Reexamination of Gender Differences in the Source Location of N1m

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Abstract

Gender differences in the source location of the auditory evoked field (AEF) component N1m have been reported previously in a small group of subjects. The present study was conducted to evaluate further the existence of gender differences in a larger sample. Neuromagnetic recordings of AEFs were obtained from young normal hearing subjects using a 1000-Hz tone burst presented at 60 dB hearing level (HL). No significant gender-related differences were observed for the N1m peak latencies following left and right ear stimulation. The stimulating parameters and larger sample used in the present study size may account for the difference in gender effects observed between the two studies.

Key Words: Auditory evoked responses, gender, neuromagnetism

Action potentials and postsynaptic potentials may be recorded from the scalp from approximately 1.5 msec up to hundreds of milliseconds following the onset of a sensory event. The ionic flow associated with these events and the corresponding intracellular and extracellular currents are the origins of voltage fields and magnetic fields. Currents occurring spontaneously in the brain are referred to as the electroencephalogram (EEG) whereas currents resulting from stimulation of a sensory pathway are referred to as an evoked potential (EP). In terms of magnetic recordings, these events are referred to as the magnetoencephalogram (MEG) and the evoked magnetic field (EMF) respectively.

In most respects, evoked magnetic fields (unlike evoked potentials) may be thought of as arising from intracellular currents. These events arise from sources within the brain and, unlike evoked potentials, the resulting magnetic fields are minimally affected by differences in the impedances of tissues interposed between source and recording device. Also, no reference electrode is required for evoked field recordings, therefore, the phenomenon of “reference contamination” is not a problem.

Neuromagnetometers are devices that are capable of sensing small changes in brain magnetic fields. The major components of the neuromagnetometer are a liquid helium filled dewar (which maintains a temperature of -269°C) containing a series of detecting coils composed of metal with superior current conducting properties. A superconducting current is generated when a magnetic field “links” the coil. The current is directed toward a very sensitive detector called a superconducting quantum interference device (SQUID) (Williamson and Kaufman, 1990). The current strength is proportional to the magnetic field that is recorded by the coil.

It is noteworthy that the recording coil can respond only to that component of the magnetic field that is normal to the axis of the detection coil. Thus, the magnetometer is more sensitive to sources located in sulci, which generate currents tangential to the measuring device. The location of these sources can be approximated with a high degree of accuracy by measuring the field over the head and determining the di-
distance between the extreme sites where the field maximally emerges and reenters the head.

Reite et al (1978, 1981), Elberling et al (1980), and Hari et al (1980) were the first to describe the auditory evoked cortical magnetic fields (AEF). Similar to cortical auditory evoked potentials (CAEP), AEFs are composed of a dominant response occurring 100 msec following stimulus onset, denoted N1m (i.e., magnetic response with a 100 msec latency). Figure 1 shows both an auditory evoked potential N1 component (N1e) recorded from the Cz electrode site, and an AEF component N1 (N1m) recorded from the anterior and posterior extrema. Notice that the waveform inverts between the two sites located over the inferior anterior scalp and posterior superior scalp regions respectively. These data support the concept that (as opposed to evoked potential techniques) magnetic field recordings make it possible to view both ends of the current dipole (in this case located in the Sylvian fissure equidistant between the two N1m extrema).

Although a great deal of information has accumulated about AEFs since they were first described in the literature, some aspects of the normal response have not been described adequately. Recently, Baumann et al (1991) reported that significant differences existed in the location of the source of the AEF component N1m when male and female subjects were compared. Specifically, the authors reported that the location of N1m was 1 cm more posterior for females than males. Also, the equivalent current dipole for N1m was oriented more downward (Psi orientation) in females.

The validity of the data obtained from the previous investigation is questioned due to a number of sampling and methodologic issues. First, with such small samples (e.g., six males and six females) it is possible that the findings obtained by Baumann et al (1991) could have occurred as a result of sampling error. Second, there are known gender differences in skull dimensions. These differences are felt to explain some of the gender differences that have been reported in short latency auditory, somatosensory and long latency visual evoked potential research (Jerger and Hall, 1980; Allison et al, 1983; Sturzebecher and Werbs, 1987; Chan et al, 1988; Jerger and Johnson, 1988; Maurizi et al, 1988; Aoyagi et al, 1990). These studies have indicated that in order to make meaningful gender-based comparisons it is important to control for head and brain size.

Interestingly, the results of these well-controlled investigations have suggested that differences in skull dimensions alone cannot explain the gender differences in brainstem auditory evoked potential measurement variables (Trune et al, 1988; Durrant et al, 1990). Additionally, there was a wide age range distribution (22–54 years) in the 12 subjects who participated in the investigation conducted by Baumann et al (1991). A breakdown of ages for each of the samples was not reported. Sub-
ject age (> 50 years of age) is known to be a source of contamination in auditory evoked potential (AEP) and AEF research (Hoke et al, 1989). In this connection, hearing sensitivity of the subjects was not reported by Baumann et al (1991). Therefore, although the stimulus intensity was reported in hearing level (HL), the authors could not assure that the stimuli were presented at equal sensation levels (SL) across subjects.

Also, the former investigators stimulated only the left ear and recorded contralateral responses. It is unknown why the investigators did not also stimulate the right ear and determine whether known interhemispheric differences in the location of N1m (Elberling et al, 1981, 1982; Pantev et al, 1986b; Hari and Mäkelä, 1988; Joutsiniemi, 1988) were influenced by gender. Finally, Baumann et al (1991) used short duration, high intensity stimuli (e.g., 200 Hz tone pips, 95 dB HL, 10 msec rise/fall time and 30 msec duration). It is unclear why a longer duration tone was not chosen.

The purpose of the present investigation was to determine whether significant differences existed in AEF component N1m variables when a larger sample of male and female subjects were compared. These paid subjects were participants in a previously reported investigation of the AEF in tinnitus, hearing loss, and normal subjects (Jacobson et al, 1991).

METHOD

Subjects

Informed consent was obtained from all subjects who participated in this investigation. Subjects were 25 young normal hearing subjects. There were 15 females (mean age 30.80 years, SD = 6.19 years) and 10 males (mean age 32.40 years, SD = 6.00 years) in this sample. Normal hearing was operationally defined as 20 dB HL or better pure-tone thresholds measured audiometrically at octave frequencies between 250 and 8000 Hz. All subjects underwent a thorough audiometric test battery including pure-tone and speech audiometry, immittance measurements, and auditory brainstem response (ABR) testing at both slow (21.3 clicks/sec) and fast (81.3 clicks/sec) stimulus presentation rates. All subjects were otologically normal. Each subject was examined by an otologist prior to being accepted into the experimental protocol. All but one of the subjects were right-handed as determined by the Edinburgh Inventory (Oldfield, 1971).

Because of the possibility of drug-induced changes in the AEF, subjects taking the following classes of drugs were excluded: (1) major tranquilizers, (2) minor tranquilizers and anxiolytics, (3) hypnotics and sedatives, (4) antidepressants, (5) anticholinergic and antihistaminic agents, (6) central nervous system stimulants, (7) anticonvulsants, and (8) narcotic analgesics.

Procedures

Neuromagnetic recordings of the AEFs were conducted in the Neuromagnetism Laboratory at Henry Ford Hospital. These measurements were made with a 7-channel DC SQUID system (Biomagnetic Technologies Inc, BTi Model 607) equipped with second-order gradiometers. The evaluation was conducted in a magnetically shielded room.

The subject's head was measured in the sagittal and coronal planes and positions Cz, T3, and T4 (International 10-20 system) were measured and marked. A grid system based upon the T3 (or T4)-nasion line was devised to ensure that the anterior and posterior extrema of the N1m were recorded with 5 to 7 probe positionings (35–49 channels) with a minimum of overlap. This system has been described elsewhere (Jacobson et al, 1991) and is a modification of a system developed by Pantev et al (1986a, b, c). Additionally, the preauricular points were marked as were the nasion and Fz. These are fiduciary points that were used by the computer to determine the point of origin of the “x,” “y,” and “z” coordinates. These coordinates are used to describe the location of N1m in three-dimensional space.

All measurements were made over the scalp contralateral to the ear stimulated. The subjects were escorted into the shielded room and placed in a lateral decubitus position (park bench position) on a comfortable padded table. A comfortable foam occluding ear plug (EAR®) was inserted in the nontest (contralateral) ear to attenuate ambient room noise. Automatic probe positioning routines were used to instruct the computer where the fiduciary points were located on each subject's head. Auditory stimulation consisted of 500 msec, 1000-Hz tone bursts (15 msec rise/fall time) presented at an intensity of 60 dB HL (Hoke et al, 1989; Pantev et al, 1989) at a rate that pseudorandomly varied from .25 Hz to .33 Hz. The stimulus timing was controlled by the signal averager component of the neuromagnetometer system. This signal
was routed through a series of gating and timing modules and finally into an amplifier module and an attenuator. The stimulus was routed to a piezo-electric transducer (Etymotic Laboratories ER3A). The output of this transducer was carried to the ear by a 7-ft length of polyethylene tubing that terminated in an earplug. This stimulus delivery system imposed a 6 msec increase in the latency of the AEFs.

The AEFs were bandpass filtered (.1-50 Hz), amplified (x 1000), digitized (250 Hz), and averaged over a 900 msec period. This averaging interval included a 200 msec prestimulus baseline period. For each waveform, the baseline was defined as the average magnitude value for the first 100 points of the evoked field waveform. A total of 80 to 100 single samples were averaged for each evoked response. Eye movement contamination was controlled by having each subject observe a visual target placed on the wall opposite them. Subjects were instructed to lie still and restrict their gaze to the target during data collection. Additionally, artifact rejection techniques were used to eliminate high amplitude (e.g., > 2000 ft) stimulus-unrelated magnetic field signals such as electrooculographic signals. An attempt was made to control alertness of subjects by requiring them to count the number of tones that were presented. A run was excluded from the investigation if the subject was incorrect in their stimulus counts by ±4. The choices of the first ear to be stimulated and whether to first define the anterior or posterior field extrema were counterbalanced across subjects.

Each subject yielded a minimum of 10 runs (e.g., 2 anterior runs, 2 posterior runs, and 1 recording obtained at the mid-point for each hemisphere). The raw data were stored initially on magnetic disk as a series of unaveraged auditory evoked fields. Following each run, these data were demultiplexed (e.g., into single samples for each of the seven channels) and data for each channel were averaged. Following signal averaging, the seven-channel AEF recording was viewed and printed.

**Data Analysis**

The software residing in the BTi 607 system permits the inverse solution of a single dipole source given the magnetic field pattern that results from multichannel AEF recordings. This solution is obtained through a least squares approximation iterative technique. Dipole moment data were calculated at the peak of N1m where the maximum number of sources were activated and the dipole strength was greatest. The goodness of fit between the magnetic field generated by the dipole source estimation of the computer and the actual observed field is denoted $r^2$ by the computer. Independent $t$-tests were used to determine whether gender differences existed for each of the N1m variables (e.g., latency, dipole strength, and the cartesian coordinates $x$, $y$, and $z$) following stimulation of the left and right ears.

**RESULTS**

The goodness of fit was good between the observed fields and those expected, given the single dipole model. The correlations ranged between .86 and .98 across gender. Accordingly, the coefficients of determination ranged between .74 and .96. The mean correlations with the single dipole model were .94 ($\pm .03$) for both the left ear and right ears across subject gender.

Mean latency and dipole moment data comparing responses from male and female subjects are shown in Table 1 for right ear stimulation and Table 2 for left ear stimulation. A visual inspection of these data showed that the mean differences for each variable were similar between males and females. In this regard, group paired comparisons (Student's two-sample $t$-tests for independent data) between these data failed to yield statistical significance (defined as a two-tailed probability of $< .05$). Table 3 is a summary of dipole moment data ($x$, $y$, and $z$ coordinates, dipole strength-$Q$, and dipole orientation-$\Psi$) reported by Baumann et al (1991) and that of the present investigators for male

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Means (SD) for N1m Dipole Parameters for Males and Females following Right Ear Stimulation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Latency (msec)</td>
</tr>
<tr>
<td>Males</td>
<td>107.60 (9.08)</td>
</tr>
<tr>
<td>Females</td>
<td>106.93 (10.22)</td>
</tr>
</tbody>
</table>
Table 2 Means (SD) for N1m Dipole Parameters for Males and Females following Left Ear Stimulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Latency (msec)</th>
<th>x (cm)</th>
<th>y (cm)</th>
<th>z (cm)</th>
<th>Psi (deg)</th>
<th>Q (nA·m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>103.20</td>
<td>1.28</td>
<td>-5.07</td>
<td>5.35</td>
<td>-140.95</td>
<td>9.16</td>
</tr>
<tr>
<td></td>
<td>(11.78)</td>
<td>(0.91)</td>
<td>(1.15)</td>
<td>(21.42)</td>
<td>(7.31)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>103.20</td>
<td>0.98</td>
<td>-4.99</td>
<td>5.35</td>
<td>-145.12</td>
<td>8.73</td>
</tr>
<tr>
<td></td>
<td>(10.19)</td>
<td>(0.84)</td>
<td>(1.32)</td>
<td>(17.05)</td>
<td>(4.94)</td>
<td></td>
</tr>
</tbody>
</table>

and female subjects. Additionally, Table 4 illustrates the between study differences in the goodness-of-fit for N1m. As may be observed, the data collected in the present investigation were slightly more compatible with a single dipole model than the data reported by Baumann et al (1991).

Recently, there has been a proposal that the power of observation of critical differences be presented in all investigations containing negative findings (Jewett, 1991). In this analysis we are interested in the power characteristics of the data we have collected to detect differences of the magnitude reported by Baumann et al (1991). To do this we note that the difference between genders that Baumann et al reported was 1.48 for the x variable and 24 for the Psi variable, the two characteristics where significance was observed. From our data we calculated the pooled standard deviation for the x and Psi variables as being 1.11 and 18.9, respectively. These are slightly higher for x and lower for Psi than those reported by Baumann et al (0.80 and 20.0 for x and Psi variables, respectively). With the sample size of 10 males and 15 females, the power of the two-sided Student’s t-test to detect these differences is 87.8 percent and 84.5 percent for x and Psi, respectively. This assumes an alpha of 0.05.

**DISCUSSION**

The present investigation was undertaken in an effort to evaluate further gender differences in the source location of N1m. Using a larger sample of young, normal, male and female subjects we were unable to support the gender difference observations of Baumann et al (1991). Additionally, there were no significant gender differences in the contralaterally recorded N1m dipole parameters when the same stimuli were presented to the right ear.

It is interesting that in the present investigation there were no significant gender-related differences noted in the peak latency of N1m. Gender differences have been reported for the ABR by many investigators (Jerger and Hall, 1980; Allison et al, 1983; Sturzebecher and Werbs, 1987; Chan et al, 1988; Jerger and Johnson, 1988; Maurizi et al, 1988; Trune et al,
The present investigation differed from that of Baumann et al (1991) in that longer duration tonal stimuli of a lesser intensity were utilized. Pantev et al (1989) have demonstrated that stimulus intensity interacts with stimulus frequency to change the source location of N1m. However, it might be expected that because the stimulus was identical for males and females, the gender differences would have been apparent.

Additionally, the dipole source estimates were examined at the peak latency of N1m (where dipole strength was greatest) instead of at the latency point where the fit with the single dipole model was strongest (Baumann et al, 1991). Rogers et al (1991) have reported previously that N1m can be modeled as sequentially activated dipoles that move in an anterior-inferior direction over a 40 msec period. Therefore, the uncontrolled variable of the point in time at which the dipole source estimates were examined would be expected to introduce more variability in the data obtained from males and females. This limitation was noted by Baumann et al (1991). In the present investigation, dipole source estimates were taken at the peak latency of N1m following left and right ear stimulation in an attempt to limit the variability associated with the time point at which the measurements were taken.

It might be agreed that one potential source of error in the present investigation was the fact that the model sphere was based on the shape of the entire head. However, because the temporal region is much flatter, the headshape sphere is much smaller than a sphere based on the curvature of the head over the temporal region. This would not appear to explain the difference between our results and those of Baumann et al (1991) because our spherical model calculations do not seem to lead to more variability. Indeed our results consistently showed a higher goodness of fit parameter (r²—see Table 4) than those obtained by Baumann et al (1991).

Finally, the sample size in the investigation of Baumann et al (1991) was small (6 males and 6 females). The authors suggested that the gender differences were genuine based on the repeatability of their measurements which, in fact, only measures the reliability and not necessarily the validity of the responses. It is our feeling that the differences observed between our study and the former investigators is probably due to sampling error. One method by which Baumann et al (1991) might have validated their observations would have been to repeat the experiment on another small sample of subjects.

The power of our test of gender differences for the x and Psi variables (87.8% and 84.5%, respectively) represents the probability of observing statistical significance if the true gender differences are at least as great as that reported by Baumann et al (1991). These power characteristics are specific to our data because they are based on our observed variability. This suggests that, at present, it is not possible to accept the conclusion that there are gender differences in N1m.

1988; Aoyagi et al, 1990; Durrant et al, 1990). The results of these investigations have indicated that the wave I-V interwave interval is shorter by approximately .2 msec for females compared with males. It might be expected that that difference would be larger for cortically generated auditory evoked potentials. However, we are unaware of any previous reports in the literature that have examined specifically gender differences in the long latency auditory evoked potential (i.e., electric) or evoked field (i.e., magnetic) N1 component. Research in long latency visual evoked potentials has suggested that the P100 component for females may be shorter by 3 msec compared with that obtained for males (Stockard et al, 1979; Allison et al, 1983). However, it is important to note that other investigators have not found these differences. Interestingly, when head circumference was taken into account, significant gender differences were not observed in P100 latency (Guthkelch et al, 1987).

It is our feeling that there are five possible explanations for the differences in the results obtained in the study by Baumann et al (1991) and those obtained by the present investigators: (1) differences in the stimulus, (2) differences in the latency point at which dipole calculations were made, (3) differences in the spherical models used to calculate dipole locations, (4) differences in the sample sizes, and (5) there are no gender specific differences in the source locations of N1m.

Table 4 Mean (SD) between Study Comparison of Goodness-of-Fit of N1m Data to a Single Dipole Model

<table>
<thead>
<tr>
<th></th>
<th>1st Session</th>
<th>2nd Session</th>
<th>Jacobson et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.94</td>
<td>0.92</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>(0.04)</td>
<td>(0.01)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>Females</td>
<td>0.90</td>
<td>0.92</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>(0.04)</td>
<td>(0.04)</td>
<td>(0.03)</td>
</tr>
</tbody>
</table>

The mean goodness-of-fit in the present investigation was better than that reported by Baumann et al (1991). Variability within the data was comparable.
differences in the source localization of N1m. Statistical power represents the probability that a given test will correctly reject the null hypothesis when, in fact, the means are different. In a test with high power (as in the current investigation) failure to reject the null hypothesis is strong evidence that the two means are equal. The assertion that gender differences exist may be accepted only if larger samples of males and females are examined and differences are observed between samples.

REFERENCES


