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Mismatch Negativity and Low Frequency Oscillations in Schizophrenia Families

L. Elliot Hong, M.D.^{1,*}, Lauren V. Moran, M.D.¹, Xiaoming Du, PhD¹, Patricio O'Donnell, M.D., PhD², and Ann Summerfelt, B.S.¹

¹Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore

²Department of Anatomy & Neurobiology and Psychiatry, University of Maryland School of Medicine, Baltimore

Abstract

Objective—Theta-alpha range oscillations have been associated with MMN in healthy controls. Our previous studies showed that theta-alpha activities are highly heritable in schizophrenia patients' families. We aimed to test the hypothesis that theta-alpha activities may contribute to MMN in schizophrenia patients and their family members.

Methods—We compared MMN and single trial oscillations during MMN in 95 patients, 75 first-degree relatives, 87 controls, and 34 community subjects with schizophrenia spectrum personality (SSP) traits.

Results—We found that 1) MMN was reduced in patients ($p < .001$) and SSP subjects ($p = .047$) but not in relatives ($p = .42$); 2) there were augmented 1–20 Hz oscillations in patients ($p = .02$ to $< .001$) during standard and deviant stimuli; 3) theta-alpha (5–12 Hz) oscillations had the strongest correlation to MMN in controls and relatives ($\Delta R^2 = 21.4\% - 23.9\%$, all $p < .001$), while delta (< 5 Hz) showed the strongest correlation to MMN in schizophrenia and SSP trait subjects; and, 4) MMN ($h^2 = .56$, $p = 0.002$) and theta-alpha ($h^2 = .55$, $p = 0.004$) were heritable traits.

Conclusions—Low frequency oscillations have a robust relationship with MMN and the relationship appears altered by schizophrenia; and schizophrenia patients showed augmented low frequency activities during the MMN paradigm.

Significance—The results encourage investigation of low frequency oscillations to elucidate the neurophysiological pathology underlying MMN abnormalities in schizophrenia.

Keywords

MMN; theta; alpha; oscillations; single trial; schizophrenia; genetics; heritability

Introduction

Schizophrenia patients often show abnormalities in mismatch negativity (MMN) (Javitt et al. 1995) although the underlying etiology is still under intense investigation. MMN is elicited by an auditory oddball series where rare deviant sounds are presented during a stream of common standard sounds (Naatanen et al. 2007). MMN typically peaks between 150 and 200 ms after stimulus onset. It is based on subtraction of time-locked components of the standard vs. rare event related potential (ERP) waveforms. Interestingly, two recent studies showed that lower range frequency theta and alpha oscillatory activities contribute to MMN in normal controls (Fuentemilla et al. 2008; Hsiao et al. 2009), and deviant stimuli are known to elicit MMN waveforms with spectral amplitude peaking in the 3–9 Hz range (Javitt et al. 2000a). Theta-alpha range neural oscillations during sensory gating were previously shown to be a robust and heritable electrophysiological component underlying the traditional ERP P50 gating (Hong et al. 2008). Specific neural oscillatory abnormalities linked to the pathology of schizophrenia may be present regardless of tasks and may influence basic neural functions of electrophysiological findings in schizophrenia. Here, we tested the hypothesis that theta-alpha neural oscillatory activities may also be associated with MMN abnormalities in schizophrenia.

MMN provides a measure of auditory sensory memory (Naatanen et al. 2007). It is closely associated with the first phase of sensory memory where short-term memory integrates consecutive incoming information to resolve component features of the sensory input (Cowan 1988). MMN also provides a passive paradigm to efficiently measure brain responses during detection of a violation of expectations to certain regularities (Herzholz et al. 2009; Kimura et al. 2010). MMN generators are demonstrated within the bilateral supratemporal plane with additional contributions from frontal and parietal cortices (Giard et al. 1994; Rinne et al. 2000; Molholm et al. 2005). The maximal effect of MMN is typically measured over frontal scalp locations (Umbricht et al. 2000; Bramon et al. 2004; Hall et al. 2007), and is thought to be the result of the supratemporal plane generators' orientations (Paavilainen et al. 2003).

Several hypotheses were proposed to explain MMN deficits in schizophrenia, including NMDA receptor dysfunction (Javitt et al. 1995) and possibly genetic liability (Hall et al. 2007). ERP is thought to be the result of summation of evoked single trial oscillatory response with superimposed gamma, alpha, theta, and delta rhythms (Basar 1980), and phase resetting of ongoing EEG oscillation (Sauseng et al. 2007). However, the mechanism of ERP amplitude formation may depend on the level of activities: when stimulus-related and ongoing activities are low the ERP amplitude is associated with a relatively linear superposition of single trial responses; but when these activities are high, extracted ERP may not be the results of a linear superposition of single trial responses (David et al. 2005). It becomes important to consider whether there are group differences in the underlying oscillatory responses during MMN, and whether such differences may contribute to the MMN dysfunction in schizophrenia, as we plan to examine in this study.

Specifically, two previous MEG and EEG studies showed that oscillatory responses to standard and deviant stimuli during MMN are primarily comprised of theta and alpha frequency oscillations (Fuentemilla et al. 2008; Hsiao et al. 2009). Deviants were different from standard only at 4–6 Hz in one study (Fuentemilla et al. 2008) and at 4–8 Hz in another (Hsiao et al. 2009); while alpha frequency contributed to about 21% of the MMN variance (Fuentemilla et al. 2008). These analyses suggest that neural oscillations in the theta-alpha range appear particularly relevant to MMN. Whether theta-alpha range activity is related to MMN in schizophrenia, or how they are related to the genetic liability of schizophrenia, remains unclear. Given our recent finding that neural oscillations at the theta-alpha range are

related to the genetic underpinning of another ERP paradigm (Hong et al. 2008), we tested whether neural oscillations in theta-alpha frequency may play a role in the generation and the genetic underpinnings of MMN and its association with schizophrenia.

Methods

Participants

We recruited the following subjects to test the hypothesis: 95 patients with schizophrenia, 87 community controls, and 74 non-schizophrenia, antipsychotic naïve, first-degree relatives of schizophrenia patients. Relatives were recruited based on availability and eligibility without stipulation on the number of family members per patient. We recruited another community group comprised of individuals with schizophrenia spectrum personality (SSP) traits but without family history of psychosis in three generations ($n=34$). The latter group was considered a non-schizophrenia sample, a special group that allowed us to test whether significant findings in schizophrenia families, if found, are present or absent in individuals with symptomatic traits but without genetic background for schizophrenia. SSP trait was based on the Structured Interview for DSM-IV Personality Disorders (SIDP) where a participant exhibited 4, 3, or 3 schizotypal, paranoid, or schizoid symptoms respectively but may or may not meet the SSP personality disorder definition. The sample included a total of 290 subjects. The Structured Clinical Interview for DSM-IV (First et al. 1997) and Personality Diagnoses (Pfohl et al. 1997) were used to make Axis I and II diagnoses. Major medical and neurological illnesses, history of head injury with cognitive sequelae, mental retardation, substance dependence within the past 6 months or current substance abuse (except nicotine) were exclusionary. Smokers were required to abstain for 60 minutes before testing. Four patients were not treated, and the rest were on one or more antipsychotic agents. Those medications that 10 or more patients were on as a single medication regimen were clozapine ($n=13$), olanzapine ($n=12$), risperidone ($n=20$), and aripiprazole ($n=11$). The rests were on single or combined first and/or second generation antipsychotic medications but less than 10 patients in any one categorization. Controls had no DSM-IV psychotic disorders or family history of psychotic illness.

Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). Most individuals were also evaluated for global functioning using the Strauss-Carpenter Level of Function (LOF) scale (Strauss and Carpenter, Jr. 1977), and completed a cognitive battery that included 16 tasks categorized into 4 domains using their z scores: memory, problem solving, processing-speed, and working-memory composite scores.

Age (18–58 range) was not significantly different between controls ($\text{mean} \pm \text{se}$: 41.8 ± 1.3) and patients (39.1 ± 1.1 , $p=0.20$) or relatives (44.7 ± 1.3 , $p=0.11$). SSP trait subjects (36.7 ± 2.0) were younger compared to controls ($p=0.04$). Gender ratios were different between the groups (%male: 57.6%, 72.2%, 58.8%, 24.2%, for controls, patients, SSP, and relatives, respectively, $p<0.001$). The sample included 78 family units (2 subjects per family): 54 patient probands and 88 relatives belonging to 32 families of size 2 (size for participating family members but not size of the actual family), 14 of size 3, 6 of size 4, and 2 of size 6; and 24 families from community controls (22 of size 2, 1 of size 3, 1 of size 4). They formed 181 informative pairs for familiarity estimates.

Laboratory procedure

EEG was recorded using Neuroscan (Charlotte, NC) SynAmp 32 channel system (30 scalp channels, VEOG and HEOG) at 1 KHz sampling rate with bandpass at 0.1–200 Hz. Subjects sat in a semi-reclining chair inside a sound-attenuated chamber. We presented a duration deviant and a pitch/duration deviant in this study. Literature has shown that duration MMN

was more robust in separating controls from schizophrenia patients than pitch MMN (e.g., Magno et al. 2008). Duration deviant was therefore our primary task. At the mean time, we explored whether one version of the duration/pitch variant could be superior to duration MMN. Subjects were presented with 2000 auditory stimuli, of which 1600 (80%) were standard tones presented at 75 dB, 60-ms, 1000 Hz; 200 (10%) were duration deviant tone at 150-ms 1000 Hz tones; and 200 (10%) duration/pitch deviant tone at 100-ms, 1500 Hz tones; a task construct closely resembled that used in another schizophrenia family study by Magno et al (Magno et al. 2008). All tones had 5-ms rise/fall time, with a stimulus onset asynchrony of 300 ms. A nose electrode served as reference (Umbricht et al. 2006). Electrode impedance was kept below 5 k Ω . FZ was used for MMN measurement because FZ typically showed the largest MMN (Javitt et al. 2000b; Umbricht et al. 2006). Eyeblink artifacts were minimized using a VEOG-based eyeblink spatial filter routine implemented in Neuroscan software. Records were then filtered at 0.1–30 Hz (Umbricht et al. 2006) in 24 octave, epoched, baseline-corrected, threshold-filter at $\pm 75 \mu\text{V}$ for artifact rejection, followed by visual inspection. MMN was scored by peak detected within a 100–250 ms post-stimulus window by an automatic algorithm followed by visual inspection of each subject's peak blind to group status and finally, subtracting averaged standard from averaged deviant waveform.

Single trial processing

Averaging across trials removes non-stationary yet potentially biologically relevant signals. Biological mechanisms during perception and especially subsequent cognitive processing are unlikely to be restricted only to uniformly time-locked activities. Evoked oscillations in single trials are defined here as measurements that include both stationary and non-stationary oscillatory responses associated with the stimulus. They may yield complementary and biologically meaningful signals to averaged evoked potentials that are based primarily on time-locked, stationary responses. Single trial analyses were performed on 10 electrodes (Figure 1A). The selection of 10 electrodes was to cover a relatively even distribution across the scalp. Single trial analysis used data from the original 0.1–200 Hz recording, epoched using a 250 ms window from 25 to 275 ms following standard and deviant stimuli. This window was wider than the 100–225ms window used for MMN averaged evoked potential peak measurement so that we could better capture both stationary and nonstationary energy in response to single trial stimulus. An 8-level biorthogonal discrete wavelet transform (DWT) was then applied to each single-trial to decompose activities into 8 “details” (D1 to D8) (Figure 2). By simulation, we estimated the frequency band of each detail: D3 corresponded to high gamma frequency activities >85 Hz; D4: gamma at 40–85 Hz; D5: low gamma at 20–40 Hz; D6: beta at 12–20 Hz; D7: theta-alpha at 5–11 Hz, D8: delta at 1–4 Hz (Hong et al. 2007). D1–D2 represented very high frequency noise and was not used. Energy within each DWT decomposition was measured by power spectrum density (PSD in dB/Hz) using a nonparametric Welch method (Welch 1967). Single trial PSD for standard and deviant stimuli was separately averaged for statistical analyses. The averaging procedure was the following: 1) extract the PSD from the 250 ms window for each detail (frequency band) of each single trial, as a single value; 2) sum the PSD values of a given frequency band from all single trials and divide the sum by the number of single trials. This is repeated for each frequency band. The results of the averaging represent the stationary and nonstationary energy post-stimulus rather than the post-stimulus time-locked activity. Oscillatory measures were scored by algorithms written in Matlab environment.

This DWT-based single trial approach is analogous to time-frequency analyses of traditional quantitative EEG measures, albeit event-related here. Other more commonly used methods for time-frequency analysis of EEG or single trial data include continuous wavelet transform

(CWT) and Fourier Transform (FT). DWT, CWT, FT each have own advantages. Both Fourier and wavelet transforms are to extract harmonic signals of a time series. As such, they are well-suited for time-frequency analysis. In CWT, the dilation and translation parameters vary continuously; in DWT, these parameters are discretized, i.e., vary by discrete values. Unlike FT that allows direct extraction of signals from user-defined frequency bands, CWT and DWT provide scales. To describe wavelet scales in terms of frequency bands, it is common to use a conversion that represents scales as frequency bands, or to use simulation to verify the frequency bands the scales represent (Hong et al. 2007). Unlike Fourier transform that relies on approximation to unbound sine waves, wavelet transform uses wavelets of limited duration that allows detection of local variation in oscillations. Unlike CWT, in biorthogonal DWT, each decomposed coefficient can have a unique frequency band and the coefficients can be mathematically independent (Daubechie 1992). The independence between frequency bands (although signals will remain correlated between neighboring bands) represents an advantageous statistical property. The advantage of CWT and Fourier transforms is that we could define any signals in any specific frequency bands, which could also be subjective. In DWT applications, the details (used as frequency bands) are not determined by the investigators but determined by the type of DWT chosen and the nature of the data. In that sense, DWT provides a rigid yet more objectively defined frequency band definition.

Statistical Methods

Oscillatory responses were compared between groups using mixed model for unbalanced repeated measures ANOVA, where 6 frequency bands and 10 channels were within subject factors, groups (patients, relatives, controls) the between subject factor, household a random effect, and if significant, age and gender covariates. Greenhouse-Geisser corrections were applied when appropriate. MMN amplitude and latency were compared using the same method but without frequency and channel. Post-hoc tests examined if patients and controls were significantly different; and if observed, whether relatives were significantly different from controls in the same frequency range and direction as the patients. The above were repeated in oscillatory responses to standard and deviant stimuli. SSP subjects formed a substantially smaller group; they were treated as special cases and were compared with controls separately and only in measures showing significant association with schizophrenia.

The contribution of oscillatory responses to MMN was explored by linear regression in which MMN amplitude served as the dependent variable and oscillatory time-frequency components served as predictor variables. We used an exploratory stepwise procedure to find the best time-frequency response (s) from deviant stimulus for predicting MMN, in which $MMN = \beta_0 + \beta_{1,1} * W_{1,1} + \dots + \beta_{i,j} * W_{i,j}$, where i is the frequency band and j the channel of the response PSD (W) of the deviant stimulus.

For familiarity calculation, we determined the genetic contribution to each measure showing significant group difference by estimating the proportion of the variance attributed to additive genetic effects, calculated using variance components analysis implemented in the SOLAR program (Almasy and Blangero 1998). The variance-components analysis decomposes the total variance of the phenotype in the family data into components that are due to additive polygenic variance and random environmental effects. Significant effects of age and sex were adjusted.

To control Type I error rates, we only performed post hoc group comparisons that were implicated by significant main effect or interaction terms. Furthermore, significance levels were corrected, e.g., thresholds for main effect and 3-way interaction were corrected for testing two oscillatory responses and their difference (standard, deviant, difference, $p < 0.017 = 0.05/3$). Significant interactions were followed by channel $\times$ group 2-way tests on

each frequency, here correcting for 6 frequency band tests ($p < 0.0083 = 0.05/6$). Significant findings were followed by comparison of simple effects (Cohen and Cohen 1983). We also examined correlations between electrophysiological measures and clinical symptom, cognition, and function. Significance levels were corrected for the number of correlations performed.

Results

MMN

There was a significant group effect on duration MMN ($F_{(2, 254)} = 10.10$, $p < 0.001$); schizophrenia patients ($p < 0.001$) but not relatives ($p = 0.42$) had reduced MMN compared with controls (Figure 3). SSP subjects also showed reduced MMN compared with controls ($p = 0.047$). Latency of the duration MMN also showed a group effect ($p = 0.026$), although there were no significant differences between controls and patients ($p = 0.12$) or relatives ($p = 0.74$). Pitch/duration MMN showed no significant group effect in amplitude ($p = 0.15$) or latency ($p = 0.73$). A repeated measure ANOVA contrasting the type of MMN (duration vs. pitch/duration) showed significant group $\times$ type interaction ($F_{(1, 181)} = 4.09$, $p = 0.045$) between patients vs. controls, supporting that the duration MMN separates patients from controls better than pitch/duration MMN, although a parametric manipulation of pitch and duration parameters is needed to confirm this assertion. Gender was not a significant covariate in any of the analyses; age was a significant covariate ($p = 0.01$) and was included in these analyses. Smoking status was not a significant covariate ($p = 0.61$). We also collected smoking severity in the smokers using Fagerstrom Test for Nicotine Dependence (FTND), and found that FTND was not significantly correlated with MMN ($r = 0.03$, $p = 0.81$). Thus, the findings are consistent with literature that neither duration MMN nor duration/pitch MMN separates controls from relatives of schizophrenia patients (Bramon et al. 2004; Magno et al. 2008; Price et al. 2006; Schreiber et al. 1992). Nevertheless, similar observations were made in a previous study (Magno et al. 2008). For the purpose of this study, we have used only duration MMN for subsequent single trial based analyses so that we can examine neural oscillations - MMN relationships within one MMN modality.

Splitting family members based on schizophrenia patients' MMN, family members of patients with reduced MMN (below the median) had significantly reduced MMN compared with family members of patients with MMN above the median (-0.42 ± 0.32 vs. -2.93 ± 0.33 , $F = 10.18$, $p = 0.002$), although neither group was significantly different from controls ($F = 3.48$, $p = 0.066$ and $F = 1.25$, $p = 0.26$, respectively). Therefore, MMN may not be significantly impaired in the combined family member sample, but reduced MMN may still be transmitted in family members of schizophrenia patients with reduced MMN, consistent with a heritable trait (see heritability estimate below).

Standard and deviant evoked oscillations

Significant group (patients, relatives and controls) and interaction effects with frequency bands and channels were found in both standard and deviant responses in 3-way tests. Data are in Figure 4A–B and statistics are in Table 1. Group $\times$ channel interactions were also present in all frequency ranges except low gamma. Post-hoc two group comparisons showed that patients had significantly increased power in beta, theta-alpha, and delta bands that covered the lower spectrum of oscillations 1–20 Hz ($p = 0.02$ to < 0.001 , most robust in theta-alpha) (Table 1). However, relatives did not significantly differ from controls in any of the frequency bands. Comparison of SSP trait subjects and controls also showed no significant group ($p = 0.08$), frequency $\times$ group ($p = 0.50$) or frequency $\times$ channel $\times$ group ($p = 0.40$) effects. Age and sex covariates were not significant in these analyses. Differences of standard and deviant evoked oscillations (standard minus deviant) showed no significant

group or interaction effects after Bonferroni corrections (Table 1). Smoking status showed no significant main effect on standard or deviant stimuli ($F = 0.35$, $p = 0.55$) or interactions on group, channel, or frequency bands (all $F = 1.78$, all $p = 0.11$). Dosages of individual medication [based only on medications where 10 or more patients were on as a single medication: clozapine ($n=13$), olanzapine ($n=12$), risperidone ($n=20$), aripiprazole ($n=11$)] showed no significant correlations with MMN or oscillatory measures (all $|r| < 0.53$, all $p > 0.09$, all based on FZ).

To summarize, there were pervasive lower range frequency oscillatory response abnormalities during standard and deviant stimuli, all in the direction of increased lower range frequency oscillatory power in schizophrenia patients. However, like MMN, the lower range frequency abnormalities were present in patients but not in first-degree relatives.

Contribution of evoked oscillations to MMN

To explore what spatial/frequency oscillatory components contribute to MMN amplitude, all frequency PSD from all sites in response to deviants were entered in a stepwise regression. In controls, 5 variables were retained: theta-alpha at FZ was the most significant predictor for MMN (R^2 change=21.4%, $F=23.19$, $p<0.001$; Figure 5), followed by delta at F8 (additional $R^2 = 6.2\%$, $p=0.009$), theta-alpha at P7 (3.6%, $p=0.041$), gamma at F8 (4.1%, $p=0.026$), and high gamma at T8 (4.4%, $p=0.017$). Note that contributions from F8 and other sites were several fold smaller than the contribution from FZ. In the relatives, theta-alpha at FZ was also the most significant predictor (R^2 change=23.9%, $F=21.40$, $p<0.001$), followed by high gamma at T7 and theta-alpha at PZ (10.2%, and 7.9% additional R^2 , respectively). Thus, although the stepwise procedure is exploratory, the frontal theta-alpha correlation to MMN amplitude was a replicable observation across non-psychosis control and family member samples.

The pattern was different in patients such that delta PSD at T8 was the most significant predictor (R^2 change=12.3%, $F=14.55$, $p<0.001$), followed by delta at PZ (9.5%) and high gamma at P8 (6.8%). Delta at FZ was not significantly correlated with MMN for either standard or deviant stimulus ($p=0.85-0.89$). In SSP trait subjects, the most significant contribution to MMN was delta at FZ (R^2 change=38.0%, $F=19.03$, $p<0.001$), followed by theta-alpha at FZ (R^2 change=23.4%, $F=9.47$, $p=0.004$).

Age was not a significant predictor for MMN in normal controls, relatives, and SSP subjects. Age was a significant contributor to MMN in the patient, explaining 8.2% of the MMN variance ($F=7.61$, $p=0.007$). This is consistent with a previous observation of age effect on MMN in schizophrenia (Kiang et al. 2009).

Overall, in the three non-psychosis groups, frontal lower range frequency oscillations were the most relevant components associated with MMN. The primary contribution from theta-alpha PSD was seen across controls and relatives. In patients and SSP individuals, the primary contribution was shifted even lower to the delta range. Theta-alpha remained a substantial contributor to MMN in SSP subjects; while in patients who had the highest theta-alpha power, the correlation between theta-alpha and MMN has all but disappeared (Figure 5). The regression slopes were significantly different between patients vs. controls ($z=2.81$, $p=0.005$), relatives ($z=3.01$, $p=0.0024$), but not SSP subjects ($z=1.2$, $p=0.11$). Findings from standard sound evoked theta-alpha PSD were similar and not described in details here; while PSD differences between standard and deviant showed no or much less correlation to MMN. Contributions of standard, deviant and standard-minus-deviant sound evoked theta-alpha to MMN are plotted at Figure 5.

Heritability

MMN amplitude measured at FZ showed significant heritability ($h^2=0.56$, $p=0.002$). Components of single trial oscillatory response that showed significant heritability were, in the order of the higher to lower heritability, deviant evoked theta-alpha at FZ ($h^2=0.55$, $p=0.004$), theta-alpha at T8 ($h^2=0.47$, $p=0.008$), delta at FZ ($h^2=0.45$, $p=0.007$), beta at FZ ($h^2=0.36$, $p=0.041$), and theta-alpha at CZ ($h^2=0.34$, $p=0.039$). None of the higher frequency responses showed significant heritability. Note that in this oddball paradigm, single trial oscillation measures yielded comparable but not higher heritability than averaging-based MMN.

Clinical correlates

Correlations were performed between MMN and theta-alpha at FZ with level of functioning (LOF), symptom (BPRS total and subscales), and cognition (4 composite scores). Based on 24 correlations ($p<0.002\approx 0.05/24$), poorer LOF was not associated with MMN ($r=-.16$, $n=225$, $p=0.02$). Poorer LOF was significantly associated with higher deviant evoked theta-alpha in the combined sample ($r=-0.31$, $n=222$, $p<0.001$), and also in controls ($r=-0.31$, $p=0.004$), patients ($r=-0.22$, $p=0.041$) and relatives ($r=-0.46$, $p<0.001$) analyzed separately. Larger MMN was significantly related to better working memory ($r=-0.27$, $n=243$, $p<0.001$), although this was not significant in individual groups, suggesting the effect was not robust or was confounded by group status. MMN was also correlated with problem solving ($r=-0.21$, $n=243$, $p=0.001$), and processing speed ($r=-0.21$, $n=243$, $p=0.001$); again neither were significant in separate groups. Theta-alpha was not significantly correlated with any cognitive domains. No symptom scales were significantly correlated with MMN or theta-alpha.

Discussion

This study applied a full spectrum analysis of evoked oscillatory activities obtained from an oddball paradigm commonly used to generate MMN. We found that augmented lower range frequency evoked oscillations were the prominent feature in schizophrenia patients. Power in the theta-alpha range was also the single most significant predictor of MMN in controls and non-ill relatives. However, this study showed that no oscillatory frequency band or MMN measure was significantly abnormal in relatives as seen in the patients. These results suggest that, although many of these measures are heritable by themselves, they may not mark the familial liability for schizophrenia.

Our study showed that lower range frequency oscillatory responses underlying the oddball paradigm are highly abnormal in schizophrenia patients. MMN to deviant sounds and lower range frequency responses in the oddball paradigm share some similar features: robustly associated with schizophrenia and significantly heritable. While initial studies with small sample sizes have reported reduced MMN in first degree relatives (Michie et al. 2002;Jessen et al. 2001), larger family member samples showed that first-degree relatives do not have reduced MMN (Bramon et al. 2004;Magno et al. 2008;Price et al. 2006;Schreiber et al. 1992). Our study that included a much larger group of family members revealed essentially the same pattern. One study in SSP subjects also showed reduced MMN (Niznikiewicz et al. 2009), which was also replicated by the current sample. Therefore, our study provided simultaneous replication of several key features of MMN previously found in schizophrenia patients, their family members, and in individuals with SSP traits.

MMN was found to be significantly heritable (0.56). Heritability calculated by SOLAR in family samples is strictly speaking familiarity. Nevertheless, this family sample based estimate closely matched two other reports of MMN heritability at 0.46 and 0.66 (Hall et al.

2006; Hall et al. 2007), estimated using twin samples. As a further support of this finding, although MMN amplitude was overall not decreased in relatives, reduced MMN in patients appears to be transmitted to their family members in contrast to family members of schizophrenia patients with higher MMN ($p=0.002$).

Fuentemilla et al showed that oscillatory responses to standard and deviant stimuli consisted primarily of 4–14 Hz oscillations and frontal MMN was associated primarily with increased theta power during the deviant trials (Fuentemilla et al. 2008). Alpha frequency contributed substantially (21%) to the MMN variance in that study. A MEG study showed that deviant stimuli were associated with 4–8 Hz oscillatory responses (Hsiao et al. 2009). Both studies were based on normal controls. Our finding of the primary correlation of theta-alpha oscillatory activities to MMN is consistent with these previous descriptions, despite the use of different analytical approaches. Interestingly, first-degree relatives with increased genetic liability for schizophrenia also showed the same relationship. In addition, previous studies were based on analyses of MMN data from phase-reset (Hsiao et al. 2009) or phase-locking (Fuentemilla et al. 2008), and results reported here were based on evoked oscillations from stationary and nonstationary signals. Future studies could further explore how these signals are similar or different in their contributions to MMN. Our selection of the discrete wavelet decomposition method also limits our ability to freely separate signals into desired frequency bands, in this case decomposing the theta-alpha band into the EEG convention of theta (5–8 Hz) and alpha (9–12 Hz) bands, although this approach provides objective, non-observer defined frequency bands.

In schizophrenia patients and SSP trait subjects, this relationship appears altered such that PSD of the delta range activities contribute most to their MMN. The commonality between patients and SSP trait subjects suggests that this change in relationship could be related to symptom states. The strongest contribution to MMN is the PSD of the oscillatory activities from central frontal site FZ, replicated in three independent groups. In schizophrenia patients, this relationship was altered and several other sites other than FZ were found associated with MMN. However, contributions from these other sites, although statistically significant, were much smaller and replications are needed to rule out spurious findings. We speculate that abnormally high levels of lower range frequency activities could have dampened the salience of the time-locked elements in ERP, reducing the normal relationship between theta-alpha and MMN in the patients. Interestingly, standard-minus-deviant PSD showed no or only small correlation to MMN. The mechanism of this is not clear. The PSD subtraction yielded differences in stationary + nonstationary energy; while MMN is a subtraction of two averaged evoked potentials that were based on time-locked signals only. Because PSD from standard and deviant are correlated to MMN in some groups (top two panels in Figure 5), a subtraction of PSD could cancel out the correlation with MMN. The mechanisms behind these intriguing relationships may need to be addressed with animal studies with simultaneous investigation of the neurobiological basis of lower range frequency activities and MMN. The important implication here is to highlight the oscillatory abnormalities in schizophrenia, particularly in low frequencies, during the oddball paradigm.

MMN dysfunction in schizophrenia is thought to be associated with an abnormality in the mismatch generator process (Naatanen et al. 1989; Javitt et al. 1995). We observed here that higher theta-alpha responses are linked to MMN in non-patient groups such that theta-alpha may be associated with passive monitoring that facilitates the mismatch generator process. However, higher theta-alpha energy in patients did not translate into higher MMN, suggesting a de-coupling of theta-alpha and MMN generation in patients. Based on the increased theta power for deviant stimuli, Fuentemilla et al (Fuentemilla et al. 2008) suggested that evoked theta oscillations could present a top-down mechanism affecting sound feature analysis. Our analysis showed that this correlation was also present in

responses to standard sounds (Figure 4 top panels), suggesting that this lower range frequency oscillation – MMN relationship was driven more by general features of the oscillatory response rather than specific to the analysis of the deviant sound feature. Therefore, the augmented lower range frequency oscillations may not be exclusively affecting MMN, but could be affecting ERPs in general. Indeed, with the short ISI (300 ms) in this MMN paradigm, the oscillatory response from one auditory stimulus overlaps with the “baseline” oscillatory activities of the next stimulus. One possible explanation of the decoupling of theta-alpha and MMN generation is that patients generate abnormally high delta-theta-alpha activity during the fast paced oddball task, which could swamp the stimulus-elicited activity leading to reduced salience of the ERP generation.

The strikingly augmented low-frequency power in patients but not in the relatives could be due to medication effects. With only 4 unmedicated patients, we lack the power to examine this directly. MMN deficit has been associated with cortical thinning (Thoma et al. 2004; Salisbury et al. 2007); it is unclear whether this could cause pervasive power increases. Artifacts such as eye blinks that occurred more often in patients could contribute to the increased power, although neither channel distribution (Figure 3A–B).

In conclusion, lower range frequency oscillations are abnormally enhanced in schizophrenia patients during MMN, but neither MMN nor these oddball-evoked lower range frequency oscillations mark the familial liability for schizophrenia. Power of the post-stimulus lower range frequency oscillations is a substantial and replicable contributor to MMN amplitude, particularly oscillatory responses in the theta-alpha range; although the relationship is altered to some extent in schizophrenia patients. Investigating lower range frequency oscillations during clinical and animal MMN research may be an important approach to elucidate the underlying pathophysiology leading to MMN deficit in schizophrenia.

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Highlights

1. Schizophrenia patients showed significantly augmented lower range frequency activities in beta, alpha, theta, and delta ranges during the MMN paradigm
2. MMN and theta-alpha oscillations were significantly heritable traits
3. Low frequency activities were robustly associated with MMN, although the exact relationships were altered by schizophrenia.

Figure 1. Channels used for data analysis (A) and standard (B), deviant (C), and duration MMN (D) grand average waveforms at FZ for normal controls, schizophrenia patients and first-degree relatives. See Figure 3 for statistics.

Figure 2.

Decomposition of time-scale (frequency) activities from a randomly selected single trial in response to a duration deviant stimulus in a schizophrenia patient, using 8-level bio5.5 discrete wavelet. Note that this graph is a technical illustration only: single trial data vary greatly from trial to trial. Time 0 indicates the onset of the duration deviant stimulus. Activities from 25ms to 275ms were extracted for calculation of power (PSD). The y-axis is scaled differently in different detail scales in this illustration. There were no discernable evoked oscillatory signals that could be easily observed from the original single trial recording (top). With the discrete wavelet transform, it appeared that very small but discernable energy changes might have appeared at detail level D3 (85Hz – 150 Hz), D6 (12–20 Hz), D7 (5–12 Hz), and D8 (1–5 Hz), as marked by the red ovals.

Figure 3. Duration and pitch/duration MMN amplitudes and latencies measured at FZ. *** $p < 0.001$; * $p < 0.05$.

Figure 4.

A–B: Oscillatory activities in response to standard and deviant sounds (mean±s.e.). The data for 10 channels are arranged as 3 groups of channels from left hemisphere (F7, T7, P7), midline (FZ, CZ, PZ, OZ), and right hemisphere (F8, T8, P8), and arranged at an anterior-to-posterior orientation. Statistics are in Table 1. PSD: power spectrum density (unit: dB/Hz). L: left

Figure 5.

Relationship of single trial evoked theta-alpha response and MMN. Top panel: standard sound evoked theta-alpha and MMN; middle panel: deviant sound evoked theta-alpha and MMN; bottom panel: standard minus deviant theta-alpha and MMN. The negative sign in most cases demonstrates that deviant sounds evoked higher theta-alpha than standard sounds in most subjects across groups. PSD: power spectrum density. SSP: Schizophrenia spectrum personality trait. The regression statistics for the SSP group excluded the outlier with MMN over 11uV.

Statistical results of group main effects and interactions. All mean and s.e. values are presented at Figure 2. “Group” is group main effect among patients, relatives, and controls. Difference: Standard-minus-deviant. Significant findings after corresponding Bonferroni corrections are in bold.

Table 1

			2-way Tests (Channel × Group)											
			3-way Overall Tests (Frequency × Channel × Group)				High Gamma (>85 Hz)				Gamma (40–85 Hz)			
Events	Statistics	Group Effect	3-way Interaction	Group Effect	Group × Channel	Group × Channel	Low Gamma (20–40 Hz)	Group Effect	Group × Channel	Beta (12–20 Hz)	Group Effect	Group × Channel	Theta-alpha (5–11 Hz)	Group Effect
Standard	F	15.20	1.92	6.73	1.86	6.07	0.79	4.55	1.84	9.67	1.92	4.55	10.92	0.65
	p	0.000	0.005	0.001	0.06	0.003	0.62	0.01	0.06	0.000	0.05	0.000	0.000	0.80
Deviant	F	12.45	1.71	5.70	1.31	4.92	3.38	3.50	2.30	7.58	1.64	3.60	14.31	0.94
	p	0.000	0.009	0.004	0.22	0.008	0.019	0.03	0.009	0.001	0.10	0.000	0.000	0.51
Difference	F	3.63	1.25	2.89	1.13	1.31	1.50	2.24	1.25	1.86	0.79	0.47	1.20	0.76
	p	0.021	0.055	0.06	0.33	0.27	0.13	0.11	0.25	0.16	0.67	0.052	0.30	0.71