Legends for figures

Figure 1. Locations of equivalent current dipoles (ECDs) under each condition in each hemisphere of a control subject superimposed on a magnetic resonance imaging slice of this subject. Circle: ECD location of MMF under tone-duration condition; triangle: that under phoneme-duration condition; and square: that under across-phoneme condition.

Figure 2. Grand mean magnetic counterpart of global field power (mGFP) waveforms under the tone-duration (top), the phoneme-duration (middle), and the across-phoneme (bottom) change condition for each hemisphere. Thick lines are for the control group and thin lines for the autism group.

Comparison between mismatch negativity amplitude and magnetic mismatch field strength in normal adults

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Abstract

Objective: The auditory mismatch negativity (MMN) or its magnetic counterpart (magnetic mismatch field; MMF) is an event-related potential or magnetic field component indexing the sensory memory. The MMN can be elicited even without requirement of active response to the stimuli; thus it has been widely used to assess the ability of stimulus-driven change detection process in healthy individuals (infants, children and adults) and persons with neuropsychiatric disorders. The authors evaluated the similarity of inter-individual variation of the response strength between MMN and MMF recordings.
Methods: Three types of MMN or MMF were recorded in ten healthy subjects: change in duration of pure-tone stimuli, change in duration of the Japanese vowel /a/, and difference between the Japanese vowels /a/ and /o/.
Results: There was no significant correlation between MMN amplitude and MMF strength under any condition and in either hemisphere.
Conclusions: These results suggest that widely used indices of MMN in the two technologies, i.e., EEG-amplitude and MEG-ECD may not be proportional in an individual. To apply MMN and MMF as clinical indices of individual ability of preattentive stage of auditory processing, further work is necessary to establish the differential significance of recording MMN and MMF in healthy subjects and patients with various illnesses.

Keywords: mismatch negativity (MMN); magnetoencephalography (MEG); event-related potentials (ERPs); auditory

1. Introduction

The auditory mismatch negativity (MMN) is an event-related potential (ERP) component indexing the sensory memory or stimulus-driven change detection process (Näätänen et al., 1978; Rinne et al., 2001). Näätänen (1992) noted that MMN reflects the detection of mismatches between the deviant stimuli and the neural trace encoding the standard stimuli. The MMN can be elicited even under passive conditions when subjects ignore the stimuli and thus can be used to index the preattentive stage of auditory processing. However, MMN is unique in that it reflects not merely early-stage auditory processing such as N100 but indexes sensory memory or change detection function. The MMN has been widely studied in an attempt to reveal the nature, mechanisms and cortical networks subserving this process. Studies of the MMN in response to changes in pure-tone stimuli have also been conducted in groups with neuropsychiatric, developmental, and neurootological disorders for further understanding of pathophysiology of the central auditory system in these disorders (Csepe and Molnar, 1997; Gene-Cos et al., 1999). The auditory mismatch response can be also measured using magnetoencephalography (MEG), and this MEG activity is called magnetic mismatch field (MMF) or magnetic counterpart of MMN (MMNm) (e.g., Alho et al., 1998a,b).

Here we encounter an important question of whether inter-individual variations of the response strength between MMN and MMF recordings are similar or not. Namely, the issue raised is whether we can judge a subject's ability of auditory sensory memory similarly by MMN and MMF recording. This question is pertinent to the application of MMN (MMF) in clinical testing of individual subjects. For example, in our previous studies, the mismatch response was found to be equally reduced in both MMN and MMF recordings in two independent samples of patients with schizophrenia compared with healthy subjects (Kasai et al., 2002a, 2003). As a group, the conclusions from the results of these two studies were common in that the auditory sensory memory process was abnormal in patients with schizophrenia. However, these group comparisons do not necessarily mean that the mismatch process can be equally measured by either MMN or MMF recording at the level of individuals.

The MMN is believed to have several generators in the bilateral temporal cortex and left (Deouell et al, 1998; Yago et al., 2001) and right (Giard et al., 1990; Kropotov et al., 1995; Alho et al., 1998b; Baldeweg et al., 1999; Kasai et al., 1999a; Rinne et al., 2000; Liasis et al., 2001) prefrontal cortex. In contrast to electrical fields, magnetic fields are not influenced by intervening tissues of different conductivities. Moreover, an MEG selectively detects tangential vectors of electrical currents, whereas an electroencephalography (EEG) is more sensitive to currents radial to the scalp. Thus, MEG recording predominantly detects the MMF generated in the superior temporal plane, while it is less sensitive to MMF from other generators such as the frontal component (Giard et al., 1990; Kasai et al., 1999a).

The MMN does not occur only with pure tone stimuli and can also be elicited by more linguistically significant stimuli such as category changes of phonemes (e.g., /a/ versus /o/; /ba/ versus /da/) (reviewed in Näätänen, 2001). Thus, it is important to use both tonal and phonetic stimuli in an MMN study, since these two types of mismatch have been widely used in previous literature. We here chose the duration deviance since it has been suggested that the MMN elicited by duration deviance has the best test-retest replicability (Kathman et al., 1999; Pekkonen et al., 1995; Tervaniemi et al., 1999) and that previous studies of MMN in patients with schizophrenia imply the clinical usefulness of MMN in response to duration change (Michie et al., 2000). Also, Kasai et al. (2001) have shown that MMF in response to pure-tone and vowel within-category changes was significantly predominant in the right hemisphere; on the other hand, vowel across-category MMF did not differ in power between hemispheres. These results suggested that the relative contribution of the left auditory cortex in the preattentive processing of speech sounds may occur only at the level of processing of the vowel across-category change. Thus, it is also important to measure MMNs in these two types of vowel conditions.

Accordingly, the present study evaluated the similarity of inter-individual variation of the response strength between MMN and MMF recordings in normal subjects. We sought to investigate how similar or different are the indices of MMN obtained in the two technologies (EEG versus MEG) when the quantification was performed using the widely used methodology: amplitude measurement in EEG and single dipole analysis in MEG. If the correlation between MMN amplitude and MMF strength was significantly high, EEG should be exclusively considered for clinical testing because of its low-cost and handiness. If the correlation is weak, however, it would be important to conduct further studies to establish the differential significance of recording MMN and MMF in healthy individuals and patients with various illnesses.

2. Methods

2.1. Subjects

Ten right-handed [determined using the Edinburgh Inventory (Oldfield, 1971); we used a laterality index ≥ 0.8 as the cutoff for right-handedness] healthy subjects participated in this study. Eight were male, and 2 were female, and their mean age was 24.3 years (SD=3.2). The exclusion criteria consisted of neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 minutes, substance or alcohol abuse or dependence, and the presence of hearing or vision impairment. This study was approved by the Ethical Committee of the Faculty of Medicine, University of Tokyo. After a complete explanation of the study to the subjects, written informed consent was obtained.

2.2. Task procedures

The task procedures were described in detail elsewhere (Kasai et al., 2002a,b,c; 2003). Briefly, the subjects were presented with auditory stimulus sequences consisting of standard stimuli (n=1080; probability=90%) and deviant stimuli (n=120; p=10%) delivered in random order, except that each deviant stimulus was preceded by at least one standard stimulus. The interstimulus interval (ISI) was 490-530 msec. These stimuli were delivered binaurally through headphones (EEG) or eartubes (MEG). The subjects were instructed to ignore the stimuli and watched a silent film to help them to do so.

The experiment consisted of three conditions. The first condition was to elicit MMN (or MMF) in response to duration change of pure tone stimuli (standard, 100-ms duration; deviant, 50-ms duration). In the second and third conditions, vowel stimuli were presented, to elicit MMN (or MMF) in response to a duration change of phoneme (Condition 2) (standard, Japanese vowel /a/ with a 150-ms duration; deviant, /a/ with a 100-ms duration) and an across-phoneme change (Condition 3) (standard, Japanese vowel /a/ with a 150-ms duration; deviant, /o/ with a 150-ms duration). These vowel stimuli were spoken by a native-Japanese-speaking actor, digitized using the NeuroStim system (NeuroScan Inc., U.S.A.), and edited to have duration of 100 or 150 ms, a loudness of 70 dBSPL and a rise/fall time of 10 ms. The frequency spectra for the vowels were as follows: /a/, formant (F) 0 = 140 Hz, F1 = 760, F2 = 1250, F3 = 2750, and F4 = 3600; /o/, F0 = 140 Hz, F1 = 480, F2 = 770, F3 = 2820, and F4 = 3600. The frequency of the pure tone stimuli was 1000 Hz, which was nearly equal to the central frequency of the formants of the vowel stimuli. The order of the three conditions was counterbalanced across the subjects.

2.3 EEG/MEG recordings

Subjects underwent the EEG and MEG experiments 2-4 weeks apart. The order of the EEG/MEG experiments was counterbalanced across subjects. For either EEG or MEG experiment, we asked the subjects to report whether and how they perceived the auditory stimuli immediately after all of the three sessions were completed. This question was to confirm that they perceived /a/ and /o/ stimuli as vowels.

2.3.1 EEG recording

Please insert Figure 1 about here.

The EEG recording procedure has been described in detail elsewhere (Kasai et al., 2002a,b,c). EEGs were recorded via a 128-electrode cap (Neurosoft, Inc.) (Fig. 1). The tip of the nose was used as the reference for all of the electrodes. Two electrodes were placed at the outer canthus and above the left eye to monitor eye movements. The sampling rate was 500 Hz/channel, and the analog filter band-pass was 0.1-100 Hz. The analysis period was 512 msec, including a 64-msec prestimulus baseline. The baseline was corrected separately for each channel according to the mean amplitude of the EEG over the 64 ms preceding the stimulus onset. Averaging and artifact rejection were conducted offline. The first 10 stimuli were automatically excluded from averaging. The EEG epochs that contained peak-to-peak amplitudes exceeding 50μV at any site and electrooculogram waves exceeding 150μV in amplitude were automatically excluded from averaging. The average waveforms were obtained separately for deviant and standard stimuli, and digitally filtered with a cutoff frequency of 30 Hz. The number of accepted responses for deviant stimuli over the channels was approximately 100 (range: 80-120) for all subjects.

The MMNs were measured in difference waveforms obtained by subtracting ERPs of standard stimuli from those of deviant stimuli (Fig. 2). The peak latency of global field power (GFP; Lehmann and Skrandies, 1980) of the grand mean waveforms was as follows: tone-duration, 162 msec; phoneme-duration, 190 msec; across-phoneme, 162 msec (Fig. 2). Individual MMN amplitudes were then determined as the averaged potential within a 100-ms time window around the above-mentioned latency for each condition.

Please insert Figure 2 about here.

2.4. MEG recording

The recording and analysis procedures were the same as those described elsewhere (Kasai et al., 2001; 2002c; 2003). Magnetic fields were recorded in a magnetically shielded room (NKK Plant Engineering Co., Japan) with a 122-channel magnetometer (Neuromag Ltd., Finland; Knuutila et al., 1993). This whole-head magnetometer consists of 61 dual-sensor units, each with two orthogonal planar gradiometers for recording maximal signals directly above the source (Hämäläinen et al., 1993). The subjects sat on a chair with their head inside the helmet-shaped magnetometer. The position of the magnetometer with respect to the head was determined at the beginning of the task under each condition by recording the magnetic fields produced by currents fed into three indicator coils at predetermined locations on the scalp. The locations of these coils in relation to the preauricular points and nasion were determined with an Isotrak 3D-digitizer (Polhemus TM, U.S.A.) before the start of the experiment. One electrode was placed at the outer canthus and another one below the left eye to monitor eye movements.

MEG epochs were averaged separately for standard and deviant stimuli online. The duration of the averaging period was 512 msec, including a 64 msec prestimulus baseline. The recording band-pass was 0.03-100 Hz, with a sampling rate of 500 Hz. The first 10 stimuli were automatically excluded from averaging. Epochs coinciding with electrooculogram movement or MEG exceeding 150μV or 3000fT/cm were also excluded from averaging. One condition lasted until 100 deviant stimuli without contamination of artifacts were accepted. Averaged responses were digitally filtered with a band-pass of 1-30 Hz.

For each subject under each condition, equivalent current dipoles (ECDs) for MMF were calculated primarily according to the method of Alho et al. (1998b). Briefly, the MMF was determined from the difference curves obtained by subtracting the response to standard stimuli from that to deviant stimuli. Then, ECDs were determined using a least-squares fit at 2-msec intervals from 100 msec to 250 msec. The calculation, using spherical head model, was performed using a subset of 44 channels over the temporal brain areas separately for each hemisphere (Fig. 4). The sphere was fitted to scalp using each individual's magnetic resonance imaging. ECDs with a maximal goodness of fit (GOF) $\geq$ 60% were included in the analysis. In this calculation, we rejected channels (0-14 channels for each hemisphere) containing artifacts until the dipole fulfilling the criteria was successfully calculated. The ECD analysis was successful for most subjects but failed for some subjects (N=2, tone-duration, right hemisphere; N=1, phoneme-duration, left hemisphere; Table 1). These failures may be due to the low signal in that hemisphere. The mean number of channels used in the ECD calculation (max=44) was: tone-duration, left: 43.3; tone-duration, right: 43.6; phoneme-duration, left: 41.3; phoneme-duration, right: 42.2; across-phoneme, left: 43.2; across-phoneme, right: 43.7. There was no significant difference between conditions (p=0.11). In most of the data, the number of channel used was 42-44 (N=54 out of 60 [10 subjects * 3 conditions * 2 hemispheres]).

2.5. Statistical analyses

EEG data

Averaged MMN amplitudes across 22 electrode sites where they were evident (Figure 1) were used in repeated measures ANOVA comparing MMN strength between conditions. Pearson's product moment correlations were used in analyses of the correlations between averaged MMN amplitude of each condition and hemisphere.

MEG data

ECD strengths were compared between conditions using repeated measures ANOVA. Pearson's product moment correlations were used in analyses of the correlations between ECD strength of each condition and hemisphere.

EEG-MEG correlation

Pearson's product moment correlations were used in analyses of the correlations between ECDs of MMF and MMN amplitudes for each of 22 electrode sites (Fig. 1) where the MMN amplitudes were maximal, for each condition and hemisphere. The same correlational analyses were performed between the ECDs of MMF and the averaged MMN amplitudes across 22 electrode sites in each hemisphere. For this analysis, nose-referenced and average-referenced data were compared. Since MMN is assumed to have a negative amplitude at frontocentral electrodes and the dipole strength of MMF has always a positive value, negative correlations were expected. The Bonferroni correction for multiple statistical correlations was used as there were no initial predictions of significance for some of the variable combinations analyzed (significant level: $p=0.00036$; 0.05/138 correlations; 1 MEG index [ECD] X 23 EEG indices [22 channel + averaged] X 3 conditions X 2 hemispheres). However, all correlations of $p<0.05$ have been reported for the reader's convenience.

3. Results

For both EEG and MEG experiments, all subjects reported that the duration of pure-tone (vowel) stimuli had sometimes been shortened abruptly for the first (second) condition and that they sparsely heard vowel /o/ among sequences of repetitive vowel /a/ for the third condition.

EEG data

Please insert Table 1 and Figure 3 about here.

The main effect of condition of the MMN amplitude was $F[2,18]=1.23$, $p=0.32$, indicating that there was no significant difference in the amplitude between deviant types (Table 1, Figure 3). There were also no significant correlations between different conditions ($p>0.06$). However, there were significant correlations between left and right hemisphere within the same deviant type for all conditions (p's=0.04, 0.03, <0.001 for tone-duration, phoneme-duration, across-phoneme condition, respectively).

MEG data

Please insert Figure 4 about here.

The main effect of condition of the ECD strength yielded a trend-level significance ($F[2,12]=3.64$, $p=0.06$). Therefore, each two types of deviants were then compared. Tone-duration vs. phoneme-duration conditions resulted in a significant difference (tone duration < phoneme duration; $p=0.02$). Comparisons between phoneme-duration vs. across-phoneme, and tone-duration vs. across-phoneme conditions, were not significant. However, the mean number of channels used in the ECD calculation (max=44) was 43.3 (left) and 43.6 (right) for the tone-duration condition, and 41.3 (left) and 42.2 (right) for the phoneme-duration condition, and not significantly different between deviant types. Moreover, mean GOF was 78.9% (left) and 85.0 (right) for the tone-duration condition, and 80.5% and 79.8 for the phoneme-duration condition, again not significantly different. There were no significant correlations between ECDs of each condition and hemisphere.

EEG-MEG correlation

Please insert Table 2 and Figure 5 about here.

There was no significant negative correlation between MEG-ECDs and MMN amplitudes for each site under any of the conditions or for either hemisphere ($p \geq 0.08$ for all correlations; Table 2, Fig. 5). No significant negative correlation was obtained between mean amplitudes of MMN and MEG-ECDs under any of the conditions or for either hemisphere. Additionally, using average reference yielded chance-level improvement in the correlation between the two indices; out of 6 conditions, correlation coefficients got better in three conditions (tone-duration, left and right; across-phoneme, left), while they got worse in the other three conditions (phoneme-duration, left and right; across-phoneme, right).

4. Discussion

To our knowledge, this is the first report to evaluate the similarity of MMN and MMF in response to both tones and speech sounds in a same group of healthy adults. Our results suggest that the inter-subject differences in response strength are not significantly replicated between MMN and MMF.

There may be several reasons for a lack of correlations between EEG and MEG indices of mismatch response. The most important consideration should be focused on the noise issue. For MMN amplitudes, there was no difference in amplitude between types of deviants. For ECD calculation, there was also no difference in GOF or number of channels used in the calculation. Therefore, we did not detect any significant difference in the level of noise between conditions either for MMN amplitude or ECD. Moreover, while the MMN amplitudes were not significantly different between types of deviants, the ECD strength showed a trend-level difference derived from a significant difference between tone-duration and phoneme-duration conditions, indicating that the data from different deviants behaved the different way between EEG and MEG. Therefore, a possibility may be ruled out that the group level correlations existed but were not shown statistically due to high amount of noise at individual level. Another possibility is that the overall noise was too high to yield correlations between MMN and MMF. However, trying to improve the noise problem by consideration of reference did not yield a better correlation between the two indices at least in this study. Thus, future investigations should be necessary to determine how the noise in MMN/MMF measurement can be reduced (Sinkkonen and Tervaniemi, 2001; Näätänen et al., 2004) and whether or not this treatment would yield better correlations between the two indices.

Other possibilities of the lack of correlations should be also discussed. First, scalp-recorded EEG and MEG reflect different aspects of electric activities arising from the neural population. Namely, in contrast to electrical fields, magnetic fields are not influenced by intervening tissues of different conductivities. Moreover, an MEG selectively detects tangential vectors of electrical currents, whereas an EEG is more sensitive to currents radial to the scalp. Therefore, it may be possible that MMN amplitude and MMF strength which were measured and calculated from the same original electric activity are not proportional. The second reason, which is pertinent to the first, may be that electrical MMN amplitude at one hemisphere may be influenced by MMN generator sources of both hemispheres due to volume conductance of the intervening tissues. This discussion is supported by the results that there were consistently significant correlations between MMN amplitude of left and right hemisphere for the same deviant type, while such correlations were not evident for ECDs. The third reason, although speculative, may be that ECD is theoretically thought to be stronger when the activations of the neuronal population subserving certain information processing in the brain synchronize in time and are regionalized, whereas the amplitude of a certain ERP component is largest when the extent and strength of the neuronal activities are maximal (Kasai et al., 2003). The fact that maximal ECD and maximal amplitude occurs in a different time and situation may result in a lack of significant correlation between the indices.

The results of the present study suggest that before MMN and MMF can be applied as clinical indices of individual ability of auditory sensory memory, further work is needed to establish the differential significance of recording MMN and MMF in healthy individuals and patients with various illnesses. Toward this end future studies should record both MMN and MMF in normal and pathological populations to assess the functional significance of these two indices at the behavioral, neuropsychological, and neurophysiological levels.

We need to comment on the methodological consideration of this study. First, the sample size was relatively small. However, since we did not find significant correlations at a very liberal level for significance of $p=0.05$ (all negative correlations were $p \geq 0.08$; Bonferroni-corrected significant level=0.00036), the conclusion would not meaningfully change even if the sample size was improved. Second, the simultaneous recording of EEG and MEG might be more optimal, however, test-retest replicability of MMN over short periods (2-4 weeks) has been shown to be very high in many studies (Escera et al., 2000; Frodl-Bauch et al., 1997; Joutsiniemi et al., 1998; Kathmann et al., 1999; Pekkonen et al., 1995; Tervaniemi et al., 1999). Third, Sinkkonen and Tervaniemi (2001) discussed optimal parameters for measurement of MMN(F). It might be an interesting question to ponder how the measurement of the electric MMN and magnetic MMF were improved to be correlated with each other.

In conclusion, the lack of significant correlation between EEG and MEG recordings of auditory mismatch suggests an important avenue for further research to establish the differential significance of recording MMN and MMF in healthy individuals and patients with various illnesses.

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Figure legends

Fig. 1

Electrode Position Map for the 128-channel EEG recording system. Channels selected for correlational analyses are indicated by dashed squares for each hemisphere.

Fig. 2

EEG Fz waveform and 2D-topography in each condition. Left, tone-duration; middle, phoneme-duration; right, across-phoneme condition. Negativity is denoted by the upward deflection. The 2-D locations of the electrodes were determined by projecting the 3-D locations onto the 2-D surface. The electrode net was first applied to the model head and the electrode positions were marked. Next, the polar coordinates (from the vertex) were used to project the location of the site onto the 2-D surface.
The latency for 2D-topography was indicated below each mapping. A, anterior; P, posterior; L, left; R, right.

Fig. 3

Individual MMN waveforms at F3 and F4 in each condition. N=10 curves were overplotted. Negativity is denoted by the upward deflection.

Fig. 4

MMF curves in each condition for a representative subject. 44 channels used in the dipole analysis was enclosed in solid pentagon for each hemisphere (shown only in the tone-duration condition). Representative channels where maximal MMF responses were evoked were encircled for each hemisphere, and enlarged curves were also shown at the bottom.

Fig. 5

Scatterplots depicting a correlation between ECD strength and MMN amplitude (mean amplitude across 22 channels) for each condition and hemisphere.

Table 1. MMN and MMF indices

	MMN amplitude* [micro-V]			MMF (ECD strength [nA·m])		
	N	Mean	SD	N	Mean	SD
Tone-duration, left	10	-1.66	0.52	10	23.1	12.9
Tone-duration, right	10	-2.04	0.58	8	29.1	12.9
Phoneme-duration, left	10	-2.02	0.62	9	35.9	19.0
Phoneme-duration, right	10	-1.72	0.84	10	27.5	14.3
Across-phoneme, left	10	-2.38	1.29	10	28.1	11.2
Across-phoneme, right	10	-2.39	1.19	10	25.7	10.3

MMN, mismatch negativity; ECD, equivalent current dipole
* Averaged MMN amplitudes across 22 electrode sites in each hemisphere.

Table 2. Correlation between MMN and MMF

			MMN (Each channel)		MMN (Averaged)	
	condition	hemisphere	Range of R value	Range of P value	R value*	P value
ECD	Tone-duration	Left (N=10)	-0.47 ~ 0.42	0.17 ~ 0.97	0.83	0.003
		Right (N=8)	-0.21 ~ 0.65	0.08 ~ 0.98	0.35	0.40
	Phoneme-duration	Left (N=9)	-0.35 ~ 0.48	0.19 ~ 0.99	0.14	0.73
		Right (N=10)	-0.42 ~ 0.44	0.2 ~ 0.96	-0.32	0.37
	Across-phoneme	Left (N=10)	-0.44 ~ 0.14	0.21 ~ 0.95	-0.20	0.57
		Right (N=10)	-0.17 ~ 0.53	0.12 ~ 0.99	0.37	0.30

*A more negative R value indicates a better correlation between ECD strength and MMN amplitude. Therefore, R=0.83 for the correlation in the tone-duration condition (left hemisphere) was not considered significant.

Figure 1.

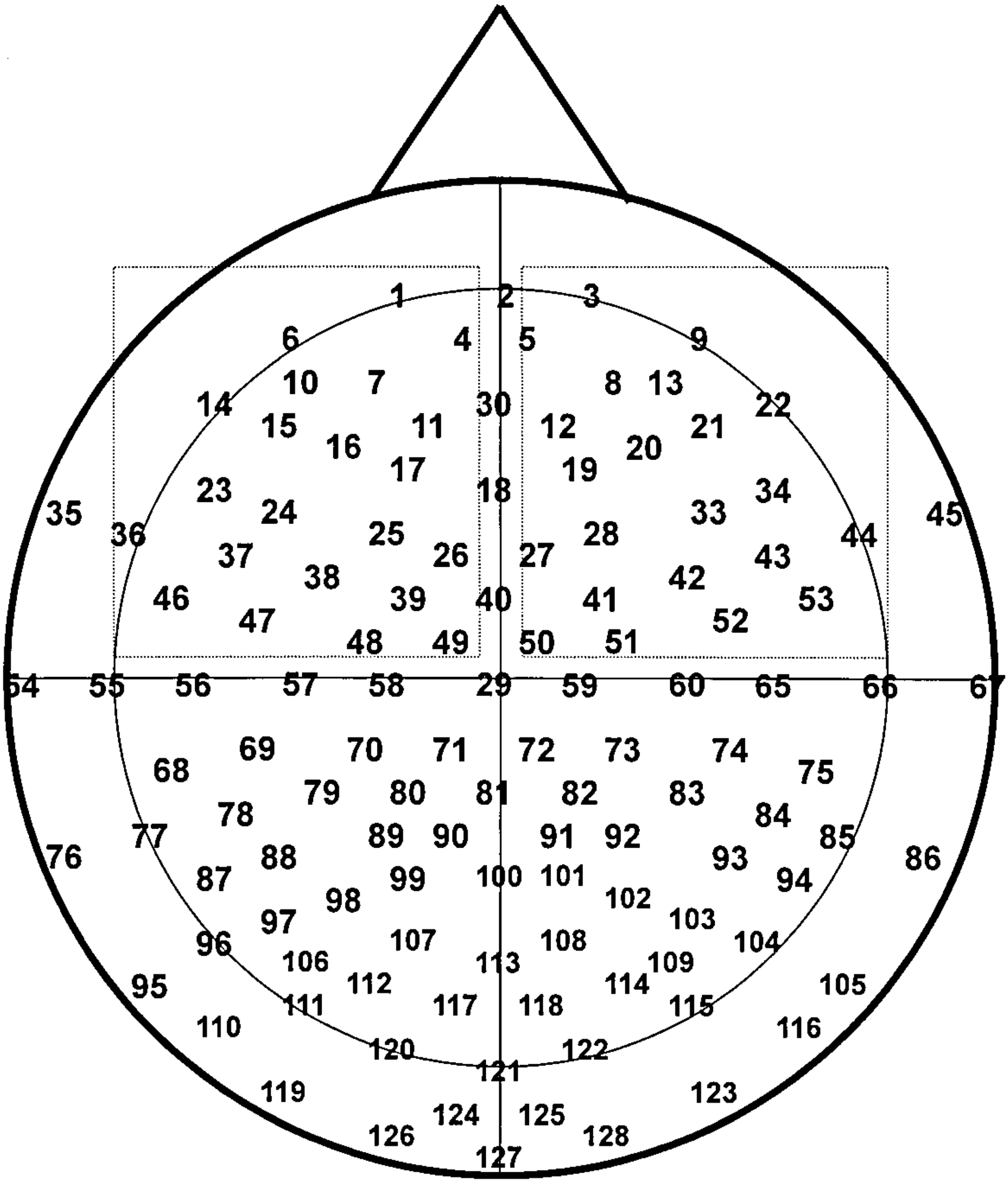
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Figure 2.

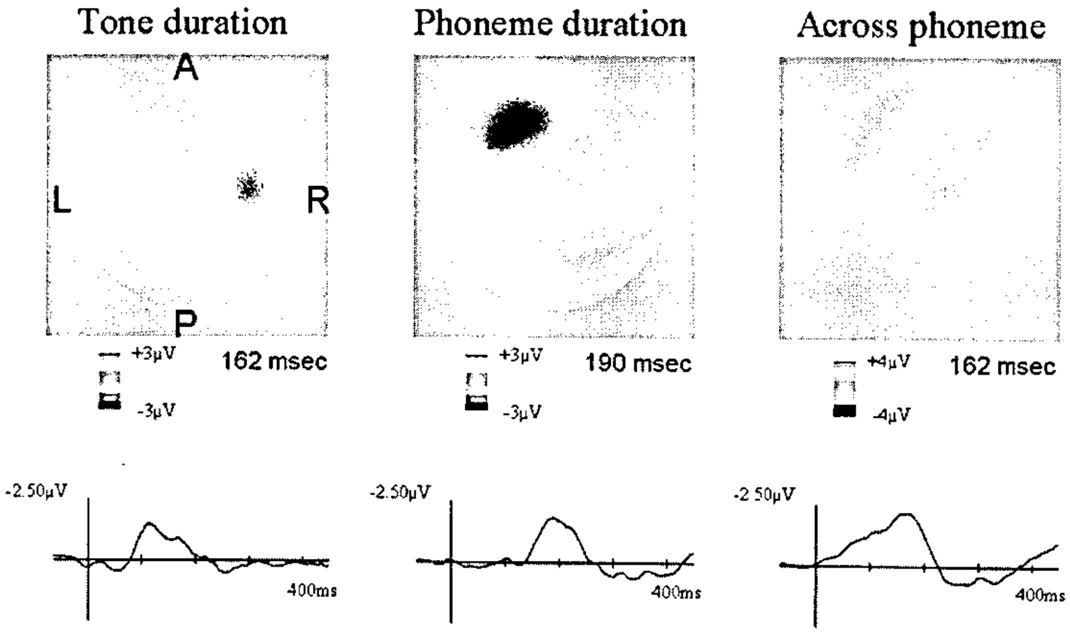
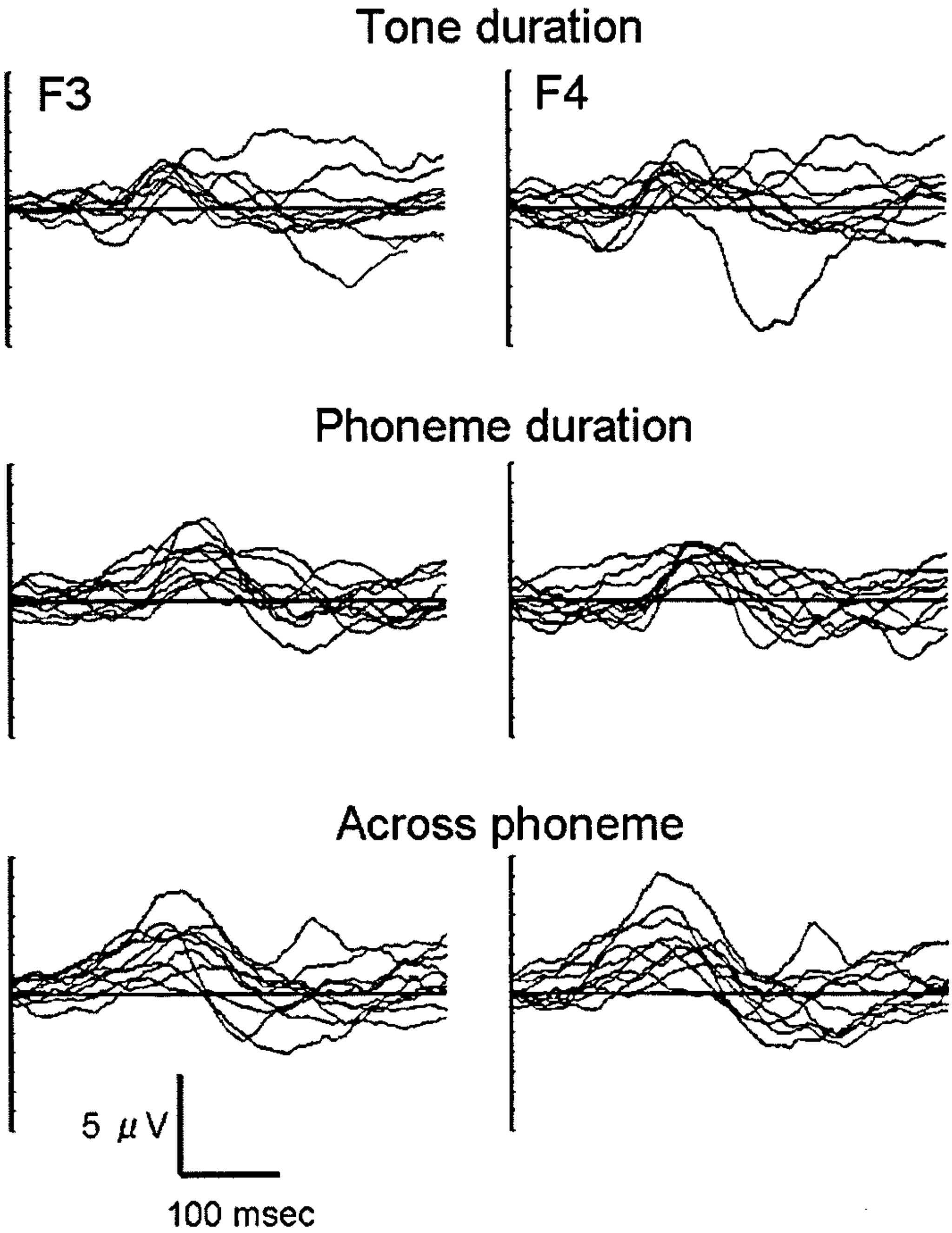

Tone duration
A
L
R
P
+3μV
-3μV
162 msec
Phoneme duration
+3μV
-3μV
190 msec
Across phoneme
+4μV
-4μV
162 msec
-2.50μV
400ms
-2.50μV
400ms
-2.50μV
400ms

Figure 3.


Tone duration
F3
F4
Phoneme duration
Across phoneme
5 μV
100 msec