathbf{t})$, called the mother wavelet. The mother wavelet is defined to have a zero average and an L^2 norm of 1, as well as satisfy a more technical admissibility condition (Daubechies, 1992). The ideal mother wavelet is well localized in both time and frequency space.

Through repeated dilation, translation, and convolution, the CWT transforms the one-dimensional time series $\mathbf{f}(t)$ into a two-dimensional array of coefficients, the two dimensions being time (u) and scale (s):

$$W_f(u, s) = \int_{-\infty}^{\infty} f(t) \frac{1}{\sqrt{s}} \Psi^* \left(\frac{t-u}{s} \right) dt.$$

The CWT is a rich, highly redundant representation of a signal, and as such has certain shortcomings that are relevant to the evoked response problem. It is a relatively intensive computation and has high storage requirements. Because the resulting coefficients (in matrix \mathbf{W}) are highly dependent, it poses the same inferential difficulties as the original time series. For these reasons, WaveDetect employs the discrete wavelet transform (DWT). The DWT differs from the CWT by being limited to dyadic scales (2^j) and to translations that are multiples of these scales ($k2^j$):

$$W_f(u, 2^j) = \sum_{t=0}^{N-1} f(t) \psi_{j,u}^*(t),$$

$$u = k2^j,$$

$$\psi_{j,u}(x) = \frac{1}{\sqrt{2^j}} \psi \left(\frac{x-u}{2^j} \right).$$

In regard to the evoked response inference problem, the DWT has an important advantage over the CWT, namely that under certain circumstances the coefficients are independent. This crucial property is explored more below. From a computational standpoint, an additional advantage of the DWT is that it can be computed with an efficient pyramid algorithm introduced by Mallat (1989) that requires merely $\mathbf{O}(N)$

operations. The storage requirement for the coefficient matrix \mathbf{W} is small; it contains approximately N coefficients.

Application of the DWT allows the analyst to focus on the coefficients for a particular scale (*cf.*, frequency in Fourier analysis). Each scale roughly corresponds to a bandpass filter. For this particular study, we used scale 2^7 , which corresponds to a filter with an approximate passband (frequency range) of 1.22 to 2.44 Hz. An example of an MEG signal and its wavelet coefficients at scale 2^7 is shown in Fig. 1.

There are two complementary inputs to the evoked response inference problem: the response (MEG channels) and the stimulus. In principle, one could compare the wavelet coefficients of the response to an appropriately downsampled stimulus waveform. A problem with this approach is that the discrete wavelet filter is not a zero phase filter; events are shifted in time. The solution that we devised was to transform the stimulus time series in the same manner as the response time series. This is appropriate because the analysis stays within the wavelet domain, rather than compare the wavelet domain to the time domain.

The WaveDetect test is summarized in Fig. 2: The analyst chooses an appropriate mother wavelet and a scale that is comparable to the timescale of the evoked response. The wavelet coefficients for that scale effectively become statistical surrogates for the raw data. The same wavelet transform is used on a stimulus time series with the same resolution, producing the same number of coefficients at the chosen scale. These coefficients are then compared using the Spearman correlation test.

There are numerous choices for the mother wavelet filter. In this study we used member 10 of the Daubechies extremal phase wavelet family, which has the smallest

support among wavelets with the same number of vanishing moments. A relatively smooth (high-numbered) filter was used to avoid artifacts associated with rougher filters (Percival and Walden, 2000). The computations were performed using the wavelet macros provided with version 8.2 of the SAS/IML® software¹.

The choice of an appropriate scale for the test is determined by several factors. First of all, the scale needs to be fine enough to capture the evoked response, which has a duration on the order of hundreds of milliseconds. On the other hand, the scale has to be coarse enough for assumptions of the WaveDetect test, elaborated below, to hold. Since the DWT only allows dyadic scales, these two requirements narrow the choices considerably. If there is still more than one potential scale, a choice can be made by checking which scale is most correlated with a clear example of an evoked response.

The validity of the WaveDetect test depends on two established properties of the DWT, one of which is not widely appreciated. The more recognized property of the DWT is that it decorrelates many types of time series, such as long memory processes. Percival and Walden (2000) demonstrated that a sufficient condition for the wavelet transform to produce decorrelated coefficients within a given scale is if the power spectrum is constant over the passband for that scale. This is true of the evoked response data for the scale under consideration, 2^7 , which spans an octave. One can also directly verify that the DWT coefficients for the chosen scale are uncorrelated.

¹ These macros are considered “experimental” in this version of SAS. Through repeated contact with the SAS Institute, however, we have verified that it is safe to use the macros with the options we have selected. The macros are “production” in the new version of SAS.

One might suspect that the decorrelating effect of the wavelet transform is merely a consequence of lowering the temporal resolution. The coefficients at scale 2^7 , for example, have a resolution of 2.44 Hz, compared to 312.5 Hz for the original time series. In fact, simply downsampling by averaging over blocks of 128 observations leaves substantial autocorrelation. This observation can be partly explained by the fact that downsampling does not eliminate correlations over longer time scales.

A second property of the discrete wavelet transform, shown by Moulin (1994), is that the coefficients are asymptotically normally distributed, provided that the mother wavelet is bounded. In other words, the wavelet coefficients at a sufficiently coarse scale are approximately normal. This can be established using a variation of the Central Limit Theorem for dependent variables. Being both uncorrelated and normally distributed, the wavelet coefficients are independent, and hence amenable to a simple correlation test.

The Pearson correlation of the wavelet coefficients of two time series estimates a quantity known as the wavelet correlation (Hudgins, 1992, Lindsay et al, 1996, Whitcher et al, 2000). We opted to use the more robust Spearman correlation coefficient rather than the Pearson correlation coefficient. Because the Spearman correlation coefficient is based on ranks, it is resistant to outliers and requires only an assumption of independence. Since we have used a different correlation coefficient the literature on the “wavelet correlation” may not be directly applicable, but we acknowledge it as relevant prior work.

In order to use the WaveDetect test for evoked responses, it is necessary to design an appropriate representation of the experimental stimulus. There are different ways to represent auditory or other stimuli in a time series. In general, the human perceptual systems are responsive to contrast and change. For the present study, this would suggest

that the analysis focus on the less frequent pitch. On the other hand, the frequent pitch has the statistical advantage of potentially producing a greater number of responses to be detected. Time efficiency is particularly important because maternal comfort limits the length of the sessions. A final consideration is that the fetus may not have a long term memory of the relative frequency of the different pitches, but simply notices when the pitch changes. These factors suggested that the most effective “stimulus”, which we denote as Novel, might be the incidence of a tone that differs in pitch from the previous tone. See Fig. 3. Note that the Novel stimulus occurs %60 more frequently than the Rare stimulus. We found that the Novel stimulus most consistently yielded a response detectable by WaveDetect; nine of the ten subjects were responsive (in at least one session). The remaining subject was responsive to the Frequent tone. (See Results.) The Rare stimulus was sometimes effective for producing a response, but because of its similarity to the Novel stimulus we have left it out of the formal analysis.

In order to design the stimulus waveform, it was necessary to further specify the time of its onset, relative to the physical stimulus, and the width of the window. There was limited independent fetal data to guide this choice. Pasman et al (1992) used EEG on preterm neonates to detect auditory evoked potentials, and found a mean latency of 187 ms for the P2 component and 347 ms for N2 component. The potential returned to baseline approximately 700 ms post-stimulus. We wanted to be sensitive to both positive and negative potentials (which would have indeterminate sign from MEG), and anticipated that fetal evoked responses could be substantially delayed relative to neonates. These considerations, and pilot testing on a small number of data sets, led us to employ two stimulus waveforms in the analysis. One waveform was an up-and-down step

function (“boxcar”) that became positive at 240 ms post-stimulus and went back to zero at 740 ms post-stimulus. (See series in Figure 3.) The other waveform was also a 500 ms “boxcar” function, but became positive at 400 ms post-stimulus. Both waveforms were tested on all subjects and sessions.

Fifty-seven contiguous sensors in the lower region of the abdomen were tested for a response. Since the fetuses had normal presentation, with their head down, this was the region of the fetal head. A Bonferroni correction was used to adjust for multiple (*i.e.*, 57) tests. The output of the remaining MEG sensors was not analyzed for two reasons. First of all, sensors near the upper part of the maternal abdomen were more likely to contain artifacts than to contain signal from the fetal head. Secondly, checking more sensors would have necessitated a larger Bonferroni correction, which would have reduced the sensitivity of the test.

The criterion for a significant response depended on the length of the session, which consisted of either 112,500 or 150,000 time points (*i.e.*, six or eight minutes). In the former case, the criterion was a correlation with an absolute value of at least .112. In the latter case, the minimum absolute correlation was .097. Our analysis was blind to the sign of the correlation because the direction of an MEG deflection cannot be unambiguously interpreted. Since a single source corresponds to a magnetic dipole, the same evoked response can be recorded as a positive deflection by one MEG sensor and a negative deflection by another.

Simulation

A simulation was performed to establish the false positive rate, nominally .05, for the WaveDetect test. In order to do this we generated random stimulus time series and compared them to two sets of actual MEG data from the study. One set, from Patient 1, consisted of six minutes of data. Another set, from Patient 2, consisted of eight minutes of data. Because the stimuli were randomly generated, positive results from the WaveDetect test were classified as errors. Hence the proportion of positive results from the simulation estimated the false positive rate of WaveDetect. The simulated pseudo-stimulus time series were compared to all 57 MEG channels, and a Bonferroni correction was included as part of the WaveDetect test. Ten thousand sessions were simulated for each patient.

Pseudo-stimulus time series were generated by randomly placing 500 ms “boxcars” (i.e., up-and-down step functions) in 1000 ms windows. If simulating a Frequent sequence, a 500 ms boxcar was placed in each 1s window with probability .8. To simulate a Novel sequence, a boxcar was placed with probability .32, which is the probability of a frequent tone following a rare tone or vice versa. When a boxcar was included in a window, it was placed according to a uniform random distribution.

It may seem odd that the method for generating a random pseudo-stimulus was not identical to the method for generating the actual stimuli that were used in the experiment. Bear in mind, however, that the purpose of the simulation was to test how often WaveDetect would find a spurious correlation if there were no relationship between the infant’s brain activity and the tones (i.e., if the null hypothesis were true). The actual experimental stimuli were correlated, because tones were played at a fairly regular 1s

interval (± 100 ms). If a patient's MEG data showed a significant relationship with a time series that was generated this way, it could simply reflect the fact that the simulated stimulus time series was correlated with the actual tones that were presented.

Results

An evoked response was detected from all ten subjects. See Tables I and II. Nine of the ten subjects responded to the Novel stimulus over the course of at least one session. For six of these nine subjects, Novel responses were observed with both the 240 ms and the 400 ms waveforms. One subject, Patient 3, only showed a Novel response detectable by the 400 ms waveform; two subjects, Patients 2 and 9, only showed Novel responses detectable by the 240 ms waveform.

The remaining participant, Patient 5, showed a response to the Frequent stimulus, delayed by 240 ms, but not to the Novel stimulus. This subject participated in only three sessions, so it is possible that a Novel response would have been detected over the course of additional recordings.

The minimum significant correlation was .112 or .097, for six or eight minute sessions, respectively. The largest observed correlation was .154.

Results from the simulation to estimate the false positive (Type I error) rate are shown in Table III. When the Novel stimulus was employed, the estimated false-positive rate from each sample data set was slightly greater than the nominal rate of .05, but significantly less than .06. When the Frequent stimulus was employed, each false positive rate was significantly less than .05.

Fig. 4 shows two examples of stimulus-triggered averages, from Patients 3 and 4, corresponding to evoked responses that were detected by the WaveDetect test. The

example from Patient 4 (panels C and D) is the same channel and session as Fig. 1, and the stimulus channels shown in Fig. 3. also came from this same session. These examples were chosen because the averages alone provide marginal or questionable evidence for an evoked response, but the WaveDetect test was nevertheless positive.

Evaluation of the test by examining stimulus-triggered averages is not entirely appropriate, however, because WaveDetect “lives” in the wavelet domain. Another view can be found in Fig. 5, which shows the WaveDetect correlation as a function of different delays until the onset of the stimulus waveform, including the two delays that were actually employed, 240 and 400 ms. A sample channel is shown from each subject. Note that the example from Patient 3 is a more delayed, but biologically plausible, response.

In the first published analysis of this data (Eswaran et al, 2002a), an evoked response was detected from eight out of ten (80%) subjects, as compared to ten out of ten (100%) in the present analysis. The older analysis differed from the present one in two distinct ways. One difference is that stimulus-triggered averaging was used, which is standard in the field, rather than the WaveDetect test. Another difference is that the original analysis did not include a check for an association between the MEG channels and the Novel stimulus shown in Fig. 3. For the two patients who did not show an evoked response to the Frequent stimulus with stimulus-triggered averaging (Eswaran et al, 2002a), we examined stimulus-triggered averages based on the Novel stimulus. One of the two patients showed a clear response to the Novel stimulus. Therefore, stimulus-triggered averaging showed a response in 90% of cases. In contrast, WaveDetect showed responses in 100%.

Discussion

The WaveDetect test is statistically valid and relatively simple to implement. As the results from this study clearly show, it is sensitive enough to detect auditory evoked responses when using fetal MEG. In at least some cases, it is more sensitive than the standard analytic technique for evoked responses, stimulus-triggered averaging.

One reason that WaveDetect can be more sensitive than averaging is that it is based on a correlation test, and is therefore capable of detecting a response that is relatively small in magnitude. In an extreme case, a change from the baseline response as small as 3-4 femtoTeslas was found to be statistically significant, because it was correlated with the stimulus waveform. An analyst who simply inspected the average would be likely to dismiss such a response as noise.

Another advantage of WaveDetect is that it accounts for multiple comparisons; the threshold for significance is adjusted to account for the fact that multiple null hypotheses are being tested. In principle, an analyst who uses the averaging method should also make such an adjustment, setting a stricter criterion for an evoked response as the number of channels under consideration gets larger. In practice, it is difficult to make such an adjustment systematically.

The SARA laboratory has also detected fetal evoked responses from visual stimulation. Initial results indicate that the WaveDetect test is also sensitive to these responses. This application will be studied in a future publication.

To our knowledge, there is no published test for evoked responses that is mathematically equivalent to WaveDetect. Nevertheless, there is some relevant work in the MEG/EEG evoked response literature. Samar et al (1995) is an early review paper on

wavelet analysis of evoked responses. Demiralp et al (1999) performed repeated measures ANOVA on DWT coefficients in order to detect evoked responses in electroencephalographic (EEG) data. EEG is based on different technology than MEG but is similar in some other regards, such as having a relatively high temporal resolution. Raz et al (1999) approached the evoked response problem by using a technique called wavelet packets that is more computationally intensive than DWT. Their analysis was based on stimulus-triggered averages, not the raw data as with our analysis. Adeli et al (2003) examined DWT coefficients visually to characterize spontaneous activity in the EEG of an epileptic patient. Quian Quiroga et al (2003) used the DWT to denoise single event-related potentials. Wavelet-based methods have also been developed for spatial data from such sources as functional MRI (Fadili and Bullmore, 2002) and PET (Turkheimer et al, 2000).

The utility of wavelet techniques is widely known among neuroscientists, but there is a tendency to use more familiar tools such as Fourier analysis, or ignore temporal correlations altogether. Adoption of wavelet methods has probably been impeded by their complexity, the myriad variations, and the lack of commercial software support for some techniques. We hope that by presenting a test that is *relatively* simple to implement and interpret we have done a small part to make wavelet techniques more acceptable to the neuroscience and obstetrics communities.

Acknowledgements

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Tables

Patient	Gest. Age (weeks)	Sessions	Novel Stim.	Freq Stim.	Either Stim.
1	30	5	2	1	3
2	33	4	1	0	1
3	33	4	1	0	1
4	34	2	0	1	1
	36	4	1	2	3
5	35	3	0	1	1
6	30	3	2	1	3
	35	3	1	1	2
7	34	4	1	1	2
	37	4	1	1	1
8	32	4	2	1	2
	36	3	1	3	3
9	31	3	1	0	1
10	32	3	3	1	3
	37	1	0	0	0

Table I

Patient	Novel - 240	Novel - 400	Frequent - 240	Frequent - 400
1	X	X	X	
2	X			
3		X		
4	X	X	X	X
5			X	
6	X	X		X
7	X	X	X	X
8	X	X	X	X
9	X			
10	X	X		X

Table II

Patient	Duration	Stimulus	False Pos. Rate	Confidence Int.
1	360 s	Frequent	.0347	.0312,.0385
		Novel	.0547	.0503,.0593
2	480 s	Frequent	.0297	.0265,.0332
		Novel	.0532	.0489,.0578

Table III

Figures

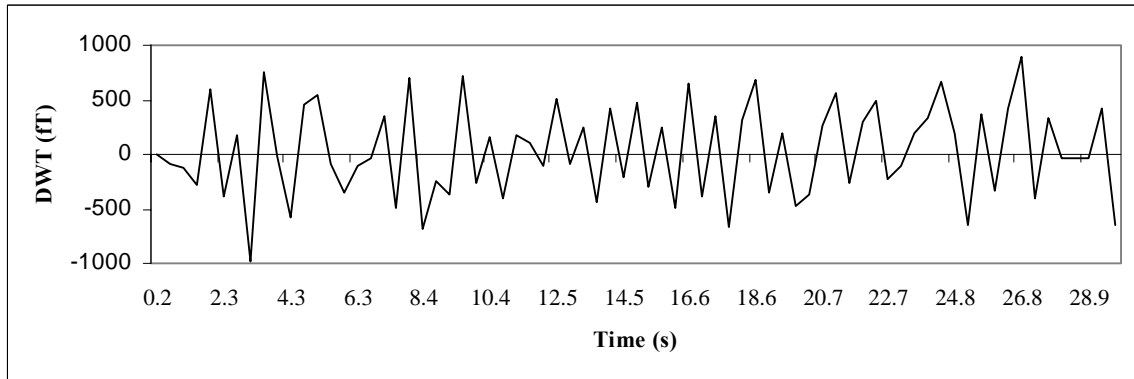
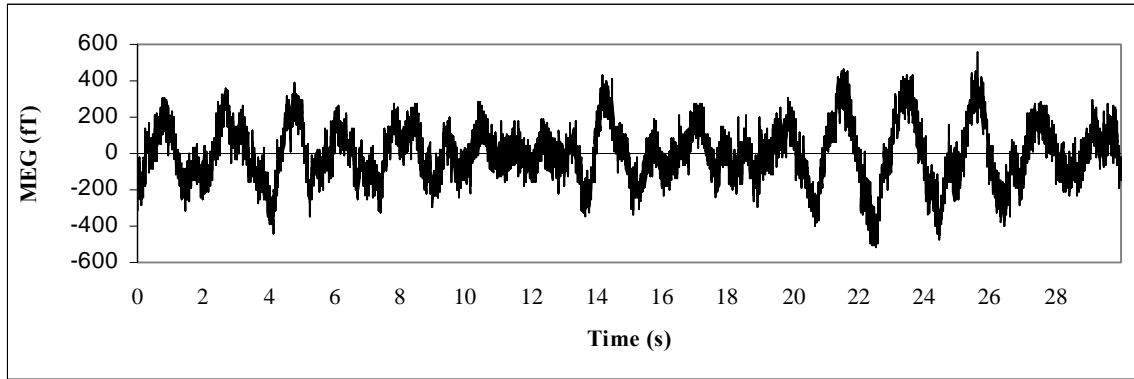


Fig. 1

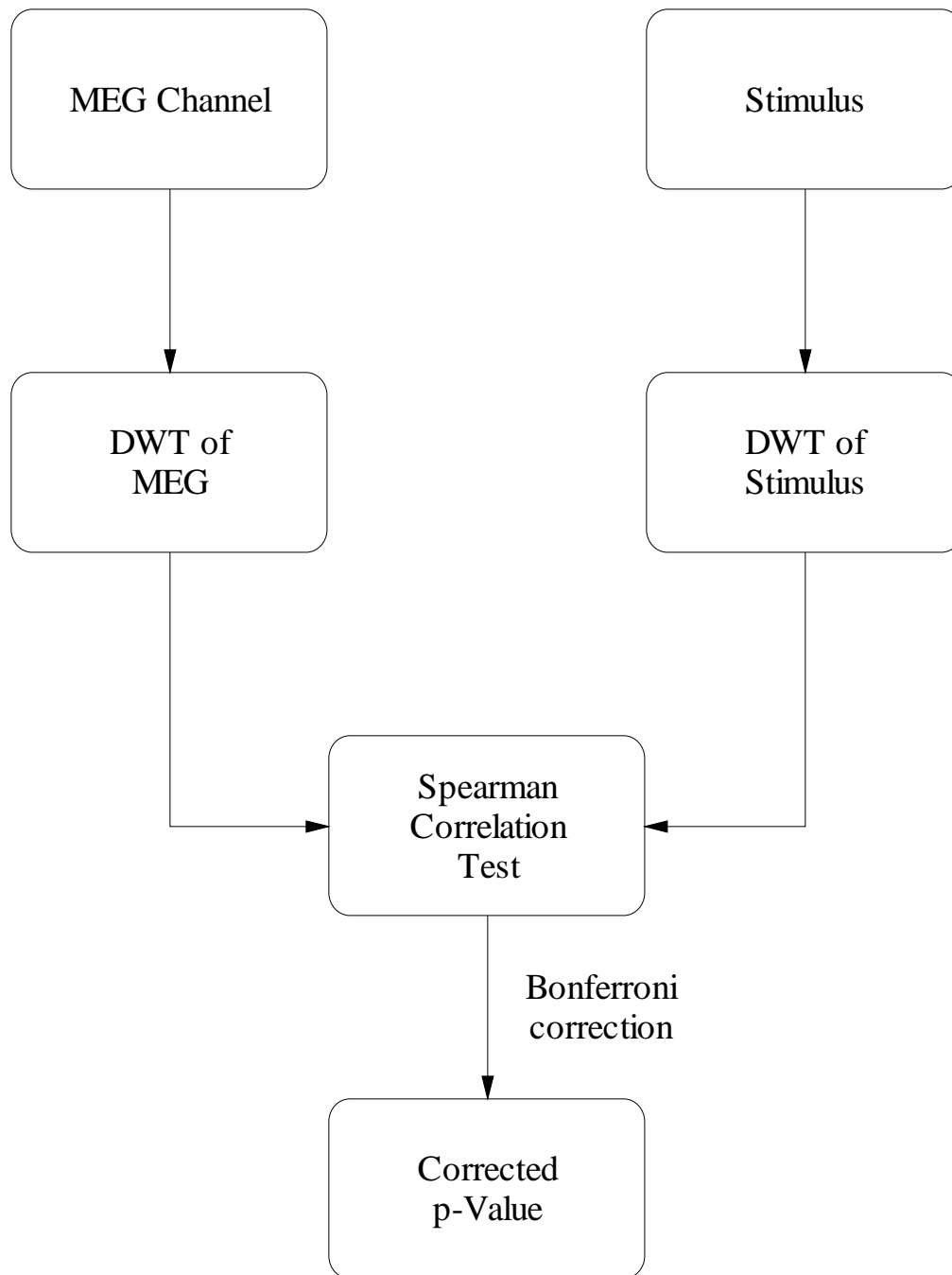
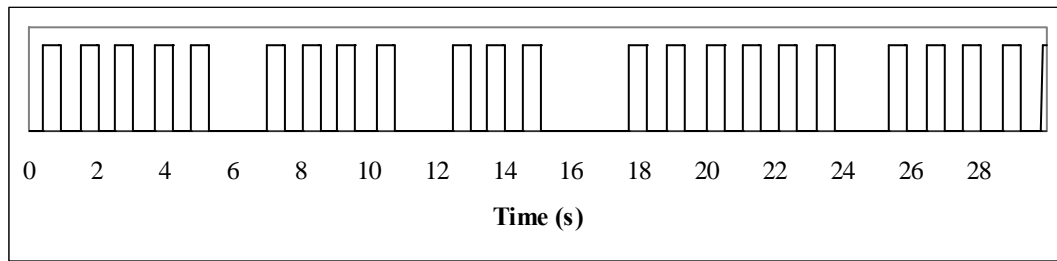
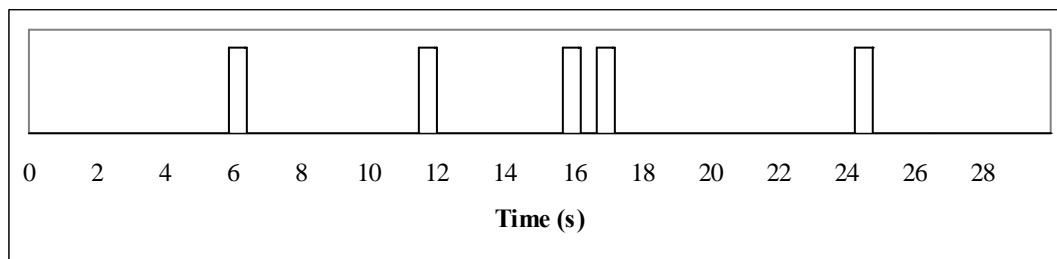


Fig. 2

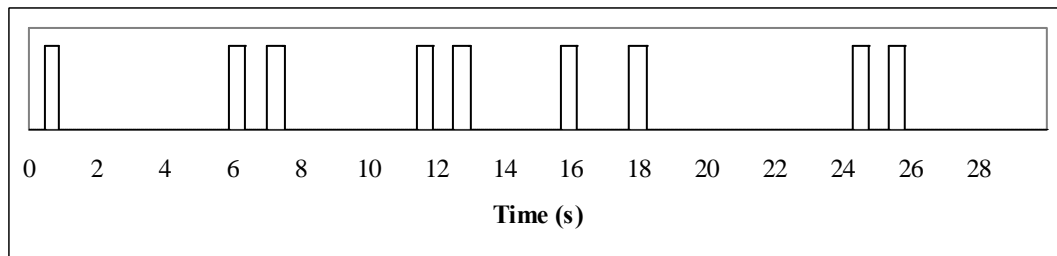
FREQUENT



RARE



NOVEL



DWT OF NOVEL

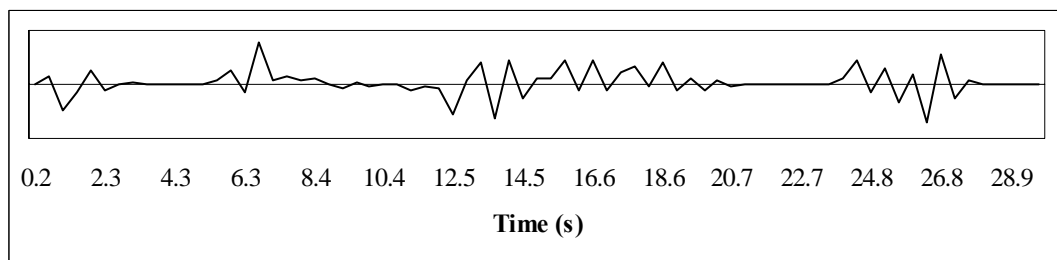


Fig. 3

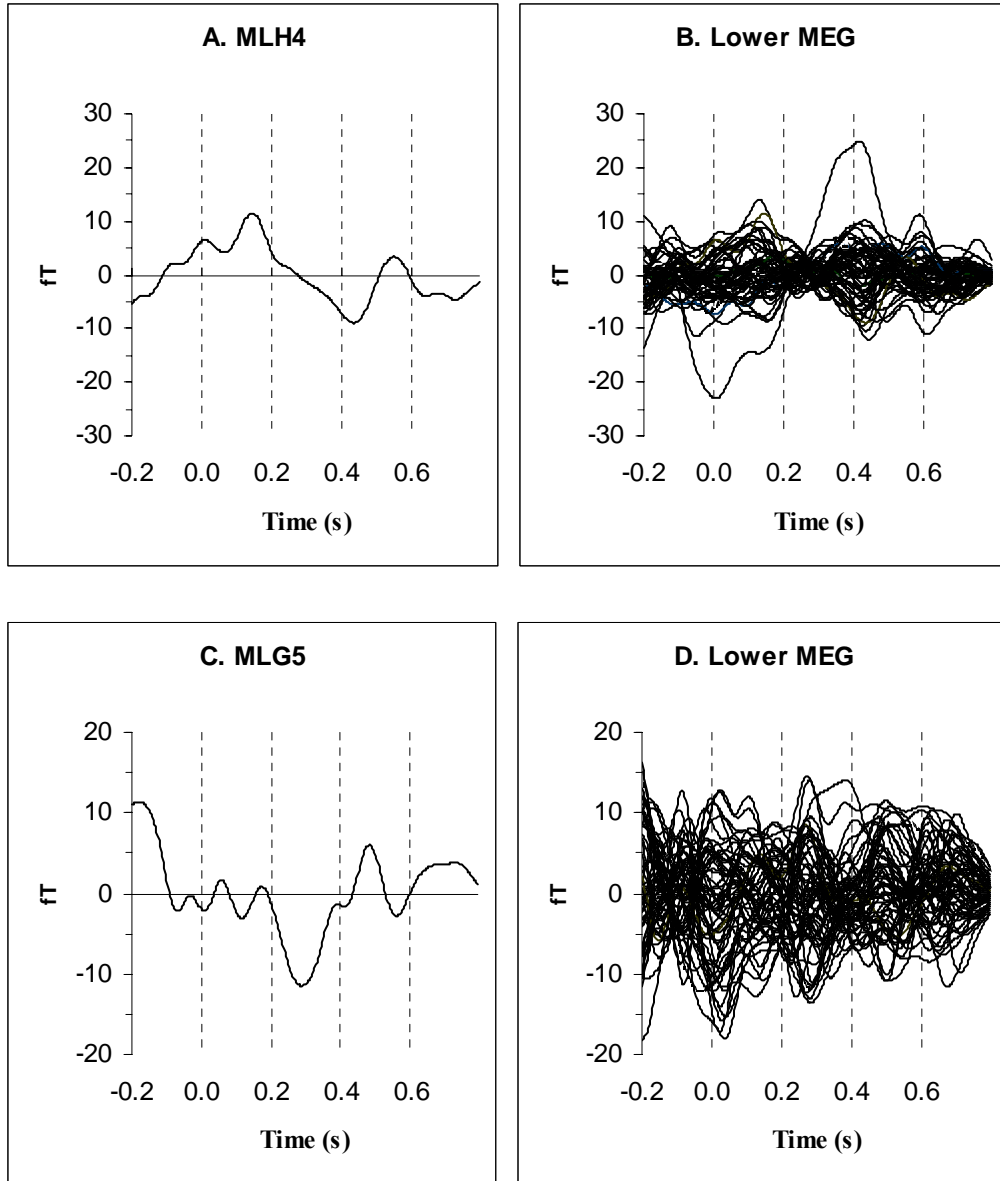


Fig. 4

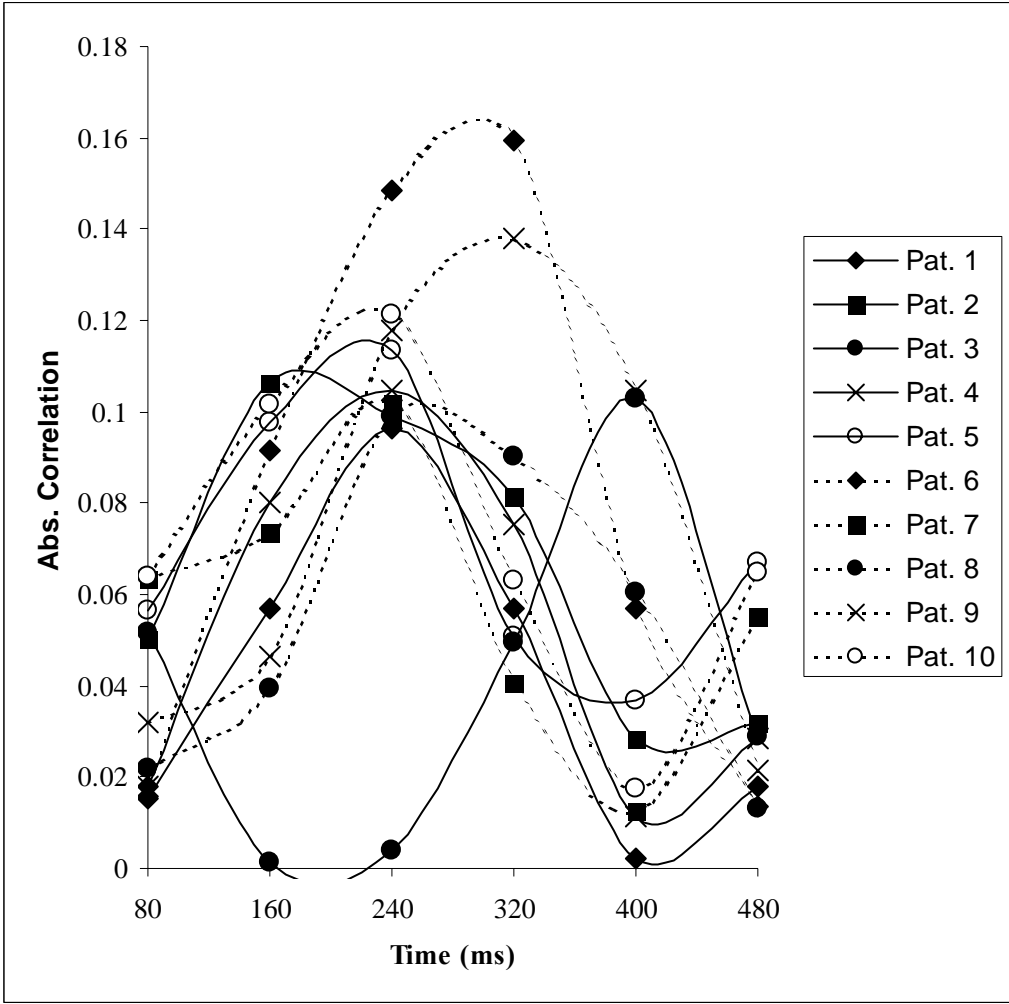


Fig. 5

Legends

Table I. Total number of sessions and sessions with responses for each subject, by gestational age (week) and type of stimulus.

Table II. Efficacy of different stimulus and delay combinations for detecting response from each subject. An 'X' indicates that a response was detected at least once with a given combination.

Table III. Results of simulation for false positive (Type I error) rate. The target (nominal) error rate was .05. $N = 10,000$. Separate results are given for the two session lengths and stimulus types. The confidence intervals are exact.

Fig. 1. Thirty second sample MEG trace (top) and corresponding DWT coefficients (bottom, scale 2^7) from Patient 4. The units on the X-axes are seconds; the units on the Y-axes are femtoTeslas.

Fig. 2. Flowchart of the WaveDetect test, for a given stimulus/sensor pair. First, the DWT is applied to the MEG and stimulus time series. Second, a Spearman correlation test is performed on the DWT coefficients from each time series. Finally, a Bonferroni correction for multiple comparisons is applied to the resulting p-value.

Fig. 3. Stimulus waveforms from the same patient/session as Fig. 1. Frequent and Novel were used in the analysis; the Rare tone is included for clarity. 30 seconds of randomized

stimulation are shown. The final panel shows the DWT coefficients for the Novel stimulus. The units on the X-axes are seconds.

Fig. 4. A. Stimulus-triggered average from Patient 3. An evoked potential was detected from this channel. B. Averages for all lower-abdomen channels from the patient/session in A. C. Stimulus-triggered average from Patient 4. An evoked potential was detected from this channel, which is the same channel shown in Fig. 1. D. Averages for all lower-abdomen channels from the patient/session in C. The units for the X-axes of all four panels are seconds; the Y-axis units are femtoTeslas.

Fig. 5. Correlation as a function of stimulus-onset delay, including the two delays that were actually employed in the analysis, i.e., 240 and 400 ms. A sample channel is shown from each subject. The Y-axis shows the absolute correlation between the wavelet coefficients for the sample channel and stimulus. The units for the X-axis are seconds.