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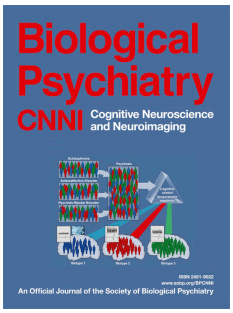

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PII: S2451-9022(23)00066-6

DOI: https://doi.org/10.1016/j.bpsc.2023.03.004

Reference: BPSC 1066

To appear in: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Received Date: 25 June 2022

Revised Date: 7 February 2023

Accepted Date: 6 March 2023

Please cite this article as: Hua J.P.Y., Roach B.J., Ford J.M. & Mathalon D.H., Mismatch Negativity and Theta Oscillations Evoked by Auditory Deviance in Early Schizophrenia, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2023), doi: https://doi.org/10.1016/j.bpsc.2023.03.004.

Mismatch Negativity and Theta Oscillations Evoked by Auditory Deviance in Early Schizophrenia

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Abstract

Background: Amplitude reduction of mismatch negativity (MMN), an event-related potential (ERP) component indexing NMDA receptor-dependent auditory echoic memory and predictive coding, is widely replicated in schizophrenia. Time-frequency analyses of single-trial EEG epochs suggest that theta oscillation abnormalities underlie MMN deficits in schizophrenia. However, this has received less attention in the early course of schizophrenia (ESZ).

Methods: ESZ (*n*=89) patients within 5 years of illness onset and healthy controls (HC; *n*=105) completed an EEG MMN paradigm (duration-deviant, pitch-deviant, duration+pitch "double-deviant"). Repeated-measures ANOVAs assessed group differences in MMN, theta inter-trial phase coherence (ITC), and theta total power, from frontocentral electrodes, after normal age-adjustment. Group differences were re-tested after covarying MMN and theta measures.

Results: Relative to HC, ESZ showed auditory deviance deficits. ESZ had MMN deficits for duration-deviants (*p*=.041), pitch-deviants (*ps*=.007) and double-deviants (*p*s<.047). ESZ had reduced theta ITC for standards (*ps*<.040) and duration-deviants (*ps*<.030). Further, ESZ had reduced theta power across deviants at central electrodes (*p*=.013). MMN group deficits were not fully accounted by theta ITC and power, and neither were theta ITC group deficits fully accounted by MMN. Group differences in theta total power were no longer significant after covarying for MMN.

Conclusions: ESZ showed reduced MMN and theta total power for all deviant types. Whereas, theta ITC showed a relatively specific reduction for duration-deviants. Although MMN and theta ITC were correlated in ESZ, covarying for the one did not fully account for deficits in the other, raising the possibility of their sensitivity to dissociable pathophysiological processes.

Keywords: auditory mismatch negativity; early schizophrenia; event-related potential; theta band oscillatory measures; time-frequency analysis

Introduction

Mismatch negativity (MMN) is elicited when a standard sound sequence is interrupted by an infrequent discriminable deviant sound(1-3). MMN indexes N-methyl-D-aspartate receptor (NMDAR)-dependent auditory echoic memory, with MMN in human(4, 5) and non-human primates(6-8) dependent on glutamate transmission at NMDARs. Critically, MMN is elicited pre-attentively(2, 3, 9-11), allowing for examination of deficits in neuropsychiatric disorders without motivational and attentional confounds(12).

MMN amplitude reduction is a well-established event-related potential (ERP) schizophrenia biomarker viewed as a reflection of NMDAR hypofunction, a leading candidate pathophysiological mechanism underlying schizophrenia(4-6, 13-15). Amplitude deficits are present in the early course of schizophrenia, including in clinical high-risk individuals (CHR-P)(16-19) and in early schizophrenia (ESZ) individuals(20-27) (i.e., within 5 years of illness onset) but see(28, 29).

Comparison of MMN magnitude deficits in CHR-P who transition to psychosis relative to first-episode psychosis (FEP) or ESZ do not support progressive worsening. Indeed, two studies including both CHR-P and FEP(18) or ESZ(17) found equivalent MMN deficits across groups. Moreover, in Erickson et al.'s meta-analysis(20), MMN deficit in CHR-P converters (Hedges g=.79) was slightly larger than the FEP effect size (Hedges g=.42), suggesting stable MMN deficits during CHR-P to FEP transition. While a large-scale study of CHR-P converters(16) showed somewhat smaller MMN deficits relative to prior CHR-P studies (mean z=0.4 relative to HC), lack of an ESZ group prevents conclusions being drawn about MMN in ESZ relative to CHR-P. In contrast, two longitudinal studies showed MMN abnormalities to worsen following a first-episode of schizophrenia(26, 30), suggesting MMN may be sensitive to

early disease progression. Meta-analyses across ESZ and chronic schizophrenia are clearer in showing larger MMN deficits in chronic schizophrenia(20, 21), consistent with MMN tracking disease progression from early to chronic illness. Aside from whether and when MMN marks disease progression, there is clear evidence of MMN deficits in ESZ. Similar evidence for deficits in deviant-related theta oscillations in ESZ has yet to be established. Accordingly, the current study addressed this gap by examining MMN and deviant-related theta metrics in a relatively large ESZ sample.

Computational accessibility for time-frequency analysis (TFA) has increased interest in parsing oscillatory frequencies and phases summed together in ERPs(15, 38, 39), such as MMN. Neuro-oscillatory synchrony provides a mechanism for communication between distributed neuronal assemblies, subserving information processing across neural circuits(40-44). Specifically, TFA allows calculation of frequency-specific inter-trial phase coherence (ITC; event-related phase consistency) and total power (event-related oscillation magnitude changes) on a millisecond scale(45, 46). Rodent(47) and human(6, 7, 34, 48-50) MMN TFA analyses have implicated theta (4-7Hz) ITC and total power increases. Mapping to theta is thought to represent interactions between cortical pyramidal neurons and somatostatin-expressing GABAergic interneurons(7). In rodents, somatostatin-type interneurons exhibit NMDAR-dependent deviance processing-related responses(51). Pharmacogenetic silencing of somatostatin-type interneurons(52) and administration of NMDAR antagonists, such as ketamine(53) and phencyclidine(47), disrupt deviance processing along with its associated theta response(52). Additionally, theta oscillations act as a gating mechanism controlling task-relevant and suppressing task-irrelevant information processing(40, 54, 55), with theta power increasing when working memory is required and decreasing when not(56).

Multiple schizophrenia studies have included MMN amplitudes along with TFA measures(33, 34, 48, 49, 57-62), but few have examined deviant-related group theta differences(49, 57, 58, 61, 62). There is evidence that deviants increase theta ITC and total power(7). Relative to healthy controls (HC), chronic schizophrenia patients show reduced theta ITC(49, 58, 62), but see(57, 61), and total power(49, 57, 61) for duration-deviants, as well as pitch-deviants(49). However, it remains unclear whether deviance-related theta deficits observed in chronic schizophrenia are similarly present in ESZ. Indeed, only one study has documented theta deficits from EEG recorded during a MMN paradigm in first-episode schizophrenia(34), but theta measurements were confined to evoked power elicited by standards and MMN correlations were not reported. Furthermore, while moderate MMN correlations with deviant-related theta ITC(61) and total power(57, 61) have been reported, including a factor analysis showing them to load on the same factor(58), there is also evidence they correlate less strongly in schizophrenia patients than HC(61). Moreover, the degree to which MMN and theta deficits account for each other in terms of sensitivity to underlying pathophysiological processes in early schizophrenia remains unclear.

As MMN neural generators differ depending on auditory deviance type(63, 64), and as MMN deficits in schizophrenia differ by deviant type in some studies(e.g., 20, 21, 24, 32, 34, 65), but not all(e.g., 17, 25, 66, 67, 68), we assessed theta oscillations and MMN to duration- and pitch-deviants. MMN variability may partially reflect pathophysiological heterogeneity, with some showing greater duration-MMN deficits and others greater pitch-MNN deficits. To maximize sensitivity to schizophrenia despite heterogeneity, we included duration+pitch "double" deviants, which we previously showed to be larger in amplitude and a better predictor of psychosis CHR-P conversion, relative to duration- or pitch-single deviants(16, 17).

To address gaps in current deviance-related theta oscillation schizophrenia literature, including minimization of confounding influences of illness chronicity (e.g., medication exposure, social/occupational dysfunction, and medical comorbidities), we assessed theta phase synchrony and power in response to duration-, pitch-, and double-deviants in ESZ and further examined their associations with, and dissociability from, corresponding MMN amplitudes. We hypothesized: 1) ESZ, relative to HC, would show MMN amplitude and theta oscillatory deficits, with greater deficits predicted for double-deviants than other deviants, and 2) MMN amplitude and theta oscillatory metrics elicited by the same deviants would be correlated, and 3) uncorrelated aspects of MMN and deviance-related theta metrics would reflect dissociable pathophysiological processes in ESZ, such that covarying for one would not fully account for deficits in the other.

Methods and Materials

Participants

ESZ patients (n=89), within five years of illness onset, were recruited from University of California, San Francisco's (UCSF) early psychosis clinic and research programs. Patients met Structured Clinical Interview for DSM-IV (SCID)(69) schizophrenia or schizoaffective criteria. Current symptom severity (positive, negative, general) was assessed with the Positive and Negative Syndrome Scale (PANSS)(70). Majority were prescribed antipsychotic medication (n=79/89; 88.76%).

HC participants (n=105) were recruited from the community and did not meet current or lifetime SCID Axis I criteria (for HC participants>16 years old) or Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version

interview(71). HC participants older than the oldest ESZ patient (age=36.17) were included when estimating normal age relationships for age-adjusted *z*-scores, but excluded for analyses.

Participants were in good physical health and fluent in English. Exclusion criteria included past year DSM-IV substance dependence (except nicotine), head injury with loss of consciousness, neurological illness, or (for HC) a first-degree relative with psychosis.

Procedure

Protocols were in accordance with UCSF's IRB and Declaration of Helsinki. Participants provided written informed consent, or for minors, parental written consent and participant assent. MMN data from HC and a subset of ESZ have been previously published focusing on MMN as a predictor of cognitive training treatment response(31). In the current manuscript, we include an expanded ESZ sample (33 additional ESZ) and examine MMN and theta oscillatory metrics and the degree to which they provide correlated versus independent information about deviance processing.

MMN Paradigms

Neurophysiological responses to auditory deviants were assessed using a two-deviant (duration-, pitch-deviant) paradigm and a single-deviant (double-deviant) paradigm described in in Biagianti et al.(31) and Supplemental Methods.

EEG Acquisition and Processing

EEG data were collected with a high-impedance BioSemi ActiveTwo recording system and a 64-channel electrode cap (BioSemi,; Supplemental Methods). Analyses focused on frontocentral electrodes (F3, Fz, F4, C3, Cz, C4) where MMN activity is maximal(15).

MMN. MMN averages for stimuli and for each participant were determined using a sorted averaging method(72) shown to reduce noise by averaging over the subset of trials that

optimizes the estimated signal-to-noise ratio (eSNR), details are described previously(17, 25) and in Supplemental Methods. Deviant-standard difference waveforms were computed by subtracting the standard tone ERP wave from deviant tone ERP wave. MMN amplitudes were identified in difference waveforms as the most negative peak between 90-290ms for all deviant types (Figure S1).

Theta ITC and Total Power. ITC was computed as 1 minus the circular phase angle variance(45). Total power was computed by averaging squared single trial magnitude values in each frequency bin on a millisecond basis. Resulting values represent change in total power relative to baseline in decibels (Supplemental Methods).

TFA standards and deviants were examined separately. To avoid trial number confounds, standards that survived sorted averaging were sub-sampled without replacement to generate standards sets with an identical trial count to the corresponding deviant (two sub-sets of standards sampled from two-deviant MMN blocks were randomly assigned to serve as standard stimulus comparators for pitch- and duration-deviants and an additional sub-set of standards sampled from one-deviant MMN blocks served as the standard stimulus comparator for duration+pitch “double” deviant). Theta ITC and total power for standards were calculated by averaging values from a 75-200ms 4-6Hz window. Theta ITC and total power for deviants were calculated by averaging values from 100-200ms 4-6Hz (duration-deviant) and 75-175ms 4-6Hz windows (pitch-, double-deviant). For standard and deviant ERP theta waveforms, see Figures S2-S3. As previous paper also found abnormalities in alpha band,(49, 61) see Figures S4-S5 for alpha (8-12Hz) activity in the same time windows mentioned above for theta.

Analyses

Outlier Winsorization and age-adjustment *z*-scoring. We Winsorized outliers(73) less than 1st quartile minus 1.5 times the interquartile range or greater than 3rd quartile plus 1.5 times the interquartile range. We removed normal aging effects while retaining pathological age-related variance(17, 31, 74). Normal aging effects were modeled in an age-regression based on a broader HC sample between 12-43 years old (*n*=121)(31).

$$z\text{-score} = \frac{\text{observed brain measure value} - \text{predicted normal value for participant's age}}{\text{root mean square error (RMSE)}}$$

Age-adjusted *z*-scores re-express, in standard deviation units (i.e., RMSE from HC age-regression model), the degree to which a participant's values deviate from the normal value expected for the participant's age (see Figures S6-S8 for age-adjustment illustrations using 121 HCs). More positive MMN *z*-scores indicate smaller MMN amplitude relative to HC norms (i.e., greater MMN deficit). More negative theta *z*-scores indicate less ITC and total power relative to HC norms (i.e., greater theta deficits). We used age-adjusted *z*-scores and restricted HC participants to those younger than the oldest ESZ patient (age=36.17; HC *n*=105). Results using raw scores and raw scores covarying for age showed similar patterns (see Table S1 for Fz/Cz MMN and theta values). Age relationships with raw metrics in HC were very weak (R^2=0.000-0.137).

MMN, theta ITC, and total power analyses. MMN differences between HC and ESZ were assessed using 2x3x2 rmANOVA with Group (HC, ESZ) as the between-subjects factor, and Deviant Type (duration, pitch, double) and Fronto-Central Lead (frontal, central) as within-subjects factors. Theta ITC and total power differences between groups were assessed using 2x2x3x2 rmANOVAs with Group (HC, ESZ) as between-subjects factor, and Stimulus Type (standard, deviant), Deviant Type (duration, pitch, double), and Fronto-Central Lead (frontal, central) as within-subjects factors. Greenhouse Geisser non-sphericity correction was applied to

within-subject factors. Significant interactions involving Group were parsed by interrogating "simple, simple main effects" of Group at each combination of other variables involved in the interaction (75) using a Bonferroni-corrected alpha=.05.

MMN, theta ITC, and total power correlations. Pearson correlations were used to investigate associations between MMN and deviant theta measures averaged across frontocentral electrodes by group. Using Meng's *z*(76), we compared the relative strength of MMN amplitude correlations with theta ITC and total power.

MMN and theta oscillatory contributions to auditory deviance processing. Analyses of covariance (ANCOVAs) were used to investigate whether group MMN differences were present when deviant-related theta ITC and total power were covaried, testing whether controlling simultaneously for these measures fully accounted for MMN group effects. Similarly, ANCOVAs were used to test whether group differences in theta ITC and total power persisted after covarying for MMN amplitude. Non-significant Group*Covariate interactions were dropped, allowing a test of the common slope of Group intercept differences controlling for the covariate. Significant Group*Covariate interactions were parsed by examining slope differences between groups and testing whether the group effect was significant at the mean levels of the covariates.

Clinical measures correlations. Spearman correlations of MMN and deviant-related theta values, averaged across frontocentral electrodes, with current symptom severity, illness duration, and chlorpromazine (CPZ) dosage equivalents(77), were calculated. Multiple comparisons with symptom severity (n=27 tests) were corrected with a false discovery rate (FDR) p_{FDR}<.05. FDR correction was not applied to CPZ so as to maximize detection of CPZ influences.

Results

Demographics

See Table 1 for demographics and clinical characteristics. Groups were not statistically different on gender (χ^2[2, *N*=194]=3.36, *p*=.067) or age (*t*[182.48]=0.69, *p*=.490).

MMN Amplitude

For MMN (Table 2 and Figure 1a), there was a significant Group*Deviant Type*Fronto-Central Lead interaction, (*p*=.002), which was parsed by examining the simple, simple main effect of Group at each combination of Deviant Type and Lead. ESZ showed reduced MMN amplitude (i.e., greater MMN *z*-scores) relative to HC at frontocentral leads for pitch deviants (*p*s=.007) and double-deviants (*p*s<.047), but not for duration-deviants, where the ESZ deficit was significant at central (*p*=.041) but not frontal (*p*=.148) leads.

Theta ITC and Power

For theta ITC (Table 3 and Figure 1b), there was a significant 4-way Group*Stimulus Type*Deviant Type*Fronto-Central Lead (*p*=.012), which was parsed by examining the simple, simple main effect of Group for specific combinations of the other variables involved in the interaction. ESZ showed lower theta ITC relative to HC for standards (which were averaged across deviant types because no differences were expected) at frontal and central leads (*p*s<.040), as well as for duration-deviants at frontal and central leads (*p*s<.030). Groups did not differ in theta ITC for pitch- or double-deviants (*p*s>.197).

For theta total power (Table 4 and Figure 1c), there was a significant 3-way Group*Stimulus Type*Fronto-Central Lead interaction (*p*=.039), which did not further interact with Deviant Type (*p*=.450). Parsing this 3-way interaction by testing simple, simple Group effects for each combination of Stimulus Type and Fronto-Central Lead, ESZ had lower theta

total power relative to HC for deviants at central (p=.013) but not frontal (p=.162) leads, whereas for standards, the groups did not significantly differ (ps>.409).

MMN Correlations with Theta ITC and Power

MMN and theta measures were highly correlated within each group (Table S2). In HC, MMN was more strongly correlated with theta ITC than total power for duration- (z=3.586, p<.001) and pitch- (z=2.116, p=.017), but not double-deviants (z=0.730, p=.233). In ESZ, MMN was more strongly correlated with theta ITC than total power across all deviants (z=2.866-4.469, ps<.002).

ANCOVA Tests of Group Effects

ESZ deficit in duration-deviant MMN amplitude at central leads (p=.041) was eliminated (p=.969) when duration-deviant theta ITC (p<.001) and total power (p=.624) were included as covariates. In contrast, ESZ deficits in pitch-deviant MMN at frontal and central leads persisted when covarying for pitch-deviant theta ITC and total power (Group effect ps<.018), with greater ITC (ps<.001) but not power (ps>.557) significantly associated with larger MMN in both groups. Similarly, the ESZ deficit in double-deviant MMN at frontal leads persisted when covarying for double-deviant theta ITC and power (p=.002), with greater ITC (p<.001) but not power (p=.131) significant associated with larger MMN in both groups. For double-deviant MMN at central leads, significant Group*ITC (p=.008) and Group*Power (p=.006) interactions indicated slope differences between groups. Parsing these interactions: 1) for theta ITC (controlling for power), HC showed a significant inverse relationship with MMN (p<.001) with ESZ showing a similar but significantly stronger relationship (p<.001; Figure 2a), and 2) for theta power (controlling for ITC), HC showed a significant inverse relationship with MMN amplitude (p=.007) not observed

in ESZ (Figure 2b). Taking these relationships into account, ESZ double-deviant MMN deficits persisted when the Group effect was tested at the mean of covariates (p=.049).

Further, ESZ deficit in duration-deviant theta ITC at frontal leads (p=.030) was eliminated (p=.106) when the significant (p<.001) inverse relationship between ITC and MMN amplitude was taken into account, whereas ESZ deficit at central leads remained significant (p=.050). ESZ deficit in theta total power averaged across deviants at central electrodes (p=.013) was eliminated (p=.771) when the significant (p<.001) inverse relationship between total power and mean MMN amplitude was taken into account.

Associations with Clinical Measures and Antipsychotic Dosage

Double-deviant MMN amplitude deficits were significantly correlated with more negative symptoms (Table S3; r_s=.218, p=.043; not significant after FDR correction). Neither MMN nor deviant-evoked theta measure z-scores showed significant correlations with estimated illness duration. Double-deviant MMN amplitude deficits (r_s=.365, p=.001) and lower theta ITC for duration- (r_s=-.247, p=.022) and double- (r_s=-.253, p=.019) deviants were significantly correlated with antipsychotic dose (CPZ), with associations remaining after accounting for symptom severity.

Discussion

Consistent with previous MMN TFA decompositions(6, 7, 34, 48-50, 58), auditory deviance processing elicited increased theta phase synchrony and total power. Findings replicate MMN amplitude findings in ESZ(20, 21, 24, 25, 27, 29), and extend them by showing deviant-related theta ITC and total power reductions.

Specifically, ESZ relative to HC showed MMN amplitude reductions for pitch- and double-deviants across frontocentral leads, and for duration-deviants at central leads, whereas

theta ITC was only reduced for duration-deviants at frontocentral sites and total power was reduced for all deviant types at central sites. Results are consistent with research indicating that different deviant types have different neuroanatomical generators(7, 78), different neurodevelopmental trajectories(32, 67), differential dependence on specific thalamic projections to the auditory cortex(49), and are differentially impacted by theta brain stimulation(79). ESZ also showed deficient frontocentral theta ITC to standards, suggesting a general deficit in theta phase synchronization likely reflecting a reduction in auditory N100 documented in prior schizophrenia studies(80). This, along with observed reduction in centrally-distributed theta power across deviant types and reduced theta phase synchrony for duration-deviants, may reflect underlying dysfunction of the recurrent inhibition generated by somatostatin-expressing GABAergic interneurons known to drive theta oscillations at the microcircuit level(7, 52, 81). These somatostatin interneurons also show action specificity(82), with optogenetic activation of interneurons resynchronizing specifically to, and firing with, theta oscillations(83, 84). Moreover, interneurons are implicated in MMN generation(52) given their amplified activity during the MMN time-window, ability to inhibit and disinhibit neighboring pyramidal neurons, and preferential inhibition of excitatory responses to frequent stimuli but not deviants(85). Further, theta oscillations serve as a gating mechanism of task-relevant and task-irrelevant information(40, 54, 55), and are strongly implicated as mediators and moderators of impaired neural and cognitive processes in schizophrenia.

MMN amplitude deficits are consistent with prior studies in early schizophrenia(20-25, 31, 34), although inconsistencies remain regarding which deviant types are most affected. Multiple studies found stronger MMN reductions for duration-deviants than pitch-deviants in schizophrenia(24, 32, 65), including recent-onset patients(21, 32, 34), with evidence that

stronger pitch-deviant MMN amplitude reductions emerge with illness chronicity(32, 34). However, other studies(17, 66, 68), including ours(25, 31), failed to find stronger MMN deficits for duration-deviants in ESZ, consistent with current results. Additionally, Biagianti et al.(31) found a double-deviant deficit for frontal leads in ESZ relative to HC; with the additional 33 ESZ in the current sample, significant duration-, pitch-, and double-deviant deficits emerged.

Duration-deviant theta ITC was relatively more deficient in ESZ, with other deviant types showing similar but non-significant ITC deficits. Thus, greater sensitivity of duration-deviance to deficits in ESZ was evident for deviant-locked theta ITC, but not MMN amplitude, suggesting an interesting dissociation between ERP- and TFA-based measures across deviant types. Non-specific theta total power reduction in ESZ across deviant types suggests that the magnitude of deviant-evoked theta oscillations does not differentially contribute to differential MMN deficits across deviant types, unlike theta phase synchrony. Whereas MMN deficits were generally present frontocentrally, theta deficits were stronger at central sites, suggesting some dissociation between neuroanatomical MMN sources(10, 86) and corresponding theta oscillations and/or differential effects of schizophrenia on their respective sources. Our results are generally consistent with chronic schizophrenia studies(49, 58, 62) reporting theta ITC deficits specifically for duration-deviants, and non-specific theta power deficits in schizophrenia across duration- and pitch-deviants(49). Some of our results converge with other evidence suggesting MMN and theta oscillations, while correlated, are dissociable. For example, in rodents, whereas acute ketamine administration increased MMN and chronic administration reduced it, ketamine produced negligible theta changes(87). Moreover, deviant-related theta oscillations span a wider time window than MMN(47, 57), encompassing the P3a that follows MMN(61). Additionally,

previous studies have reported only modest to moderate correlations between them(57, 58, 61), with evidence that correlations are attenuated in schizophrenia(61).

While many prior studies assess deviant-related theta oscillations and MMN, few directly examined their interrelationship. In a large sample of schizophrenia patients and HC, Hochberger and colleagues showed MMN amplitude and deviant-related theta ITC, along with other deviant processing metrics, to load on the same "deviance detection" factor, whereas theta evoked power and ITC to standards loaded on a separate "sensory registration" factor(58). Additionally, Hong et al.(59) found MMN amplitudes were significantly predicted by evoked power in theta-alpha (5-11Hz) in HC and in delta band (1-4Hz) in schizophrenia patients. Similarly, Lundin et al.(61) found MMN amplitudes were predicted by deviant-related theta ITC (but not total power) in HC, but significantly less so in schizophrenia. While these papers document convergence of MMN and theta metrics, they do not address the possibility that meaningful signals are contained in aspects of each that are uncorrelated with the other.

In the current study, we assessed whether ERP and TFA measures provided unique or redundant information. Interestingly, ESZ deficits in MMN amplitudes for pitch-deviants at frontocentral sites and double-deviants at frontal sites, but not duration-deviants at central sites, were still significant after covarying for deviant-related theta ITC and total power. For double-deviant MMN deficits at central sites, there was significant inverse relationship with 1) theta ITC (controlling for power) that was present in both groups but significantly greater in HC, and 2) theta power (controlling for ITC) that was present in HC, but not ESZ. These results suggest that pitch- and double-deviant MMN group deficits were not fully accounted by ITC and power. Additionally, ESZ duration-deviant ITC deficits at central leads remained significant after controlling for MMN, highlighting non-redundant information provided by MMN and theta ITC.

In contrast, group differences in deviant-elicited theta total power were no longer significant after covarying for MMN, suggesting greater redundancy between MMN and theta metrics. Importantly, group effect sizes were larger for MMN than theta TFA measures (Tables 2-4), suggesting that deviant-related theta metrics may not be as sensitive to auditory deviance processing deficits in schizophrenia as MMN, although ESZ deficit in duration-deviant theta phase synchrony at central leads appeared to contain disease-related information unaccounted for by duration-deviant MMN itself. If observed deficits in MMN and deviance-related theta in ESZ arose exclusively from the same underlying pathophysiological mechanism, covarying for one should eliminate the deficit in the other. This was clearly not the case in many instances.

Consistent with previous research(88), auditory deviance processing was not associated with symptom severity. There were no correlations with illness duration in ESZ. However, a limitation is that correlations might be obscured by imprecise estimates of age of illness onset from the SCID and/or attenuated by the restricted range of illness duration in an ESZ sample. In contrast, MMN reduction for double-deviants and theta ITC reduction for duration- and double-deviants were correlated with increased antipsychotic dose. These associations were significant after accounting for symptoms, suggesting this relationship is not a reflection of clinical severity in patients prescribed higher doses. However, presence of double-deviant MMN deficits in unmedicated CHR-P individuals who transition to full psychosis(16) argues against MMN and theta ITC deficits in ESZ being exclusively a consequence of antipsychotics. Moreover, other studies show no significant association between antipsychotic dosage and MMN(22, 49) but see(89). Thus, more research is needed before conclusions can be drawn about susceptibility of neurophysiological auditory deviance indices to deleterious antipsychotic medication effects. Additionally, future studies including ESZ subgroups could provide clinically useful

information, as MMN deficits have been found to be particularly pronounced in low-functioning schizophrenia(35-37, 67, 90). As ESZ abnormalities were not uniform across deviant types, we recommend inclusion of multiple deviant types in future MMN/theta studies. Moreover, as theta ITC and power were differentially sensitive to ESZ, future schizophrenia studies should assess both in addition to MMN. As with prior MMN studies, effects were most evident at frontocentral midline electrodes, suggesting that a more limited electrode montage could be used to increase efficiency in future studies.

Acknowledgments

This work was supported by NIMH (MH076989 [DHM]), Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Mental Illness Research and Treatment, the Medical Research Service of the San Francisco Veterans Affairs Health Care System, and the Department of Veterans Affairs Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), and University of Missouri dissertation funds (JPYH). JMF was supported by a Senior Research Career Scientist Award from the Department of Veterans Affairs. Manuscript writing by JPYH was supported by the Department of Veterans Affairs Sierra Pacific Mental Illness Research, Education, and Clinical Center (MIRECC). The aforementioned funding sources had no role in the study design, data collection, analysis and interpretation of data, writing of the report, and in the decision to submit the article for publication.

Disclosures

DHM received compensation as a consultant for Boehringer-Ingelheim, Cadent Therapeutics, Neurocrine Biosciences, Gilgamesh Pharma, Recognify Life Sciences, and Syndesi Therapeutics. The other authors report no biomedical financial interests or potential conflicts of interest. JPYH, JMF, and DHM are United States Government employees. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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Table and Figure Legends

Table 1. Demographic and Clinical Characteristics (Mean ± SD) of Participant Groups

Table 2. Repeated Measures Analysis of Variance of Mismatch Negativity (MMN) Amplitude

Table 3. Repeated Measures Analysis of Variance of Theta Inter-trial Phase Coherence (ITC)

Table 4. Repeated Measures Analysis of Variance of Theta Total Power

Figure 1. Healthy control (HC) and early illness schizophrenia (ESZ) groups *z*-adjusted means and standard errors for a.) MMN (more positive MMN *z*-scores indicate greater MMN deficits relative to HC), b.) theta inter-trial phase coherence (ITC), and c.) theta total power.

Figure 2. Mismatch negativity (MMN) double-deviant associations with theta ITC and theta total power residuals. a) For theta ITC (controlling for power), healthy controls (HC) showed a significant inverse relationship with MMN with early illness schizophrenia (ESZ) showing a similar but significantly stronger relationship. b*)* For theta power (controlling for ITC), HC showed a significant inverse relationship with MMN amplitude that was not observed in ESZ.

Table 1

Demographic and Clinical Characteristics (Mean ± SD) of Participant Groups

	HC (*n*=105)	ESZ (*n*=89)
Demographics		
Gender (% male / female)	58.10 / 41.90	70.71 / 29.29
Age (Range: 12-36)	23.01 ± 6.35	22.48 ± 4.24
Ethnicity (%)		
American Indian / Alaska Native	2.88	0.00
Asian American	17.14	25.84
Black / African American	5.71	4.49
More Than One Race	12.38	13.48
Native Hawaiian / Pacific Islander	0.00	1.12
White / Caucasian	60.95	51.69
Not Reported	0.95	3.37
Medication (%)		
Chlorpromazine equivalents (mg)	---	301.54 ± 332.75[a]
Antipsychotic medication	---	88.76
(typical, atypical, unknown)	---	(1.27, 94.94, 3.80)
Clinical Symptom Severity		
PANSS Positive	---	14.05 ± 5.04
PANSS Negative	---	16.84 ± 6.48
PANSS General	---	33.36 ± 8.86

Note. *SD*=standard deviation; HC=healthy control; ESZ=early illness schizophrenia; PANSS=Positive and Negative Syndrome Scale.
[a]Chlorpromazine equivalents for 3 ESZ participants missing.

Table 2

Repeated Measures Analysis of Variance of Mismatch Negativity (MMN) Amplitude

Effect	*F*	*p*	Partial eta^2	Follow-Up Tests
Group	**8.610**	**.004**	**.043**	**HC<ESZ**
Deviant Type	0.319	.723	.002	
Fronto-Central Lead	1.906	.169	.010	
Group*Deviant Type	1.019	.361	.005	
Group*Fronto-Central Lead	0.694	.406	.004	
Deviant Type*Fronto-Central Lead	**8.298**	**.000**	**.041**	
Fronto-Central Lead Effect for Duration-Deviants	0.744	.390	.004	
Fronto-Central Lead Effect for Pitch-Deviants	0.017	.898	.000	
Fronto-Central Lead Effect for Double-Deviants	**10.056**	**.002**	**.050**	**F>C**
Deviant Type Effect at Frontal Leads	1.061	.348	.011	
Deviant Type Effect at Central Leads	0.487	.615	.005	
Group*Deviant Type*Fronto-Central Lead	**6.320**	**.002**	**.032**	
Group Effect for Duration Deviants at Frontal Leads	2.108	.148	.011	
Group Effect for Duration-Deviants at Central Leads	**4.213**	**.041**	**.021**	**HC<ESZ**
Group Effect for Pitch-Deviants at Frontal Leads	**7.487**	**.007**	**.038**	**HC<ESZ**
Group Effect for Pitch-Deviants at Central Leads	**7.320**	**.007**	**.037**	**HC<ESZ**
Group Effect for Double-Deviants at Frontal Leads	**10.380**	**.001**	**.051**	**HC<ESZ**
Group Effect for Double-Deviants at Central Leads	**3.989**	**.047**	**.020**	**HC<ESZ**

Note. HC=healthy control; ESZ=early illness schizophrenia; F=Frontal; C=Central. More positive MMN *z*-scores indicate greater MMN deficits relative to HC.

Table 3

Repeated Measures Analysis of Variance of Theta Inter-trial Phase Coherence (ITC)

Effect	*F*	*p*	Partial eta^2	Follow-Up Tests
Group	**7.658**	**.006**	**.038**	**HC>ESZ**
Stimulus Type	0.114	.736	.001	
Deviant Type	0.669	.497	.003	
Fronto-Central Lead	0.030	.863	.000	
Group*Stimulus Type	0.010	.921	.000	
Group*Deviant Type	1.626	.201	.008	
Group*Fronto-Central Lead	0.037	.848	.000	
Stimulus Type*Deviant Type	2.790	.069	.014	
Stimulus Type*Fronto-Central Lead	2.557	.111	.013	
Deviant Type*Fronto-Central Lead	1.028	.355	.005	
Group*Stimulus Type*Deviant Type	0.791	.442	.004	
Group*Stimulus Type*Fronto-Central Lead	0.320	.572	.002	
Group*Deviant Type*Fronto-Central Lead	0.113	.880	.001	
Stimulus Type*Deviant Type*Fronto-Central Lead	2.349	.098	.012	
Group*Stimulus Type*Deviant Type*Fronto-Central Lead	**4.533**	**.012**	**.023**	
Group Effect for Standards Averaged Over Deviant Types at Frontal Leads	**4.289**	**.040**	**.022**	**HC>ESZ**
Group Effect for Standards Averaged Over Deviant Types at Central Leads	**5.342**	**.022**	**.027**	**HC>ESZ**
Group Effect for Duration-Deviants at Frontal Leads	**4.777**	**.030**	**.024**	**HC>ESZ**
Group Effect for Duration-Deviants at Central Leads	**8.198**	**.005**	**.041**	**HC>ESZ**
Group Effect for Pitch-Deviants at Frontal Leads	1.675	.197	.009	
Group Effect for Pitch-Deviants at Central Leads	0.609	.436	.003	
Group Effect for Double-Deviants at Frontal Leads	1.506	.221	.008	
Group Effect for Double-Deviants at Central Leads	0.407	.524	.002	

Note. HC=healthy control; ESZ=early illness schizophrenia.

Table 4

Repeated Measures Analysis of Variance of Theta Total Power

Effect	*F*	*p*	Partial eta^2	Follow-Up Tests
Group	3.795	.053	.019	
Stimulus Type	1.528	.218	.008	
Deviant Type	0.451	.627	.002	
Fronto-Central Lead	0.438	.509	.002	
Group*Stimulus Type	1.622	.204	.008	
Group*Deviant Type	0.389	.670	.002	
Group*Fronto-Central Lead	0.974	.325	.005	
Stimulus Type*Deviant Type	0.102	.902	.001	
Stimulus Type*Fronto-Central Lead	2.904	.090	.015	
Deviant Type*Fronto-Central Lead	0.301	.739	.002	
Group*Stimulus Type*Deviant Type	0.628	.533	.003	
Group*Stimulus Type*Fronto-Central Lead	**4.302**	**.039**	**.022**	
Group Effect for Standards at Frontal Leads	0.683	.409	.004	
Group Effect for Standards at Central Leads	0.173	.678	.001	
Group Effect for Deviants at Frontal Leads	1.966	.162	.010	
Group Effect for Deviants at Central Leads	**6.320**	**.013**	**.032**	**HC>ESZ**
Group*Deviant Type*Fronto-Central Lead	0.460	.631	.002	
Stimulus Type*Deviant Type*Fronto-Central Lead	0.260	.771	.001	
Group*Stimulus Type*Deviant Type*Fronto-Central Lead	0.797	.450	.004	

Note. HC=healthy control; ESZ=early illness schizophrenia.