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Finding the missing stimulus mismatch negativity (MMN): Emitted MMN to violations of an auditory gestalt

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Abstract

Deviations from **repetitive auditory stimuli** evoke a **mismatch negativity** (MMN). Counter-intuitively, omissions of repetitive stimuli do not. Violations of patterns reflecting complex rules also evoke MMN. To detect a MMN to missing stimuli, we developed an **auditory gestalt task** using one stimulus. Groups of 6 pips (50 msec duration, 330 msec stimulus onset asynchrony (SOA), 400 trials), were presented with an inter-trial interval (ITI) of 750 msec while subjects (n=16) watched a silent video. Occasional deviant groups had missing 4th or 6th **tones** (50 trials each). Missing stimuli evoked a MMN ($p < .05$). The missing 4th (-0.8 uV, $p < .01$) and the missing 6th stimuli (-1.1 uV, $p < .05$) were more negative than standard 6th stimuli (0.3 uV). MMN can be elicited by a missing stimulus at long SOAs by violation of a gestalt grouping rule. Homogenous stimulus streams appear to differ in the relative weighting of omissions than strongly patterned streams.

The mismatch negativity (MMN) event related potential (ERP) is a neurophysiological signal of stimulus processing extracted from the electroencephalogram (EEG). The MMN elicited by simple changes in stimulus parameters (pitch, loudness, duration, location, etc) reflects activity of pre-conscious, pre-attentive sensory memory within sensory cortex, and serves as a metric of stimulus deviance likely sent to frontal lobe mechanisms that may engage an alerting orienting response to the source of change from a repetitive environmental pattern. MMN reflects the output of a low-level mechanism for detection of change from stimulus regularities in the environment. It occurs very early in perception within the information processing stream, and is little affected by top-down executive functions like attention (Näätänen 1990). Although for many years thought to be exclusively found in auditory echoic memory, a similar potential is evident within visual iconic memory (Winkler et al 2005, see Pazo-Alvarez et al 2003 for review). Still, the MMN to small stimulus deviations within the auditory system remains the most widely studied. Early MMN theory focused on the distinction between the MMN being a purely sensory response because the deviant tone recruited different sensory cortex populations, versus the MMN reflecting the difference between a memory trace of the specific single standard stimulus versus the current stimulus (Näätänen 1990).

Simple stimulus parameter MMN studies (one repetitive identical tone and a physically different deviant) have been unable to show a MMN to a missing stimulus, unless the tones were played very rapidly (100 or 125 msec stimulus onset asynchrony (SOA), but not >150 msec, Yabe et al 1997. Herein SOA refers to onset-to-onset of tones, whereas inter-stimulus interval, ISI, refers to offset-to-onset). This suggested that the tones were within a critical

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temporal window of integration, and thus the missing stimulus represented a violation not simply because of its absence per se, but because it was not there to form a compound stimulus with the preceding stimulus. Using depth recordings, Hughes et al (2001) did not report MMN-like responses to omissions of tones regularly spaced 1.2 sec apart, although they did report MMN-like responses to a missing second tone of 100 msec duration tone pairs with a 200 msec SOA (100 msec tone duration + 100 msec ISI). Because omissions of tones at longer ISIs violate stimulus regularity, it remains paradoxical that omissions at SOAs > 150-200 msec do not elicit MMNs.

As mentioned, stimulus parameter deviations are generally slight changes in the pitch, duration, or location of short tone pips (oddball stimuli), but MMN can also be elicited by stimuli that are affected by learning. For example, phonemes that deviate slightly from a repetitive train generate MMN only if that phoneme is relevant in one's native language (Aaltonen et al 1987, see Näätänen 2001 for review). MMN is also elicited by deviations from learned patterns of sounds (see Kujala et al 2007 for review), exceptions from a purely bottom-up nature for MMN, indicating the influence of acquired knowledge in "automatic" perception. Hence, the simple stimulus parameter deviant MMN may only scratch the surface of the cortical processing that may be reflected in MMN activity. In the last several years, research in psychiatrically-well participants has changed the conceptualization of MMN, what it reflects, and the complexity of how it may be elicited. Rather than being elicited solely by low-level bottom-up analysis of repetitive stimulus patterns, physical parameter changes which can be analyzed mainly in primary auditory cortex, MMN can be elicited by a host of complex abstracted or second-order rules, and by deviations from complex learned rules. This "automatic auditory intelligence" can form rules based on stimulus change trends and learned tone patterns such as a melody (see review Näätänen et al 2010). The "complex memory MMN" depends on more sophisticated processing than the simple stimulus parameter MMN, necessitating the more complicated circuit architecture of secondary cortical association areas, and may include parietal and frontal processing modules in addition to secondary auditory cortex (see Schröger et al 2007). For example, if a rule that the second tone in a pair is always a higher pitch than the initial tone, a MMN is elicited if the second tone is lower (Saarinen et al 1992, Korzyukov et al 2003). Alho et al (1996) showed that complex MMN could be elicited by a deviation from a serial tone pattern (i.e., a tune). The melody E4, C5, G4, E5, C4 was the standard pattern, and a deviant was E4, C5, A4, E5, C4. The deviant A4 elicited a MMN, which could only occur if the overall melody had been abstracted as a complex rule. Atienza and Cantero (2001) claimed that the MMN to violations of an 8 tone pattern could also be evoked during REM sleep after learning. Standard stimuli were 365 msec long tones comprising 8 segments of different frequencies with no logical pattern from one segment to the next, resulting in an abstract sequence. The deviant was identical, except that the 6th segment was 15% higher in pitch. Responses to learned pattern violations was shown as well by Sculthorpe et al (2009) for an alternating 8 tone pattern, where the standard comprised alternating tones (ABABABAB) and the deviant comprised alternating tone with a repeat (ABABBBAB). These studies have supported a different model of MMN generation than the comparison of the current stimulus with a backward-looking memory trace of a previous standard stimulus. Rather, it seems more likely that MMN reflects a comparison of a forward-looking prediction of what should occur, be it based on a single repetitive tone or a complex pattern of tones, with what actually occurred (see Winkler 2007).

The ability of the auditory system to use simpler abstracted rules to form groups of stimuli based on implicit patterns has been examined. At longer ISIs (1.3 sec, 50 msec duration tones), deviants presented regularly (every 5th tone) evoked a MMN. However, at short ISIs (100 msec), the deviants did not evoke a MMN, presumably forming a unit with the preceding tones (Sussman, 1998). van Zuijen et al (2004) presented subjects with a constant

stream of 100 msec duration tones at an ISI of 87.5 msec. Four identical tones were played (an implicit group), with a new group at this constant rate indicated by a different pitch. An extra (fifth) tone elicited a MMN in both musically skilled and unskilled participants. Again, however, these groups appear to form only at relatively short ISIs. A crucial aspect of the simple grouping rule studies described immediately above is that the SOA and ISI were constant; that is, the groups were formed by implicit groupings of stimulus parameters or repetitive parameter changes.

Using a somewhat more complex rule, Atienza et al (2003) examined the time course of this implicit grouping of 30 msec duration tones into a “larger acoustic event”, and suggested such an integration interval did not exceed ITIs of 240 msec. Subjects were presented 6 tones with a SOA of 120 msec. The ITI was varied between 150, 180, 240, and 360 msec. Within each train, tones alternated between 2 frequencies. Deviant trains began with a repetition of the same frequency (i.e., 2 standard trains: a,b,a,b,a,b a,b,a,b,a,b. Standard train followed by deviant train: a,b,a,b,a,b, b,a,b,a,b,a). Atienza et al argued that if a rule expecting alternating frequencies of 6 tones was developed, the first tone of a deviant train (where the frequency did not change) should elicit a MMN if it violated an expectancy for an alteration within the ~250 msec temporal integration interval described above. They described a MMN to the deviant under 240 msec, but not at 360 ITI, presumably outside the integration of the alternating rule expectancy. Although this may imply that the auditory system did not develop an overarching expectancy for the group of tones as a whole, it is important to note that the deviant always occurred every other train, and was thus predictable as a larger pattern.

Here we describe a method to form overarching groups of a single repetitive stimulus via manipulation of the ISI, based on the gestalt grouping principle of proximity. As shown in Figure 1A, which illustrates the visual analog of the task, 6 stimuli which are close together and separated from other similar bunches of close together stimuli form implicit groups. This simple abstraction based on temporal proximity, forming groups of stimuli with constant ISIs separated by a longer ITI, was used to determine whether violation of such a grouping principle would elicit an MMN to an omitted stimulus (Figure 1B,C) at SOAs over 250 msec.

Method

Subjects

Sixteen subjects underwent EEG recording while watching a silent nature video. All subjects were normal hearing as assessed by audiometry. Subjects were 34.4 years of age (± 12.1 , range 20-53), and included 9 M and 7 F. Subjects received \$15/hour for participation. The study was approved by the McLean Hospital IRB.

EEG Recording

EEG was recorded from a custom 74 channel Active2 high impedance system (BioSemi), comprising 72 scalp sites including the mastoids, and 2 cheek sites below the middle of the eyes and level with the nosetip. The EEG amplifier bandpass was open (DC) to 104 Hz (24 dB/octave rolloff) digitized at 512 Hz, referenced to a common mode sense site (near PO1). Processing was done off-line with BrainVision Analyzer2 (Brain Products GMBH). EEG was filtered between 0.75 and 20 Hz; the relatively high low cutoff was to remove DC drifts and skin potentials, the high cutoff was to remove muscle and other high frequency artifact. Data were rereferenced to averaged cheeks. Epochs (350 msec) were extracted from the EEG based on stimulus triggers, including a 50 msec prestimulus baseline. Epochs were baseline corrected, and DC detrended by subtraction of the line between baseline (-50 to 0)

and the last 50 msec of the epoch. Epochs were subsequently rejected if any site contained activity $\pm 50 \mu\text{V}$. MMN was analyzed by comparison of the differential averaged amplitude between 150 and 200 msec between standards and deviants, and visualized through subtractions (rule-breaking deviant minus last position standard).

Stimuli

Sounds were created with Ace of Wave and presented using Presentations. Binaural auditory stimuli were presented using Etymotic 3A insert earphones, with loudness confirmed with a sound meter and artificial ear canal. All tones used were the same: 1 kHz, 75 dB, 50 msec pips with 5 msec rise/fall times. Importantly, any MMN activity cannot be due to release from N1 adaptation for missing tones as with a differently pitched deviant: There was no stimulus. Temporal proximity was used to form discrete groups, with a SOA within groups of 330 msec (Figure 1). Six tones formed the standard group. Groups were separated by an ITI of 750 msec. There were 2 deviant groups, one with a missing 4th position tone, and one with a missing 6th position tone. Twenty percent of the groups formed deviants (2 deviants/8 standards), with a total of 50 deviant groups of each type (10% each deviant). Deviant groups never immediately followed one another. Digital triggers were embedded for missing stimuli based on the expected delivery time (330 msec from the onset of the preceding tone).

Analysis

MMN was measured over 150 to 200 msec from standard, missing 4th, and missing 6th tone ERP waveforms. Analysis was performed at Fz, where MMN is typically largest, and subjected to repeated measures ANOVA with the Huynh-Feldt epsilon used to correct for 3 levels. Followup comparisons were performed using t-tests. Subtraction waves were subjected to CSD analysis to infer source-sink topography, expected to indicate a superior temporal source for the missing stimulus MMN. Interpolation was done using spherical splines, with the order of splines set to 4, the maximum degree of Legendre polynomials set to 10, and a default lambda of $1e-5$.

Results

As indicated in Figure 2, missing stimuli that violated the expected group of 6 stimuli appear to elicit a MMN response. Amplitude at Fz between 150 and 200 msec was compared between the final tone of groups (standard) and the two deviants. Missing stimuli evoked a MMN ($F_{2,30} = 6.1$, $p = .006$, $\epsilon = 0.98$). Both the missing 4th stimulus ($-0.8 \mu\text{V}$, $t_{15} = 2.8$, $p = .013$) and the missing 6th stimulus ($-1.1 \mu\text{V}$, $t_{15} = 3.7$, $p = .002$) were significantly more negative than the standard stimulus ($0.3 \mu\text{V}$).

As indicated in Figure 3, subtraction waveforms inverted at the mastoids with the averaged cheek reference, although this was not as robust as expected. The use of averaged cheeks rather than the nosetip may have attenuated the response. Reference-independent CSD maps indicate a source-sink pattern consistent with bilateral superior temporal plane auditory cortex generators. There were bilateral inferior posterior sources and bilateral frontal sinks, with just one major source - sink pair in each hemisphere. The sink-source pattern appeared slightly greater over the right hemisphere, consistent with the behavior of MMN.

Discussion

The implicit grouping of tone pips via the gestalt principle of proximity appears to occur automatically within the auditory system. Violation of this auditory gestalt elicited a MMN to a stimulus omission that must be based on a violation of an expectancy for a group of 6 stimuli. The MMN occurred to stimuli that were spaced 330 msec apart, presumably outside

the temporal integration interval, and to groups separated by 3/4 of a second. Thus, MMN can be elicited by missing stimuli at relatively longer ISIs if an overarching expectation is developed. We suggest that the use of a relatively simple abstracted rule based largely on bottom up information is sufficient to form such an expectancy.

This auditory gestalt was based on inserting a longer ITI between groups of tones. Without this manipulation, missing stimuli at such a SOA will not elicit a MMN. Hughes et al (2001) suggested that imprecision in timing estimation of when the omitted stimulus should have occurred resulted in an inability for signal averaging to detect a MMN. An alternative possibility is that the ISI of basic streams of uniform repetitive stimuli is not necessarily weighted heavily in detection of deviance. Nordby, Roth, and Pfefferbaum (1988a) presented homogeneous streams of stimuli with occasional deviant pitched tones and shorter ISI tones. They reported that the pitch and the time deviants elicited a MMN. However, in a companion paper Nordby, Roth, and Pfefferbaum (1988b) presented patterns of stimuli, of alternating pitch (high, low, high, low, etc) and alternating ISI (short, long, short, long, etc), and found repeats of the pitch elicited MMN, whereas repeats of an ISI did not, although both violated the overarching alternating stimulus pattern. They suggested that ISI changes may have less salience than pitch or stimulus characteristics. We suggest that with a 2 stimulus pattern, this lack of salience of timing information may result in a reduction of the weighting of timing deviance, such that a MMN is not evoked.

Random changes in the SOA of continuous repetitive stimuli caused by a stimulus omission may be treated with some flexibility by the auditory system, perhaps a more ecologically valid approach to naturally occurring sound patterns which may contain more temporal variability than typical in MMN experiments. Only when a rigid overarching pattern is detected among tones (such as auditory gestalts) will a missing stimulus elicit a MMN. That is, the system must know what to compare at what time scales. For example, Winkler, Schröger, and Cowan (2001) presented subjects with six identical tones separated by 0.5 sec followed by a deviant stimulus. When the ISI of the deviant stimulus was increased beyond 0.5 sec, the MMN became attenuated, absent at a 10 sec ISI. However, when the ISI between standard tones was lengthened to 7 seconds, a deviant at 7 seconds elicited MMN. This was interpreted as indicating the “memory trace” of the standard stimulus had not decayed after 7 to 10 seconds, as had been proposed in some earlier studies, but that the preattentive auditory system could integrate deviance at longer ISIs between tones when relevant to the overall pattern. Takegata et al (2001) showed largest MMNs to “early” deviants when SOA and ISI between standard tones were constant. Collectively, these data suggest that SOA/ISI need strong regularity to result in the MMN when violated.

Although relatively small, the missing stimulus MMN observed here was largest frontally, relatively more positive at the mastoids, and demonstrated a source-sink pattern consistent with sources in the superior temporal plane. On the other hand, the polarity inversion and the source-sink pairs were not as robust as might be expected, and appeared to be somewhat stronger in the right hemisphere, despite a lack of evidence of asymmetry in the deviant waveforms. Still, the sinks were not central, as would be expected for N2b, and are consistent with a source in auditory cortex. Both tone analysis and holistic group analysis are thought to be right hemisphere functions, so the CSD results are not unreasonable. The results here should be considered a first step to demonstrating the presence of an emitted MMN to a missing stimulus.

Occurrence of MMN to a missing stimulus (here) and to violations of rules in the absence of repetitive stimuli (Saarinen et al 1992, Alho et al 1996, Atienza et al 2003, Korzyukov et al 2003) indicate that MMN is not simply an index of stimulus change, but rather reflects an index of deviance from a prediction of what will occur in the environment (cf. Naatanen et

al 2010). Friston and colleagues have developed a model of MMN based on a hierarchical Bayesian model, proposing that hierarchical levels within sensory cortex generate a predictive model of the environment, then learn precisely which parameters are crucial for minimizing the error of the model. Not only is error caused by changes in feed-forward sensory information via release from stimulus adaptation for standards, but also by the “distance” from the prediction and the actual stimulus. Note that the omission of a stimulus should not cause release from stimulus adaptation, so most error will be prediction error. May & Tiitinen (2010) argued that the MMN to an omission stimulus at short SOAs within the temporal window of integration (e.g., Yabe et al 1997) might be explained by a sensory offset response due to violation of the rapid presentation rate or oscillating steady-state response induced by the rapid presentation rate. It is not clear that such a sensory adaptation model can explain the MMN to the missing stimulus in the current experiment, with a 330 msec SOA. (Some have argued that a circuit can be developed to detect an omission (Regan 1989), but a body of work in the “emitted” P300 showed a lack of sensory potentials to omitted stimuli that generated N2 and P3 (Squires et al 1975, Ford et al 1976, Ruchkin & Sutton 1978).) Each level of the local (intrinsic) and long-range (extrinsic) hierarchy modulates, via feedback, processing of the prior level, by providing it priors (generative rules) based on its own estimations. MMN reflects the error of the predictive model. Garrido and colleagues (Garrido et al, 2009a,b) have used dynamic causal modeling (DCM) to test models of simple MMN generation. DCM “explains” activity in time or space based on activity in a prior time or space. Using dipoles within physiologically plausible areas, they showed that MMN to simple tone differences was generated in primary then in secondary temporal lobe, with subsequent processing in right inferior frontal gyrus. This is similar to the general physiological model of MMN, with the addition of secondary association cortex. We speculate that the missing stimulus MMN emitted here reflects error of the expectancy developed by primitive auditory intelligence through abstraction of auditory gestalt groupings within secondary auditory association cortex. However, it is not entirely clear that a cortical model based on MMN to deviants within simple homogenous streams of stimuli apply to pattern-based MMN, although a highly plausible and parsimonious possibility.

The development of expectations based on simple auditory gestalt proximity groupings appears to occur, and violations of such expectations appears sufficient to elicit a MMN at relatively long ISIs. Further work is necessary to confirm this finding, to examine the time course of this effect and the duration of the expectation, and to determine the effect of providing cross-modal cues to obviate any time of occurrence estimation errors at substantially longer ISIs.

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A. Standard Groups**B. Standard Groups and Missing 4th Deviant****C. Standard Groups and Missing 6th Deviant****Figure 1.**

Panel A. Stimuli separated by regularly spaced increases in ISI form implicit groups via the gestalt principle of proximity, here into groups of six notes. Most people see 3 groups of notes rather than a sequence of notes with variable SOAs. Panel B. Omissions of stimuli at the 4th position violate the Gestalt grouping rule. Panel C. Likewise, omissions of stimuli at the 6th position violate the Gestalt grouping rule. In this study, tones were 50 msec in duration, with a SOA of 330 msec. Trials were separated by 750 msec.

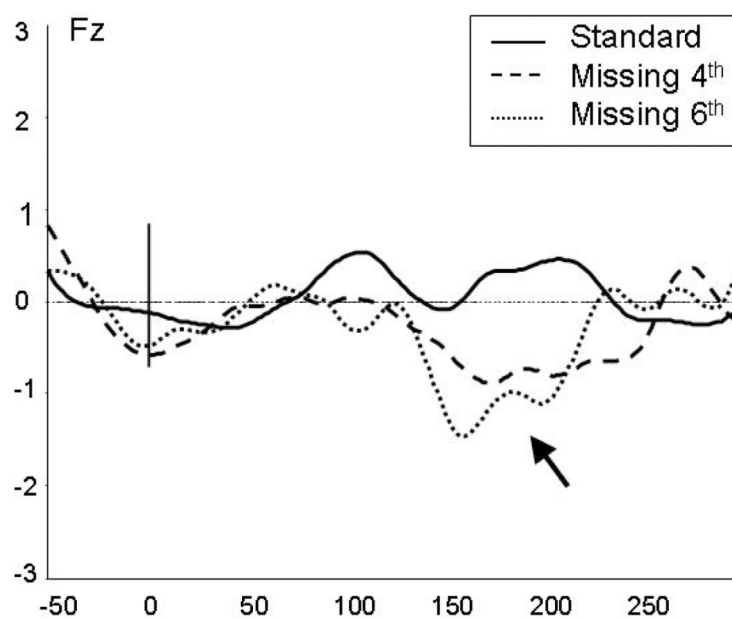


Figure 2. ERP responses at Fz to standard tones, and time-locked to the expected occurrence of the missing 4th and 6th tones of the group. Note the presence of a relative negativity between 100 and 200 msec to the stimuli that were not there.

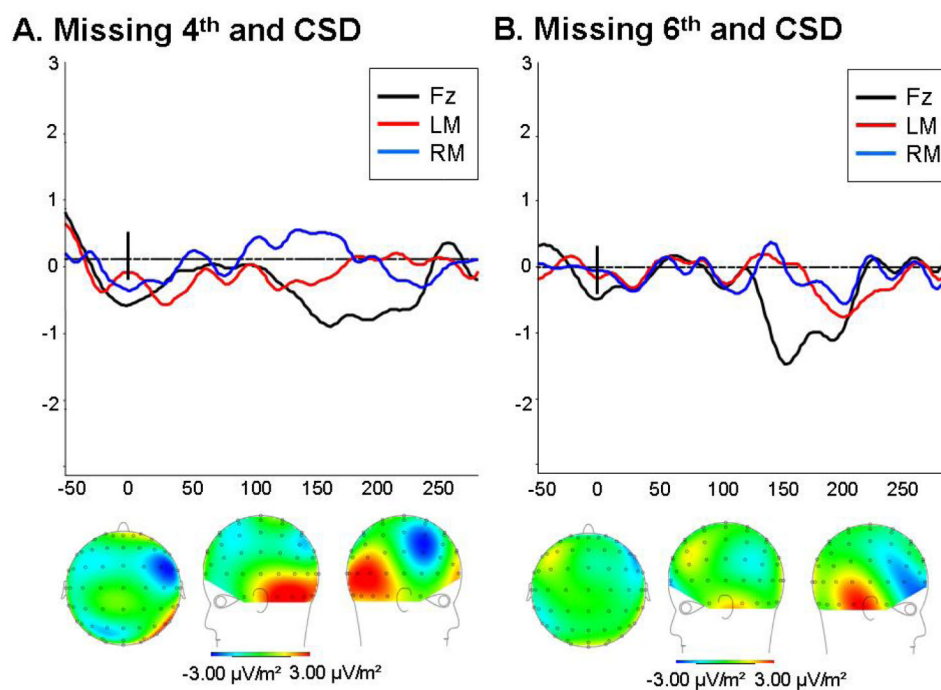


Figure 3.

Difference waveform for the missing stimuli minus the standard stimuli. Panel A presents the mastoids overlaid on Fz with the corresponding CSD maps below for 150-200 msec for the missing 4th tone MMN. Panel B presents the same data for the missing 6th tone MMN difference waveform.