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Title: Duration Mismatch Negativity and P3a in First Episode Psychosis and Individuals at Ultra-High Risk of Psychosis

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Abstract

Background: Reduction in a pre-attentive measure of auditory change detection, mismatch negativity (MMN), is one of the most consistent findings in schizophrenia. Recently, our group showed a reduction in MMN to changes in the duration and intensity of background sounds in those within 5 years of illness onset whereas reduced MMNs to changes in sound frequency were only seen in patients with longer illness duration. In this report, we examine whether reduced MMN as well as P3a, another index of auditory deviance detection, to duration changes is evident even earlier in the illness, that is, in individuals in the first episode of a psychosis (FEP) and individuals identified as being at ultra-high risk of developing schizophrenia (UHR).

Methods: MMN and P3a were measured in 30 UHR individuals, 10 FEP individuals and 20 healthy controls (CON) to both long (100 ms) and short (50 ms) duration deviant sounds.

Results: MMN was reduced to both duration deviants not only in the FEP group but also in the UHR group. P3a amplitude was also reduced in the UHR group but at trend level only in FEP. However, MMN and P3a reductions were unrelated in both UHR and FEP groups suggesting that they reflect distinct deficits.

Conclusions: These results suggest that MMN as well as P3a to duration deviants are reduced in very early stages of a psychotic illness including those in an at-risk mental state. Both should be considered as potential markers of the prodrome.

Introduction

The last 10-15 years has seen the burgeoning of research into the prodromal phase of schizophrenia. Results from this research are promising and suggest that a variety of neurobiological changes are detectable prior to a diagnosis of schizophrenia, including cognitive (1-6), structural (7-10) and electrophysiological (11-14) changes. The ability to improve the identification of individuals who are more likely to make a transition to schizophrenia would allow for targeted early intervention in the prodromal phase of the illness, thus aiming for better long-term outcomes as some recent studies have demonstrated (15-17).

A useful tool in the investigation of neural processes is event-related potentials (ERPs). ERPs allow one to probe sensory, perceptual and cognitive processes with high temporal resolution and are important electrophysiological biomarkers of schizophrenia (18). One of the most reliable ERP markers is an amplitude reduction of mismatch negativity (MMN:19, 20). MMN is an early negative ERP component elicited by any discriminable but relatively infrequent change in a repetitive background of auditory stimulation (21). MMN is the result of an automatic memory-based comparison process that detects a discrepancy between the neural representation of the regularity of recent stimulation and the representation of the deviant sound (22). It is generally accepted that MMN reflects sensory "echoic" memory in audition essential for sound perception, attention and memory (23). Reduced MMN in schizophrenia is associated with impaired proverb interpretation and verbal memory (24) and poor level of functional status across psychological, social and occupational domains (25).

MMN sources originate in the areas of the brain that first detect and process the sound violation (Heschl's gyrus and posterior superior temporal gyrus) with a

likely subsequent contribution from prefrontal brain areas (inferior frontal gyrus) involved in determining whether the deviation is of sufficient novelty for the allocation of attentional resources (26-31). Hence, the activation of an auditory change detection mechanism as indexed by MMN often triggers automatic re-orienting of attention to potentially important events in the unattended auditory environment, reflected in the generation of a frontocentrally distributed P3a component (23, 26, 32). Although not as widely investigated in schizophrenia as the P3b elicited by stimuli that require active attention, a number of studies have reported reduced P3a to novel irrelevant stimuli in schizophrenia in active odd-ball tasks (33, 34). Recently there has been increased interest in the schizophrenia literature in the P3a that follows MMN elicited during passive odd-ball tasks (35-37).

To date, there have been only three studies that have examined MMN in individuals at high-risk of schizophrenia. Of these, two examined MMN with electroencephalography (EEG: 11, 12) and the other utilised magnetoencephalography (MEG: 13). Brockhaus-Dunke et al (12) examined MMN to both frequency and duration decrement deviants (i.e., deviant sounds that differed from standards by a decrease in pitch and sound duration, respectively). They observed a significantly reduced MMN to duration deviants in patients with schizophrenia compared to controls and a non-significant reduction in MMN amplitude in at risk individuals. A second study by the same group, Bodatcsh et al (11), similarly found MMN amplitude to a duration decrement in their at-risk group was intermediate between a healthy control and a first episode group but did not differ significantly from either. Importantly, they also found that duration MMN, unlike frequency MMN, contributed to the prediction of transition to schizophrenia within 24 months. Shin et al (13) examined MMN to a duration increment deviant and found a significant decrease in

the MMNm dipole moment in the at risk group relative to controls. None of the previous studies examined P3a following MMN.

In order to further characterise MMN in subjects who are in a potentially prodromal state, the current study examined MMN to both duration increment and decrement deviants in individuals clinically identified to be at ultra-high risk of developing schizophrenia (UHR) based on the Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria (38). They were compared with small sample of individuals experiencing their first episode psychosis (FEP) and healthy controls (CON). MMN to both duration increments and decrements were examined, as our previous research suggests that duration increment (long) deviants are superior to duration decrement (short) deviants for revealing schizophrenia-related deficits (39-41). We have also previously shown that MMN to duration increments is reduced in unaffected first degree relatives (39) and reduced in patients with a relatively recent illness onset (< than 5 years) (42). We were therefore interested in determining the sensitivity of MMN to duration increments versus decrements in revealing possible prodrome-related deficits in a group identified as being at-risk of developing schizophrenia as well as deficits in a group of first episode patients. Based on this previous research we hypothesised that duration increments would discriminate better between CON, FEP and UHR groups than duration decrements. Research also suggests that nose referenced MMN data consistently show reduced MMN over frontocentral sites in schizophrenia compared to healthy controls (43) but often, although not invariably (see 46), normal amplitude MMN reversal over mastoids (44-46). We therefore utilised nose-referenced data to determine whether this pattern of reduced frontocentral but unaffected mastoid MMN amplitudes were also evident in UHR and FEP groups. There are to our knowledge no studies to date that have

examined both the MMN and P3a ERP components acquired in the same paradigm in at-risk and first episode groups. Hence, we examined not only whether FEP and UHR groups showed P3a amplitude reductions relative to CON, but also whether MMN amplitude predicted P3a amplitude.

Methods and Materials

Participants

Sixty-one young adults (mean age 19 +/- 3.5 years, 20 male) volunteered for the study. Forty were outpatients of a local mental health service focussed on identifying and treating young people at risk of developing psychosis. Of these, 11 met CAARMS (38) criteria for FEP (mean age 21 +/- 2.7 years, 5 male) and were in remission at time of assessment. The remaining 30 met criteria for UHR for development of psychosis (mean age 17 +/- 3.6 years, 10 male). Identification of the ultra-high risk cohort was based on meeting clinical criteria for at least one of three groups according to the CAARMS (38). Briefly, the three groups were those with 1) Attenuated Psychotic Symptoms, 2) Brief Limited Intermittent Psychotic Symptoms, and 3) Trait and State Risk Factors, that required a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as marked decline in social or occupational functioning. Twenty-one of the UHR subjects met criteria for attenuated psychotic symptoms. Four met brief limited intermittent psychotic symptoms criteria. One met trait and state criteria and four were categorised with both attenuated psychotic symptoms and trait and state factors. Seven individuals in the UHR group received sub-therapeutic antipsychotic pharmacotherapy (e.g. 0.5 mg/day risperidone) for a brief period (< 1 month) which was discontinued following psychiatric review and 8 individuals in the FEP group were receiving low-dose

treatment with atypical antipsychotics at the time of the MMN recording. To date, of the 30 UHR participants, 6 have made a confirmed transition (UHR-T) to a psychotic disorder based on SCID criteria (47). Three have been diagnosed with Schizoaffective Disorder, one with Schizophrenia paranoid type, one with Schizophrenia undifferentiated and one with Psychosis not otherwise specified. Although twenty-four have not transitioned (UHR-NT), some could still be in the prodromal phase and develop schizophrenia at some time in the future. In addition to the CAARMS, symptom severity of seventeen UHR and seven FEP participants was rated using the Schedule for Assessment of Positive Symptoms (SAPS) and Schedule for Assessment of Negative Symptoms (SANS) (48). The majority of UHR participants rated between none and mild on global rating scales with a median rating of questionable or mild. The FEP participants exhibited more delusions (p=.06), affective flattening (p=.01) and avolition (p=.002) than UHR participants.

Twenty participants in the control (CON) group were students attending the University of Newcastle (mean age 20 +/-2.4 years, 5 male). Participants in the CON group were excluded if they had a personal history of mental illness based on the SCID (47) or had a first or second-degree biological relative with a history of a psychotic disorder.

Participants were screened for neurological conditions, serious head injury, and hearing impairments via audiometric assessment. One individual in the FEP group was excluded due to a diagnosis of central epilepsy. Ethics approval was obtained from the University of Newcastle. All participants gave their written informed consent to participate.

Stimuli and Procedure

Two MMN sequences were generated using the Neuroscan STIM package. Tones were presented binaurally over headphones while participants watched a silent cartoon. Subjects heard 8 blocks of 300 auditory tones (1000 Hz, 70.5dB SPL) of short (50 ms) and long (100 ms) duration with a regular inter-stimulus interval (offset to onset interval) of 600 ms. In half the blocks, 7.5% of tones (deviants) were of long duration and 92.5% (standards) were short, whereas in the other half of the blocks, deviants were short and standards were long duration. Each sequence lasted approximately 4 minutes. Short and long deviant blocks alternated.

EEG data were acquired and processed with Neuroscan software and hardware (Neuroscan, El Paso, Texas). The data were continuously sampled at 500 Hz from three midline sites (Fz, Cz and Pz) and the left and right mastoids, each referred to the nose. Vertical and horizontal electrooculogram was monitored by electrodes above and below the left eye and 1 cm to the side of the outer canthi of each eye respectively. Impedances were kept below 5 kΩ.

Data Analysis

Segments of the continuous record contaminated by movement artefacts were identified and manually marked for deletion. Eyeblink artefact was corrected with procedures implemented in Neuroscan (49). The data were filtered (bandpass 1-12 Hz) and epoched with a 100 ms pre-stimulus and 450 ms post-stimulus periods. Separate averages were then obtained for each standard and deviant stimulus in each stimulus sequence. Epochs containing artefacts exceeding +/- 100 μV were excluded from averages.

MMN to short and long duration sounds was obtained by subtracting the standard from the deviant ERP for each stimulus duration (50 or 100 ms) thus

controlling for the physical attributes of the stimulus. Peak detection software was used to extract peak latencies at Fz, Cz, and the mastoids from individual subject MMN waveforms using a latency window of 140-270 ms. Mean amplitudes of MMN were then computed over 50-ms windows surrounding identified peaks. The same procedures were used for identifying peak latencies and mean amplitudes of P3a at Fz, Cz and Pz using a latency window of 250-400 ms and N1[1] mean amplitude in both standard and deviant ERPs at Fz and Cz using a latency window of 50-150 ms.

Age differed significantly across the groups ($F(2,57) = 9.70$, $p < .001$): the UHR group was younger than both the control and FEP groups (Bonferroni adjusted $p = .002$ for both comparisons). MMN measures were initially analysed as mixed model omnibus ANCOVAs with age as a covariate, a Group (CON, UHR and FEP) factor and 2 repeated measures factors; Deviant Duration (short and long) and Site (Fz, Cz, left mastoid, right mastoid). Homogeneity of age regressions was satisfied for both MMN measures.

P3a measures were analysed as mixed model ANCOVAs with Group (CON, UHR and FEP) and two repeated measures factors, Deviant type (short and long) and Site (Fz, Cz and Pz). Age was fitted as a single covariate for P3a latency and amplitude. Homogeneity of age regressions was satisfied for both P3a measures.

Greenhouse-Geisser corrected degrees of freedom and p-values are reported when sphericity was violated and Bonferroni multiple comparisons undertaken where appropriate.

To examine whether MMN and P3a components generated in response to duration increments and decrements covaried, we examined Spearman correlations between MMN and P3a amplitudes in each group separately. Relationships between

global symptom ratings on SAPS and SANS and MMN and P3a amplitude in the UHR and FEP groups were also determined using Spearman correlations.

Results

MMN Analysis

As the initial omnibus ANCOVA indicated age did not significantly predict MMN amplitudes, and its inclusion in the model did not change any of the main or interaction effects, ANOVAs are reported. MMN amplitude exhibited main effects of group ($F(1,57) = 5.61$, $p = .006$), duration ($F(1,57) = 4.21$, $p = .045$) and site ($F(1.54, 93.14) = 227.44$, $p < .000$). Both group and duration interacted with site (group x site: $F(3.09, 87.99) = 5.32$, $p = .017$; duration x site: $F(1.85, 105.44) = 5.82$, $p = .005$), primarily due to the polarity reversal of MMN at mastoid relative to scalp sites. Separate analysis conducted on midline sites (Fz, Cz) resulted in significant duration ($F(1,57) = 10.89$, $p = .002$) and group ($F(2,57) = 8.18$, $p = .001$) effects only. MMN amplitude at midline sites was larger in response to a duration increment. Both FEP and the UHR groups showed highly significant reductions in MMN amplitude relative to CON (FEP: $p = .001$; UHR: $p = .009$) across both deviant types, although the effect size of the reduction was slightly larger for a duration increment than decrement: FEP vs. CON, Cohen's $d = -1.29$ and -1.00 for duration increment and decrement respectively and for UHR vs. CON, Cohen's $d = -.76$ and $-.56$ respectively (see Figure 1 and Table 1). There were no significant group or duration deviant differences at the mastoids.

These main effects were maintained when the MMN data were re-referenced to the average of the mastoids (see Supplemental 2) except that interactions with site were no longer significant.

Age did not significantly predict MMN latency and was removed from the analysis. MMN peak latency exhibited an effect of site ($F(2.15,122.77) = 14.30$, $p < .001$), peak latency being earlier at both left and right mastoid sites than midline sites (Fz, Cz: all p-values < .05), an effect of duration ($F(1,57)=8.06$, $p=0.006$) due to MMN peak latency being earlier to the long than the short deviant, and a significant interaction between duration and group ($F(2,57)=3.77$, $p=0.029$). None of the Bonferroni comparisons of simple group effects were significant. However inspection of means suggested MMN peak latency to short duration deviants was longer in the FEP group than controls ($p = .089$) whereas MMN peak latencies to long duration deviants were similar across the three groups (see Table 1). Re-referenced MMN data for latency again provided similar results to those obtained above (see Supplemental 2).

The distribution of MMN amplitudes of the 6 individuals who transitioned (UHR-T; see Figure 2A) indicate 75% of MMN amplitudes generated by these prodromal individuals to short and long deviants are smaller than median MMN amplitudes of those that have not transitioned at the time of assessment (UHR-NT). With such small transition numbers and the preliminary nature of the data, these results should be interpreted with caution.

P3a Analysis

Age was not a significant predictor of P3a amplitude or latency. ANOVA results are reported for both measures. There was a trend towards an effect of deviant type ($F(1,57)=3.62$, $p=0.062$), due to P3a to long duration deviants being larger, and a significant main effect of group on P3a amplitude ($F(2,57)=4.01$, $p=0.024$). UHR produced a significantly smaller P3a than CON ($p=0.035$) and FEP showed a similar

trend (p=0.105) but unlike MMN, there was no consistent evidence for the effect size to be larger for duration increments: FEP vs. CON, Cohen's d = -.45 and -.67 for duration increment and decrement respectively and for UHR vs. CON, Cohen's d = -.76 and -.29 respectively (see Figure 1 and Table 2). Both deviants produced typical frontocentral scalp topography of P3a peaks ($F(1.62, 92.12)=24.71$, $p<.001$), with larger amplitudes at Fz and Cz than Pz (both p-values < .001). No site interactions were significant.

There were no group differences in P3a peak latencies. In general, Cz produced an earlier P3a peak than either Fz or Pz (site effect: $F(1.31, 74.89)=17.98$, $p<.001$), P3a peak latency at Pz was particularly prolonged to long duration stimuli (duration x site interaction: $F(1.64, 93.63)=5.13$, $p<.012$; see Table 2).

A similar distribution pattern to that seen for MMN amplitudes is also seen in the P3a amplitudes of the 6 individuals who transitioned (UHR-T; see Figure 2B), with approximately 75% of P3a amplitudes generated by these prodromal individuals to short and long deviants being smaller than median P3a amplitudes of those that have not transitioned at the time of assessment (UHR-NT).

Relationship of MMN amplitude to P3a amplitude and global symptom ratings

For both deviant types, correlations (two-tailed) between MMN and P3a were evident only in the control group (long duration: r_s = -.41, p = .077; short duration: r_s = -.56, p = .010). For the UHR and FEP groups, the correlations were negligible (r_s ranging from -.07 to .16). There were no significant associations between SAPS and SANS and global symptom ratings and MMN and P3a amplitudes in the UHR and FEP groups.

Discussion

We investigated automatic auditory processing utilising long and short duration deviants and two neurophysiological markers of auditory deviance detection, MMN and P3a, in individuals identified as being at ultra-high risk of schizophrenia and those in their first episode of psychosis compared with healthy controls. Although effect sizes of group differences in MMN amplitude were somewhat larger for long than short duration deviants, our results did not support the hypothesis that a long duration deviant would discriminate better between healthy controls, individuals at ultra-high risk of schizophrenia and first episode psychosis individuals. However, our results clearly indicate that those identified as at risk show substantial deficits in pre-attentive stages of auditory processing as measured by MMN at midline sites, whereas MMN at the mastoids was not reduced. These findings mirror those often reported in patients with an established schizophrenic illness (44-46). We have also shown that individuals experiencing their first episode of psychosis produce reduced MMN compared to healthy controls. Again, MMN at the mastoids was not significantly reduced.

P3a was also reduced in individuals who are at risk of psychosis, but this was not the case for those in their first episode, possibly because of the smaller sample and reduced power. MMN amplitude was a significant predictor of P3a amplitude only for the control group. MMN and P3a appear to be dissociated in both the first episode and ultra-high risk groups and therefore could represent distinct deficits in the early stages of schizophrenia and in those who are potentially prodromal. Neither MMN nor P3a amplitudes correlated with global symptom ratings,

In demonstrating that MMN to duration deviants provides a sensitive marker of at-risk mental states, our data extend previous ERP research by Brockhaus-Dunke

et al (12) and Bodatsch et al (11) who found similar but non-significant reductions in MMN to short duration deviants in at-risk groups. Although it is tempting to suggest that the greater sensitivity of our MMN paradigm is due to the inclusion of long duration deviants, this conclusion is not warranted statistically although data from Shin et al (13) are consistent with such an interpretation: their MEG study also found a significant reduction in MMNm dipole moment to a long duration deviant in at risk individuals. Nonetheless, it is clear that short duration deviants provide important predictive information about transition since Bodatsch et al (11) demonstrated that MMN amplitude contributed not only to the prediction of transition to schizophrenia but also to an individualised estimate of risk (of psychosis). Even though our own transition data are preliminary, some interesting trends are apparent.

However, while our data suggest impairments in MMN in both individuals with a recent onset of illness and those who are at-risk and potentially prodromal, it is acknowledged that there remains controversy as to whether MMN reduction occurs early in the illness or not. Some reports (50, 51) have found impairments in MMN in patients with recent onset schizophrenia. Others report that MMN reduction only appears with increasing illness duration (52-54). Our recent findings reported in Todd et al (42) that MMN to different deviant dimensions are differentially sensitive to illness duration may go some way towards accounting for inconsistencies in the literature: Todd et al found a reduction in MMN to duration and intensity increment deviants but not frequency for those patients who were at an early stage of their illness, but in contrast, patients with a longer length of illness showed a reduction in MMN to frequency but not duration and intensity deviants. The current study extends these findings: reduced frontocentral MMN to duration deviants suggests underlying

abnormalities in auditory system function in not only those experiencing their first episode of psychosis but also those in an "at-risk" mental state.

The polarity reversal of MMN at the mastoids with a nose reference has given rise to speculation regarding the roles of different sources contributing to the MMN (26, 55, 56). Schönwiesner et al (29), based on findings from a combined fMRI and EEG study, proposed a hierarchical model of automatic change processing in which the primary auditory cortex, the posterior superior temporal gyrus and the mid-ventrolateral prefrontal cortex are involved in the initial detection of an acoustic change, analysis of the change and a subsequent novelty judgement of the change, respectively. Based on this hierarchical model, the current findings and those of other studies reporting reduced MMN at frontocentral sites but no reduction at mastoids in established schizophrenia (44, 45, 57) (however see 58) suggest that the initial detection of acoustic change is adequate in individuals at high risk of developing psychosis as well as in those either in their first episode or a more enduring illness, but that difficulties occur later in the analysis of this acoustic change and/or judgements about the novelty of the change.

Our P3a results also suggest impairments in novelty detection in the UHR group. There have been only a few schizophrenia studies that have examined the P3a component subsequent to MMN in a passive paradigm. Valkonen-Korhonen et al (59) and Hermens et al (35) report reductions in P3a in first-episode psychosis individuals. Our study provides evidence, albeit at trend level, of similar reduction of P3a in a young first episode group, but extends these findings by showing a reduction in P3a in individuals at high risk of developing a psychotic illness, suggesting that this ERP component is also impaired prior to psychosis onset. Horvath et al (60) have suggested that the process indexed by P3a is activated by significant events in a

general sense and the P3a would therefore be modulated by the results of analysis of sensory memory and/or by the potency of the stimuli to affect behaviour. However, as our data also show that P3a reductions are unrelated to MMN reductions and therefore presumably independent of the outcome of analysis by sensory memory, the reduction in P3a amplitude in the UHR group may be more strongly linked to a separate deficit in processing the salience of the stimuli and relevance to behaviour. It should be noted that others have also observed that P3a component can be dissociated from MMN (61, 62).

There are two limitations of the current study. The first is the small sample of first episode patients available for assessment, a limitation that may account for inconsistent effects on P3a amplitude in the high risk and first episode groups. A second limitation is the heterogeneity of the prodromal sample. Within the follow-up period although six UHR participants made the transition to psychosis (20%), the number of false negatives remains unknown. Future follow-up of UHR individuals will provide further information as to whether lower MMN and P3a amplitudes in the prodrome can provide an indication of a higher risk of developing a schizophrenia spectrum disorder.

In summary, our results indicate that there is a reduction in the amplitude of the MMN and P3a to both short and long deviants in young people identified as at risk of developing a psychotic disorder. Therefore, reduced duration MMN and P3a amplitudes may be markers of the prodromal phase of schizophrenia and provide promise in terms of identifying individuals who are at risk for early intervention.

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Endnotes/Footnotes

[1] The N1 analysis and associated Table and Figure can be found in Supplemental 1.

[2] There are a number of outliers evident for both MMN and P3a measures. Non-parametric median tests of group differences on MMN and P3a amplitude measures at Fz when averaged over long and short duration deviants were still significant for MMN (p=0.002) and showed a trend for P3a (p=0.115)

Legends

Table 1: Mean Amplitude (μV) and Peak Latency (ms) (SD in parenthesis) of Mismatch Negativity peak for each deviant type in CON (Control), UHR (Ultra-High Risk of psychosis) and FEP (First Episode Psychosis) groups at each electrode site. RM = right mastoid, LM = left mastoid.

Table 2: Mean Amplitude (μV) and Peak Latency (ms) (SD in parenthesis) of the P3a peak for short and long deviants in CON, UHR and FEP groups at each electrode site.

Figure 1: Mismatch negativity difference waves (MMN) at the Fz, Cz, Right Mastoid (RM) and Left Mastoid (LM) for A: Duration Decrement Deviant, B: Duration Increment Deviant. For Control, UHR (Ultra-High Risk of psychosis) and FEP (First Episode Psychosis) groups.

Figure 2: Distribution of (A) MMN mean amplitudes and (B) P3a mean amplitudes elicited by long duration deviants and short duration deviants at the frontal central electrode site (Fz) for CON (Control), FEP (First Episode Psychosis), UHR-NT (Ultra-High Risk of psychosis individuals who have not transitioned to psychosis to date) and UHR-T (Ultra-High Risk of psychosis individuals who have made a confirmed transition to a psychotic disorder) groups[2]. Horizontal bars represent median MMN and P3a amplitudes for the groups.

Table 1

Table 1

	Fz		Cz		RM		LM	
	Amp	Latency	Amp	Latency	Amp	Latency	Amp	Latency
Short duration								
CON	-1.37	206.0	-1.29	207.2	0.68	194.8	0.81	198.4
	(0.95)	(24.64)	(0.82)	(23.65)	(0.42)	(26.06)	(0.59)	(34.2)
UHR	-0.92	218.47	-0.99	214.8	0.88	198.93	0.89	200.93
	(0.58)	(21.55)	(0.53)	(20.91)	(0.66)	(25.98)	(0.81)	(27.17)
FEP	-0.76	227.6	-0.57	218.6	0.82	206.4	0.68	208.8
	(0.35)	(30.78)	(0.51)	(39.82)	(0.68)	(28.8)	(0.57)	(26.82)
Long duration								
CON	-1.97	212.2	-1.74	210.0	0.84	201.9	1.02	191.4
	(0.86)	(22.55)	(0.92)	(19.7)	(0.54)	(32.95)	(0.73)	(30.63)
UHR	-1.31	199.47	-1.2	199.73	0.92	197.53	0.95	187.6
	(0.72)	(20.98)	(0.76)	(20.86)	(0.71)	(24.75)	(0.78)	(20.41)
FEP	-1.00	205.8	-0.87	214.00	0.76	202.8	0.65	180.4
	(0.5)	(34.13)	(0.59)	(21.21)	(0.46)	(15.7)	(0.41)	(23.85)

Table 2

Table 2

	Fz		Cz		Pz	
	Amp	Latency	Amp	Latency	Amp	Latency
Short duration standard						
CON	1.12 (1.0)	303.7 (30.0)	1.04 (0.94)	303.5 (34.67)	0.57 (0.77)	321.8 (46.09)
UHR	0.91 (0.48)	312.4 (32.42)	0.76 (0.57)	297.8 (21.87)	0.47 (0.69)	311.8 (42.98)
FEP	0.57 (0.62)	319.60 (35.0)	0.37 (0.67)	313.8 (36.4)	0.34 (0.75)	324.4 (42.34)
Long duration standard						
CON	1.49 (1.18)	313.8 (32.51)	1.4 (1.17)	303.2 (28.86)	0.9 (0.97)	340.9 (35.5)
UHR	0.83 (0.60)	308.8 (29.04)	0.75 (0.62)	303.47 (31.77)	0.39 (0.48)	331.8 (44.15)
FEP	1.97 (1.05)	316.6 (38.98)	1.0 (0.88)	304.2 (36.02)	0.58 (0.66)	345.4 (34.14)

Figure 1

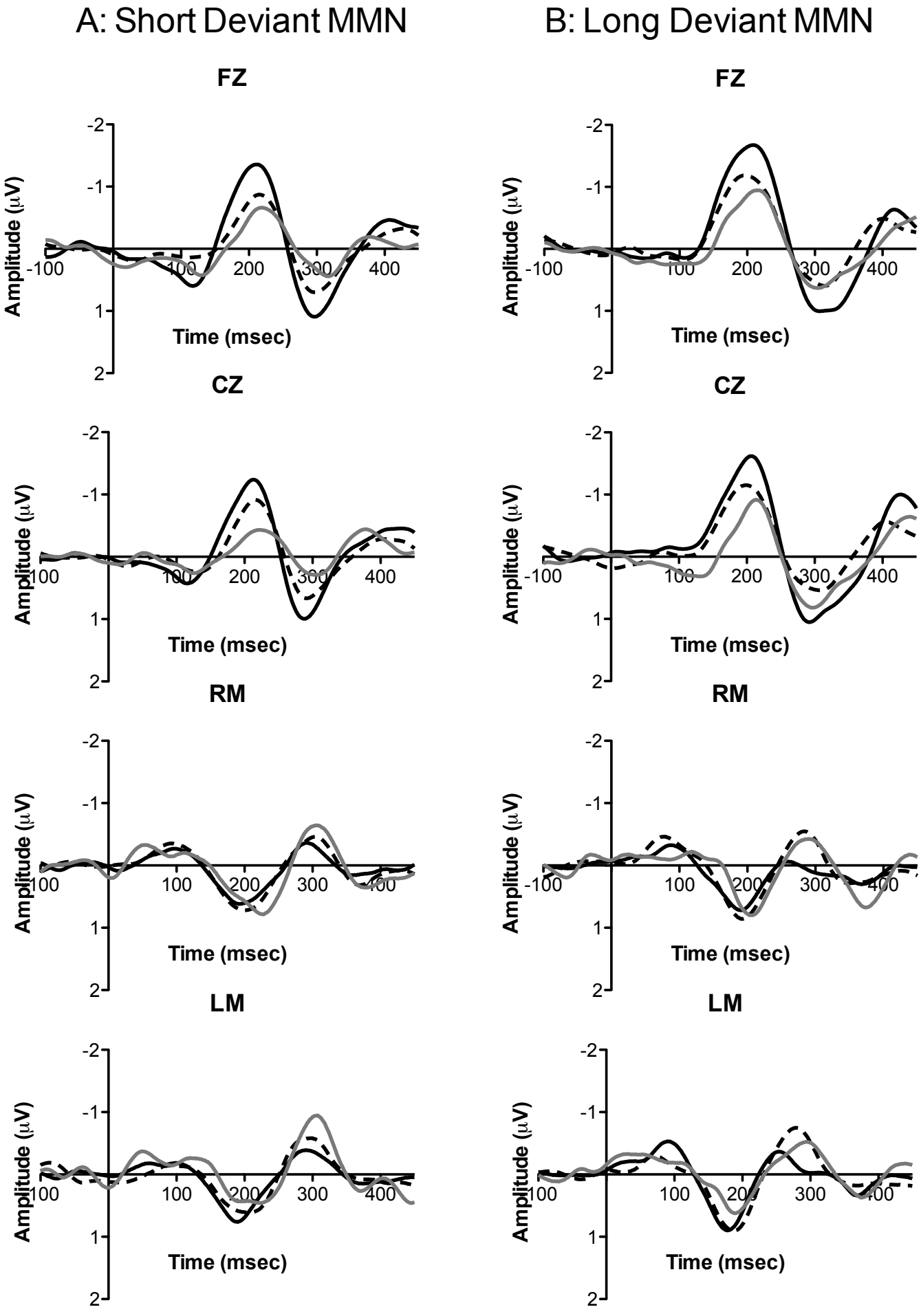
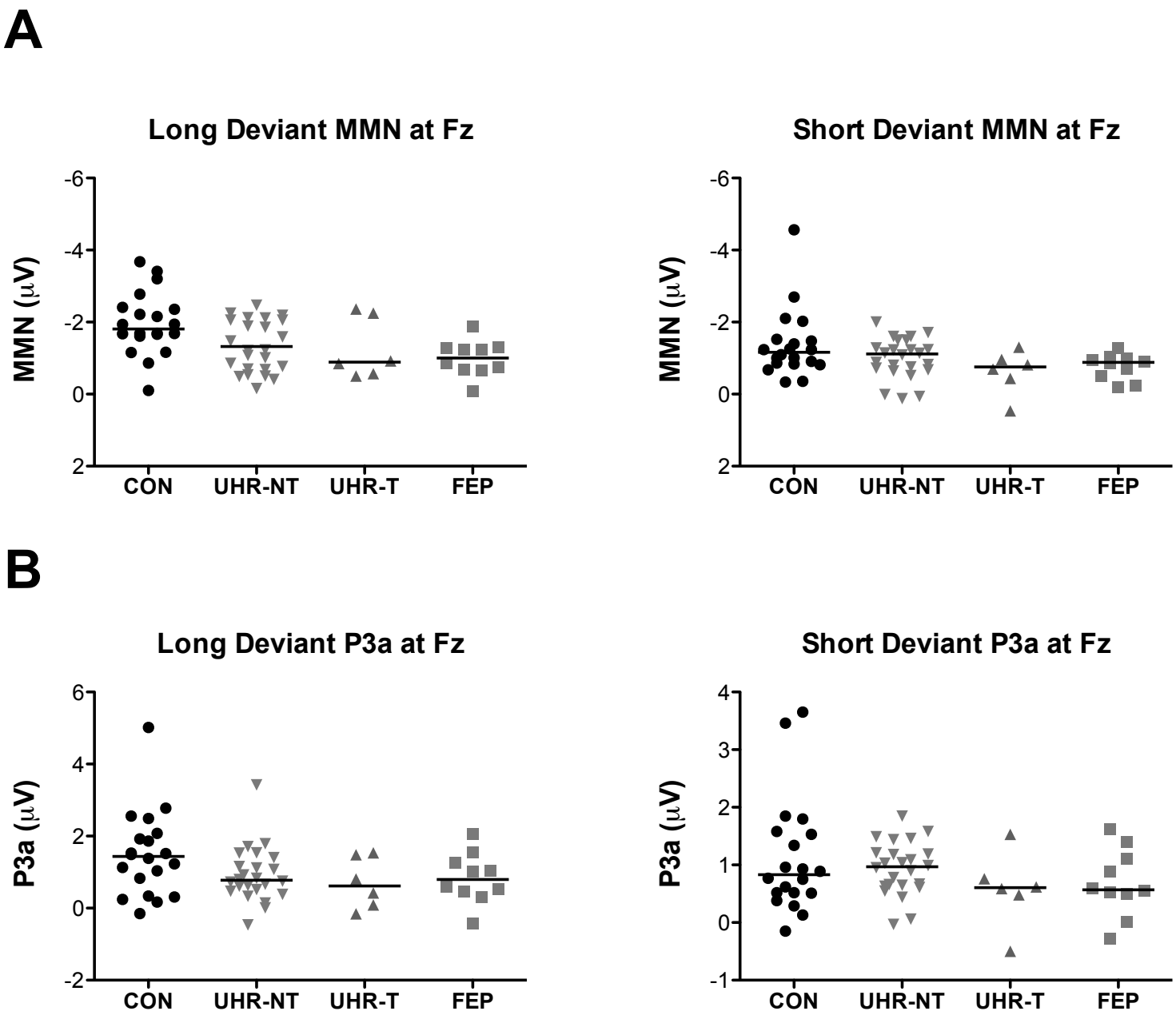

A: Short Deviant MMN
B: Long Deviant MMN
FZ
CZ
RM
LM
Amplitude (μV)
Time (msec)
-2
-1
1
2
-100
100
200
300
400
Control
UHR
FEP

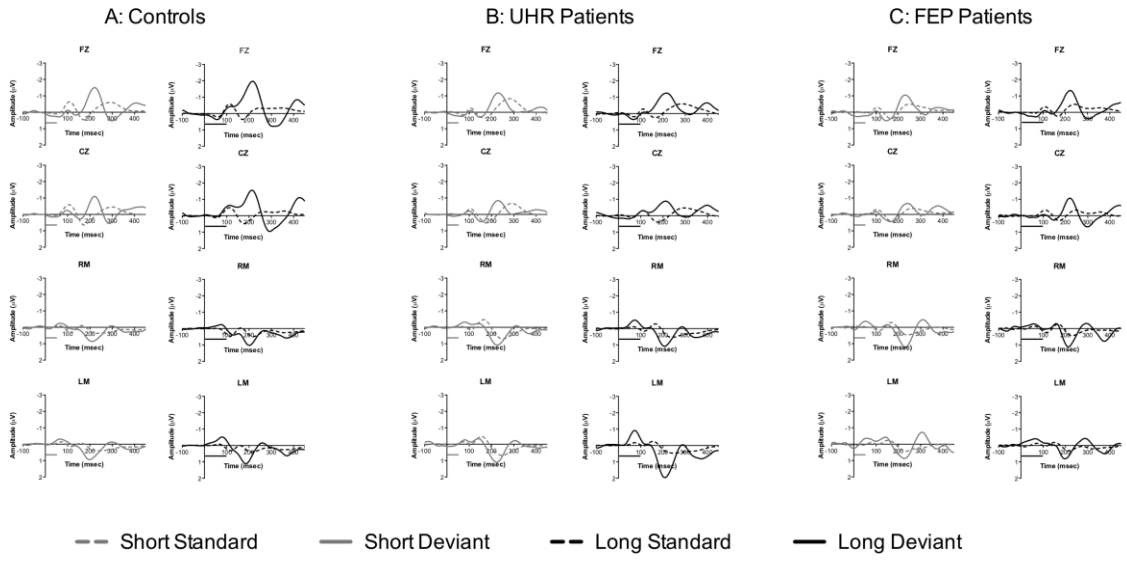
Figure 2


A
Long Deviant MMN at Fz
MMN (μV)
-6
-4
-2
0
2
CON
UHR-NT
UHR-T
FEP
Short Deviant MMN at Fz
MMN (μV)
-6
-4
-2
0
2
CON
UHR-NT
UHR-T
FEP
B
Long Deviant P3a at Fz
P3a (μV)
6
4
2
0
-2
CON
UHR-NT
UHR-T
FEP
Short Deviant P3a at Fz
P3a (μV)
4
3
2
1
0
-1
CON
UHR-NT
UHR-T
FEP

Supplemental 1

N1 Analysis

Age was a significant predictor ($F(1,56)=8.66$, $p=0.005$) of N1 amplitude: younger individuals produced larger (more negative) N1 peaks. N1 amplitude was larger at Cz than Fz (site effect: $F(1,57)=4.15$, $p=0.046$) and larger for standard than deviant stimuli (stimulus effect: $F(1,57)=5.44$, $p=0.023$) but Group only approached significance ($F(1,56) = 2.68$, $p = .078$. That is, after adjusting for the regression of N1 amplitude on age, N1 amplitude was smaller in the FEP group overall than the CON and UHR. This pattern of results can be seen in Supplemental Figure 1. There were no interactions involving group nor were there interactions between stimulus and duration. Therefore, there is no evidence in these data that N1 amplitude differences between deviants and standards contributed to the MMN difference waveform, or to the group differences in MMN, particularly for the long duration deviant. N1 differences between deviants and standards (larger for standards) in fact resulted in a positive shift of the MMN subtraction waveform over the N1 latency range (see Supplemental Figure 1).



Supplemental Figure 1: Grand average event-related potentials (ERPs) at the Fz, Cz, Right Mastoid (RM) and Left Mastoid (LM) to short duration deviants and standards for A: Controls, B: UHR (Ultra-High Risk of psychosis) and C: FEP (First Episode Psychosis) groups. Lines indicate stimulus duration.

Supplemental Table 1: Mean Amplitude (μV) (SD in parenthesis) of N1 for short and long duration tones in CON (Control), UHR (Ultra-High Risk of psychosis) and FEP (First Episode Psychosis) groups at Fz and Cz electrode sites

	Fz		Cz	
	N1 Amp Standard	N1 Amp Deviant	N1 Amp Standard	N1 Amp Deviant
Short duration				
CON	-0.58 (0.34)	-0.21 (0.88)	-0.53 (0.34)	-0.31 (0.78)
UHR	-0.17 (0.50)	-0.15 (0.57)	-0.25 (0.48)	-0.29 (0.67)
FEP	-0.22 (0.14)	-0.11 (0.68)	-0.25 (0.18)	-0.21 (0.5)
Long duration				
CON	-0.53 (0.40)	-0.46 (0.72)	-0.47 (0.40)	-0.69 (0.79)
UHR	-0.22 (0.37)	0.33 (0.66)	-0.27 (0.42)	-0.49 (0.62)
FEP	-0.28 (0.26)	-0.05 (0.79)	-0.31 (0.2)	-0.09 (0.8)

Supplemental 2

Re-referenced MMN

Supplemental Table 2 shows the mastoid re-referenced MMN mean amplitudes and latency for each group. Consistent with the nose referenced data, re-referenced MMN amplitude exhibited main effects of group ($F(1,57) = 4.57$, $p = .014$), duration ($F(1,57) = 9.59$, $p = .003$) and site ($F(1, 57) = 4.62$, $p = .036$). MMN mean amplitude was larger to a duration increment and larger overall at the Fz electrode site. Both the FEP and UHR groups displayed lower MMN mean amplitudes to both deviant types in comparison to the CON group. However only the reduction in the FEP group reached significance (FEP: $p= .014$). Effect sizes were again larger for a duration increment than decrement and exhibited a similar pattern to the nose referenced data, although overall effect sizes were slightly smaller in the re-referenced data: FEP vs. CON, Cohen's d = -1.07 and -0.43 for duration increment and decrement respectively and for. UHR vs. CON, Cohen's d = -.64 and -.34 respectively. The reduced effect sizes in the mastoid re-referenced data relative to the nose referenced data is perhaps not surprising given that MMN at the mastoids in the nose-referenced data did not exhibit group differences.

Re-referenced MMN peak latency exhibited an effect of duration ($F(1,57)=15.03$, $p<.001$) due to peak latency being earlier to the long than short deviant and significant three-way interaction between duration, site and group ($F(2,57)=6.29$, $p=.003$). None of the Bonferroni comparisons of simple group effects were significant. However inspection of means suggested MMN peak latency was shorter in the CON compared to either the UHR or FEP groups.