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Automatic Auditory Processing Deficits in Schizophrenia and Clinical High-Risk Patients: Forecasting Psychosis Risk with Mismatch Negativity

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Abstract

Introduction—Only about one third of patients at high risk for psychosis based on current clinical criteria convert to a psychotic disorder within a 2.5-year follow-up period. Targeting clinical high-risk (CHR) individuals for preventive interventions could expose many to unnecessary treatments, underscoring the need to enhance predictive accuracy with non-clinical measures. Candidate measures include event-related potential (ERP) components with established sensitivity to schizophrenia. Here we examined the mismatch negativity (MMN) component of the ERP elicited automatically by auditory deviance in CHR and early illness schizophrenia (ESZ) patients. We also examined whether MMN predicted subsequent conversion to psychosis in CHR patients.

Method—MMN to auditory deviants (duration, frequency, and duration+frequency "double deviant") were assessed in 44 healthy controls (HC), 19 ESZ, and 38 CHR patients. Within CHR patients, 15 converters to psychosis were compared to 16 non-converters with at least 12 months of clinical follow-up. Hierarchical Cox regression examined the ability of MMN to predict time to psychosis onset in CHR patients.

Results—Irrespective of deviant type, MMN was significantly reduced in ESZ and CHR patients relative to HC, and in CHR converters relative to non-converters. MMN did not significantly differentiate ESZ and CHR patients. The duration+frequency double deviant MMN, but not the single deviant MMNs, significantly predicted the time to psychosis onset in CHR patients.

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Conclusions—Neurophysiological mechanisms underlying automatic processing of auditory deviance, as reflected by the duration+frequency double deviant MMN, are compromised prior to psychosis onset, and can enhance the prediction of psychosis risk among CHR patients.

Keywords

event-related potential; schizophrenia; mismatch negativity; clinical high risk for psychosis; psychosis; auditory cortex; longitudinal

Among individuals at clinical high-risk (CHR) for psychosis, 29–36% will convert to a psychotic disorder within a 2–3 year follow-up period (1, 2). Targeting CHR patients for early intervention based solely on clinical criteria could expose many patients to unnecessary treatments, underscoring the need to enhance predictive accuracy with non-clinical measures. Candidate measures include electroencephalography (EEG)-based event-related potential (ERP) components with established sensitivity to schizophrenia. Among such ERP components, the mismatch negativity (MMN) shows promise as a biomarker of psychosis risk (3–7).

Auditory MMN, a neurophysiological measure of stimulus feature analysis (8), is a negative ERP component elicited automatically by any discriminable deviant sound occurring during a series of repeated “standard” sounds (9). MMN is thought to reflect “echoic” memory because the detection of deviance depends on a short-term representation of the preceding sequence of standard sounds (9, 10). Larger MMN amplitude is associated with greater feature deviance and lower deviance probability (9). Importantly, MMN is pre-attentive; its elicitation does not require attention to the auditory stream or to the deviant stimulus (9, 11, 12). As such, it allows study of auditory pathophysiology in schizophrenia while minimizing cognitive, attentional, and motivational confounds.

MMN amplitude is reduced in schizophrenia (13, 14), including chronic (4, 15–30), recent onset (4, 5, 18, 28, 31), and unmedicated (3, 15, 21, 32, 33, but see 34) patients. Studies of MMN in first episode schizophrenia are mixed, with some finding reduced frequency-deviant (22) or duration-deviant (3, 20, 35, 36) MMN, at least in a subgroup with no college education (18), but others finding normal duration- (26) or frequency-deviant (3, 26, 30, 34, 37) MMN amplitudes that subsequently decline over 2.5 months (34) to 1.5 years (38), in one case in association with left Heschel’s gyrus volume decline (38). Genetic studies are also mixed, with some showing MMN deficits in first-degree relatives of schizophrenia probands (39–41) but others showing no familial effects (26, 42–44) or weak genetic effects based on patient twin data (44, 45). In addition, reduced MMN has recently been observed in CHR patients (3–7), indicating that MMN is compromised prior to psychosis onset. Importantly, two of these CHR studies (3, 6) found greater MMN deficits in CHR patients who subsequently converted to psychosis.

Although MMN deficits in schizophrenia are not always observed (13), study results may depend on the type of MMN elicited. Indeed, MMN is not a unitary ERP component; rather, distinct neural generators contribute to MMN depending on which stimulus features are deviant (46–51). There is some evidence that duration-deviant MMN is more sensitive to schizophrenia than frequency-deviant MMN (13, 19, 31). All previous CHR studies (3–7)

examined duration-deviant MMN, but only one examined frequency-deviant MMN (3), finding it to be normal in CHR patients. Nonetheless, frequency-deviant MMN deficits have been observed in schizophrenia (13, 18, 38), suggesting that pathophysiological heterogeneity across patient samples may also contribute to inconsistent MMN findings. If some schizophrenia or CHR patients are more deficient in duration-deviant MMN, while others are more deficient in frequency-deviant MMN, single-deviant MMN paradigms may yield weak and inconsistent group effects. Multi-deviant paradigms, in which two or more deviant types are presented along with standards within a single sequence, have been used to overcome this limitation (31, 52). Another approach, adopted in the current study, is to combine deviance features such as duration and frequency within a single stimulus, potentially facilitating detection of MMN deficits regardless of which MMN type is more deficient in a given patient. Prior studies (53–57) have shown that when two features of a stimulus are deviant, the deviant features are processed in parallel, with MMN showing additive (53, 55) or at least enhanced (55–57) amplitude relative to the amplitudes of corresponding single-deviant MMNs.

The current study examined MMN in CHR patients, in early illness schizophrenia patients (ESZ), and in healthy controls. Both duration- and frequency-deviant MMNs were assessed in two single-deviant paradigms. Based on prior studies (3, 13, 18, 21, 30, 38), we hypothesized that duration-deviant MMN would be more deficient than frequency-deviant MMN in both CHR and ESZ patients. In addition, we implemented a third paradigm that combined duration and frequency deviance within a single stimulus. We hypothesized that this “double-deviant” MMN, relative to the single-deviant MMNs, would show enhanced sensitivity to ESZ and CHR patients, and further, would be the best predictor of subsequent psychosis among CHR patients.

Method

Participants

Participants included 19 early illness schizophrenia patients (ESZ; within 5 years of initial hospitalization or initiation of antipsychotic medication) based on the Structured Clinical Interview for DSM-IV (SCID) (58), 38 clinical high risk (CHR) patients meeting the Criteria of Prodromal States (COPS) (59) based on the Structured Interview for Prodromal Syndromes (59, 60), and 44 healthy controls (HC). CHR patients who converted to a psychotic disorder within 24-months of study entry (converters n=15) were compared to CHR non-converters (n=16) who’d been followed clinically for at least 12 months. CHR patients (n=7) who dropped out of the study before the 12-month follow-up were excluded from converter vs. non-converter sub-group comparisons but were included in survival analyses predicting time to psychosis onset. Mean time from ERP assessment to psychosis onset in CHR converters was 10.4 months (sd=9.0). In non-converters, the mean clinical follow-up interval was 28.6 months (sd=8.8). Interviews were conducted by a trained research assistant, psychiatrist, or clinical psychologist. HC with a past or current DSM-IV Axis I disorder (based on a SCID) or a first-degree relative with a psychotic disorder were excluded. Exclusion criteria for all groups included substance dependence or abuse within the past year, a history of significant medical or neurological illness or head injury resulting

in loss of consciousness, and abnormal audiometric testing. CHR patients were recruited from the Yale Psychosis Prodrome Research Clinic. ESZ patients were referred by community clinicians. HC were recruited by advertisements and word-of-mouth. The study was approved by the institutional review board of Yale University. Adult participants and parents of minors provided written informed consent, and minors provided written assent.

Symptom Ratings

ESZ symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (61) within 1 month (mean ± sd = 15.7 ± 10.4 days) of ERP assessment; CHR symptoms were rated using the Scale of Prodromal Symptoms (SOPS) (59, 60) within 2 weeks (mean ± sd = 11.4 ± 3.1 days) of ERP assessment. Ratings were based on consensus of a trained research assistant and a psychiatrist or clinical psychologist.

MMN Paradigm

Auditory stimuli were presented to participants at 78 dB SPL (sound pressure level) via Etymotic ER3-A insert earphones. Each MMN paradigm consisted of two runs, with each run comprising a fixed pseudorandom sequence of 875 tones, of which 90% were standards (50ms, 633 Hz) and 10% were deviants: For duration (DUR) MMN, deviants were 100ms, 633 Hz; for frequency (FREQ) MMN, deviants were 50ms, 1000 Hz; for double-deviant (DBL) MMN, deviants were 100ms, 1000 Hz. All tones had 5ms rise/fall times and were presented with a 510 ms stimulus onset asynchrony. The order of MMN paradigms (DUR, FREQ, DBL) was fixed. Participants were instructed to ignore auditory stimuli while they silently read a book.

Data Acquisition and Pre-processing

EEG was recorded from a 20-channel (standard 10–20 scalp locations) electrode cap (Physiometrix, Inc.) and additional mastoid and nose electrodes, using a linked-ears reference and an FPz ground. EEG was digitized at 1000 Hz and bandpass filtered between 0.01 and 100 Hz during acquisition using a Neuroscan Synamps amplifier (Neuroscan, Herndon, VA). Subsequently, continuous EEG data were high-pass filtered at 1 Hz and parsed into 600 ms epochs (−100 to 500 ms) for each stimulus type. Vertical and horizontal electro-oculograms, recorded from electrodes above and below the left eye and at the outer canthi of both eyes, respectively, were used to correct EEG for eye movement and blink artifacts (62). After baseline-correction (−50 to 0 ms pre-stimulus baseline), EEG epochs containing amplitudes exceeding +/−100 μV in any fronto-central electrode (F3, Fz, F4, C3, Cz, C4) were rejected. Next, ERP averages for standards and deviants were generated using a sorted averaging technique previously shown to reduce noise in the MMN waveform by averaging over the subset of trials that optimizes the estimated signal to noise ratio (eSNR) (63). Briefly, single-epoch root mean squared (RMS) amplitude values for each trial are calculated and sorted in ascending order for each stimulus type. The subset of sorted trials selected for ERP averaging are associated with the largest eSNR, which is the ratio of the number of trials to the variance of the amplitude values across trials. Details of this method are presented in Supplemental Materials. The number of trials contributing to ERP averages did not differ between groups (all ps >.59). ERPs for standards and deviants were then low-pass filtered at 30 Hz and subtracted to derive a deviant-standard difference wave. MMN

amplitude was defined as the most negative peak between 90 and 290 ms in each participant's difference wave.

Statistical Correction for Normal Aging Effects

In order to compare ESZ patients with the younger CHR patients on MMN, we needed to control for normal brain development and aging effects (27). Accordingly, normal aging effects on MMN were modeled in the HC (age range 12 – 38 years) by regressing MMN amplitudes on age separately for each deviant type and electrode. Resulting regression equations were used to derive predicted "normal" MMN amplitudes for each participant (patients and HC) based on his/her specific age. Differences between observed and age-specific predicted MMN amplitudes were then divided by the standard error of regression (from the HC regression model), yielding age-corrected MMN z-scores for all groups. This method, which has been used in previous brain imaging and ERP patient studies to control for normal aging effects (64–66), is preferable to ANCOVA models because it preserves pathological aging effects (e.g., abnormal brain maturation trajectories) while only removing normal aging effects. The resulting age-corrected MMN z-score expresses, in standard units, the degree to which a participant's MMN amplitude deviates from the normal value expected for his/her age.

Statistical Analysis

Group differences in MMN z-scores were assessed using a 4-way repeated measures analysis of variance (ANOVA) with Group (ESZ, CHR, HC) or Conversion Group (Converter, Non-Converter) as the between-subjects factor and Deviant Type (DUR, FREQ, DBL), Fronto-Central Lead (Frontal, Central), and Lateral Lead (Left, Midline, Right) as within-subjects factors. Significant effects were parsed using *post-hoc* Tukey-Kramer tests. Greenhouse-Geisser non-sphericity correction was applied to within-subjects effects with more than two levels. In addition, four Bonferroni-corrected (alpha = .05/4 = .0125) planned contrasts compared converter and non-converter CHR sub-groups to HC and ESZ groups on MMN z-scores averaged across the deviant types and six fronto-central leads.

Hierarchical Cox regression was performed to model the relationship between MMN amplitude and the time to psychosis onset (i.e., "survival time") among CHR patients. To test whether the DBL MMN has greater predictive power than the DUR and FREQ MMNs, raw MMN amplitudes (in microvolts) averaged over the six fronto-central leads were entered hierarchically in two separate regression models. In one model, DUR and FREQ MMNs were entered as a block in the first step, then DBL MMN was entered second. In the other model, DBL MMN was entered first followed by entry of DUR and FREQ MMN as a block in the second step. All CHR patients were included, with censoring of those who did not convert to psychosis. Alpha was set to p=.05.

To assess correlations with symptom severity, raw MMN amplitudes for each deviant type (average of the six fronto-central leads) were correlated with positive and negative symptom subscales from the PANSS in the ESZ group and from the SOPS in the CHR group.

Because only a minority of CHR patients was taking antipsychotic medication, all analyses were repeated with 27 antipsychotic-free CHR patients.

RESULTS

Demographic Differences Between Groups

Demographic data are shown in Table 1. Gender and handedness (67) did not differ between groups. Age significantly differed between groups. P*ost-hoc* tests showed ESZ to be significantly older than both CHR and HC groups, whereas the CHR vs. HC age difference was not significant. All group comparisons of MMN used age-corrected z-scores. Parental socioeconomic status (PSES) (68) significantly differed between groups, with *post-hoc* tests showing lower PSES in the two patient groups relative to the HC group. Accordingly, all ANOVAs were repeated using PSES as a covariate. CHR converters did not differ from non-converters in gender, handedness, age, or PSES. For baseline SOPS ratings, converters had marginally more severe positive symptoms and significantly more severe negative symptoms than non-converters.

Correlations Among MMN Deviant Types

DUR and FREQ MMN z-scores were moderately correlated in each group (HC r=.39, p<.01; ESZ r=.38,p=.11; CHR r=.41, p=.01). DBL MMN correlated more highly with FREQ MMN (HC r=.75, p<.001; ESZ r=.82, p<.001; CHR r=.79, p<.001) than with DUR MMN (HC r=.41, p<.01; ESZ r=.39, p=.10; CHR r=.51, p=.001), suggesting a greater contribution of frequency deviance than duration deviance to the double-deviant MMN.

Group Differences in MMN

Nose-referenced ERP difference waves showing the expected MMN polarity reversal at mastoid leads are presented in Supplementary Materials. Grand average ERP difference waves, scalp topography maps, and mean amplitude values (raw voltage and z-score) for DUR, FREQ, and DBL MMN are presented in Figure 1. These figures show MMN amplitude across deviant types to be reduced in both ESZ and CHR groups relative to the HC group. In the ANOVA of MMN z-scores, a significant Group effect emerged, with *post-hoc* tests showing significantly smaller MMN amplitudes in the ESZ and CHR groups compared to the HC group, but no difference between the ESZ and CHR groups (see Table 2). There were also marginally significant Group×Lateral Lead and Group × Fronto-Central Lead × Deviant Type effects. These interactions mainly involved variation in the strength of Group effects and or Deviant Type effects across scalp electrode sites. In no case did they reveal a noteworthy absence of a Group effect or a significant dependence of the Group effect on MMN Deviant type. Accordingly, we do not present a full description of these interaction effects here. Instead, a full parsing of these interaction effects is presented in the Supplemental Materials and in Table 2.

ANOVAs were repeated in the subset of antipsychotic-free CHR patients (n=27) and in the full sample using PSES as a covariate. Both re-analyses yielded results similar to those presented above.

Conversion Effects in MMN

Grand average ERP difference waves, scalp topography maps, and mean amplitude values (raw voltage and z-score) for DUR, FREQ, and DBL MMN show CHR converters to have smaller (i.e., less negative) MMN amplitudes than non-converters (Figure 2). Results of the 4-way (Converter Group × Deviant Type×Fronto-Central Lead × Lateral Lead) ANOVA of MMN z-scores, are presented in Table 2. A marginally significant Conversion Group effect indicated that converters had greater MMN deficits than non-converters. While the Conversion Group effect did not interact with Deviant Type, it significantly interacted with the Fronto-Central Lead × Lateral Lead effect. Since the basic finding of a Conversion Group effect that did not significantly depend on MMN Deviant Type was not altered by the interaction effects involving scalp topography factors, these interaction effects are not presented here. Instead, a full parsing of these interaction effects is presented in the Supplemental Materials and in Table 2.

MMN z-scores averaged over leads and deviant types were subjected to a one-way ANOVA with planned comparisons of the CHR conversion sub-groups with the ESZ and HC groups. Converters (p=.002), but not non-converters (p=.506), showed a significant MMN deficit relative to HC. In addition, ESZ patients showed significant MMN deficits relative to non-converters (p=.011) but not converters (p=.740).

Converters were also compared to the smaller subgroup (n=11) of non-converters who were followed for at least 24 months. For MMN z-scores (averaged over six fronto-central leads), the Conversion Group effect only showed a trend (F(1,24)=3.58, p=.070). However, for MMN raw amplitudes, the Conversion Group effect reached significance (F(1,29)=4.78, p=0.037), with no significant effects for Deviant Type (F(2,28)=1.89, p=0.18) or Conversion Group × Deviant Type (F(2,28)=1.16, p=0.31).

Survival Function for Conversion to Psychosis

In the first of two hierarchical Cox regression models predicting the time from ERP assessment to psychosis conversion in CHR patients, DUR and FREQ MMN raw amplitudes entered as a block in Step 1 did not produce a significant overall increment in prediction (χ^2=2.63, p=0.27), and neither MMN produced a significant predictive increment over and above the other (DUR: Wald(1)=0.17, p=.68, Exp(B)=1.06, FREQ: Wald(1)=1.59, p=.21, Exp(B)=1.24). However, at Step 2, entry of DBL MMN significantly improved prediction of time to psychosis onset (χ^2=8.41, p=0.004, DUR: Wald(1)=0.07, p=0.79, Exp(B)=0.97, FREQ: Wald(1)=1.86, p=0.17, Exp(B)=0.7,DBL: Wald(1)=7.3, p=0.007, Exp(B)=2.23). In the second model, DBL MMN entered at Step 1 significantly predicted time to psychosis onset (χ^2=9.06, p=0.003; Exp(B)=1.63, Wald(1)=7.53, p=.006), and DUR and FREQ MMNs failed to significantly improve this prediction when entered as a block in Step 2 (χ^2=1.99, p=0.37). In the final model, with all three MMN deviant types entered as predictors, a significant hazard ratio was produced by the DBL MMN (Exp(B)=2.23, p=.007) but not the DUR (Exp(B)=0.97, p=.79) or FREQ (Exp(B)=0.70, p=.17) MMNs. When DBL MMN was the sole predictor, the significant hazard ratio indicated that a unit decrease in MMN (i.e., 1 microvolt less negative MMN amplitude) is associated with a 1.63-fold increase in the risk for conversion to psychosis. As suggested by Hosmer and Lemeshow

(69), we illustrate this effect by showing the estimated cumulative survival functions, indicating the probability of *not* converting to psychosis, for the three MMN values corresponding to the quartiles of the DBL MMN in the CHR sample (see Figure 3).

Correlations with Clinical Symptoms

MMN amplitudes did not significantly correlate with PANSS or SOPS positive and negative symptom scores in ESZ or CHR groups, respectively.

Discussion

This study directly compared the sensitivity of MMN elicited by three deviant types to schizophrenia and to a putatively prodromal clinical syndrome associated with high risk for psychosis. ESZ and CHR patients showed reduced MMN, irrespective of deviant type, relative to healthy controls, but did not differ from each other. CHR patients who converted to psychosis within 24 months of their ERP assessment showed a significant MMN deficit, again irrespective of deviant type, relative to CHR non-converters. Whereas the MMN deficit in CHR converters was comparable to the ESZ MMN deficit, MMN in the non-converters was essentially normal. In addition, while group differences in MMN did not depend on deviant type, the double deviant MMN, but not the single deviant MMNs, significantly predicted the time from ERP assessment to psychosis onset in CHR patients.

Our results corroborate five previous studies (3–7) reporting MMN deficits in CHR patients, providing strong evidence that deficient automatic processing of auditory deviance, possibly reflecting compromised sensory echoic memory (9, 10), predictive coding (70), synaptic plasticity (71), and/or glutamatergic NMDA receptor function (72–76), predates psychosis onset. Moreover, our observation of MMN deficits in the subset of antipsychotic-free CHR patients who converted to psychosis is consistent with prior studies showing that MMN deficits are not related to anti-psychotic use (3, 15, 21, 32, 33, but see 34) or dose (77).

Among individuals meeting CHR criteria, only 35% are expected to convert to psychosis within a 2–3 year follow-up period (1, 2). Of the remaining 65%, most will never develop a psychotic disorder. This relatively low conversion rate tempers enthusiasm for early interventions in CHR patients, particularly with drugs that have significant side effects such as antipsychotics. Preventive interventions with CHR patients would not only expose many patients to unnecessary treatments, they also potentially expose patients to societal stigma (78), making the clinical utility of the CHR syndrome a matter of ongoing debate (79–82). If consideration of biomarkers can improve the predictive validity of the CHR syndrome, the risk-benefit ratio may be tipped in favor of early intervention with the subset of CHR patients at greatest risk for psychosis. Consistent with two prior reports (3, 6), our study indicates that reduced MMN in CHR patients is associated with increased risk for imminent conversion to psychosis. Challenges remain in translating these findings into a clinically useful prognostic test, but their replicability across three different CHR samples suggests that the time is ripe for future studies to address these challenges.

From the standpoint of distinguishing CHR vs. HC and converter vs. non-converter groups, the three types of MMN assessed (duration, frequency, duration+frequency double deviant)

produced comparable group effects. These results did not support the hypothesis, based on prior schizophrenia studies (3, 13, 18, 21, 30, 38), that duration-deviant MMN is more sensitive than frequency-deviant MMN to early schizophrenia and its putative prodrome. Moreover, our finding of reduced frequency-deviant MMN in CHR patients is inconsistent with findings of normal frequency-deviant MMN in first episode schizophrenia (3, 26, 30, 34, 37). It is also inconsistent with one report showing normal frequency-deviant MMN in CHR patients (3), although the other CHR MMN studies only examined duration-deviant MMN (4–7). MMN paradigm differences and patient heterogeneity within and between studies may have contributed to these inconsistencies. However, relatively few first-episode and CHR studies to date have directly compared frequency- and duration-deviant MMN, and most have relied on relatively small samples. Accordingly, more research is needed before definitive conclusions can be drawn about the status of frequency- and duration-deviant MMN in CHR and first-episode patients.

The double-deviant MMN did not yield significantly larger group effects than the single-deviant MMNs, inconsistent with our hypothesis. However, when the time from ERP assessment to psychosis conversion among CHR patients was considered, only the double-deviant MMN significantly predicted psychosis onset after controlling for the correlations among the three MMN deviant types. This finding, which replicates and extends findings from Bodatsch and colleagues (3), suggests that the neuroanatomically distinct MMN generators associated with processing different dimensions of auditory deviance (54, 57, 83) may be heterogeneously compromised across schizophrenia (84) and CHR patients, with no single-deviant MMN being optimally sensitive to disease in all patients (52). While the double-deviant MMN was more strongly related to the frequency MMN than the duration MMN, its ability to predict psychosis onset over and above the single deviant MMNs suggests that it may be particularly useful for purposes of clinical prediction in CHR patients. Moreover, the double-deviant MMN appears to assess neurophysiological processes associated with multi-feature auditory deviance detection that are not assessed by separate assessment of MMN to each deviance feature, at least from the standpoint of processes related to psychosis risk.

There were no associations between MMN and symptoms in either patient group, consistent with much of the prior literature (13, 14) but inconsistent with several studies showing MMN to correlate with negative symptoms (15, 28, 85) or hallucinations (85–88). Variability in symptom correlations across studies may arise for many reasons, including failure to distinguish contributions of trait severity and clinical state fluctuations to symptom ratings, as well as attenuation of relationships associated with studying medicated patients (89).

In conclusion, this study demonstrates MMN reduction in and CHR patients. Moreover, among CHR patients, the greater the MMN reduction, the more imminent the risk of psychosis. MMN is a promising biomarker of psychosis risk that may improve the accuracy of psychosis prediction when combined with clinical risk criteria. Future studies should extend the follow-up period in order to track within-patient clinical and neurophysiological illness progression from the prodrome through the early stages of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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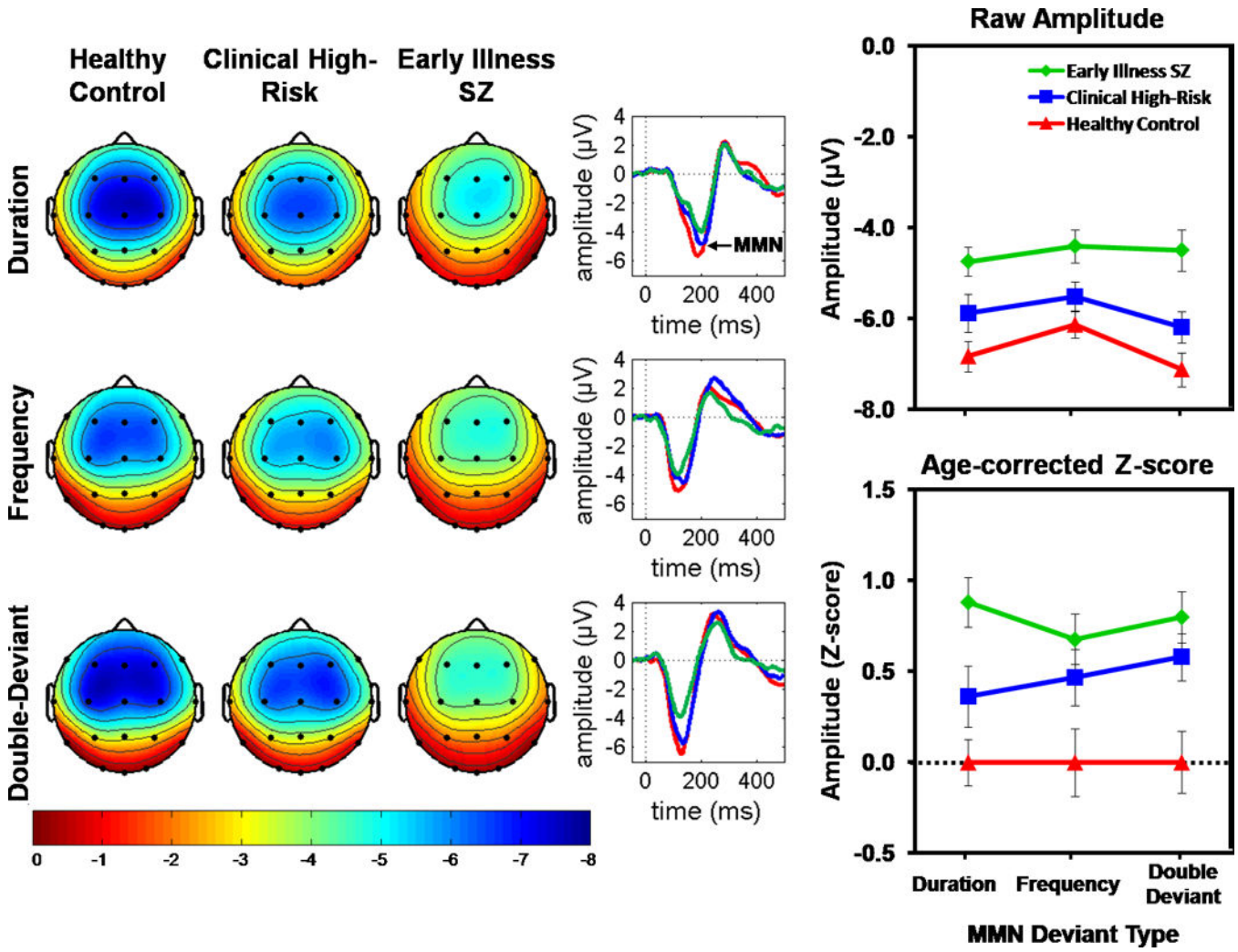

Figure 1. Mismatch Negativity (MMN) for each Group and Deviant Type

On the left, scalp voltage topography maps of MMN amplitudes are shown for each group and deviant type. MMN topography maps show the group means of MMN amplitudes associated with subject-specific median peak latency across the six fronto-central leads (F3, Fz, F4, C3, Cz, C4). All maps are plotted on the same voltage scale (μV) as indicated in the legend. In the center, ear-referenced ERP difference waveforms averaged across the six fronto-central leads for Duration, Frequency, and Double-Deviant MMN are shown for each group. On the right, line graphs show group means and standard errors for raw MMN amplitude in microvolts (top) and MMN age-corrected z-scores (bottom). Healthy Controls are shown in red, Clinical High Risk patients in blue, and Early Illness Schizophrenia (SZ) patients in green. MMN is reduced in Early Illness SZ and Clinical High Risk patients relative to Healthy Controls across deviant type.

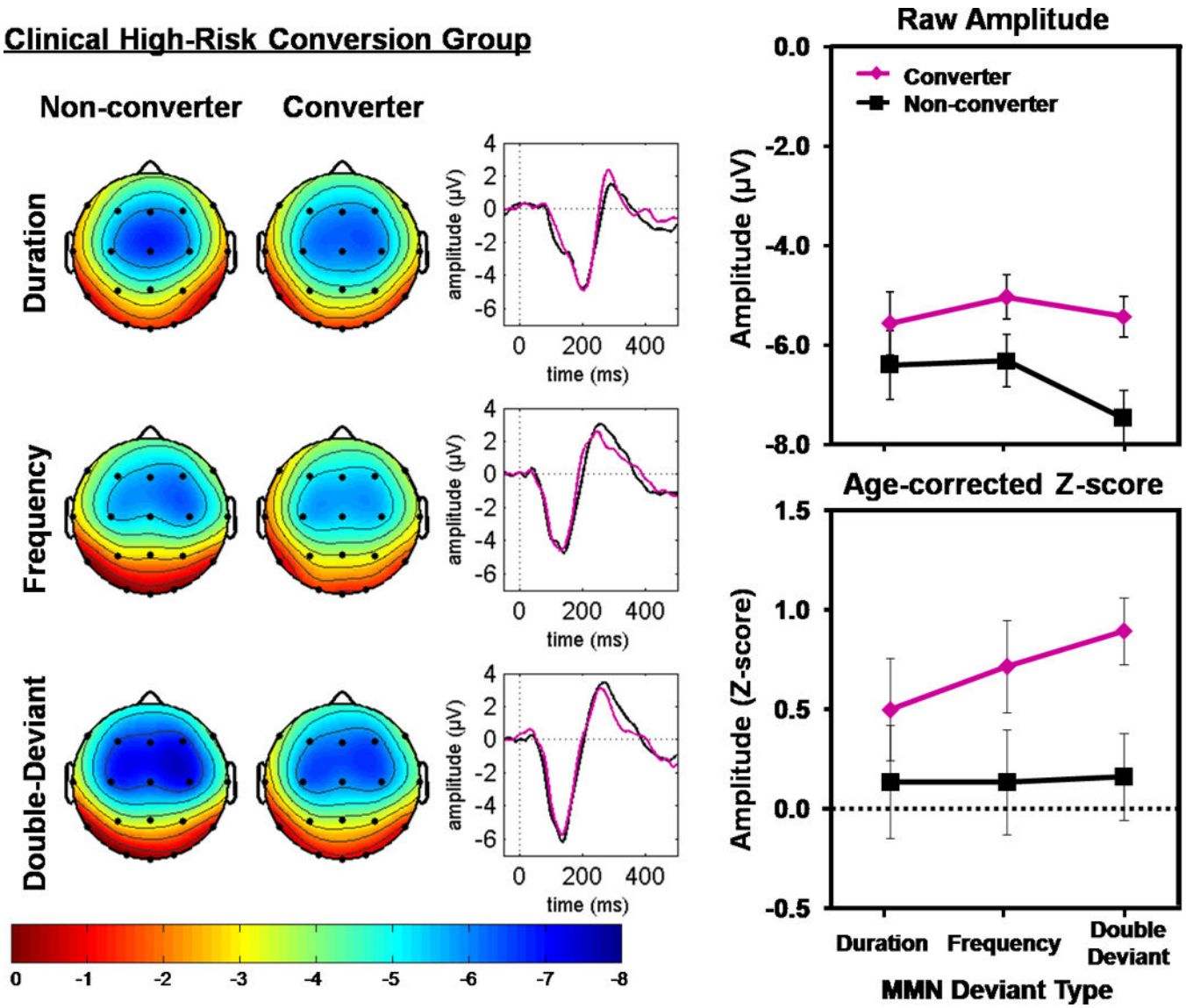

Figure 2. Mismatch Negativity (MMN) for each Clinical High-Risk Conversion Group and Deviant Type

On the left, scalp voltage topography maps of MMN amplitudes are shown for each group and deviant type. MMN topography maps show the group means of MMN amplitudes associated with subject-specific median peak latency across the six fronto-central leads (F3, Fz, F4, C3, Cz, C4). In the center, ear-referenced ERP difference waveforms averaged across the six fronto-central leads for Duration, Frequency, and Double-Deviant MMN are shown for both groups. On the right, line graphs show (top) group means and standard errors for raw MMN amplitude in microvolts and (bottom) MMN age-corrected z-scores. Converters to psychosis are shown in magenta and non-converters are shown in black. MMN is reduced in converters relative to non-converters across deviant type. Individual subject butterfly plots are shown in Figure S3 of the Supplementary Materials.

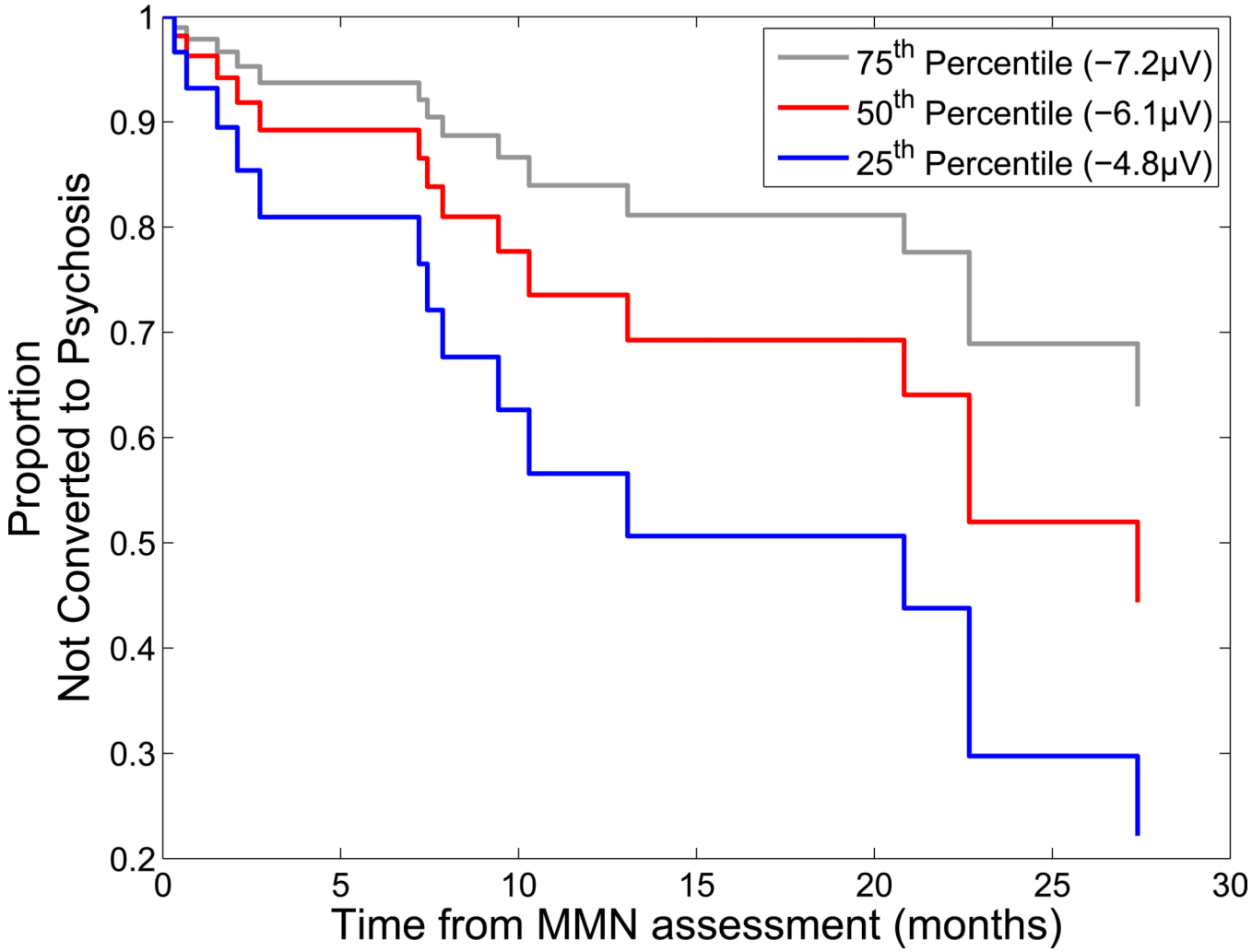

Figure 3. Estimated Survival Functions for Quartiles of the Double-Deviant Mismatch Negativity (MMN) in Clinical High-Risk Patients Showing Psychosis Conversion Risk

A Cox regression analysis shows that a greater Double-Deviant MMN deficit in CHR patients is associated with an earlier transition to psychosis. To illustrate this finding, estimated cumulative survival functions are plotted for the amplitude values corresponding to the quartiles of the double-deviant MMN in the CHR group: Lower quartile (25th percentile) of MMN = −4.8 μV (blue line); Middle quartile (50th percentile) of MMN = −6.1 μV (red line); Upper quartile (75th percentile) of MMN = −7.2 μV (gray line).

Table 1

Group Demographic Data

	Early Illness Schizophrenia Patients n = 19		Clinical High-Risk Patients n= 38		Healthy Controls n = 44					Clinical High-Risk Patients					
										Converters n= 15		Non-Converters n = 16			
Demographic/Clinical Measure	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2**	***p*-value**	***Post-hoc* contrasts**	**N**	**%**	**N**	**%**	**χ^2**	***p*-value**
Gender							2.2	0.34						0.05	0.83
female	4	21.1	15	39.5	17	38.6				6	40.0	7	43.8		
male	15	78.9	23	60.5	27	61.4				9	60.0	9	56.3		
Handedness[a]							1.8	0.78						1.01	0.60
right	16	84.2	31	81.6	37	84.1				13	86.7	12	75.0		
left	1	5.3	3	7.9	5	11.4				1	6.7	1	6.3		
ambidextrous	2	10.5	4	10.5	2	4.5				1	6.7	3	18.8		
Diagnostic Subtype															
paranoid	11	57.9													
disorganized	1	5.3													
undifferentiated	2	10.5													
catatonic	1	5.3													
residual	1	5.3													
schizoaffective	3	15.7													
Clinical High-Risk Syndrome (COPS)[b]															
APS			38	100.0						15	100.0	16	100.0		
BIPS			1	2.6						1	6.7	0	0.0		
GRD			1	2.6						1	6.7	0	0.0		
Antipsychotic type															
atypical alone	13	68.4	10	26.3						5	33.3	3	18.8		
typical alone	0	0	0	0						0	0	0	0		
atypical and typical	3	15.8	1	2.6						0	0	0	0		
none	2	10.5	27	71.1						10	66.7	13	81.3		
unknown	1	5.3	0	0						0	0	0	0		

	Early Illness Schizophrenia Patients n = 19		Clinical High-Risk Patients n= 38		Healthy Controls n = 44					Clinical High-Risk Patients					
										Converters n= 15		Non-Converters n = 16			
Demographic/Clinical Measure	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2**	***p*-value**	***Post-hoc* contrasts**	**N**	**%**	**N**	**%**	**χ^2**	***p*-value**
	M	SD	M	SD	M	SD	F	*p*-value	*Post-hoc* contrasts	M	SD	M	SD	F	*p*-value
Age, years[c]	23.91	6.17	17.4	3.5	19.99	5.5	10.83	<0.001	ESZ>HC[†] ESZ>CHR[†] CHR=HC	17.47	2.2	15.88	3.3	2.48	0.13
Parental Socioeconomic Status[d]	40.44	9.06	36.6	15.22	28.02	13.17	6.96	0.002	HC<ESZ[†] HC<CHR[†] CHR=ESZ	36.70	13.4	35.34	18.0	0.06	0.82
PANSS Positive Symptom Total[e]	18.71	5.78													
PANSS Negative Symptom Total[e]	17.14	6.11													
SOPS Positive Symptom Total			11.03	4.96						12.45	5.07	9.0	4.91	3.74	0.06
SOPS Negative Symptom Total			10.74	6.35						14.40	5.05	6.69	5.71	15.77	<0.001

Note. Values are given as number and percentage of subjects for gender, handedness, diagnostic subtype, prodromal criteria, and antipsychotic type. Group means with the standard deviation for age, parental socioeconomic status, PANSS, and SOPS are reported. Gender and handedness were analyzed with Pearson chi-square tests. Age and parental socioeconomic status were analyzed with one-way ANOVA and Tukey-Kramer *post hoc* tests.

Abbreviations: HC, healthy controls; PD, prodromal patients; ESZ, early illness schizophrenia patients; PANSS, Positive and Negative Syndrome Scale; SOPS, Scale of Prodromal Symptoms; APS, Attenuated Positive Symptoms; BIPS, Brief Intermittent Psychotic Symptoms; GRD, Genetic Risk and Deterioration.

[a] The Crovitz-Zener (1962) questionnaire was used to measure handedness.

[b] Prodromal criteria APS, BIPS, and GRD are not mutually exclusive.

[c] Age range (years): ESZ = 13.8–37.5 years; CHR = 12.4–26.6 years; HC = 12.4–37.9 years; Converters = 14.8–21.4 years; Non-Converters = 12.4–24.2 years.

[d] The Hollingshead (1975) four-factor index of parental socioeconomic status (SES) is based on a composite of maternal education, paternal education, maternal occupational status, and paternal occupational status. Lower values signify higher socioeconomic status. SES data could not be retrieved from two early illness patients.

[e] PANSS symptom ratings were collected from 14 of the 19 early illness schizophrenia patients.

[†] Significant at $p<0.05$, two-tailed.

Table 2

Analyses of Diagnostic Group and Psychosis Conversion Effects on Mismatch Negativity.

	Group Effects (HC, CHR, ESZ)[a]				Conversion Group Effects (Converter, Non-converter)[b]			
Effect	**df**	**F**	**p-value**	**Follow-Up Tests[c]**	**df**	**F**	**p-value**	**Follow-Up Tests[c]**
Group	2, 98	8.63	**<.001**	CHR>HC*, ESZ>HC***, CHR=ESZ	1,29	4.07	**0.053**	Converter>Non-converter*
Deviant Type (DUR, FREQ, DBL)	2,196	0.37	0.639		2, 58	0.74	0.441	
Fronto-Central Lead (Frontal, Central)	1,98	0.02	0.889		1,29	1.66	0.208	
Lateral Lead (Left, Midline, Right)	2,196	1.61	0.205		2,58	6.45	**0.009**	Left>Midline*, Midline>Right*
Group x Deviant Type	4,196	0.67	0.579		2, 58	0.57	0.512	
Group x Fronto-Central Lead	2,98	2.38	0.098		1,29	0.10	0.756	
Group x Lateral Lead	4,196	2.52	**0.053**		2, 58	1.26	0.284	
Lateral Lead effect in HC	2, 86	0.00	1.000					
Lateral Lead effect in CHR	2,74	7.73	**0.004**	Left>Midline*, Midline>Right*				
Lateral Lead effect in ESZ	2,36	0.21	0.747					
Group effect at Left (F3, C3) leads	2,98	10.23	**<.001**	CHR>HC***, ESZ>HC***, CHR=ESZ				
Group effect at Midline (Fz, Cz) leads	2, 98	8.25	**<.001**	CHR>HC*, ESZ>HC***, CHR=ESZ				
Group effect at Right (F4, C4) leads	2, 98	6.62	**0.002**	CHR=HC, ESZ>HC**, CHR=ESZ				
Group x Lateral Lead x Deviant Type	8,392	1.15	0.330		4,116	0.52	0.681	
Group x Fronto-Central Lead x Deviant Type	4,196	2.50	**0.054**		2,58	1.54	0.226	
Group x Fronto-Central Lead for DUR	1,98	1.27	0.285					
Group x Fronto-Central Lead for DBL	1,98	1.75	0.180					
Group x Fronto-Central Lead for FREQ	1,98	4.39	**0.015**					
Fronto-Central Lead effect in HC	1,43	0.00	0.999					
Fronto-Central Lead effect in ESZ	1,18	0.24	0.627					
Fronto-Central Lead effect in CHR	1,37	9.67	**0.004**	Frontal>Central**				
Group effect at Frontal Leads	2,98	5.59	**0.005**	CHR>HC*, ESZ>HC*, CHR=ESZ				
Group effect at Central Leads	2,98	3.64	**0.030**	CHR=HC, ESZ>HC*, CHR=ESZ				
Fronto-Central Lead x Deviant Type in HC	2,86	0.00	1.000					
Fronto-Central Lead x Deviant Type in ESZ	2,36	1.67	0.204					
Fronto-Central Lead x Deviant Type in CHR	2,74	7.31	**0.003**					

	Group Effects (HC, CHR, ESZ)[a]				Conversion Group Effects (Converter, Non-converter)[b]			
Effect	**df**	**F**	**p-value**	**Follow-Up Tests[c]**	**df**	**F**	**p-value**	**Follow-Up Tests[c]**
Deviant Type effect at Frontal Leads	2,74	2.51	0.108					
Deviant Type effect at Central Leads	2,74	0.78	0.461					
Fronto-Central Lead effect for DUR	1,37	0.34	0.566					
Fronto-Central Lead effect for FREQ	1,37	9.67	**0.004**	Frontal>Central**				
Fronto-Central Lead effect for DBL	1,37	2.63	0.113					
Group x Deviant Type at Frontal Leads	2,196	0.99	0.401					
Group x Deviant Type at Central Leads	2,196	0.61	0.621					
Group x Fronto-Central Lead x Lateral Lead	4,196	1.75	0.148		2, 58	3.87	**0.035**	
Group x Fronto-Central Lead effect on Left					1,29	0.24	0.629	
Group x Fronto-Central Lead effect on Midline					1,29	1.31	0.262	
Group x Fronto-Central Lead effect on Right					1,29	0.40	0.535	
Group x Lateral Lead effect at Frontal leads					1,29	0.19	0.764	
Group x Lateral Lead effect at Central leads					1,29	2.37	0.122	
Fronto-Central Lead x Lateral Lead in Nonconverters					1,15	2.25	0.132	
Fronto-Central Lead x Lateral Lead in Converters					1,14	5.55	**0.016**	
Lateral Lead effect at Frontal leads					2,28	3.59	**0.051**	Left=Midline, Midline>Right*
Lateral Lead effect at Central leads					2,28	3.58	**0.049**	Left>Midline*, Midline=Right
Fronto-central Lead effect on Left					1,14	0.44	0.518	
Fronto-central Lead effect on Midline					1,14	4.95	**0.043**	Frontal>Central*
Fronto-central Lead effect on Right					1,14	0.19	0.670	
Group x Deviant Type x Fronto-Central x Lateral Lead	8,392	0.94	0.476		4,116	0.73	0.537	

[a] Repeated measures ANOVA comparing Healthy Control (HC), Clinical High Risk (CHR), and Early Illness Schizophrenia (ESZ) groups across the three deviant types (DUR, FREQ, DBL) using age-corrected mismatch negativity (MMN) z-scores. DUR=Duration deviant type; FREQ=Frequency deviant type; DBL=Double-deviant type.

[b] Repeated measures ANOVA comparing converters and non-converters to psychosis across DUR, FREQ, and DBL deviant types using age-corrected MMN z-scores. More positive MMN z-scores indicate greater MMN deficits relative to HC.

[c] Between group comparisons are based on *post-hoc* Tukey tests. Between lead comparisons are based on Helmert contrasts.

* $p \leq 0.05$,

** $p \leq 0.01$,

*** $p \leq 0.001$