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Longitudinal Relationships between Mismatch Negativity, Cognitive Performance, and Real-World Functioning in Early Psychosis

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Abstract

Background: Reduced mismatch negativity (MMN) is observed in early psychosis (EP) and correlated with cognition and functioning, but few studies have examined their longitudinal relationships and diagnostic specificity. We examined MMN, neuro- and social-cognition, and functional measures in EP patients with schizophrenia-spectrum (SZ) or bipolar disorder (BD) over a 1-year follow-up.

Methods: 54 EP patients (SZ: n=24; BD: n=30) and 42 healthy controls completed baseline measures: MMN, neuro- and social-cognition, and functional assessments. 30 EP patients completed 12-month follow-up assessments. Patients and controls were compared on MMN at baseline and follow-up, and diagnostic subgroup analyses were performed. Associations amongst MMN, neuro- and social cognition, and clinical measures were examined and predictive models of follow-up outcomes were conducted.

Results: EP patients showed significantly reduced MMN compared to controls at baseline ($p = 0.023$). MMN was impaired in SZ patients at baseline ($p = 0.017$) and follow-up ($p = 0.003$); BD patients did not differ from controls at either timepoint. MMN was associated with symptom

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severity and functioning at baseline, and with social cognition and functioning at follow up, but was not predictive of functional outcomes at follow-up.

Conclusions: MMN abnormalities were evident in EP SZ-spectrum disorders at both timepoints, but not in BD at either timepoint. MMN was associated with functioning cross-sectionally, but did not predict future functional outcomes. However, deficits in MMN were associated with social cognition, which may have downstream effects on community functioning. Implications for targeted interventions to improve social processing and community outcomes are discussed.

Keywords

Early Psychosis; Longitudinal; Mismatch Negativity; Cognition; Functioning

1. Introduction

Mismatch negativity (MMN) is an event-related potential (ERP) that represents an early pre-attentive automatic change detection process occurring in the auditory cortex (see Naatanen et al., 2007; Naatanen et al., 2012 for review). MMN can be elicited using a passive auditory oddball paradigm in response to various types of infrequent deviants (e.g., duration, pitch). Reduced duration-deviant MMN (dMMN) amplitude is a robust observation in patients with chronic schizophrenia spectrum disorders (SZ) with large effect sizes (Cohen's d ~ 1) (Erickson et al., 2016; Umbricht and Krljes, 2005). In chronic bipolar disorder (BD), studies also find evidence of abnormal MMN, albeit to a lesser degree than in SZ (Hedge's g ~ 0.40) (Chitty et al., 2013; Erickson et al., 2016; Hermens et al., 2018). Accordingly, MMN has been interpreted as an index of neurobiological phenotype that is shared across psychotic and related disorders (Light and Naatanen, 2013; Javitt et al., 1996) consistent with the Research Domain Criteria (RDoC) framework (Insel et al., 2010). In patients experiencing a first episode of psychosis (FEP), dMMN deficits are also reported, with smaller effect sizes (Cohen's d ~ 0.4) (Haigh et al., 2017; Hsieh et al., 2019) than in chronic illness, indicating deficits are present early in the disease course and continue worsening over the course of the illness.

In addition to MMN and other neurophysiological abnormalities, FEP patients exhibit deficits across a broad array of domains, including neurocognition, social cognition, and daily functioning. Numerous studies have reported that neurocognition deficits are present early in psychosis (Zabala et al., 2010; Gonzalez-Ortega et al., 2013; Bora and Murray, 2014) and are associated with poorer community functioning (Leeson et al., 2011; Gonzalez-Ortega et al., 2013; Green and Harvey, 2014; Torgalsboen et al., 2015). Social cognition refers broadly to the cognitive functions relevant to perception and processing of social information (Harvey and Penn, 2010) including emotion processing, social perception, theory of mind (TOM)/mental state attribution, and attributional style/bias, as well as more complex concepts such as social metacognition (Pinkham et al., 2016). Although social cognition and neurocognition are often correlated, they appear to exist as at least partially distinct constructs (Sergi et al., 2007), and social cognition may be even more strongly associated with functional outcomes (Fett et al., 2011; Ohmuro et al., 2016). However, longitudinal findings regarding associations amongst neurocognition, social

cognition, and outcomes in FEP have been mixed (Gonzalez-Ortega et al., 2019; Stouten et al., 2014).

MMN generation is shown to be sensitive to N-methyl-D-aspartate-type receptor (NMDAR) dysfunction in both primates (8) and in humans (Gunduz-Bruce et al., 2012; Rosburg and Kreitschmann-Andermahr, 2016; Rowland et al., 2016), which is associated with cognition and functioning in both healthy adults and people with psychosis. Accumulating evidence shows that MMN abnormalities in people with SZ and related disorders are tied to downstream functional deficits including measures of social skills, work, independence in daily living, and global ratings of psychosocial functioning (Baldeweg et al., 2004; Light et al., 2007; Naatanen et al., 2011; Light and Braff, 2005; Kawakubo et al., 2007; Wynn et al., 2010; Rasser et al., 2011). These findings suggest that MMN may be associated with other core symptom domains in psychosis such as neurocognition and social cognition, as well as functional outcomes, making it a promising neurophysiological biomarker (Javitt and Freedman, 2015).

Few studies in FEP have examined neurocognition and social cognition in association with electrophysiological biomarkers. Kaur et al. (2011) reported that FEP patients with SZ-spectrum or affective-spectrum disorders exhibited MMN impairments, and that impaired dMMN was correlated with mental control ($r=-0.33$) and verbal learning ($r=-0.34$).) Using low resolution brain electromagnetic tomography (LORETA) to examine dMMN deficits in early stage SZ patients and associations with neuropsychological performance, Miyanishi et al. (2013) found that poor working memory was associated with decreased dMMN current density in the frontal lobe. In terms of functioning, associations appear more complex. In the early course of SZ, dMMN amplitude is significantly and negatively correlated with functioning, and working memory is significantly and positively correlated with functioning; however, neurocognition and dMMN were not correlated with one another (Koshiyama et al., 2018), consistent with associations observed in chronic SZ patients (Light and Braff, 2005; Kawakubo and Kasai, 2006; Kiang et al., 2007; Rasser et al., 2011).

MMN studies are typically reported using cross-sectional designs. Only two studies have examined longitudinal changes or diagnostic specificity in early stages of psychosis, with conflicting findings. Koshiyama et al. (2017) found that dMMN deficits were present in FEP patients at baseline and had no progressive reduction over time, whereas Salisbury et al. (2007) reported intact MMN at baseline with progressive reductions over time in people with SZ but not in people with BD. To the best of our knowledge, no study has examined the longitudinal associations among MMN, neurocognition, social cognition, and community functioning in the same cohort of FEP patients. In the present study we report baseline and 12-month follow-up measures from a cohort of early psychosis (EP) patients with SZ-spectrum or BD disorders to examine: 1) MMN differences between controls and EP patients and between diagnostic groups at baseline and follow-up, 2) associations between MMN and neurocognition, social cognition, and functioning at baseline and follow-up, and 3) the predictability of baseline MMN, neurocognition, social cognition, and symptom severity to functional outcomes at follow-up. We employed both interview-based and performance-based measures of functioning in order to assess real-world community functioning (e.g. independence in daily living, role functioning, and social interest/

engagement) and performance-based functional capacity. We hypothesized that i) people with EP would exhibit impairments in MMN compared to controls at both timepoints, but that deficits would be more pronounced in patients with SZ than BD, ii) MMN would be significantly associated with neurocognition, social cognition, and community functioning at both timepoints, and iii) baseline MMN, neurocognition, social cognition, and symptom severity would be independently predictive of both community functioning and functioning capacity at follow-up.

2. Methods and Materials

2.1 Subjects

The sample consisted of 54 EP patients and 42 healthy control (HC) subjects. Patients consisted of 24 SZ-spectrum diagnoses and 30 BD with psychotic features, as assessed by the Structured Clinical Interview for DSM-IV (SCID) and review of medical records at initial assessment. Patients were recruited from outpatient clinics, inpatient hospital units, flyers posted at McLean Hospital, and physician referrals. Study inclusion criteria were: 1) ages 18 to 45; 2) fluent in English; 3) IQ>70; 4) diagnosis of SZ, schizoaffective disorder, schizophreniform disorder, psychotic disorder NOS, psychotic depression, or psychotic BD; and 5) EP defined as within the first 3 years of illness onset (Table 2). Exclusion criteria consisted of: 1) diagnosed neurological disorder; 2) brain injury including stroke, loss of consciousness, coma; 3) diagnosed alcohol or drug dependence within 6 months; 4) chronic medical problem that could interfere with study participation, e.g. blindness, deafness, 5) ECT within the past 6 months. The averaged follow-up period for SZ patients was 284.08 days (SD=85.50, range 179–417) and for BD patients was 287.87 days (SD=121.19, range 155–518). HC subjects were recruited from the Partners Research Portal and subject to the same exclusion criteria plus the following: no current or past history of psychotic or affective disorders, no substance abuse or previous chronic dependence, and no first-degree relative with a history of psychosis or BD. The study was approved by McLean Hospital Institutional Review Board. All subjects provided written informed consent after receiving a complete description of the study.

2.2 Clinical assessments

Clinical measures included the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Young Mania Rating Scale (YMRS) (Young, et al., 1978), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Medication information was collected at each assessment timepoint. Antipsychotics included first- and second-generation antipsychotic medications and were converted into chlorpromazine (CPZ) equivalents based on the recommendations of Baldessarini (2013).

2.3. Cognitive assessments

Neurocognition.—Neurocognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). The MCCB consists of 10 tasks across 7 domain scores, including Processing Speed, Attention, Working Memory, Verbal Learning, Visual Learning, Problem Solving, and Social Cognition, and also produces a Composite score. Several studies suggest that the MCCB social cognition composite is less

strongly correlated with the neurocognition domain scores (Lewandowski et al., 2014; Van Rheenen et al., 2017) and may even serve as a partial mediator between neurocognitive functioning and community outcomes (Ospina et al., 2018). Based on these findings and our aims of examining specific associations between MMN and neurocognition/MMN and social cognition separately, we calculated a mean MCCB neurocognitive composite score without the social cognition domain score, and report the social cognition domain separately. All scores are reported as age and sex adjusted T scores generated using the MCCB scoring software.

Social Cognition.—Social cognition was assessed using two measures: the Awareness of Social Inference Test (TASIT)-Part Two (McDonald et al., 2003) which measures social inference/Theory of Mind, and the MSCEIT subtest from the MCCB, which measures social and emotional reasoning. The TASIT is comprised of fifteen brief video clips depicting everyday social interactions between two actors. The dialogue is often ambiguous, requiring participants to integrate cues from face, prosody, gesture, and social context (Channon et al., 2005; Leitman et al., 2006; McDonald, 1999). Participants answer 4 questions per video that probe understanding of the intentions, beliefs, and meanings of the speakers and their exchanges. Scores range from 0 to 64. Studies have found deficits in social perception in people with SZ using the TASIT (Kern et al., 2009; Leitman et al., 2006; Sparks et al., 2010. The MSCEIT consists of a series of vignettes read aloud to participants as they follow along in their booklets. Participants are asked to answer questions about effective responses or likely emotional reactions based on the vignettes. Scores are calculated using the MSCEIT scoring algorithm included in the MCCB scoring package, and age and sex adjusted norms are generated in T scores.

2.4. Functional assessments

Functional capacity was assessed using the UCSD Performance-Based Skills Assessment, Brief (UPSA-B) (Mausbach et al., 2007). The UPSA-B is a performance-based measure consisting of two subscales, financial and communication, designed to evaluate ability to perform everyday tasks (Mausbach et al., 2007). Total scores range from 0 to 100; higher scores reflect better performance (McKibbin et al., 2004; Leifker et al., 2009; Patterson and Mausbach, 2010; Green et al., 2011).

Community functioning was evaluated using the Multnomah Community Ability Scale (MCAS) (Barker et al., 1994; Zhou et al., 2018; Monaghan et al., 2019), an interview-based measure developed for use in psychiatric populations that probes several aspects of community functioning including independence in daily living, instrumental role functioning, and social interest/engagement. We used an abbreviated 11-item version to assess community functioning independent of cognitive impairment and symptom severity (Lewandowski et al., 2013). Items are scored 1–5, and higher scores indicate better functioning. We examined the MCAS total and the social and independence factors previously identified by Martin et al. (2015). Studies have demonstrated good predictive validity of MCAS, with poorer scores associated with subsequent hospitalizations (Barker et al., 1994; Zani et al., 1999).

2.5. Electrophysiological recordings and processing

The electroencephalogram (EEG) was recorded continuously using the BioSemi Active Two system (BioSemi Inc, Amsterdam, Netherlands) at a digitization rate of 512 Hz, with a bandpass of DC–104 Hz, and a Common Mode Sense (CMS) as the reference (PO2 site) using a 64-channel electrode cap. EOG electrodes were placed below and at the outer canthi of the left eye. A duration MMN paradigm was used to elicit MMN. Stimuli consisted of 1200 trials presented to the subjects through foam insert earphones. 85% of the stimuli were standard tones (1000Hz, 100ms), and 15% were duration deviant tones (1000Hz, 150ms), with an inter-stimulus interval 200ms and stimulus-onset-asynchrony 300 ms after standards and 350 ms after deviants. Participants were instructed to watch a silent cartoon/video clips (BBC natural program, Charlie Brown) during the stimulus presentation.

Data were processed using BrainVision Analyzer 2 (Brain Products GmbH, Munich, Germany). Data processing was performed offline and blind to group membership using automated procedures. Signals were re-referenced to an average of the mastoids and bandpass filtered between 0.01 to 20 Hz using a zero phase shift Butterworth filter. Data were segmented by stimulus marker from −100 to 400 ms. Segments were baseline corrected using −100 to 0 ms pre-stimulus time and eye-blink corrected using established measures (Gratton et al., 1983). Artifact rejection for individual channels was performed and a given segment was rejected if the voltage gradient exceeded 50 μV/ms, amplitude was +/−100 μV, or the signal was flat (<0.5 μV for >100 ms). MMN waveforms were generated by subtracting ERP waveforms in response to standard tones from the ERPs generated in response to the deviant tones. The MMN amplitude was measured as the peak amplitude between the time window of 100 to 250 milliseconds.

2.6 Statistical Analysis

Statistical analyses were carried out using STATA 15 (StataCorp, College Station, Texas). Duration MMN amplitudes at the Fz electrode were analyzed. Comparisons of control versus patient demographics and clinical features were performed using two-tailed unequal-variance t-tests and Fisher’s exact tests. Linear regression analyses were conducted to examine whether impaired MMN in patients would be observed at each timepoint and diagnostic specificity, controlling for age and sex. Patients’ longitudinal changes were assessed using linear mixed effects models, accounting for interaction between diagnostic group and time.

Relationships between MMN, community functioning (MCAS), functioning capacity (UPSA), neurocognition, social cognition, and symptom severity at baseline and follow-up were assessed using stepwise linear regression analyses (Likelihood Ratio Tests, LRTs) and partial correlational analyses controlling for significant predictors in the regression model to quantify the strength of associations. In the stepwise regression model, MMN was the outcome variable; age, sex, real-world functioning (UPSA, MCAS), social cognition (TASIT, MATRICS-social subscore), symptom severity (PANSS), and composite neurocognition (the average of all six MATRICS subscores except the social subscore) were included as predictors. Two separate analyses were run, one for baseline and one for follow-up. CPZ was initially included as a covariate but was not a significant predictor in the

models at either timepoint; this variable was dropped from the regression models. Prediction of real-world functioning at 12-month follow-up (MCAS or UPSA) was assessed using two separate stepwise regression models. In the first model, baseline demographics (age, sex), MMN, composite neurocognition, social cognition, and symptoms (PANSS total) were entered as predictors, and follow-up MCAS, or UPSA, was the outcome variable. In the second model, baseline demographics (age, sex), MMN, composite neurocognition, social cognition, and symptoms (PANSS total) were entered as predictors, and follow-up MCAS Independence subscore, or MCAS Social subscore, was the outcome variable.

3. Results

3.1 Comparison of demographics and clinical variables

Group analyses revealed significant differences between patients and healthy controls in education, composite neurocognition, MCAS, and UPSA at baseline (Table 1A). At follow-up patients had significantly lower MCAS than healthy controls (Table 1B). Patients with SZ had significantly higher PANSS General and PANSS Total scores and lower MCAS functioning than those with BD (Table 2).

3.2 Comparisons of MMN between groups

Results of regression analyses including all patients showed that at baseline, MMN of patients differed significantly from controls ($\beta = 0.672$, $p = 0.023$), while at follow-up the group difference was at the trend level (Figure 1A).

Comparisons by diagnostic group revealed that relative to controls MMN was significantly impaired in the SZ group at both baseline ($\beta = 0.884$, $p = 0.017$) and follow-up ($\beta = 1.283$, $p = 0.003$). Conversely, there were no significant differences between BD patients and controls at either timepoint (baseline: $\beta = 0.502$, $p = 0.140$; follow-up: $\beta = -0.051$, $p = 0.895$) (Figure 1B). Post hoc analyses revealed that SZ and BD patients did not differ significantly from each other at baseline ($\beta = -0.409$, $p = 0.328$), but did differ at follow up ($\beta = -1.291$, $p = 0.021$) with the SZ group showing greater impairment. The time by diagnosis interaction was not significant.

3.3 MMN in relationship with functioning, social cognition, and neurocognition

In two separate analyses (baseline and follow-up), the stepwise regression model included age, sex, UPSA, MCAS, TASIT, MATRICS-social subscore, PANSS, and composite neurocognition as predictors. Patient and control groups differed on full scale IQ (FSIQ), with patients performing slightly better than controls (Table 1). However, FSIQ was not correlated with MMN ($r=-0.0001$, $p=0.9991$), and therefore we chose not to include FSIQ as a predictor in the regression models. Results of baseline stepwise regression showed that MMN was significantly correlated with MCAS ($p = 0.03$; partial correlation = −0.39) and PANSS total ($p = 0.02$; partial correlation = −0.33). At follow-up stepwise regression, MMN was significantly associated with TASIT ($p = 0.024$; partial correlation = −0.580), MCAS ($p = 0.019$; partial correlation = −0.567), and MATRICS social cognition ($p = 0.008$; partial correlation = 0.528). Post-hoc analyses examining MCAS sub-domains showed that MMN was significantly associated with MCAS social sub-domain ($p = 0.027$; partial correlation =

−0.488) at follow-up. Interrelationships among neurocognition, social cognition, and functioning measures were presented in the supplementary table (Table S1 and S2).

3.4 Predictions of patients' real-world functioning at follow-up

Baseline demographics (age, sex), MMN, composite neurocognition, social cognition, and symptoms (PANSS total) were included in stepwise regression models to predict follow-up UPSA, MCAS, MCAS Social subscore, or MCAS Independence subscore. None of the baseline clinical variables were found to be significant predictors of follow-up UPSA total score. Baseline composite neurocognition ($\beta = 0.431$, $p = 0.048$) was a significant predictor of follow-up MCAS total score, while diagnosis was a predictor of follow-up MCAS total at a trend level. Analyses examining specific domains of function revealed that baseline diagnosis ($\beta = -2.772$, $p = 0.023$) and baseline composite neurocognition ($\beta = 0.317$, $p = 0.024$) were predictive of follow-up MCAS Social subscore, while baseline composite neurocognition was predictive of follow-up MCAS Independence subscore at a trend level.

4. Discussion

To our knowledge, this study is the first to investigate the relationships among MMN, neurocognition, social cognition, performance-based functional capacity and community functioning in a transdiagnostic cohort of EP patients, as well as the relationships amongst MMN, neurocognition, social cognition, and later functional outcomes. As a group, patients with early psychosis had impaired MMN at study entry compared to controls; however, we found unanticipated differences by diagnosis in which MMN abnormalities were pronounced in people with SZ-spectrum disorders but people with BD did not differ from controls. MMN did not change significantly in either group, remaining stably impaired in people with SZ and no different from controls in people with BD. Across the patient groups MMN was associated with symptom severity and functioning at baseline, and with social cognition and functioning at follow up. Baseline diagnosis and neurocognition were predictive of later functional outcomes, particularly in social and independent functioning domains.

4.1 Comparisons of MMN between groups

The present findings support previous evidence that MMN impairment is a trait biomarker in people with SZ-spectrum illness – present at illness onset and in ultra-high risk populations, and consistently impaired over time – but do not support this conclusion in people with BD with psychosis (Haigh et al., 2017; Hall et al., 2007; Hall et al., 2009; Hsieh et al., 2019; Erickson et al., 2016; Perez et al., 2014). At baseline, symptom severity was associated with MMN across patient groups. However, post-hoc analyses revealed that in SZ patients, healthier MMN amplitude was associated with less PANSS total score ($r = 0.21$), whereas in BD, higher MMN amplitude was associated with higher PANSS total score ($r = -0.41$), suggesting that MMN may be a trait marker of illness in SZ, and may also reflect state symptom severity in BD. Supporting this possibility, Kaur et al. (2011) found MMN impairments in both SZ and affective disorders, but reported that the affective disorders group actually exhibited higher symptom severity than the SZ group, potentially driving higher levels of state-related MMN abnormalities.

Previous work has reported that MMN abnormalities may progress with duration of illness (Salisbury et al., 2017). Meta-analyses report that FEP patients already exhibit abnormalities in MMN, but that the magnitude is smaller in FEP than in chronicity, suggesting a progressive nature to MMN impairment, as proposed by Salisbury et al. (2007). Our findings support the presence of MMN abnormalities at the early course of illness in people with SZ-spectrum disorders; however, progressive changes in MMN were not apparent in our sample. Given our relatively short follow-up period of one year, it is possible that worsening MMN may occur more slowly over time, perhaps associated with illness burden, rather than deteriorating precipitously after an initial episode.

4.2 MMN in relationship with functioning, social cognition, and neurocognition

Our results revealed a significant association between MMN and daily functioning in EP. Greater MMN abnormalities were associated with greater functional impairment using interview-based community functioning (MCAS) measures at both timepoints. These findings are consistent with observed MMN-functioning associations in chronic SZ and BD patients (Light and Braff, 2005; Kawakubo and Kasai, 2006; Kiang et al., 2007; Wynn et al., 2010; Rasser et al., 2011; Hermens et al., 2018). Only three previous reports have examined the relationship between MMN and functioning in early psychosis. Hermens et al. (2010) found a significant correlation between MMN amplitude and quality of life in first episode psychosis, and Koshiyama et al. (2018) showed a significant correlation between MMN impairment and lower global functioning (GAF) in early SZ patients. Murphy et al. (2020) reported significant associations between MMN and social functioning using the Global Functioning: Social and Role scales. In the present study we used an interview measure assessing several aspects of community functioning, including independence in daily living, instrumental role functioning, and social interest and engagement. Thus, we were able to extend the literature by demonstrating that MMN was associated with real-world functioning across several domains independent of symptom severity, and that the MMN-community functioning relationship was particularly relevant to the social domain (e.g., social acceptability, social interest, social effectiveness, and social network) consistent with Murphy et al. (2020), similar to findings in people with chronic SZ.

We found that, as expected, healthier MMN was associated with higher social influence ability (TASIT) and better real-world functioning (MCAS) at follow-up. However, we found an unanticipated correlation between MMN and social-t score, showing better MMN was associated with less social emotional ability. Correlations matrix (Table S1b) showed that in the whole sample social-t score was positively correlated with neurocognition, MCAS, and TASIT, as one would expect. The unanticipated correlation between MMN and social-t score was driven by the BD group ($r= 0.64$), while in SZ MMN was negatively associated with social-t score ($r= -0.14$). Future studies are warranted to gain better insight of social emotion and MMN in BD patients.

4.3 Predictions of patients' real-world functioning at follow-up

While we found associations between MMN and functional measures at both timepoints cross-sectionally, contrary to our hypothesis, baseline MMN was not a significant predictor of later functional outcomes. Additionally, a post-hoc mediation analysis failed to find a

significant mediation effect of social cognition, although it should be noted that this analysis was likely underpowered. Kaur et al. (2013) also failed to find MMN at frontocentral sites as a predictor of functional outcome; rather, they reported MMN at the mastoids (M1/M2) as predictors. Accordingly, more research is needed before definitive conclusions can be drawn about the utility of MMN in predicting later functioning status. While MMN was not a significant predictor of later functioning, diagnosis and neurocognition at baseline were independently predictive of later functional outcomes, particularly in the social and independent functioning domains, in keeping with previous associations between neurocognition and functioning in FEP (Stouten et al., 2014; Dickerson et al., 2008; Nuechterlein et al., 2011). Of note, while neither MMN nor social cognition were predictive of future functional outcomes, both were associated with functioning at each timepoint suggesting that impairments in MMN may impact functioning cross-sectionally, perhaps via associations with social cognition. These findings have implications for the development of targeted interventions to improve social processing with MMN serving as a potential mechanism of action.

Several limitations should be noted. First, we focused on relatively short-term clinical and functioning outcomes one year after baseline assessment. Thus, the relationships amongst MMN, social cognition, neurocognition, and functional measures occurring after a one-year period are yet to be established. Second, while effects of antipsychotic medications on MMN were not significant in our sample, which is consistent with literature (Korostenskaja et al., 2005; Leung et al., 2007; Pekkonen et al., 2002; Umbricht et al., 1998), a relatively high degree of missingness may have reduced our power to detect significant associations. Also, we were unable to examine potential effects of other medication classes on MMN, and there is a dearth of research assessing the medications effects on MMN. Third, while the UPSA is commonly used to assess functional capacity, some components are outdated and alternative performance-based measures may better capture functioning particularly in young people. Forth, HC were not retested. It is possible HC may have had some increase at re-testing that cannot be ruled out. However, we have reported high and significant reliability for MMN amplitude (ICC=0.67 for peak amplitude) in a prior study (Hall et al., 2006). Lastly, we included the PANSS Total score but not the positive, negative, and general subscales separately due to concerns about overfitting given the relatively modest sample size. A recent study found that positive symptoms specifically were correlated with MMN amplitude in people with SZ (Koshiyama et al., 2020), although an earlier study found no association between symptom severity and MMN (Erikson et al., 2017). Future work in larger samples examining specific associations between MMN abnormalities and PANSS subscales are needed.

In conclusion, we found evidence of early auditory processing deficits by the time of first episode that persisted over time in people with SZ but not with BD, and associations with state clinical symptoms in both SZ and BD, suggesting that MMN may act as a trait-marker of illness in SZ-spectrum disorders and a state marker of symptom severity transdiagnostically. Additionally, our findings suggest that MMN abnormalities are associated with social cognition and may affect community functioning, particularly in the social domain, making it a promising biomarker and a potential treatment target in early psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. B.

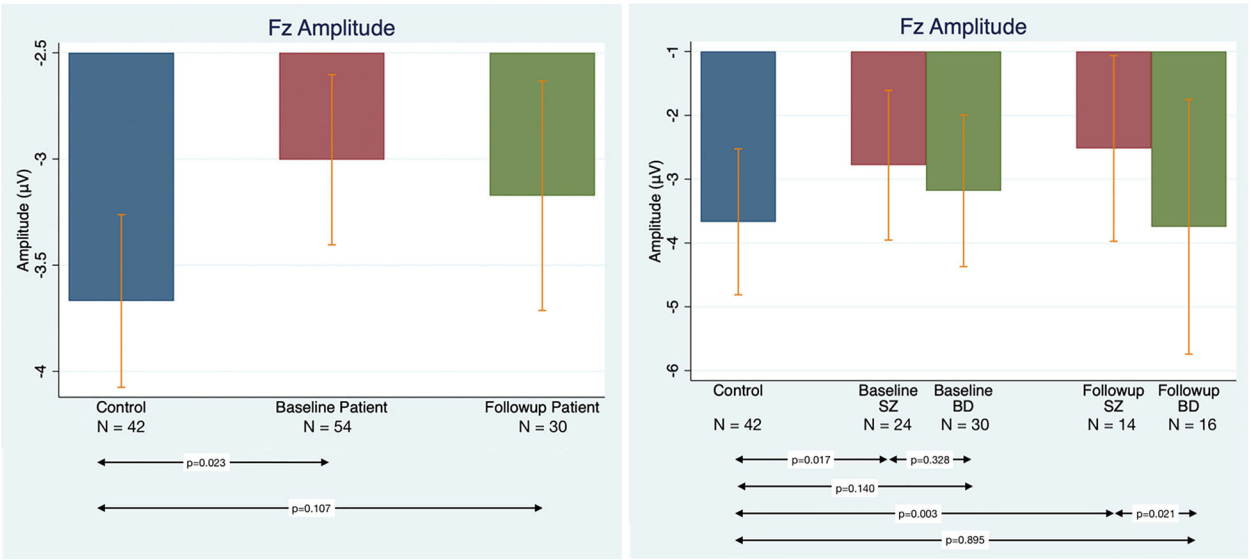

Figure 1.

Comparisons of MMN by Group and Diagnosis. Figure 1A) (left): Average Fz amplitudes for different groups. Amplitude for control subjects (blue), early psychosis (EP) patients at baseline (red), and EP patients at 12 months (green). Figure 1B) (right): MMN for control subjects (blue), SZ patients at baseline and 12 months (red), and BD patients at baseline and 12 months (green). (Note: vertical bars represent standard deviations.)

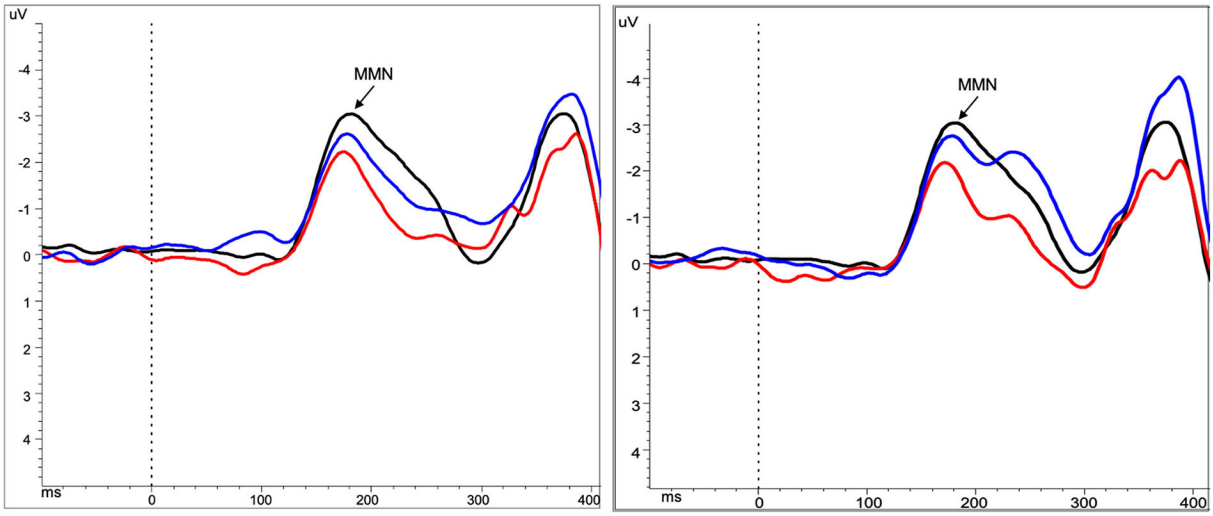

Figure 2.

Grand average MMN waveforms at Fz for control subjects (black), SZ (red) and BP (blue) patients at baseline (left) and follow-up (right)

Note: Peak detection window for MMN was between 120–250ms. HC baseline mean = 185.73 ms, SD = 19.17, range 160–242 ms; Patients baseline mean = 180.52 ms, SD = 19.88, range 139–248 ms; Patients follow-up mean = 179.69 ms, SD = 21.89, range 135–236 ms.

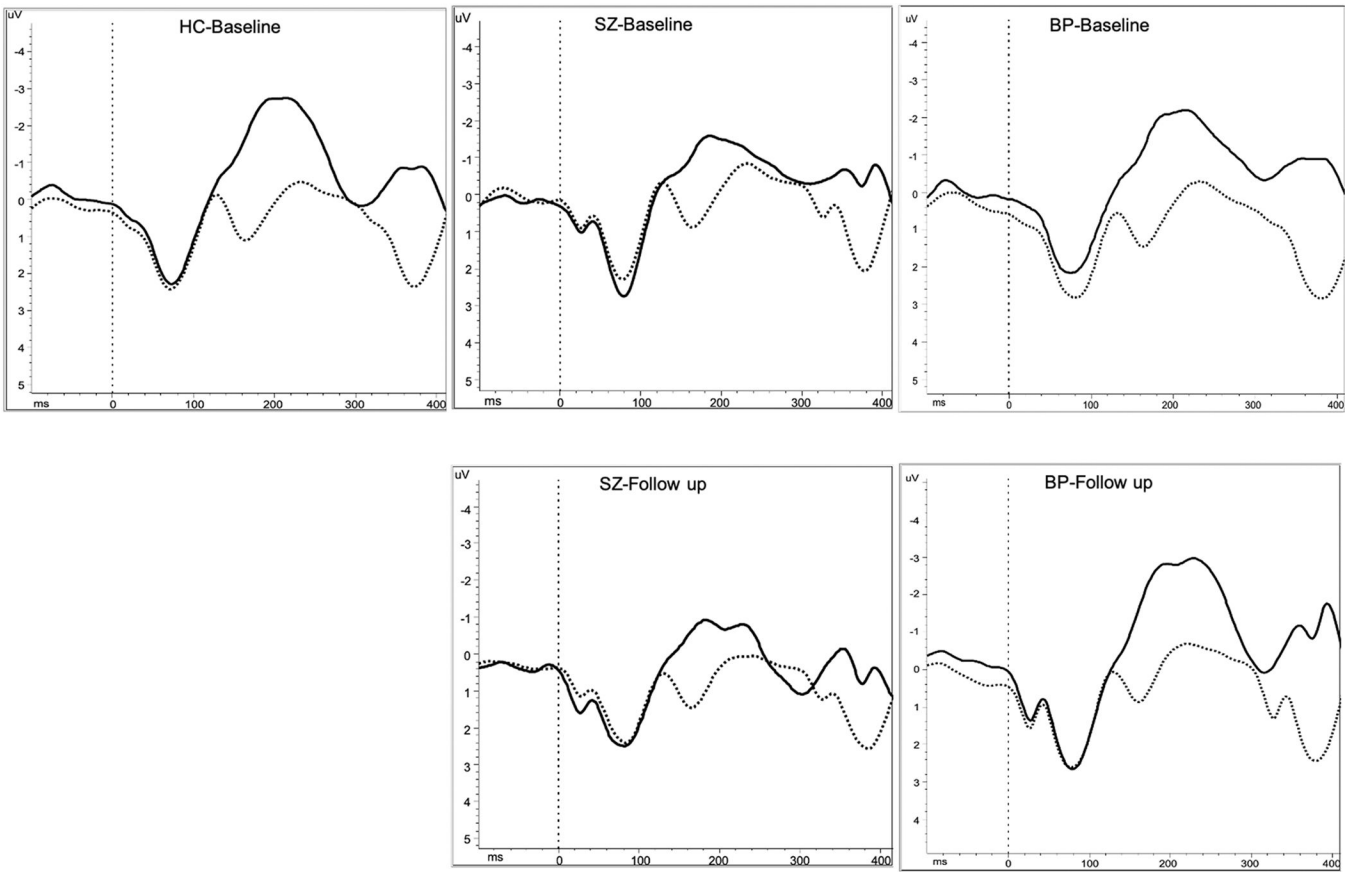

Figure 3.

Grand average waveforms of standard (solid) and target (dotted) tones at Fz for control subjects (left), SZ (middle) and BP (right) patients at baseline (top) and follow-up (bottom)

Table 1:

Group comparison (patients versus controls) of demographic, cognitive, and functional measures at baseline (A) and follow up (B)

(A) Baseline						
	Controls		Patients at Baseline		Statistic (df)	p value
	Mean (Std Errors)	N	Mean (Std Errors)	N		
Age	22.83 (0.58)	42	23.07 (0.51)	54	−0.31 (88.09)	0.756
Male (counts and %)	24 (57.14%)	42	33 (61.11%)	54	0.15	0.834
Education	**15.5 (.25)**	**42**	**14.78 (0.23)**	**54**	**2.13 (90.12)**	**0.036**
Full Scale IQ (FSIQ)	**113.25 (1.076)**	**42**	**116.42 (1.021)**	**54**	**−2.14 (90.99)**	**0.035**
MATRICS Social Subscore	54.18 (1.15)	40	51.88 (1.44)	50	1.25 (86.92)	0.215
Composite neurocognition	**50.90 (0.86)**	**40**	**45.90 (0.95)**	**49**	**3.91 (87.00)**	**<0.001**
MCAS total score	**54.76 (0.11)**	**33**	**46.08 (0.95)**	**53**	**9.04 (53.30)**	**<0.001**
TASIT	56.06 (0.78)	33	54.63 (0.92)	35	1.19 (64.96)	0.240
UPSA total score	**84.60 (1.45)**	**33**	**78.50 (2.00)**	**35**	**2.47 (61.15)**	**0.017**
(B) Follow-up						
	Controls		Patients at Follow-Up		Statistic (df)	p value
	Mean (Std Errors)	N	Mean (Std Errors)	N		
Age	22.83 (0.58)	42	24.033 (0.75)	30	−1.26 (58.96)	0.213
Male (counts and %)	24 (57.14%)	42	20 (66.67%)	30	0.67	0.469
Education	15.5 (.25)	42	14.97 (0.33)	30	1.30 (58.44)	0.199
MATRICS Social Subscore	54.18 (1.15)	40	53.64 (2.48)	25	0.20 (34.37)	0.846
Composite neurocognition	50.90 (0.86)	40	48.89 (1.52)	25	1.15 (39.17)	0.257
MCAS total score	**54.76 (0.11)**	**33**	**48.69 (1.02)**	**29**	**5.90 (28.61)**	**<0.001**
TASIT	56.06 (0.78)	33	54.25 (1.30)	24	1.19 (38.95)	0.241
UPSA total score	84.60 (1.45)	33	83.95 (2.25)	24	0.24 (41.01)	0.809

Table 1A) (top): Average baseline demographic, cognitive, and functional measures, represented by mean and standard errors, were compared between patients and controls. Bolded text represents significant differences between groups. Table 1B) (bottom): Average follow-up demographic, cognitive, and functional measures, represented by mean and standard errors, were compared between patients and controls. Bolded text represents significant differences between groups.

Table 2:

Comparisons of demographic, cognitive, functional and clinical measures by patient diagnostic group at baseline

	SZ Patients		BD Patients		Statistic (df)	p value
	Mean (SD)	N	Mean (SD)	N		
Age	22.67 (3.96)	24	23.4 (3.61)	30	t = −0.71 (52)	0.4805
Male (counts and %)	16 (66.67%)	24	17 (56.67%)	30	$\chi^2 = 0.1346$	0.714
Education	14.33 (1.55)	24	15.13 (1.74)	30	t = −1.76 (52)	0.0838
Full Scale IQ (FSIQ)	116.49 (8.22)	24	116.36 (7.01)	30	t = 0.062 (52)	0.951
Duration of Illness (yr)	1.45 (1.35)	24	1.17 (1.0)	29	t = 0.88 (51)	0.38
Age of Onset	21.21 (4.05)	24	22.21 (3.82)	30	t = −0.92 (52)	0.36
MATRICS Social Subscore	50.14 (9.40)	21	53.14 (10.68)	29	t = −1.028 (48)	0.3091
Composite neurocognition	42.10 (8.22)	21	46.19 (9.88)	30	t = −1.56 (49)	0.1261
MCAS total score	**42.83 (8.42)**	**23**	**48.57 (4.23)**	**30**	**t = −3.24 (51)**	**0.0021**
TASIT	53 (5.70)	14	55.71 (5.09)	21	t = −1.47 (33)	0.1500
UPSA total score	74.87 (12.50)	14	80.92 (11.03)	21	t = −1.51 (33)	0.1410
CPZ	205.94 (201.73)	21	154.38 (188.66)	28	t = 0.92 (47)	0.3627
PANSS Positive	15.13 (6.41)	23	12.03 (6.27)	30	t = 1.77 (51)	0.0835
PANSS Negative	13.30 (4.51)	23	11.37 (3.75)	30	t = 1.71 (51)	0.0936
PANSS General	**30.87 (5.47)**	**23**	**27.07 (7.19)**	**30**	**t = 2.11 (51)**	**0.0398**
PANSS Total	**59.30 (12.29)**	**23**	**50.47 (14.53)**	**30**	**t = 2.34 (51)**	**0.0231**

Average baseline demographic, cognitive, and functional measures, represented by mean and standard deviation, were compared between SZ and BD patients. Bolded text represents significant differences between groups.