MMN amplitude in first-degree relatives of psychotic disorders: links with cognition and
schizotypy

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Abstract

Background: Mismatch negativity (MMN) amplitude is reliably reduced in psychotic disorders. While several studies have examined this effect in first-degree relatives of individuals with schizophrenia, few have sought to quantify deficits in relatives of individuals with other psychotic disorders. While some studies conclude that, compared to healthy subjects, first-degree relatives of schizophrenia show reduced MMN, others contradict this finding, a discrepancy which extends to two recent meta-analyses. Furthermore, though MMN is often shown to be associated with cognitive impairments and clinical symptoms in psychotic disorders, to our knowledge no studies have sought to examine these relationships in studies of first-degree relatives. Method: The present study sought to clarify the extent of MMN amplitude reductions in a large sample of siblings of individuals with diverse psychotic disorders (n=65), compared to cases with psychosis (n=220) and never psychotic comparison subjects (n=252). We further examined associations of MMN amplitude with cognition and schizotypal symptoms across these groups. Results: We found that MMN amplitude was intact in siblings compared to cases with psychosis. MMN amplitude was associated with cognition and schizotypal symptoms dimensionally across levels of familial risk. Conclusions: The present results imply that MMN amplitude reductions emerge as a result of, or in conjunction with, clinical features associated with psychosis. Such findings carry important implications for the utility of MMN amplitude as an indicator of inherited risk, and suggest that this component may be best conceptualized as a marker for clinical symptoms and cognitive impairments, rather than risk for psychosis per se.

Keywords: Mismatch Negativity (MMN), Psychosis, Schizophrenia, Genetic Risk, Schizotypy

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The mismatch negativity (MMN) is reliably reduced in schizophrenia. Most often studied through auditory paradigms, the MMN is an event-related potential (ERP) elicited by the presentation of an unexpected stimulus. Most often, MMN paradigms vary the duration (MMN-D) or frequency (MMN-F) of a stimulus, with expectations set through the more frequent presentation of the standard stimulus (Näätänen, 1995). A relative deficit in MMN amplitude is one of the most replicated psychophysiological impairments in schizophrenia (Erickson, Ruffle, & Gold, 2016; Umbricht & Krljes, 2005); evidence suggests reductions are also present across other psychotic disorders (Donaldson et al., 2020; Erickson et al., 2016). Reduced MMN amplitude is often associated with worse cognitive functioning (Donaldson et al., 2020; Erickson et al., 2016; Javitt, Doneshka, Grochowski, & Ritter, 1995; Näätänen, Sussman, Salisbury, & Shafer, 2014) and greater psychotic symptoms (Donaldson et al., 2020; Fisher et al., 2011; Fisher, Labelle, & Knott, 2008, 2012; Light et al., 2015); though see (Erickson et al., 2017).

Several studies have examined MMN in samples at genetic high risk for schizophrenia (Earls, Curran, & Mittal, 2016; Erickson et al., 2016). While some conclude that, compared to healthy subjects, first-degree relatives of schizophrenia show reduced MMN (Jessen et al., 2001; Michie, Innes-Brown, Todd, & Jablensky, 2002; Şevik et al., 2011), others contradict this finding, demonstrating MMN amplitude reductions in only patients, not relatives (Ahveninen et al., 2006; Bramon et al., 2004; Hong, Moran, Du, O'Donnell, & Summerfelt, 2012; Magno et al., 2008). This discrepancy extends to two recent meta-analyses; one compared patients with schizophrenia, individuals at clinical high-risk, and relatives of patients with schizophrenia across eight studies and found no significant differences between relatives and controls (Erickson

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et al., 2016), while the second demonstrated a significant difference between these groups (Earls et al., 2016). Overall, studies of MMN amplitude in relatives of schizophrenia are few, and limited in sample size. It is possible this lack of clarity is due to such limitations, as several recent studies demonstrate that while MMN amplitude is *heritable*, it is not reduced in relatives of individuals with psychosis (Hall et al., 2009; Ramlund et al., 2016). Indeed, studies report heritability estimates of about 50-60% (Hall et al., 2006; Hall et al., 2009b), suggesting genetic effects, while contributory, are not wholly deterministic of MMN amplitude.

Fewer studies have examined MMN in relatives of individuals with psychotic disorders other than schizophrenia, despite considerable overlap in symptoms (APA, 2013; Reininghaus et al., 2016). Studies of MMN in siblings of individuals with diverse psychotic disorders include one sample of patients with bipolar disorder and their siblings (Hall et al., 2009) and one mixed psychosis sample comprised predominantly of schizophrenia-spectrum disorders (N= 21; 88% of the sample; Ramlund et al., 2016). However, diagnostic instability among cases, particularly early in illness, is high. Many early course cases initially diagnosed as other than schizophrenia-spectrum eventually are diagnosed as schizophrenia-spectrum disorders (Bromet et al., 2011; Heslin et al., 2015; Ruggero, Carlson, Kotov, & Bromet, 2010; Ruggero et al., 2011), complicating comparisons between sibling groups. Thus, further study of MMN amplitude in first-degree relatives of individuals with psychotic disorders other than schizophrenia are needed in order to examine this putatively genetically transmitted neural marker of psychosis in samples at familial risk for developing a psychosis-spectrum illness.

Reduction in MMN amplitude is often associated with poor cognitive functioning in schizophrenia (Baldeweg, Klugman, Gruzelić, & Hirsch, 2004; Näätänen, Kujala, Kreegipuu, Carlson, Escera, Baldeweg, & Ponton, 2011; Näätänen et al., 2014) and other psychotic disorders

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(Donaldson et al., 2020; Hermens et al., 2010; Kaur et al., 2011; Thompson et al., 2005). Thus far, only one study to our knowledge has sought to extend this relationship to first-degree relatives of individuals with psychotic disorders. This study, including individuals with schizophrenia and their relatives, shows associations between MMN and cognitive functioning in a sample of patients, relatives, and controls (Hong et al., 2012). This relationship did not reach significance when relatives were examined separately and is inconclusive. To our knowledge, these effects have not been replicated, nor extended to relatives of individuals with other psychotic disorders. Examination of the relationship between MMN and cognition across levels of familial risk for psychosis represents an important next step in elucidating the degree to which this relationship is dimensional. Given relationships present in cases with psychosis and never psychotic subjects (Donaldson et al., 2020), we expect this relationship to extend to siblings of individuals with psychosis.

Additionally, reduction in MMN amplitude is associated with psychotic symptoms in psychotic disorders in studies with large sample sizes or targeted recruitment of symptoms (Donaldson et al., 2020; Fisher et al., 2011; Fisher et al., 2008, 2012; Light et al., 2015); though one recent-meta analysis concludes the opposite (Erickson et al., 2017, likely due to effects collapsed across symptoms and MMN deviant types; Donaldson et al., 2020), and is reduced in schizotypal personality disorder (SPD; Niznikiewicz et al., 2009). First-degree relatives of individuals with schizophrenia report psychotic-like experiences at a higher than average rate (Johnstone et al., 2000; Kendler, 1985; Tarbox & Pogue-Geile, 2011) and are at increased risk for schizophrenia and SPD (Asarnow et al., 2001; Erlenmeyer-Kimling et al., 1995). The presence of psychotic symptoms in individuals with psychotic disorders is associated with increased symptoms of schizotypy in their first-degree relatives (Fanous, Gardner, Walsh, &

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Kendler, 2001), suggesting that it reflects etiology similar to psychiatric symptoms. However, to our knowledge no studies have reported on the association between MMN amplitude and schizotypal traits in relatives of individuals with psychotic disorders.

The aim of the present study is to clarify the extent of MMN amplitude reductions in siblings, and thereby the extent to which reduced MMN amplitude in cases may reflect genetic and shared environmental vulnerability for psychosis. This examination follows a previous study with this sample demonstrating associations between reduced MMN amplitude, auditory hallucinations, and cognitive functioning in psychotic disorders (Donaldson et al., 2020) and seeks to extend these findings across familial liability for psychosis. To accomplish this aim, we examined the relationships among MMN amplitude, cognitive functioning, and schizotypy traits across three groups (people with psychotic disorders, unaffected biological siblings, and never-psychotic comparison subjects), seeking to clarify whether MMN indexes clinical and cognitive impairments across levels of familial risk for psychosis. We hypothesize that reduced MMN amplitude will be associated with worse cognitive functioning and greater schizotypy, and that these relationships will not differ between groups. The present study will provide insight into whether reduced MMN amplitude reflects risk for psychosis, which may be present but attenuated in siblings of individuals with psychosis, or factors associated with the illness itself. This study utilizes a sample of individuals with diverse psychotic disorders and their biological siblings, allowing us to extend relationships that exist transdiagnostically amongst psychotic disorders to their first-degree relatives.

Method

Participants

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Study participants consisted of individuals with mixed psychotic disorders (N=220, including schizophrenia-spectrum disorders, mood disorders with psychosis, and other psychotic disorders), biological siblings not diagnosed with a psychotic disorder (N=65), and 252 never-psychotic zip-code- and demographically-matched comparison subjects (NP). All study participants were drawn from the 20-year follow up of the Suffolk County Mental Health Project (Bromet et al., 2011; Kotov et al., 2017), an epidemiologic study of first admission psychosis. Sample characteristics are presented in **Table 1**. MMN amplitude in cases with psychosis and never-psychotic comparison subjects in a similar, partially overlapping sample has previously been reported; MMN amplitude was reduced in cases, and shown to correlate with cognitive functioning and auditory hallucinations (Donaldson et al., 2020). We sought to examine whether similar relationships extend to siblings.

Measures

Clinical and neuropsychological assessments were completed by each participant at study visits concurrent with the MMN task. Diagnosis was determined using the structured clinical interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2001), information from which was used by study psychiatrists to generate consensus diagnoses. Psychotic symptoms were absent in sibling and NP groups by design; thus, dimensional measures of schizotypy were used. Schizotypal symptoms were assessed using the Schedule for Nonadaptive and Adaptive Personality (SNAP; Clark, Simms, Wu, & Casillas, 1993). The SNAP yields three subscales in its assessment of schizotypal traits—eccentric perceptions, mistrust, and detachment—which were used independently in the present analyses (Cicero, Jonas, Li, Perlman, & Kotov, 2019).

Cognitive functioning was assessed during a comprehensive neuropsychological battery, including the Controlled Oral Word Association Test (Ruff, Light, Parker, & Levin, 1996),

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Verbal Paired Associates and Visual Reconstruction from the Wechsler Memory Scale-Revised (both immediate and delay trials; Wechsler, 2012), Symbol-Digit Modalities, Letter-Number Sequencing, and Vocabulary from the Wechsler Adult Intelligence Scale-R (Silverstein, 1982), Trails A and B (Reitan, 1955), and the Stroop Test (Trenerry, Crosson, DeBoe, & Leber, 1989). A single composite score reflecting performance across these tasks was computed using an exploratory factor analysis, described in further detail in previous studies (Jonas et al., 2019; Martin et al., *Under Review*).

Task

The auditory MMN task was administered in the background of a visual picture/word matching task (Donaldson et al., 2020; Mathalon, Roach, & Ford, 2010). 2458 tones were presented at an interval of 500 ms, at 78 dB and 633 Hz, with 10ms rise/fall. 80% of tones were considered ‘standards’, while 10% deviated in duration (MMN-D, 100ms) and 10% deviated in frequency (MMN-F, 1000 Hz). This task is described in further detail in Donaldson et al (2020). As differences in MMN-D are shown to be most relevant to prediction of psychosis (Lepock et al., 2018; Randeniya, Oestreich, & Garrido, 2018), analyses in the present study focus on this component.

Psychophysiological Data Acquisition and Preprocessing

EEG data were acquired using an ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). 34 scalp electrodes were placed according to the international 10/20 system. Signal was digitized at 24-bit resolution at a sampling rate of 1024 Hz and referenced to a common mode sense active electrode forming a monopolar channel. Electrodes were placed above and below and at the outer canthi of each eye in order to record horizontal and vertical electrooculogram.

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Offline data analyses were completed using Brain Vision Analyzer (Brain Products, Munich, Germany). Linked mastoids served as the reference, and data were band-pass filtered from .1 to 30 Hz. Ocular correction was used to remove eye movements, and a trial-wise artifact rejection was applied based on a 50+ mV step between trials or 75 mV difference within trials. Baseline correction was applied with reference to a 200-ms pre-stimulus window. ERPs were stimulus-locked to onset of standard and deviant tones, and the MMN was computed at Fz as a difference wave (duration deviant minus standard). Standard tones were scored with respect to the time window of the deviant, at 180-230 ms for MMN-D.

Statistical Analyses

IBM SPSS Statistics (Version 26.0, IBM, Armonk, NY) was used for statistical analyses, save for paired t-tests which were computed using the following packages in the R programming environment (R Core Team, 2020): magittr (Bache & Wickham, 2014) and dplyr (Wickham, François, Henry, & Muller, 2020). Differences between groups in demographic factors were assessed using one-way analyses of variance (ANOVAs) and chi-square goodness of fit tests.

Group Differences. Differences in MMN amplitude, schizotypy, and cognition between cases, siblings, and never-psychotic participants were examined using an ANOVA, with group as the between-subjects factor and MMN-D amplitude as the dependent variable. Tukey post-hoc analyses were used to query hypothesized differences between each of these groups. Finally, paired samples t-tests were performed in which MMN amplitude in cases was compared to MMN amplitude in their matched biological sibling, using a subset of the present sample restricted by the size of the sibling group.

Clinical Relationships. Associations of MMN with cognition were assessed using bivariate Pearson correlations. A hierarchical regression model was then employed to examine

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group differences in this relationship. MMN amplitude was the dependent variable, with cognition, dummy-coded group (cases, siblings, or NP), and their interaction entered sequentially into the model. A non-significant cognition X group interaction term indicated the relationship between MMN and cognitive functioning did not differ systematically by group (Donaldson et al., 2020; Sheffield et al., 2017). The same analysis plan was carried out for each of the three schizotypy subscales, which were centered prior to forming interaction terms.

Results

Group Differences

MMN Amplitude. A significant main effect of group on MMN-D ($F(2, 532)=10.39$, $p<.001$) emerged; Tukey HSD post-hoc analyses revealed that MMN-D in cases was significantly reduced compared to NP (Cohens $d=.37$, $p=.000$; as described in a similar sample in Donaldson et al., 2020). MMN-D was lower in cases than in siblings (Cohens $d=.48$, $p=.002$), and siblings did not differ from NP (Cohens $d=.12$, $p=.64$)¹. Group differences in MMN-D amplitude are displayed in **Figure 1**. Paired t-tests confirm that MMN-D amplitude differs significantly between cases and their paired siblings ($t(46)=2.83$; $p=.007$). Group differences in MMN-D amplitude remained controlling for age, gender, and race ($p<.001$).

Clinical and Cognitive Measures. Significant differences emerged in cognition ($F(2,477)=56.33$, $p<.001$). Tukey HSD follow-up analyses revealed that cognition in cases differed from NP (Cohens $d=.99$, $p<.001$) and siblings (Cohens $d=.82$, $p<.001$), while siblings did not differ from NP (Cohens $d=.23$, $p=.46$). Group differences in cognitive functioning are presented in **Table 2**. Group comparisons in schizotypal traits revealed significant group effects

¹Siblings of cases with schizophrenia spectrum (N=34) and other psychotic disorders (N=31) did not differ from each other ($p=.94$) and accordingly were entered as a single group in further analyses.

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on dimensions of mistrust ($F(2,464)=40.85, p<.001$), detachment ($F(2,470)=35.12, p<.001$), and eccentric perceptions ($F(2,477)=29.54, p<.001$). Tukey HSD follow-up analyses revealed that schizotypal traits were elevated in cases compared to siblings (mistrust Cohens $d = .64$, detachment Cohens $d = .86$, eccentric perceptions Cohens $d = .71$, all $p<.001$) and NP (mistrust Cohens $d = .85$, detachment Cohens $d = .76$, eccentric perceptions Cohens $d = .65$, all $p<.001$), while siblings did not differ significantly from NP (mistrust Cohens $d = .23$, detachment Cohens $d = .11$, eccentric perceptions Cohens $d = .04$; **Table 2**). Overall group differences in cognition and schizotypy remained when controlling for age, gender, and race (all $p<.001$).

Relationships of MMN with cognitive and clinical measures.

Bivariate correlations revealed significant associations between lower MMN amplitude and worse cognitive functioning ($r=-.23, p=.000$), greater mistrust ($r=.14, p=.003$), greater detachment ($r=.10, p=.040$), and greater eccentric perceptions ($r=.11, p=.013$). Results are displayed in **Figure 2**. Follow-up hierarchical regression analyses show that these relationships did not differ based on group status (case vs sibling vs NP; **Table 3**).

Discussion

It is unknown whether MMN deficits are a marker of genetic and environmental vulnerabilities to psychosis or a consequence of psychotic disorders themselves. Studies of MMN in siblings of people with psychotic disorders have had small sample sizes, and did not examine associations of the component with clinical or cognitive correlates. The present study sought to address this gap in the literature, and to characterize MMN amplitude and its relationships across levels of familial risk for psychosis. By comparing MMN amplitude in cases with diverse psychotic disorders, their siblings, and never-psychotic subjects, we were able to highlight the specificity of the deficit in MMN amplitude to individuals affected by psychosis,

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revealing intact MMN amplitude in siblings. Furthermore, this study sought to extend relationships between MMN and both cognitive and clinical functioning in psychotic disorders across the continuum of familial psychosis risk. By evaluating relationships between MMN and clinical variables across these groups, we revealed associations between MMN amplitude and overall cognitive functioning dimensionally across the spectrum of psychosis risk. We further provide first evidence regarding dimensional associations between MMN and schizotypal traits.

The finding that MMN amplitude was not reduced in siblings of those with psychotic disorders replicates some previous studies (Ahveninen et al., 2006; Bramon et al., 2004; Hong, Moran, Du, O'Donnell, & Summerfelt, 2012; Magno et al., 2008), including one recent meta-analysis (Erickson et al., 2016), while contradicting others (Jessen et al., 2001; Michie, Innes-Brown, Todd, & Jablensky, 2002; Şevik et al., 2011). Our inclusion of siblings of individuals with a diverse array of psychotic disorders extends these previous null findings to a broader sample. These results are consistent with earlier work in bipolar disorder (Hall et al., 2009) and in one small mixed psychosis sample (Ranlund et al., 2016). Taken together, these results do not support the notion that MMN amplitude offers a genetically-transmitted marker for psychotic disorders broadly defined.

Both cognition and schizotypy were associated with MMN amplitude, a relationship which did not differ based on group status. While this finding echoes previous work revealing relationships between MMN and cognition in psychosis samples (Baldeweg et al., 2004; Näätänen, Kujala, Kreegipuu, Carlson, Escera, Baldeweg, & Ponton, 2011; Näätänen et al., 2014; Donaldson et al., 2020; Hermens et al., 2010; Kaur et al., 2011; Thompson et al., 2005), the extension of this relationship to unaffected siblings is novel. This analysis was based on 535 observations, but may be underpowered due to the relatively small size of the sibling group

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($n=65$); thus, the present results would benefit from replication with a larger group of first-degree relatives of individuals with psychosis. Similarly, to our knowledge no prior studies have characterized relationships of MMN amplitude with schizotypal traits. The present study not only illustrates that MMN is associated with symptoms of schizotypy, in line with prior work demonstrating reduced MMN amplitude in SPD (Niznikiewicz et al., 2009), but also shows these relationships are consistent across cases with psychosis, their siblings, and comparison subjects. Furthermore, results demonstrate relationships with MMN amplitude across domains of schizotypal traits. Mistrust and eccentric perception scales are strongly correlated with measures of paranoia and psychoticism, respectively (Cicero et al., 2019). The present findings echo previous associations between MMN and positive symptoms in psychotic disorders (Donaldson et al., 2020; Fisher et al., 2011; Fisher et al., 2008, 2012; Light et al., 2015). Conversely, the detachment subscale correlates with measures of social anhedonia and negative schizotypy (Cicero et al., 2019), replicating some less consistent associations between MMN and negative symptoms (Baldeweg et al., 2004; Javitt, Shelley, & Ritter, 2000) and extending these relationships dimensionally across familial risk.

These results suggest that MMN amplitude tracks clinical and cognitive functioning across levels of vulnerability to psychosis. Indeed, it is possible that prior findings of decreased MMN in siblings did not reflect vulnerability per se, but attenuated symptoms and/or cognitive impairment in siblings in these samples. Several prior studies suggest that cognitive deficits are present to an attenuated degree in first-degree relatives of psychotic disorders (Arts, Jabben, Krabbendam, & Van Os, 2008; Bromet et al., 1996; Hill et al., 2013; Russo et al., 2017; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, MacDonald III, & Carter, 2006; Touloupoulou et al., 2005; Zalla et al., 2004). It may therefore be the case that while the MMN

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does not carry sufficient power as a candidate biomarker for familial risk, reduction in MMN amplitude may reflect attenuated symptoms or clinical high risk for psychosis. Consistent with this interpretation, there is emerging evidence that MMN is in fact reduced in individuals at clinical high risk for psychosis (Perez et al., 2014; Erickson, Ruffle, & Gold, 2016; Atkinson, Michie, & Schall, 2011) and may predict conversion to psychotic disorders (Perez et al., 2014; Bodatsch et al., 2011; Shaikh et al., 2012; Naatanen et al., 2015). Further work is needed in this area to tease apart relationships of MMN amplitude with clinical, cognitive, and genetic risk factors in order to fully evaluate its effectiveness as a candidate marker of genetic risk for psychotic illness.

A strength of the present study is our large transdiagnostic sample of individuals with psychotic disorders. Furthermore, our inclusion of siblings of both schizophrenia spectrum and other psychotic disorders allowed us to investigate a broad range of vulnerabilities, a novel addition to the literature. One limitation of this study is the small sibling group. However, paired analyses limited to individuals with psychotic disorders and their own relatives confirm our overall group results are likely robust to the impact of unequal sample sizes. Further, the overall lack of cognitive impairment in our sibling group is contrary to several prior studies (Arts, Jabben, Krabbendam, & Van Os, 2008; Bromet et al., 1996; Hill et al., 2013; Russo et al., 2017; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, MacDonald III, & Carter, 2006; Touloupoulou et al., 2005; Zalla et al., 2004) which may have impacted the present findings. Finally, future studies utilizing approaches such as twin designs and molecular genetic analyses will be an important step in yielding deeper knowledge regarding these relationships.

In sum, the present study demonstrates associations of MMN amplitude with cognition and schizotypal traits across levels of familial risk for psychotic disorders. Results extend

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previous examinations restricted primarily to siblings of individuals with schizophrenia-spectrum disorder to risk for psychotic disorders broadly defined. While no significant reductions of MMN amplitude were observed in siblings of individuals with psychotic disorders in the present sample, associations with clinical and cognitive variables emerged across study groups. This pattern of effects may imply that MMN amplitude reductions emerge as a result of, or in conjunction with, clinical features associated with psychosis. Such findings carry important implications for the utility of MMN amplitude as an indicator of inherited risk, and suggest that this component may be best conceptualized as a marker for transdiagnostic psychotic symptoms, negative symptoms, and cognitive dysfunction, rather than risk for psychosis per se.

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Tables & Figures

Table 1. Sample Characteristics

	Cases	Siblings	NP	Cases v. Siblings v. NP
	N (%)	N (%)	N (%)	
Gender	—	—	—	$X^2=10.85^{**}$
Female	91 (42.3)	40 (65.6)	110 (44.4)	—
Male	124 (57.7)	21 (34.4)	138 (55.6)	—
Race ¹	—	—	—	$X^2=17.19^{**}$
Asian	5 (2.3)	1 (1.5)	2 (.8)	—
African American	25 (11.4)	9 (13.8)	14 (5.6)	—
White	168 (76.8)	53 (81.5)	223 (89.2)	—
More than one race	9 (4.1)	0 (0)	4 (1.6)	—
Other/Unknown	12 (5.5)	2 (3.1)	7 (2.8)	—
Ethnicity	—	—	—	$X^2=4.1$
Hispanic/Latino	30 (13.9)	6 (9.8)	20 (8.1)	—
Antipsychotic Medication	126 (58.3)	1 (1.6)	4 (1.6)	$X^2=217.80^{***}$
	Mean (SD)	Mean (SD)	Mean (SD)	Cases v. Siblings v. NP
Age (years)	47.9 (8.6)	49.1 (9.0)	50.5 (8.8)	$F=5.04^{**}$

¹Due to the small number of individuals identifying as a race other than Caucasian, group differences were examined as white vs other. *Indicates a significant difference ($p<.05$) between groups; **Indicates $p<.01$; *** $p<.001$.

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Table 2. Cognition & Schizotypy Across Groups

	Cases	Siblings	Neighbors	Group Comparison
	Mean (SD)	Mean (SD)	Mean (SD)	
Cognition ¹	-.44(1.0)	.26(.67)	.41(.67)	F=56.33***
Case v NP	—	—	—	p=.000**
Case v Sibling	—	—	—	p=.000**
Sibling v NP	—	—	—	p=.460
Mistrust	6.32(5.2)	3.41(3.8)	2.60(3.3)	F=40.85***
Case v NP	—	—	—	p=.000**
Case v Sibling	—	—	—	p=.000**
Sibling v NP	—	—	—	p=.418
Detachment	6.70(4.2)	3.38(3.5)	3.77(3.5)	F=35.13***
Case v NP	—	—	—	p=.000**
Case v Sibling	—	—	—	p=.000**
Sibling v NP	—	—	—	p=.779
Eccentric Perceptions	3.21(3.4)	1.40(1.2)	1.45(1.7)	F=29.54***
Case v NP	—	—	—	p=.000**
Case v Sibling	—	—	—	p=.000**
Sibling v NP	—	—	—	p=.980

¹Overall cognition score derived factor analytically from scores on a large neuropsychological functioning battery. NP = never psychotic; *p<.05; **p<.01; ***p<.001.

Table 3. Hierarchical Regression

Model	Predictors	R ²	ΔR ²	p value
Cognition	Cognition	.05	.05	.000**
	Group	.07	.01	.038*
	Interaction	.07	.01	.220
Mistrust	Mistrust	.02	.02	.003**
	Group	.04	.02	.021*
	Interaction	.04	.01	.277
Detachment	Detachment	.01	.01	.040*
	Group	.03	.02	.004**
	Interaction	.04	.01	.318
Eccentric Perceptions	Eccentric Perceptions	.01	.01	.013*
	Group	.04	.02	.003**
	Interaction	.04	.01	.321

¹Cases vs Siblings vs Neighbors; *p<.05, **p<.01

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Figure 1. ERP Waveforms and Scalp Distributions

Note. Duration mismatch negativity (MMN) amplitude in cases, siblings, and never psychotic comparison subjects. MMN amplitude scored as difference wave at electrode Fz. Highlighted area represents mean amplitude utilized in analyses. NP = never psychotic; ms = milliseconds; μV = microvolts.

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Figure 2. Relationships of MMN Amplitude with Cognition and Schizotypy

Note. Scatterplots illustrating associations between duration mismatch negativity (MMN-D) and measures of overall cognition score (A) and schizotypal symptoms, including eccentric perceptions (psychoticism) (B), detachment (C), and mistrust (C). Effects are illustrated across cases, siblings, and never-psychotic comparison subjects (neighbors).

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