Possible Neuronal Refractory or Recovery Artifacts Associated with Recording the Mismatch Negativity Response

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Abstract

The mismatch negativity (MMN) is an event-related potential that involves a negative voltage shift of baseline electroencephalographic (EEG) activity in the approximate latency window of the N_1 and P_2 cortical potentials in response to new or novel sounds. The MMN is present at birth and has been hypothesized to serve as an automatic preconscious detector of changes in the auditory environment. Research paradigms used to extract the MMN response from EEG activity have a potential problem related to neuronal refractoriness or recovery. Both N_1 and P_2 are known to increase in amplitude with longer interstimulus intervals (ISIs). The MMN extraction procedures involve mathematical subtraction of waveforms elicited by standard sounds (with short ISIs) from those recorded to rare deviant sounds (with longer ISIs). Any ISI-dependent amplitude changes in N_1 and/or P_2 could therefore alter the morphology of the resulting difference wave and lead to misinterpretation of the nature of the underlying MMN generators. We tested 12 young females and found that the MMN can be influenced by ISI-dependent refractory effects that may modify the waveform morphology. This has important clinical implications since the MMN is being investigated as an assessment tool.

Key Words: Attention, auditory event-related potentials, auditory evoked potentials, memory, mismatch negativity, neural recovery, neural refractoriness

Abbreviations: ANOVA = analysis of variance, CNS = central nervous system, EEG = electroencephalographic, ERP = event-related potential, ISI = interstimulus interval, LAEP = late auditory evoked potential, MMN = mismatch negativity

B eginning with the discovery (Hillyard et al, 1973) of electrophysiologic signs of selective attention in the human brain, investigations of the neural correlates of higher-level cognitive processing have become a major focus in both the clinical and basic neurosciences. Various forms of experimental paradigms involving the measurement of auditory event-related potentials (ERPs) have been used in this

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research. In the summer of 1975, Näätänen et al (1978) discovered the existence of a form of ERP that appeared to be unique compared with other forms of ERPs (e.g., the P_{300}) known at the time. This potential, which has come to be known as the mismatch negativity (MMN), involves a negative voltage shift of baseline electroencephalographic (EEG) activity in response to any discriminable change in a repetitive sound. The MMN frequently overlaps the latency window of the N_1 and P_2 components of the late auditory evoked potential (LAEP) and, unlike other ERPs, appears to be present at birth (Alho et al, 1990). The MMN does not require attention or a behavioral response from the test subject (Näätänen and Teder, 1991; Novak et al, 1992) and has been found to occur in sleeping

adults (Nielsen-Bohlman et al, 1988) and some comatose patients (Kane et al, 1993). The MMN can be recorded to small changes in a wide variety of basic attributes of sounds (e.g., frequency, intensity, duration, omission of sounds, spatial and phonetic changes, etc; see Näätänen and Kraus, 1995, for a recent review). This response has been hypothesized to be a reflection of an automatic, preattentive, or preconscious brain mechanism that serves to automatically detect or register changes in the ongoing auditory environment. If this is true, the MMN could potentially serve as a clinical tool for objectively evaluating the discriminatory powers of the central auditory system in patients who cannot be tested using behavioral measures.

Many investigators (e.g., see Näätänen and Kraus, 1995, for a recent review) believe that the MMN response reflects the activity of specialized groups of neurons in the brain that have become conditioned to respond when new sounds are presented that exhibit some physical difference from sounds that have occurred repetitively in the recent past. A memory trace for the repetitive sounds is laid down, and then, when the new sound occurs, a group of special "comparator" units fire in response to this new sound.

Three laboratory paradigms have been developed to extract the MMN response from EEG activity. The most commonly used procedure involves presentation of an oddball sequence of repetitive sounds in which "deviant" sounds are randomly interspersed among "standard" sounds, with the former sounds differing in some specific way (e.g., frequency, intensity) from the latter. The standard sounds are typically presented more frequently than the deviant sounds, with probabilities of occurrence (in different experiments) ranging from 75 percent to near 100 percent. A difference wave is then computed in which the waveform elicited by the standard stimulus is subtracted from the response to the deviant stimulus. A second technique for deriving the MMN involves recording the response to a train of deviant stimuli presented alone and subtracting this response from the response to the same deviant stimulus when it is presented as part of the oddball sequence. A third technique involves running consecutive trial blocks with the standard stimulus in one test run becoming the deviant stimulus in the other and then subtracting the response to the stimulus when it was a standard from the response to the same stimulus when it was a deviant. Although the first procedure has become the virtual standard in the field, a few labora-

tories also use the second technique. No recent studies, to our knowledge, have used the third procedure (probably because of time limitations).

All three MMN extraction techniques described above have a potential technical problem related to neuronal refractoriness or recovery. It is well known (Nelson and 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 LAEP (e.g., N_1, P_2). With all three extraction techniques, the MMN response is estimated or indirectly derived from the calculation of difference waves associated with the recording of the obligatory LAEP components in different stimulus contexts (e.g., deviant in oddball vs deviant alone). Any ISI-dependent amplitude changes in the LAEP could therefore be erroneously interpreted as reflecting changes in the underlying MMN generator(s). Experiments that use the first and third extraction techniques inherently involve deviant stimuli that have longer ISIs than is the case for the standard stimuli, whereas the second technique, as it has been frequently used (e.g., Picton et al, 1985; Kraus et al, 1992), may involve ISIs during deviant-alone runs, which are shorter than ISIs for deviant stimuli when they are presented in the oddball sequence. Earlier studies (Näätänen et al, 1989a, b) that investigated this possible refractory artifact concluded that the MMN response was not contaminated by such effects.

During the past few years, however, there has been a shift (Näätänen and Kraus, 1995) in MMN research away from studies with normal volunteers to investigations of the possible clinical utility of the response. Important new research programs (Kraus et al, 1996, 1999) are being developed to investigate the clinical value of the MMN for identifying central nervous system (CNS)-based learning and communication problems in young children. The majority of the studies are using either the first or second (or both) extraction techniques listed above where neural refractoriness may be an uncontrolled variable. These investigations are beginning to report MMNs in different clinic populations that are absent, are smaller in amplitude, or have latencies that are longer than "normal" (Alho et al, 1994; Korpilahti and Lang, 1994; Pekkonen et al, 1995, 1996; Kraus et al, 1996; Cheour et al, 1997; Kazmerski et al, 1997; Gaeta et al, 1998). Since neural refractory or recovery functions are also known to vary with different forms

of CNS dysfunction (Shagrass et al, 1971; Papan-icolaou et al, 1984; Shucard et al, 1984), it is possible that in some studies, the MMN response and neural refractory effects may temporally overlap, which could result in erroneous interpretations of the clinical significance of altered waveform morphology. The present investigation was undertaken, therefore, to further investigate the relationship between the MMN response and neural refractoriness.

METHOD

Participants

A group of 12 young females (mean age: 23.3 years; range: 19–26) was tested in this project. All participants were volunteers from the university student body and had pure-tone audiometric thresholds of 20 dB HL or better at both ears for octave frequences from 250 to 8000 Hz. Tympanometry screening revealed normal middle ear function (ASHA, 1990). All 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 and Procedures

Stimuli and Test Procedures

Tones were presented to the right ear at 65 dB pSPL with insert receivers (Etymotic ER-3A) while participants were reading a self-selected book in a sound-treated and electrically shielded booth. As described, three different experimental paradigms have been developed to record the MMN response. The present participants received a series of test runs that allowed extrac-

tion of a MMN response with each of the three procedures. Table 1 shows the stimulus format for the present project. The order in which the five types of test runs were administered to individual participants was counterbalanced using Latin square logic.

The first MMN extraction procedure (i.e., the deviant-in-oddball method) involved administering oddball tonal sequences with deviant tones interspersed among standard tones and then subtracting the waveform elicited by the standard stimuli from the waveform elicited by the deviant stimuli. Test run 1 was used for this comparison. The standard and deviant stimuli consisted of 1100- and 1000-Hz tone pulses (50 msec duration, 10-msec rise–fall times), respectively. Each oddball run involved the presentation of 1190 standard and 210 deviant stimuli. The probability of occurrence of the standard tones was 85 percent, whereas that for the deviant tones was 15 percent. Stimuli were presented in a pseudorandom sequence with an ISI of 500 msec. At least three standard stimuli separated presentations of deviant stimuli. 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. The responses to standard stimuli immediately following deviant stimuli were also excluded from response averages.

The second MMN extraction procedure (i.e., the deviant-alone method) involved presentation of oddball sequences containing standards and deviants plus presentation of separate test runs involving deviant stimuli alone. Waveforms recorded to the deviant stimuli in test run 1 were compared with those from runs 3, 4, and 5. ISIs of 500, 1050, and 2150 msec were used in these deviant-alone test runs. An ISI of 500 ms was used during all administrations of test run 1. The waveform elicited by the deviant-alone condition was subtracted from that of the

Table 1   Five Types of Stimulus Test Runs Administered to the Participants, Plus Which Test Runs Were Used in Deriving MMN Responses with Each of the Three Extraction Methods

Test Run	Standard (kHz)	Deviant (kHz)	ISI (msec)	No. of Stimuli	MMN Method
1	1.1	1.0	500	1400	FF/DO/DA
2	1.0	1.1	500	1400	FF
3	–	1.0	500	210	DA
4	–	1.0	1050	210	DA
5	–	1.0	2150	210	DA

MMN = mismatch negativity, ISI = interstimulus interval, FF = flip-flop, DO = deviant in oddball, DA = deviant alone.

deviants when they were part of the oddball sequence.

The third procedure (i.e., the flip-flop method) involved administering two oddball test runs in which the stimulus frequency that served as the deviant in one test run was made to serve as the standard stimulus in the other run. Test runs 1 and 2 were used in this comparison. The waveform elicited by the stimulus when it was the standard was subtracted from the same stimulus when it served as the deviant.

Electrophysiologic Recording and Data Analysis Procedures

EEG activity was recorded from a vertex electrode site (i.e., C_z re the 10-20 system) referenced to the nose. Electrodes placed vertically above and below the left eye were used to monitor ocular movements. Electrode impedances were maintained below 3000 ohms. Individual sweeps of time-locked EEG activity extended from –50 to +500 msec relative to stimulus onset. EEG activity was amplified 1000 times, analog filtered (1–70 Hz, 24 dB/octave slope), and digitized at an analog-to-digital rate of 500/sec with a PC-based NeuroScan system and SynAmps 16-bit amplifiers. The digitized epochs were sent to a microcomputer for offline averaging and digital filtering (1–40 Hz, 24 dB/octave). The 50-msec 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 epoched EEG files prior to averaging. Ocular movement artifacts were digitally removed from the epochs (Semlitsch et al, 1986). Epochs containing artifacts exceeding ± 50 μV were rejected from averaging.

RESULTS

Figure 1 shows the overlaid grand-averaged group waveforms along with the difference waves for each of the three MMN extraction techniques. Figure 2, in contrast, shows the response obtained with the deviant-alone method when two longer (i.e., 1050 and 2150 msec) ISIs were employed in deviant-alone test runs. These grand averages were used to facilitate identifying MMN components of individual difference waves for each participant. Although different methods have been proposed (e.g., Kraus et al, 1993a, b; Sharma et al, 1993; Dalebout and Fox, 2000) for defining the MMN waveform, we chose
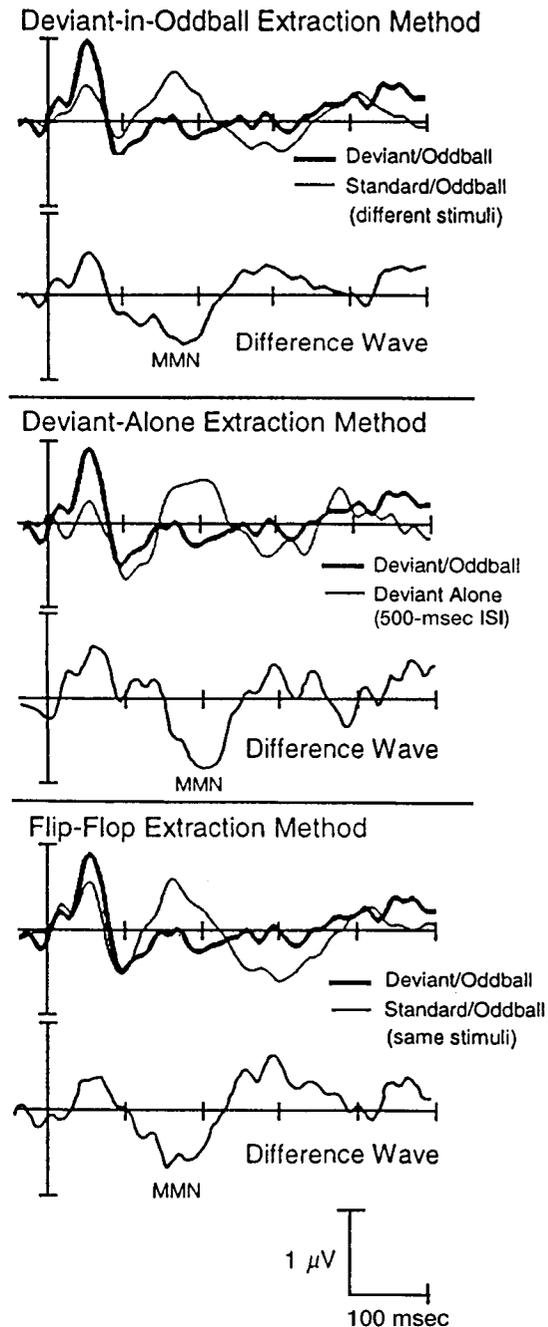

Figure 1 Mismatch negativity (MMN) responses derived with each of three electroencephalographic extraction procedures. Group-averaged waveforms from 12 young adults are shown.

to define it in terms of voltage negativity in individual difference waves relative to baseline. The method of performing baseline corrections with the present NeuroScan system involves averaging the voltages from the prestimulus data points and then subtracting these data from the single sweeps of epoched EEG files prior to averaging. MMN peak amplitude was
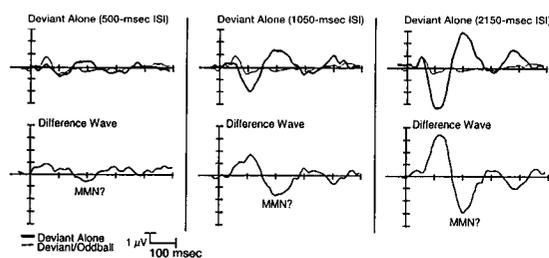
Figure 2 Effects of changing interstimulus intervals on the mismatch negativity (MMN) responses (group-averaged waveforms) derived with the deviant-alone MMN extraction technique.

defined as the maximum negative peak between 100 and 400 msec. MMN onset and offset latencies were defined as the first points preceding and following this negative peak where the waveform intersected baseline. To examine possible differences between the three MMN extraction techniques and effects related to differences in the ISIs used in the three deviant-alone test conditions, MMN amplitude areas were calculated. Amplitude area was defined in msec $\times$ μV for the area under the line drawn from the MMN onset to offset points. For this computation, waveform data (i.e., latency and amplitude coordinates) were converted to ASCII format and exported for area analyses. The respective waveform peaks were independently selected by each of four experienced examiners (LJW, MC, CRD, and JLC) with a required three-quarters consensus. Table 2 shows the means and standard deviations of these area data obtained with each of the five MMN extraction procedures.

Two one-way repeated-measures analyses of variance (ANOVAs) were used to analyze the present data. Whereas the first ANOVA found no significant difference (F = .121, df = 2, 33, p = .70) among the three MMN extraction procedures with respect to amplitude area, the second ANOVA found a significant main effect (F = 6.98, df = 2, 33, p = .003) for the three deviant-alone test conditions. Post hoc tests using the Tukey Honest Significant Difference revealed

that whereas the 500- and the 2150-msec ISI conditions were significantly different (p = .002), the other two comparisons were not (p $\geq$ .10). Finally, previous studies have reported that the MMN response, although small in amplitude, also tends to exhibit considerable subject-to-subject variability (Kurtzburg et al, 1995; Lang et al, 1995; McGee et al, 1997; Dalebout and Fox, 2000). As shown in Figure 3, considerable individual variability also occurred with the experimental data of the present project. To evaluate the incidence of MMNs in individual participants, our team of examiners (again with a required three-quarters consensus) examined individual difference waves obtained with the deviant-in-oddball, flip-flop, and deviant-alone (500-msec ISI condition only) extraction procedures. This analysis indicated that 85 percent of the difference waves showed "definite" as opposed to "questionable" evidence of the presence of a MMN response. No differences were seen between extraction procedures.

DISCUSSION

Although the present experiment provides support for the existence of the endogenous MMN phenomenon, it also provides strong evidence that ISI-dependent neural refractory or recovery effects may, with some experimental protocols, overlay and modify the apparent morphology of the MMN response. The presence of possible artifacts related to neuronal refractoriness may be especially problematic for interpretation of MMNs derived with the deviant-alone extraction method whenever the ISIs of the stimulus sequences differ in the oddball and deviant-alone test conditions. With both the deviant-in-oddball and flip-flop methods, the waveforms elicited by the deviant stimuli exhibited negative voltage baseline shifts in the temporal region of the N_1 and P_2 components of the LAEP. This effect has been traditionally interpreted to constitute the MMN response. The negative baseline shift observed

Table 2 Means and SDs (in μV) of the Area Data Obtained with Each of the Five MMN Extraction Procedures

	DO	FF	DA (500)	DA (1050)	DA (2150)
Mean	33.9	32.8	30.4	70.1	122.5
SD	26.6	27.3	35.4	59.8	78.7

For the DA extraction procedure, three interstimulus intervals were used (500, 1050, and 2150 msec).
MMN = mismatch negativity, DO = deviant in oddball, FF = flip-flop, DA = deviant alone.

Deviant-in-Oddball Method

Deviant-Alone Method (500-msec ISI)
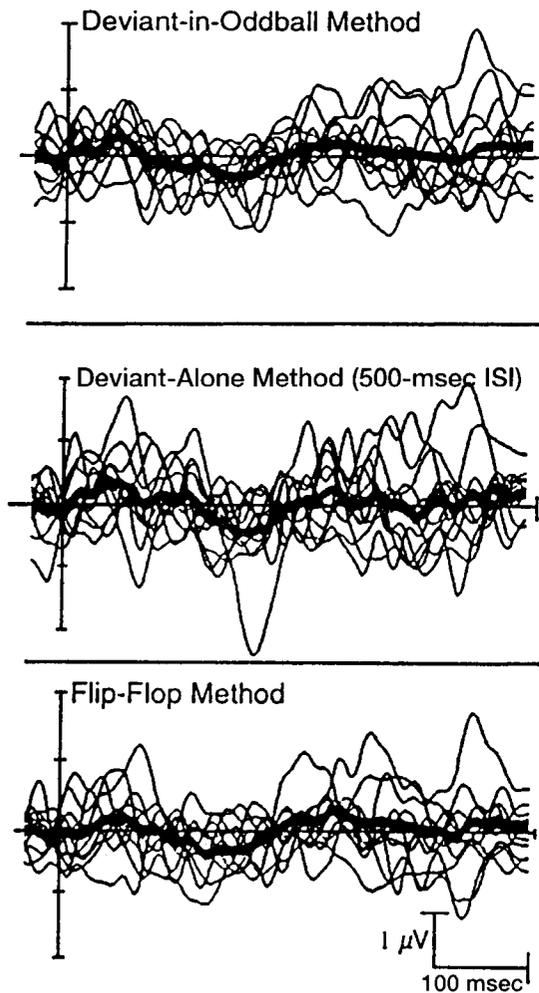
Flip-Flop Method

Figure 3   Group-averaged difference waves (*thick line*) and individual participant difference waves (*thin lines*) illustrating variability in the MMN response.

Standard/Oddball
Deviant/Oddball
Deviant Alone

Figure 4   Grand-averaged waveforms recorded from C_z to standard stimuli in an oddball sequence (*thin solid lines*), deviant stimuli in an oddball sequence (*thick solid lines*), and deviant stimuli presented alone with interstimulus intervals of (*A*) 500, (*B*) 1050, and (*C*) 2150 msec (*dotted lines*).

with the present deviant-alone procedure when the ISIs on deviant-alone and oddball runs were similar (i.e., 500 msec) also supports the existence of a MMN response. However, as depicted in Figure 4, increasing ISIs during deviant-alone test runs to more closely match the ISIs of the deviant stimuli when they occurred in oddball runs has the effect of substantially increasing $N_1–P_2$ peak-to-peak amplitudes. As shown in Figure 2, these ISI-dependent refractory effects can dramatically alter the morphology of the resulting difference waves.

In earlier years, when MMN investigators were mainly focusing on developing a normative database using healthy young participants, neuronal refractory effects were not as much of a concern as they are now that investigators are beginning to look for MMN changes related to specific forms of CNS pathology. Experiments that
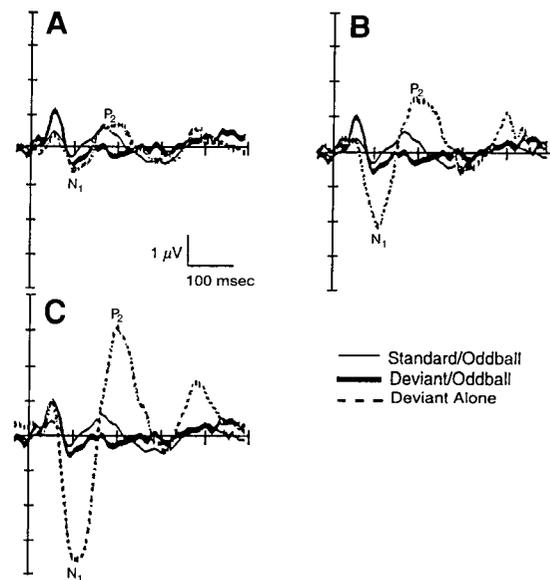
were designed to identify the normal morphologic changes in the MMN that result from altering stimulus, training, or other task-related variables would probably not be affected as much by artifacts related to neural refractoriness since this latter variable would be expected to remain relatively constant in young participants. However, with the recent switch in emphasis from conducting normative studies to investigations of changes in the MMN with different forms of CNS pathology, this neural refractory issue becomes more critical. Without knowledge of the specific changes in neuronal refractory functions that occur with different CNS pathologies, researchers cannot rule out the possibility that observed differences in the MMN reflect artifacts related to refractoriness. Experiments that separately measure both the MMN response plus neural refractory functions for the same stimuli in groups of normal participants and listeners with specific CNS pathologies are needed. This would allow investigators to be more confident that the MMN reflects a form of endogenous attentional processing rather than artifacts associated with neuronal refractoriness or recovery.

The present project, therefore, shows that the use of difference waves to identify the MMN response may be vulnerable to artifacts related to neuronal refractoriness. The deviant-alone MMN extraction method appears to be espe-

cially susceptible to this problem. However, Näätänen and others (see Näätänen, 1990, and Näätänen and Kraus, 1995, for recent literature reviews) have argued that when deviant and standard stimuli are presented together in odd-ball runs, as they are in the deviant-in-oddball and flip-flop procedures, refractory effects are not a concern. These investigators believe that when the differences between the standard and deviant stimuli are small, the negative voltage shift in the deviant waveform reflects the activity of special "difference detectors" (comparator units) rather than that of units selectively tuned to the deviant stimuli. In two earlier studies, Näätänen et al (1989a, b) provided evidence that the MMN response can be elicited by deviant stimuli that involve decreases in intensity and temporal duration. At the time these studies were performed, Näätänen and his colleagues were unaware of any published evidence for the existence, in the brain, of neurons that are tuned to specific intensity or duration features of sounds. These authors therefore concluded that the MMN response to decreases in intensity or duration most likely reflect endogenous attentional processes rather than activation of new neural units. However, numerous subsequent single-unit studies with a variety of species (bats, cats, chinchillas, and monkeys) have reported evidence for the existence of both intensity- (Pfingst and O'Connor, 1981; Suga and Manabe, 1982; Phillips and Orman, 1984; Phillips et al, 1985, 1995) and duration-specific (Ehrlich et al, 1997; He et al, 1997; Guang-Di and Chen, 1998; Brand et al, 2000; Casseday et al, 2000; Covey, 2000) neural units in the mammalian brain. Such findings would seem to question the conclusions of Näätänen et al (1989a, b), at least with respect to the underlying nature of the MMN response to changes in these two sound parameters.

Thus, it appears that the question of whether the MMN response reflects activity of special comparator units or activation of different neural populations is still not completely resolved. The present authors believe that insufficient research information 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. Until we know much more about neural tuning processes in the brain than we do at present, researchers must be cautious in assuming that neural refractory artifacts are not present in specific experiments. The presentation of deviant sounds intermingled among standard sounds in oddball runs may involve more complex neural events than presenting deviant sounds alone. We may be dealing with complex neural processes in which some neural units selectively fire to the standard stimuli, other units fire to the deviant stimuli, and yet other units may be selectively tuned to some stimulus feature related to the combination of the two types of sounds (e.g., "pattern" changes). 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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