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A Comparison Of The Mismatch Negativity and A Differential Waveform Response

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## Abstract

A mismatch negativity response (MMN) and a new “differential” waveform were derived in an effort to evaluate a neural refractory or recovery effect in adult listeners. The MMN was elicited using oddball test runs in which the standard and deviant stimuli differed in frequency. To derive the differential waveform, the same standard and deviant stimuli were presented alone. MMN responses were obtained by subtracting the averaged responses to standards from the deviants. The differential waveforms were obtained by subtracting the averaged responses to standards presented alone from deviants presented alone. Scalp topography for the MMN and differential waveforms were similar. A significant ( $p < .05$ ) positive and negative correlation was found between the earlier and later components of the bimodal MMN and the N1 and P2 component of the differential waveform, respectively. Further, N1 and P2 of the differential waveform were significant ( $p < .05$ ) predictor variables of early and late peak amplitudes of the MMN. These results suggest that refractory effects may overlay/modify the morphology of the MMN waveform.

Key words: auditory event-related potentials, mismatch negativity, neural recovery

## An Evaluation Of The Mismatch Negativity and A Differential Waveform Response

The mismatch negativity response (MMN) has been extensively investigated as a cortical response that possibly indexes an early pre-attentive auditory discrimination process and the underlying sensory memory upon which the discriminative process depends. This derived auditory event-related potential (ERP) has been examined under a variety of laboratory conditions in an attempt to understand a listener's capacity for storage and comparison of auditory information (for recent reviews see Näätänen 1995; Picton et al 2000,). The MMN is elicited by occasional deviant stimuli in a sequence of otherwise identical stimuli, even in the absence of attention (Näätänen et al 1978, 1992; Cowan, 1995), possibly reflecting an automatic change detection mechanism. Näätänen et al (1978) proposed the memory trace hypothesis, interpreting the MMN as a memory-related process rather than an activation of new afferent elements specifically tuned to the deviant stimuli.

It has been well documented (Davis et al 1966; Nelson & Lassman, 1968, 1973, 1977; Butler, 1973; Budd et al 1998) that increasing the interstimulus interval (ISI) between adjacent sounds in a stimulus train will result in increased amplitudes of the exogenous components of the late auditory evoked potential (e.g., N1, P2). The most common laboratory method employed to derive the MMN involves an oddball paradigm employing a train of repetitive, homogeneous tones (i.e., "standards"), which are interspersed with tones that differ acoustically (i.e., "deviants") from the standards. The deviant stimuli evoke negativity between 100 and 200 ms that is not evident in response to the standard stimuli. This negativity is typically expressed by a difference wave (i.e., the waveform response to the deviant minus the standard) referred to in the scientific literature as the MMN. Most acoustic features that are discernable have been reported

to be able to elicit the MMN (e.g., changes in intensity, frequency, duration, rise time, and perceived location).

One of the major technical drawbacks of this oddball approach is that the standards are presented more frequently in the stimulus trains than the deviants. This technique inherently involves comparing ERPs obtained from two sequences of stimuli that differ, not only in a particular stimulus feature, but also in their repetition rate (i.e., the “inter-standard interval” is shorter than the “inter-deviant interval”). Thus any inter-standard/deviant dependent amplitude changes in the ERPs could be erroneously interpreted as reflecting changes in the underlying MMN generator(s). Some researchers who investigated the possibility of a neural refractory artifact concluded that such effects did not significantly contaminate the MMN response (Näätänen et al 1989a, b; Schroger & Wolff, 1996; Takegata & Morotomi, 1999; Deacon et al 2000; Jacobsen & Schroger, 2001; Czigler et al 2002). Others, however, have reported to the contrary. For example, Butler (1968, 1972) and Butler et al (1969) demonstrated that when stimuli were interleaved between trains of test stimuli, the N1-P2 amplitude to the test stimuli decreased relative to when the test stimuli were presented alone. That is, increasing the separation in frequency between the test stimuli and the interleaved stimuli resulted in a smaller decrease in the N1 amplitude. Picton et al (1978) and Näätänen et al (1988) latter replicated these effects. These findings were interpreted as reflecting refractory effects of the N1 generators.

It has been suggested that there may be two possible sources for the negativity in the MMN (Scherg et al 1989). The first is the refractoriness of the N1 generators and the second a process that represents cerebral processing of the acoustic difference between stimuli. Scherg et al using a dipole source analysis confirmed a two-component model of the MMN with sequential but partly overlapping activities. The earlier component “corresponded to the N1 dipole sources

and the latter to a more anteriorly located dipole with an orientation more lateral than N1” (p. 336). Additional dipole modeling studies have confirmed these general findings (Sams et al 1991; Tiitinen et al 1993). The two-component model supports the notion that the difference in the response to the deviant versus the standard stimuli reflects an independent MMN component that is spatially and functionally different than the N1 response (e.g., Näätänen 1995). Further, it is thought that this neural population responds exclusively to changes in acoustic stimuli.

An alternative interpretation is, however, plausible. May et al (1999) offered another explanation following their computational and experimental examination of post-stimulus inhibition/refractory mechanisms underlying the MMN. In a paradigm similar to Butler’s (1968) original work, they compared responses to tonal stimuli presented as deviants among standards (i.e., an oddball condition) versus deviants presented alone. They predicted the response to the tone should be attenuated and delayed in the oddball condition due to post-stimulus inhibition. This prediction is contradictory to the model that assumes the MMN response results from a mechanism(s) that respond(s) exclusively to change. Positive evidence that the MMN is elicited by a change detection mechanism (e.g., Näätänen et al 1978, 1992; Cowan, 1995) would be a larger response to the deviant in the oddball condition than to the deviant in the alone condition. Their findings were consistent with their predictions (i.e., response to the deviant was attenuated and delayed in the oddball condition) suggesting that the response to the stimulus in the oddball condition and the alone condition originate from the same source. They concluded that “the differences in amplitude between the deviant and the standard responses, generated at their respective tonotopic locations, is due to different combinations of adaptation and lateral inhibition at the deviant and standard locations. The MMN, then, is the activity produced by the

population mapping the deviant frequency” (May et al 1999, p. 116) and not to a neural population that responds exclusively to the changes in stimulation.

The issue of a possible artifact related to neuronal refractoriness has recently become more critical since there has been a change in emphasis from conducting normative studies to investigating differences in the MMN which result from various forms of central nervous system (CNS) pathologies. Researchers have reported a significantly greater attenuation of the MMN response for stimuli delivered at longer ISIs in specific clinical populations including the elderly (Gaeta et al 1992; Woods 1992; Pekkonen et al 1996), children with CATCH-22 syndrome learning problems (Kraus et al 1996; Cheour et al 1997), and those suffering from Parkinson's disease (Pekkonen et al 1994), Alzheimer's disease (Kazmerski et al 1997), chronic alcoholism (Ahveninen et al 2000; Grau et al 2001), and coma (Kane et al 1993). Since certain neural refractory functions are also known to vary with different forms of CNS dysfunction (Shagrass et al 1971; Alho et al 1994; Ornitz et al 1974; Papanicolaou et al 1984; Shucard et al 1984), it is possible that in some studies, the MMN response and neural refractory effects may temporally overlap. If that were the case, erroneous interpretations of the clinical significance of the altered waveform morphology could result.

We recently reported results from our laboratory that provided evidence that neuronal refractory or recovery effects for stimulus changes involving both frequency (Walker et al 2001) and speech (Cranford et al 2003) can substantially alter the morphology of the difference wave from which the MMN is measured. While in both experiments we confirmed the existence of an endogenous MMN phenomenon, there was also evidence to suggest that strong ISI-dependent stimulus response amplitude effects may overlap and interfere with identification of the MMN response. That is, MMNs to tonal and speech stimuli from young adults obtained with the

oddball paradigm described above evidenced ISI-dependent amplitude changes in N1 and/or P2 that altered the morphology of the difference waves.

The present project was designed to further investigate the possible influence of neural refractory or recovery effects on the MMN. In a single ERP recording session, the same acoustic stimuli were presented to listeners in two different test paradigms. First, ERPs were recorded with a traditional oddball paradigm to derive the MMN response. Second, ERPs were recorded with a paradigm to derive a “differential waveform” that reflected amplitude changes related to differences in stimulus presentation rates (i.e., neural refractoriness). It was hypothesized that there would be a relationship between the magnitude of neural refractory effects and the amplitude of the MMN. Such a relationship could suggest that the two neural phenomena are functionally linked.

## Methods

### *Participants*

Twelve young adult females ( $M = 21$  years; Range: 20-24) participated. All participants presented with normal middle ear function as assessed with immittance audiometry (American Speech-Language-Hearing Association, 1997) and normal hearing sensitivity defined as having pure-tone thresholds of  $\leq 20$  dB HL (American National Standards Institute, 1996) at octave frequencies from 250 to 8000 Hz. In addition, participants were right handed with negative histories of neurologic disorders, head trauma and/ or surgery, otologic disease (including otitis media), vertigo or persistent tinnitus, ototoxic drug use, speech and language disorders, or significant occupational and recreational noise exposure.

### *Apparatus*

A double wall sound-treated electrically shielded audiometric suite (Industrial Acoustics Corporation), meeting specifications for permissible ambient noise (American National Standards Institute, 1999), served as the test environment. Participants were tested with a PC-based Neuroscan system and Synamps 16-bit amplifiers. Tonal stimuli generated by the evoked potential system were applied to an insert earphone (Etymotic ER-3A) at 70 dB pSPL.

### *Procedure*

As indicated above, the present project involved presentation of the same acoustic stimuli in two different test paradigms. ERPs were recorded with a traditional paradigm to derive the MMN response and ERPs recorded with a second paradigm to derive a differential waveform that reflected amplitude changes related to differences in stimulus presentation rates (i.e., neural refractoriness). With both paradigms, tones were presented to the right ear of participants while they read a self-selected book. The MMN was elicited using two oddball test runs in which the standard and deviant stimuli were tone pulses differing in frequency (i.e., 1000 Hz and 1200 Hz, 50 ms duration, 10 ms rise/fall time). The two oddball runs were designed such that the standard in the first oddball was the deviant in the second oddball and vice-versa. The stimulus format for the two types of oddball test runs is shown in Figure 1a and 1b. Each oddball run involved the presentation of 1190 standards and 210 deviant stimuli. The probability of occurrence of the standard tones was 85% while that for the deviant tones were 15%. Stimuli were presented in a pseudo random sequence with an ISI of 500 ms. Each oddball run was designed so that at least three standards separated presentations of each deviant stimulus. In each test run, 20 standard stimuli preceded the occurrence of the first deviant stimulus. These 20 stimuli were not included in the response average. Responses to standard stimuli immediately following the deviant stimuli

were excluded from the response averages. MMN responses were derived by the traditional approach where the averaged ERP waveforms of the standards were subtracted from that recorded for the deviants in each of the two oddball runs (i.e., runs “a” and “b” in Figure 1). We employed this approach to extract the MMN because of its popularity with assessing both normal and clinical populations (e.g., Groenen et al 1996; Sasaki et al 2000; Sabri & Campbell, 2001; Näätänen et al 2004). Furthermore, earlier research from our group (Walker et al 2001) lead us to believe that, under comparable test conditions (i.e., same stimulus deviance, ISI, and recording parameters), the MMNs elicited from other extraction techniques are not significantly different.

To derive the differential waveform, each participant was presented with four additional test runs. In each of these runs, the standard or deviant stimuli from the original oddball test sequences were presented alone (i.e., "standard-alone " and "deviant-alone" test conditions). The stimulus sequences used in each of these control runs were derived directly from the respective oddball sequences that were employed to elicit the MMN. For example, during deviant-alone test runs, the amplitude of the standard stimuli were attenuated well below hearing thresholds while the deviant stimuli were presented at their original amplitude levels. Thus on each control run, the respective deviant or standard stimuli were presented with a variable ISI that matched those used in the oddball runs. The stimulus format for each of the two stimulus-alone and two deviant-alone control runs are illustrated in Figure 1c-f. The differential waveforms were obtained by subtracting the waveforms elicited during runs in which each stimulus served as a standard-alone from runs in which it served as the deviant-alone (i.e., deviant-alone control run “e” minus standard-alone control run “d” and deviant-alone control run “f” minus standard-alone control run “c” in Figure 1).

Thus, using the two test paradigms, two MMNs and two differential waveforms were derived for each of the 12 young listeners. The order of presentation of the six types of test runs for each participant was determined using Latin square design. Electroencephalogram (EEG) activity was recorded from eleven electrode sites (i.e., F<sub>3</sub>, F<sub>Z</sub>, F<sub>4</sub>, C<sub>3</sub>, C<sub>Z</sub>, C<sub>4</sub>, P<sub>3</sub>, P<sub>Z</sub>, P<sub>4</sub>, M<sub>1</sub>, and M<sub>2</sub>) placed according to the 10-20 system (Jasper, 1958). Electrodes were positioned vertically above and below the left eye to monitor ocular movements. All electrodes were referenced to the tip of the nose. Electrode impedance was maintained below 3000 ohms. Individual sweeps of time-locked EEG activity extended from -50 to +500 ms relative to stimulus onset. EEG activity was amplified 1000 times, analog filtered (i.e., 1-70 Hz, 24 dB/octave slope), and digitized at an analog-to-digital rate of 500/s. The digitized epochs were sent to a microcomputer for offline averaging and digital filtering (i.e., 1-40 Hz, 24 dB/octave). The 50 ms prestimulus recording was used to establish a baseline to correct for the DC level of background EEG activity. The voltages from the prestimulus data points were averaged and then subtracted from the single sweeps of epoch EEG files prior to averaging. Ocular movement artifacts were digitally removed from the epochs (Semlitsch et al 1986). Epochs containing artifacts exceeding  $\pm 50 \mu\text{V}$  were rejected from averaging.

With the MMN and differential waveforms derived for each participant overlaid, four peak amplitude values were determined: the peak amplitude of the MMN segment that fell within the N1 latency window of the differential waveform (i.e., the early component of the MMN); the peak amplitude of the MMN segment that fell within the P2 latency window of differential waveform (i.e., the late component of the MMN); N1 amplitude of the differential waveform; and P2 amplitude of the differential waveforms. Peak amplitude was defined relative

to baseline. The respective waveform peaks were independently selected by each of three experienced examiners (SE, LW, JLC) with a required two-thirds consensus.

### Results

Group averaged waveforms recorded from  $C_z$  comparing ERPs recorded for standards in the alone run and standards in the oddball run are displayed in Figure 2.<sup>1</sup> The N1 and P2 amplitude for standards in the alone run and standards in the oddball run were similar (cf. -0.73 vs. -0.75  $\mu\text{V}$  and 0.98 vs. 0.96  $\mu\text{V}$ , for N1 and P2 respectively).<sup>2</sup> There is no significant difference between the mean peak amplitude for both N1 [ $F(1, 10) = .059, p = .81, \eta^2 = .006, \phi = .056$ , at  $\alpha = .05$ ] and P2 [ $F(1, 10) = .054, p = .82, \eta^2 = .005, \phi = .055$ , at  $\alpha = .05$ ] averaged ERPs recorded for the standard in the oddball condition versus the standard alone (i.e., averaged responses in oddball runs in Figure 1a and 1b versus 1c and 1d). Figure 3 displays group averaged ERP waveforms recorded from  $C_z$  for deviants in the oddball run and deviants in the alone run (i.e., averaged responses in oddball runs in Figure 1a and 1b versus 1e and 1f). In contrast to Figure 2, N1 and P2 amplitude for deviants in the alone run was much larger, as expected, than for deviants in the oddball run (cf. -2.83 vs. -1.34  $\mu\text{V}$  and 4.04 vs. 1.74  $\mu\text{V}$ , for N1 and P2 respectively). A significant difference in average amplitude between both N1 [ $F(1, 10) = 16.41, p = .002, \eta^2 = .62, \phi = .95$ , at  $\alpha = .05$ ] and P2 [ $F(1, 10) = 19.34, p = .001, \eta^2 = .66, \phi = .97$ , at  $\alpha = .05$ ] ERPs recorded was found for deviants alone versus deviants in the oddball condition.

Grand averaged MMNs and differential waveforms were constructed by averaging respective waveforms from all participants as a function of electrode site. The two group-averaged MMNs and two differential waveforms recorded from  $C_z$  are shown in Figure 4. The two different MMNs and group-averaged differential waveforms at each electrode site were

compared using an Intra-class Correlation statistic (Neuroscan 4.0). This statistical measure permits one to compare data point differences between two waveforms at 275 points along the latency axis. As expected, the results revealed a high level of correlation between the two MMNs for all the electrode locations ( $M = 0.85$ ; Range = 0.70 to 0.96) and the two group-averaged differential waveforms ( $M = 0.96$ ; Range = 0.90 to 0.99). Similar results were also seen with Scherg et al (1989) who concluded that the magnitude of the recorded MMN depended on the magnitude of the deviance between the standards and the deviants, but is not significantly affected by the direction of the frequency change. Since both the group-averaged MMNs and differential waveform were highly correlated, the data were pooled together to create single MMN and differential waveform for subsequent statistical analyses.

The group-averaged MMN and differential waveforms recorded from the nine scalp locations plus the left and right mastoids are illustrated in Figure 5. In general, evidenced from the MMNs at all 11 scalp electrode sites, maximum negative amplitudes were located at midline and frontal locations (i.e.,  $C_Z$  and  $F_Z$ ). Also, Figure 5 illustrates similar scalp topography between the MMN and differential waveforms. That is, amplitude maxima were frontal and central (i.e.,  $F_Z$  and  $C_Z$ ). Further, all frontal and central waveforms were bimodal. Finally, Figure 5 also shows indication of the presence of a polarity reversal for both the MMN and differential waveform components when ERPs were recorded from the posterior scalp sites (i.e.,  $P_3$ ,  $P_Z$ , and  $P_4$ ). This polarity reversal is even more apparent at the left and right mastoid sites (i.e.,  $M_1$  and  $M_2$ ).

To investigate the relationship between amplitudes of the N1 and P2 components of the differential waveform and the early and later components of the bimodal MMN at  $C_Z$  and  $F_Z$ , correlation and linear regression analyses were performed. Statistically significant positive

correlations were found between N1 amplitude of the differential waveform and the peak amplitude of the MMN segment that fell within the N1 latency window of the differential waveform at both  $C_Z$  ( $r = 0.73, p = .0006$ ) and  $F_Z$  ( $r = 0.84, p < .0001$ ). Linear regression analyses revealed a statistically significant relation between N1 amplitude of the differential waveform and the peak amplitude of the MMN segment that fell within the N1 latency window of the differential waveform at both  $C_Z$  ( $p = .0010$ ) and  $F_Z$  ( $p < .0001$ ). That is, as N1 amplitude of the differential waveform increases the peak amplitude of the MMN segment that fell within the N1 latency window of the differential waveform increases. The bivariate scatterplots and respective linear regression lines for the peak amplitude of the MMN segment that fell within the N1 latency window of the differential waveform as a function N1 amplitude are presented in Figure 6. Statistically significant negative correlations were found between P2 amplitude of the differential waveform and the peak amplitude of the MMN segment that fell within the P2 latency window of the differential waveform at both  $C_Z$  ( $r = -0.49, p = .031$ ) and  $F_Z$  ( $r = -0.47, p = .036$ ). Linear regression analyses revealed a statistically significant relation between P2 amplitude of the differential waveform and the peak amplitude of the MMN segment that fell within the P2 latency window of the differential waveform at both  $C_Z$  ( $p = .032$ ) and  $F_Z$  ( $p = .037$ ). That is, as P2 amplitude of the differential waveform increases the peak amplitude of the MMN segment that fell within the P2 latency window of the differential waveform decreases. The bivariate scatterplots and respective linear regression lines for the peak amplitude of the MMN segment that fell within the P2 latency window of the differential waveform as a function P2 amplitude are presented in Figure 7.

## Discussion

The findings of the present study are twofold. First, these research findings are similar to numerous previous investigations that have demonstrated, when recorded with a standard oddball sequence, the existence of the MMN response which represents some form of preconscious endogenous neural process in the brain conditioned to respond to acoustic stimulus change (e.g., Näätänen 1995; Picton et al 2000). Our MMN response is similar in scalp topography but slightly smaller in amplitude. The reduced MMN amplitude is likely the result of different stimulus parameters employed (e.g., standard and deviant frequency separation and ISIs) and recording parameters. The electrode montage used in the present investigation probably influenced this variation of the typical scalp topography of the MMN. The MMN is usually reported to be larger frontally than centrally when a mastoid or earlobe reference is used (Woldorff et al 1991; Näätänen et al 1993). However with a nose reference, typically larger peak amplitudes are recorded for the central electrodes rather than the frontal electrodes (Sasaki et al 2000). Typical latency window for frequency deviants for MMN falls between 50 to 175 ms with ISIs of 0.5 and 1.5 ms (Pekkonen et al 1995). The MMN elicited at  $C_z$  in the present investigation fell between 29.7 ms and 119.4 ms with a mean peak amplitude of 1.17  $\mu\text{V}$  (range = 0.1 to 2.8  $\mu\text{V}$ ). Previous studies (Alho et al 1986; Novak et al 1990; Paavilainen et al 1991) report that MMN was found to invert in polarity at the mastoids below the auditory cortex especially when a nose reference was used. Such a polarity reversal of the MMN was also witnessed in the present investigation. Figure 5 shows the presence of a polarity reversal for both the MMN and differential waveform components when ERPs were recorded from the left and right mastoid sites (i.e.,  $M_1$  and  $M_2$ ). Moreover, the voltage distribution, though minimal, is asymmetric as reported in literature with predominant right superior frontal negativity (Giard et

al 1995). The mean peak amplitude of the MMN recorded at C<sub>4</sub> was 1.43  $\mu$ V (range = 0.88 to 2.5  $\mu$ V) while that recorded at C<sub>3</sub> was 1.37 $\mu$ V (range: 0.36 to 2.2  $\mu$ V).

The second finding was a significant relation between the amplitude of the MMN response and the magnitude of the differential waveform when the same standard and deviant stimuli were presented alone with variable ISIs matching those used in oddball runs. Specifically, the earlier component of the bimodal MMN was positively correlated with the early N1 component of the differential waveform, while the later occurring MMN component was negatively correlated with the later P2 differential waveform. Further, N1 and P2 of the differential waveform were significant predictor variables of early and late peak amplitudes of the MMN. These results suggest that refractory effects may overlay/modify the morphology of the MMN waveform consistent with previous findings (Butler 1968, 1972; Butler et al 1969; Picton et al 1972; Näätänen et al 1988; May et al 1999). As stated earlier, in the standard oddball approach, the standards are presented more frequently and with shorter ISIs in the stimulus trains than the deviants. This technique intrinsically involves comparing ERPs obtained from two sequences of stimuli that differ, not only in a particular stimulus feature, but also in their ISI. Consequently, any ISI-dependent amplitude changes in the ERPs (i.e., neural refractory or recovery effect) may influence the morphology of the MMN and hence interpretation of MMNs. These ISI-dependent refractory effects can dramatically alter the morphology of the resulting difference waves for both tonal and speech stimuli for this MMN extraction technique and others (Walker et al 2001; Cranford et al 2003). It is important to note, however, that the use of correlation and regression measures do not infer any kind of cause-effect relationship. While the present study found significant associations between two different ERP difference waves that were designed to isolate the MMN and neural refractory effects related to stimulus rate

differences, one could not conclude that refractoriness is the cause of the MMN phenomenon. At present, the statistical analyses only confirmed the associative and predictive relationship between the variables.

Näätänen et al (1989 a, b), in developing his “echoic memory theory”, argued that the topographical distribution of the MMN (with larger amplitudes over the right hemisphere) was different and independent of the topographical distribution of the N1-P2 ERP complex (which favors a contralateral distribution). While the present authors are not aware of any research that has investigated the scalp distribution of ISI-dependent neuronal refractory or recovery effects associated with different components of the late auditory evoked potential response, numerous MMN studies have shown that the scalp distribution of the MMN response does change depending on the nature of the stimulus feature being studied. For example, Giard et al (1987) and Paavilainen et al (1991) have found that the topography of the MMN is different when elicited by changes in intensity, frequency, or temporal duration. In the present study, similar scalp topographies for the MMN and refractory effects were found, with fronto-central amplitude maxima, for both neural phenomena. Further studies are needed to determine whether this topographic similarity occurs for changes involving intensity or duration. The present study also found evidence of overlap in electrode sites (i.e., posterior scalp locations as well as left and right mastoid sites) where polarity reversals in both the MMN and neural refractory effects were found. Although it is presently believed that the MMN may have multiple sites of origin (Csépe 1995), which is probably also true for refractory events, the findings herein support the possibility that both the MMN and refractory effects may share at least some common neural sources.

Näätänen et al (1987) have shown that, at least for simple stimuli, MMN amplitude increases when the ISI is shortened during oddball test runs, provided that the intervals between the deviants remain unchanged. This is in contrast to the fast decrement of the amplitude of N1 and P3b ERP components (Mantysala & Näätänen, 1987). The explanation offered for this phenomenon was that, when the repetition rate of the standard stimuli increases, the memory trace evoked by it becomes more intense. This strengthened memory trace is believed to be the cause of the more robust MMN. However, another possible explanation for this phenomenon could be that with the ISI of the standards changing independent of the deviants in the oddball, the disparity between the ISIs of the standards and deviants is heightened, which allows the occurrence of enhanced neuronal refractory effects.

At present, the laboratory test paradigms that are most commonly used to extract the MMN involve both changes in acoustic features (i.e., physical differences between standards and deviants) and changes in ISIs. We believe that whether the MMN phenomenon may involve activation of special neural units that have been conditioned to respond to stimulus change (i.e., “comparator” units or “deviance detectors”, e.g., Winkler et al, 1996), or responses of new neural units that are selectively tuned to the deviant rather than the standard stimuli is an issue that is still not resolved. Neuronal refractoriness may have been an uncontrolled variable in many earlier MMN studies. It is also well known that, in all sensory modalities, the later the occurrences of the neural components, the more prolonged are the refractory periods (Allison, 1962). The N1 and P2 components of the late auditory evoked potential have been reported to have recovery periods of seven seconds or longer (e.g., Nelson & Lassman, 1973; Picton et al 1976). Since the longest ISI with which MMNs can be recorded is at least ten seconds long

(Schroger & Winkler, 1995), this temporal overlap in the two respective functions opens the possibility that the two neural processes may not be functionally independent.

Recently Ulanovsky et al (2003) demonstrated a form of stimulus-specific adaptation of single neuron responses in the cat primary auditory cortex that is suggestive of a neural correlate of the MMN. Responses were recorded in the primary auditory cortex and medial geniculate body to tonal stimuli during an oddball paradigm where the probability of occurrence, frequency, and amplitude of the standard and deviant tones was manipulated. The responses to the deviant were stronger than the standard indicative of neuronal adaptation. This differential adaptation was more prominent when the frequency difference between the two was larger and when the deviant probability was smaller. This stimulus-specific adaptation was not evident in the medial geniculate body. A “difference signal” was calculated by subtracting the responses to the standard from the deviant stimuli. The difference signal and the MMN shared many of the same characteristics. The authors concluded that their results “provide the first direct evidence that neuronal adaptation has the right properties to account for MMN. Our comparison between MMN and DS [difference signal] suggests that a specific kind of adaptation, namely SSA [stimulus-specific adaptation] in single auditory cortex neurons, may underlie cortical MMN” (p.396).

Finally, those that have examined animal studies with a variety of mammalian species (including primates) have strongly suggested that the numbers of distinct neural populations in the brain that are selectively tuned to various simple and complex features of sounds may be far more extensive than previously believed (Covey, 2000). For example, although Näätänen et al (1989a, b) earlier reported MMNs can be recorded to decreases in both intensity and temporal duration and interpreted this as strong support of an endogenous origin for this response, there is

now evidence that questions this. Researchers evaluating single unit studies with animals have reported evidence for the existence of both intensity-specific (Pfungst & O'Conner, 1981; Suga & Manabe, 1982; Phillips & Orman, 1984; Phillips et al 1985, 1995) and duration-specific (Ehrlich et al 1997; He et al 1997; Guang-Di & Chen, 1998; Brand et al 2000; Casseday et al 2000; Covey, 2000) neural units in the mammalian brain. Thus, we believe that insufficient research data is currently available to determine how much of a difference, or what kinds of differences, are needed between standard and deviant stimuli before different populations of neural units would be activated. The activation of special neural units that are selectively tuned to stimulus "change", as required by current attention theories of the MMN process, could be only one of many possible complex-tuning mechanisms that exist in the brain.

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## Footnote

<sup>1</sup>We chose to evaluate waveforms recorded from  $C_z$  for two reasons. First our previous work focused on response recorded from  $C_z$  (Walker et al 2001; Cranford et al 2003). Second, it has been suggested that attentional processes influence the topographical distribution of the MMN (Woldorff et al 1991; Näätänen et al 1993). Further, the N2b process that is activated with attention is more strongly represented in the central electrodes ( $C_z$ ) rather than the frontal electrodes ( $F_z$ ).

<sup>2</sup>Data from one participant's was lost for these analyses of N1 and P2 ERPs.

## Figure Captions

*Figure 1.* Stimulus paradigm used in the two oddball conditions ('a' and 'b') and four 'alone' test conditions ('c', 'd', 'e', and 'f').

*Figure 2.* Group averaged waveforms recorded from C<sub>Z</sub> comparing ERPs recorded for standards in the alone run and standards in the oddball run.

*Figure 3.* Group averaged waveforms recorded from C<sub>Z</sub> comparing ERPs recorded for deviants in the alone run and deviants in the oddball run.

*Figure 4.* Group averaged waveforms recorded from C<sub>Z</sub> comparing MMNs from the two oddball paradigms and differential waveforms from the respective standard and deviant-alone control runs.

*Figure 5.* Grand averaged overlaid MMNs and differential waveforms recorded from eleven electrode sites.

*Figure 6.* Bivariate scatter plots and respective linear regression lines illustrating relationship between N1 amplitude of the differential waveform and the peak amplitude of the MMN segment that fell within the N1 latency window of the differential waveform at both C<sub>Z</sub> (filled squares) and F<sub>Z</sub> (open circles). Regression line equations for predicting the peak amplitude (μV) of the MMN as a function of N1 amplitude of the differential waveform at C<sub>Z</sub> =  $-.45 + .21 \times \text{N1 amplitude of the differential waveform}$ ;  $r^2 = .53$  and F<sub>Z</sub> =  $-.23 + .31 \times \text{N1 amplitude of the differential waveform}$ ;  $r^2 = .70$ .

*Figure 7.* Bivariate scatter plots and respective linear regression lines illustrating relationship between P2 amplitude of the differential waveform and the peak amplitude of the MMN segment that fell within the P2 latency window of the differential waveform at both C<sub>Z</sub> (filled squares) and F<sub>Z</sub> (open circles). Regression line equations for predicting the peak amplitude (μV) of the

MMN as a function of P2 amplitude of the differential waveform at  $C_Z = -.553 - .176 \times P2$

amplitude of the differential waveform;  $r^2 = .24$  and  $F_Z = -.485 - .187 \times P2$  amplitude ( $\mu V$ ) of the differential waveform;  $r^2 = .22$ .













