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Abnormal Complex Auditory Pattern Analysis in Schizophrenia Reflected in an Absent Missing Stimulus Mismatch Negativity

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Abstract

The simple mismatch negativity (MMN) to tones deviating physically (in pitch, loudness, duration, etc.) from repeated standard tones is robustly reduced in schizophrenia. Although generally interpreted to reflect memory or cognitive processes, simple MMN likely contains some activity from non-adapted sensory cells, clouding what process is affected in schizophrenia. Research in healthy participants has demonstrated that MMN can be elicited by deviations from abstract auditory patterns and complex rules that do not cause sensory adaptation. Whether persons with schizophrenia show abnormalities in the complex MMN is unknown. Fourteen schizophrenia participants and 16 matched healthy underwent EEG recording while listening to 400 groups of 6 tones 330 ms apart, separated by 800 ms. Occasional deviant groups were missing the 4th or 6th tone (50 groups each). Healthy participants generated a robust response to a missing but expected tone. The schizophrenia group was significantly impaired in activating the missing stimulus MMN, generating no significant activity at all. Schizophrenia affects the ability of “primitive sensory intelligence” and pre-attentive perceptual mechanisms to form implicit groups in the auditory environment. Importantly, this deficit must relate to abnormalities in abstract complex pattern analysis rather than sensory problems in the disorder. The results indicate a deficit in parsing of the complex auditory scene which likely impacts negatively on successful social navigation in schizophrenia. Knowledge of the location and circuit architecture underlying the true novelty-related MMN and its pathophysiology in schizophrenia will help target future interventions.

Keywords

Complex MMN; Prediction error; Psychosis; Sensory adaptation; Temporal lobe

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Compliance with Ethical Standards

Conflict of interest The Authors have no conflicts of interest, no competing interests, and no financial relationships with commercial interests.

Introduction

Mismatch negativity (MMN) is a neurophysiological index of stimulus deviance elicited preattentively (Näätänen 1990). Auditory MMN elicited by deviance in a simple physical parameter (pitch, duration, intensity, etc.; hereafter referred to as simple MMN) is reduced in a variety of disorders (Näätänen et al. 2012, 2014). Simple pitch and duration deviant MMNs show large effect sizes (Cohen's $d = \sim 1$) for reductions in long term schizophrenia (Salisbury et al. 2002; Umbricht and Krljes 2005; Erickson et al. 2016). MMN reductions at psychosis onset and their development during the early disease course remain controversial (Erickson et al. 2016; Salisbury et al. 2016; Haigh et al. 2016; Todd et al. 2008).

MMN was originally thought to reflect the pre-attentive comparison of the current sound to a memory trace of previous sounds (Näätänen 1990; Sams et al. 1985). This memory-trace explanation of MMN has more recently been incorporated into a prediction of stimulus regularity framework (Winkler 2007; Winkler et al. 2009). Modules in auditory cortex form a prediction of patterns in the auditory environment that feed back to sensory areas. MMN reflects feed forward prediction error used to adapt the predictive model. In these so-called "cognitive" models, MMN reflects communication between (at least) two separate cortical modules (sensory and cognitive). The alternative sensory adaptation model (e.g., May and Tiitinen 2010) suggests MMN is an epiphenomenal sensory effect. Tone repetition leads to stimulus-specific adaptation (SSA), causing smaller evoked responses to standard tones. The deviant activates non-adapted sensory cells, which show larger evoked responses. Hence, MMN is just differential sensory activity that appears to index deviance, yet no special area performs any novelty-detection process. Animal recordings in primary auditory cortex (Ulanovsky et al. 2003; Fishman and Steinschneider 2012) suggest SSA does play a role in the generation of simple MMN, and recent work in rat somatosensory cortex has identified a late (200 ms) response to deviants (Musall et al. 2015).

For long term schizophrenia, where simple MMN is robustly deficient, the question arises whether MMN deficits reflect prediction defects or basic sensory defects. The location and cortical architecture for understanding pathophysiology in schizophrenia will be substantially different for these two models of MMN. Knowledge about the local circuit is important for development of targeted, biologically-based pharmacologic interventions (Lewis and Sweet 2009).

Research undertaken to minimize the contribution of SSA has indicated that standard tones need not be identical sounds and that MMN can be elicited by deviations from complex patterns. For example, among standard tone pairs in which the second tone is always relatively higher in pitch than the first tone, a rare deviant second tone that is relatively lower in pitch than the first tone generates a complex MMN (Korzyukov et al. 2003; Saarinen et al. 1992). If the standard pattern comprises alternating tones (AB, AB), MMN is elicited by a tone repeat (AA; Sculthorpe et al. 2009). However, our reading of the literature suggests that complex MMN tends to be somewhat smaller than simple MMN, implying that while a true novelty or regularity deviance detection process exists, SSA likely contributes at least in part to the simple MMN.

A complex MMN task that removed all possible contributions of SSA would be valuable for isolating true deviance detection processes and locations, and clinically for determining whether MMN deficits in schizophrenia were due to deficits in deviance detection or in sensory adaptation. Salisbury (2012) showed that MMN could be elicited by the absence of a tone. Occasional missing 4th and 6th tones amidst groups of 6 identical tones elicited a MMN in healthy subjects. MMN could only occur at these relatively long SOAs (greater than 150 ms, see Yabe et al. 1997) if participants used proximity to form an auditory Gestalt grouping of tones. While a rule based on the number of items is not a particularly complex rule, it still needs to be abstracted as a group characteristic that cannot be predicted by any physical parameter of the stimulus itself. This Gestalt principle of proximity (in this case temporal proximity) is one of pattern abstraction. Thus, forming a perceptual group of items is very much an abstract rule, because it cannot be calculated from any individual element. By contrast a simple MMN evoked by a change in pitch, for example, can be easily detected because of a change in the physical stimulus. This missing stimulus MMN cannot be due to activity in non-adapted sensory neurons, since there is no actual stimulus, and the stimulus is too short to cause an off potential. It may, however, reflect sensory steady-state reverberation due to entrainment of the rapid stimulation in sensory cortex (May and Tiitinen 2010). If the presentation of a series of tones causes the cortex to begin to oscillate, an oscillatory N1 could be misinterpreted as a MMN to an expected but missing stimulus. This possibility can be assessed by examining the period following the last tone in the standard group of 6 tones.

Complex MMN to pattern violations has been largely understudied in schizophrenia. Alain et al. (1998b) examined abstract rule-based MMN in schizophrenia. Using alternating tones, they reported marginally significant complex MMN reduction in schizophrenia at Fz ($p = 0.052$) only for a nose reference, not mastoids. Todd et al. (2014) examined “simple” MMN to four types of deviants, and contrasted those MMNs in a second task where the deviants were paired; the first deviant type (pitch deviant cue) was always followed by the second deviant type (linked duration deviant), and the third deviant type (intensity deviant cue) was always followed by the fourth deviant type (linked pitch glide deviant). Although overall MMN was smaller in schizophrenia, like controls, patients showed a reduction in MMN to the linked deviants relative to the random deviant task. Todd et al. interpreted the reduction in the linked deviant MMNs as reflecting the abstraction of a rule predicting the occurrence of the linked deviant after the cue, such that its occurrence should be an expected event. In that sense, complex MMN was relatively unimpaired in schizophrenia. However, it is possible that the reduced MMN to the linked pair relates to the fact that it followed a deviant, which affects the representation of the standard, which becomes weaker. The studies examining impaired complex MMN in schizophrenia are sparse and the results are equivocal at best. The purpose of the current experiment was to determine if participants with long-term schizophrenia could perform complex pre-attentive pattern abstraction as reflected in the generation of MMN to a missing but expected tone, and to rule out that the missing stimulus MMN is actually just the ebbing end of an induced sensory oscillation.

Materials and Methods

Participants

Fourteen participants with schizophrenia were compared with 16 healthy control participants (14 controls overlap with Salisbury 2012). Groups were matched for age, gender, handedness, and parental socioeconomic status (patients' families were slightly *more* affluent than controls; Table 1). As expected, patients had lower SES than controls, consistent with social and occupational impairment as a disease consequence. Patients were medicated, and moderately symptomatic.

This study conforms with the World Medical Association's Declaration of Helsinki. All participants provided informed consent, and were paid for participation. All procedures were approved by the McLean IRB. In addition, the McLean IRB provided approval for deidentified data to be analyzed elsewhere. The University of Pittsburgh IRB also approved the study.

Stimuli

All tones used were the same: binaural 1 kHz, 75 dB, 50 ms pips with 5 ms rise/fall times, created with Ace of Wave and presented using Presentation over Etymotic 3A insert earphones. Loudness was confirmed with a sound meter and artificial ear canal. Six tones formed the standard group, with a stimulus onset asynchrony of 330 ms. Groups were separated by 800 ms. Thus, the complex rule to be abstracted by each participant's perceptual system according to the Gestalt principle of proximity was that tones were presented in groups of six. This could be determined only by analysis of the temporal relationship between tones and expectation for six tones. There were two 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 ms from the onset of the preceding tone).

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). The Active2 system is a high impedance recording system that uses active noise cancellation. Processing was done off-line with BESA 6 (BESA GMBH) and BrainVision Analyzer2 (Brain Products GMBH). First, using BESA, EEG was filtered between 0.5 and 20 Hz to remove DC drifts and muscle and other high frequency artifact. ICA was used to remove one vertical and one horizontal EOG component explaining the most variance and displaying a symmetrical topography. Next, in BrainVision Analyzer2, data were rereferenced to averaged mastoids. Four averages were constructed: the standard 4th tone occurring in the group immediately preceding the deviant 4th group; the standard 6th tone occurring in the group immediately preceding the deviant 6th group; the deviant missing 4th

tone; and the deviant missing 6th tone. Epochs were extracted from the EEG (400 ms including a 50 ms prestimulus baseline), baseline corrected by the average prestimulus voltage, DC detrended between baseline (−50–0) and the last 50 ms of the epoch, rejected if any site contained activity $\pm 50 \mu\text{V}$, and averaged. Because there is no sensory component to a missing stimulus, subtractions of the standard from the deviant were not performed. MMN was analyzed by comparison of the averaged amplitude between 150 and 200 ms between standards and deviants.

To assess whether the short series of tones entrained sensory cortex and the missing stimulus MMN actually reflected the tail end of an entrained steady state response, activity following the 6th tone of the standard trains was assessed. By logical extension, if 5 tones entrained the cortex, then 6 tones should as well. Averages were constructed 280 to 680 ms following the present 6th tones that preceded a missing 6th block. Hence, the ERP to a missing 6th tone (expected 330 ms after a present 5th tone) could be compared to the ERP to a missing 7th tone (unexpected after a present 6th tone). Additionally, because the auditory evoked responses can be described in the alpha band, we performed wavelet analyses of the full train duration and subsequent activity (300 ms prior to the first tone of a train and the following 2400 ms) to determine whether alpha activity lasted longer to 6 tone trains than 5 tone trains, which would occur with entrainment. Continuous wavelets used the Morlet transform in 0.5 Hz linear steps from 0.5 to 20 Hz, with Morlet's constant of four (enabling a full wavelet to fit in the 300 ms pre-stimulus baseline), and Gabor normalization.

Statistical Methods

Group demographics were compared using t-tests and Chi squared tests. Analysis was performed at F1, Fz, and F2, and FC1, FCz, and FC2, frontocentral sites where MMN is typically largest, with repeated measures ANOVA. Group was the between subjects factor, and Stimulus (actual or missing), position (4th or 6th), chain (F or FC), and Site (left, middle, or right) were within subjects factors. The Huynh–Feldt epsilon corrected for three levels of site. Current Source Density (CSD) analysis with spherical splines was used to visualize source-sink topography (order of splines = 4, maximum degree of Legendre polynomials = 10, lambda of $1e-5$), implemented in BrainVision Analyzer2. For analyses of possible entrainment, activity in healthy participants after the missing 6th tone and after the missing 7th tone at FCz were compared to zero via t test.

Procedure

After audiometry (within 30 dB nHL, no more than 15 dB differences between ears), participants heard tones while watching a silent video of ocean wildlife. No instructions about the tone pattern were provided. Subjects were instructed to attend the video, ignore the tones, remain vigilant, not to blink, and to sit as still as possible.

Results

Overall Activity in the MMN Window

Groups did not differ in overall amplitude collapsed across present and absent stimuli, although the difference reached trend-level ($F(1, 28) = 3.0$, $p = 0.095$, partial $\eta^2 = 0.096$) for patients to show less negative activity.

Actual versus Missing Tones

Missing tones generated marginally more negative activity ($F(1, 28) = 4.1$, $p = 0.052$, partial $\eta^2 = 0.129$) but this differed between groups (Group $\times$ Stimulus, $F(1, 28) = 4.6$, $p = 0.04$, partial $\eta^2 = 0.142$). Followup analyses for actual versus missing stimuli within groups revealed a missing stimulus MMN (significantly more negative to a missing stimulus) was present in healthy controls ($F(1, 15) = 9.1$, $p = 0.009$, partial $\eta^2 = 0.377$, Fig. 1a) but not in schizophrenia ($F(1, 13) < 0.01$, $p = 0.93$, partial $\eta^2 = 0.001$, Fig. 1b). Followup analyses for each tone separately between groups revealed no significant difference in the activity in the MMN window elicited by an actual tone ($F(1, 28) = 0.2$, $p = 0.663$, partial $\eta^2 = 0.007$). However, group comparisons revealed controls were significantly more negative than patients to a missing but expected stimulus ($F(1, 28) = 11.8$, $p = 0.002$, partial $\eta^2 = 0.296$).

Fourth or Sixth Position

There was no effect of stimulus position (4th or 6th, $F(1, 28) = 1.5$, $p = 0.227$, partial $\eta^2 = 0.052$), and no interaction between type of stimulus (actual versus missing) and position ($F(1, 28) = 0.07$, $p = 0.798$, partial $\eta^2 = 0.002$).

F versus FC chain

Although there was no omnibus difference in activity between the frontal (F) and fronto-central (FC) chains ($F(1, 28) = 1.8$, $p = 0.185$, partial $\eta^2 = 0.062$), there was more negative F chain activity for missing stimulus MMN in both groups (stimulus $\times$ chain, $F(1, 28) = 8.5$, $p = 0.007$, partial $\eta^2 = 0.234$).

Laterality

Groups differed in laterality for 4th and 6th stimuli (Position $\times$ Site $\times$ Group, $F(2, 55) = 3.9$, $p = 0.026$, $\epsilon = 1$, partial $\eta^2 = 0.122$) driven by a more negative response on the right to 4th tones and a more negative response on the left to 6th tones in schizophrenia (Position $\times$ Site, $F(2, 26) = 3.6$, $p = 0.043$, $\epsilon = 1$, partial $\eta^2 = 0.215$).

Topography and CSDs

Figure 2 presents scalp topography (mastoid reference) and CSD maps (reference-free) for the missing stimulus MMN. Because patients showed no missing stimulus MMN, Fig. 2 is restricted to control participants. The scalp topography shows maximum negativity more anteriorly, consistent with MMN. The current source-sink pattern is consistent with anterior temporal lobe sources.

Entrainment

Figure 3a presents waveforms and 3b wavelet heat maps for the missing 6th tone and the period following a present 6th tone (corresponding to a missing 7th tone) for healthy participants. There was a small ($-0.4 \mu\text{V}$) N1-like potential at 100 ms that was significantly different from zero ($t_{15} = 3.8$, $p = 0.002$) for the “missing” 7th tone. By contrast, this N1 oscillation was not present to the missing 6th tone ($0.3 \mu\text{V}$, $p > 0.47$) where the larger later negativity (MMN) was observed (150–200 ms).

Discussion

Healthy control participants showed a small but robust negativity to missing stimuli that likely reflects a complex MMN. Primitive auditory intelligence was able to use the Gestalt principle of proximity to form a perceptual group. This response was entirely absent in schizophrenia. Successful navigation of the environment depends on rapid, effortless parsing of the auditory scene into separate events. Novel sounds and the cessation of sounds potentially indicating threat must be pre-attentively detected. Separating the voice of one’s interlocutor from background conversation and noises must be accomplished rapidly in realtime for effective social behavior. Such complex pre-attentive pattern analysis is deficient in schizophrenia, providing increasing evidence that sensory-perceptual deficits impinge on cognitive and social processes (Javitt 2009; Salisbury et al. 2010).

Impaired development of predictive models in schizophrenia may be related to cortical gray matter loss (Hirayasu et al. 1998; Kasai et al. 2003) and synapse reduction in secondary cortex superficial layers (Sweet et al. 2009; Konopaske et al. 2006) possibly related to aberrant NMDA receptor mechanisms (Salisbury et al. 2007; Javitt et al. 1996; Baldeweg and Hirsch 2014). To the extent that MMN reflects communication between primary and secondary cortices, the secondary processing modules may not have the rich circuit architecture necessary to support pattern extraction and prediction.

Complex MMN paradigms may isolate novelty-detection with minimal contribution from adaptation. MMN been shown to changes in ISI for noise burst (Ford and Hillyard 1981) and tone repetitions (Alain et al. 1998a; Nordby et al. 1988), for violations of a tone sequence or “melody” (Schröger et al. 1992; Alho et al. 1996), and to a descending pitch second tone among standard pairs of ascending pitch (Korzyukov et al. 2003; Schröger et al. 2007). Using the “controlled” MMN paradigm Jacobsen and Schröger (2001) detected an earlier SSA N1 component and a later MMN component. Later work was unable to differentiate sources for these two components, both overlapping in STG (Maess et al. 2007). Thus, it cannot be ruled out that both simple and complex MMN may arise in superficial layers of primary auditory cortex (Javitt et al. 1996; see Musall et al. 2015) within a sensory column. We speculate that simple sensory-memory MMN may reflect relatively more primary cortical processing and that complex MMN reflects more secondary cortical processing. Future studies designed for localization of simple and complex MMN are needed to assess this conjecture.

May and Tiitinen (2010) suggested two mechanisms to explain the missing stimulus MMN. Prior to Salisbury (2012), MMN was observed only to missing tones at rates under ~150 ms

apart (Yabe et al. 1997; Tervaniemi et al. 1994). May and Tiitinen (2010) showed that fast stimulation rates caused a positive sustained response in auditory cortex that resolved back to baseline after stimulation stopped (i.e., during the response to a missing stimulus). The sustained positivity did not develop at the rates used in the current experiment. The second suggestion was that the missing stimulus MMN was entrained response resonance. If entrainment occurred to 5 tones, logically it should occur to 6 tones. We saw no evidence for any such activity (Fig. 3a, b). Thus, the response to the expected but missing tone is not an epiphenomenon caused by an oscillation to the repeated tones themselves. The missing stimulus paradigm reported here generates a complex MMN that is abnormal in schizophrenia, at least for prediction of tones based on timing.

Michie (2001) suggested that the brain defect in schizophrenia was more sensitive to duration deviance than pitch deviance. Umbricht and Krljes (2005) reported a pitch MMN effect size of 0.94, and a duration MMN effect size of 1.24. In this missing stimulus paradigm patients and controls showed good separation for the missing 4th tone ($d = 0.93$) and the missing 6th tone ($d = 0.72$) as indicated by only partially overlapping distributions (Fig. 4). Prediction of tone occurrence, abnormal here in schizophrenia, may tap into deficits in time estimation similarly as duration MMN. Current research is underway to determine whether providing visual cues improves the missing stimulus MMN in schizophrenia, and whether other abstract rule violations that do not depend on timing are likewise impaired.

Complex MMN to a missing but expected stimulus is impaired in chronic schizophrenia. The complex MMN reported here likely contains little to no activity reflecting release from sensory adaptation or from steady-state entrainment in sensory cortex. To that extent, the results suggest that detection of novelty and pattern deviance in perceptual groups occurs at a cognitive level within auditory cortex, and this process is highly impaired in schizophrenia.

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Fig. 1.
a ERP waveforms to standard 4th and 6th stimuli and to missing 4th and 6th stimuli in healthy controls. The *arrow* indicates the MMN elicited by missing stimuli. Note that missing stimuli, by definition, do not evoke sensory activity. **b** ERP waveforms to standard 4th and 6th stimuli and to missing 4th and 6th stimuli in schizophrenia. The *arrow* indicates where the MMN elicited by missing stimuli was expected. Note that the waveforms to missing stimuli show very little negativity in schizophrenia

Fig. 2. Scalp topography (averaged mastoids reference), CSD map (reference free), and BESA6 dipole solution for the missing 4th and 6th tone elicited MMN in healthy subjects. All are consistent with a temporal source, inferior and medial to that for the simple stimulus parameter MMN

Fig. 3.

N1 entrainment following tones. **a** Comparison of activity following the unexpected last 5th tone (missing 6th tone) and following the expected last 6th tone (missing 7th tone). Note the small N1 entrainment following the present and expected last 6th tone. A later, larger MMN occurs to the unexpected missing 6th tone. **b** Duration of alpha activity for the tone trains. Evoked potentials can be described in the low alpha range. If entrainment to the trains causes the missing 6th MMN, alpha activity to 6 tones should last longer than activity to 5

tones. The *arrow* labelled “No N1” indicates where an oscillatory N1 would have occurred. Such does not occur, suggesting a qualitatively different event to a missing but expected tone

Fig. 4. Distributions of subjects for missing 4th and 6th MMN. Groups show a fairly good amount of separation, reflected in large effect sizes

Table 1

Demographic and clinical variables

	Patients	Controls	Statistics
Age	34.5 (12.8)	35.4 (11.6)	$t = 0.21, p = 0.84$
Gender	9 M/5 F	10 M/6 F	$\chi^2 = 0.02, p = 0.89$
Parental SES	1.4 (0.7)	2.2 (1.1)	$t = 1.7, p = 0.10$
SES	3.9 (1.2)	2.4 (1.1)	$t = 3.0, p = 0.008$
MiniMental	29.1 (0.8)	29.5 (0.5)	$t = 1.5, p = 0.16$
Handedness	0.7 (0.2)	0.8 (0.1)	$t = 0.6, p = 0.57$
Medication	434.6 (291.6)		
PANSS total	67.8 (22.8)		
PANSS positive	19.6 (7.1)		
PANSS negative	15.1 (6.5)		
Years illness	13.4 (13)		

Medications are expressed in chlorpromazine equivalents