

Associations of Mismatch Negativity With Psychotic Symptoms and Functioning Transdiagnostically Across Psychotic Disorders

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Mismatch negativity (MMN) amplitude has been widely shown to be diminished in schizophrenia and, more recently, in other psychotic disorders. Although there is considerable evidence linking MMN reduction to cognitive and functional deficits in schizophrenia, there is little evidence of associations with specific psychotic symptoms. Further, it is unclear if MMN reductions relate to specific symptoms, cognitive, and functional deficits transdiagnostically across different psychotic disorders. The present study examines MMN amplitude in a large cohort of cases diagnosed with psychotic disorders including schizophrenia and schizoaffective disorder ($N = 116$); bipolar disorder and major depressive disorder ($N = 75$); and other psychotic disorders ($N = 25$), as well as individuals with no psychotic disorder diagnoses ($N = 248$). Furthermore, we examined the association of MMN with symptoms, cognitive functioning, and real-world functioning to determine whether these relationships differ by diagnosis. Results showed that MMN amplitude was reduced in cases overall compared to never-psychotic individuals, with no differences between psychotic disorders. Furthermore, there were transdiagnostic associations of reduced duration MMN (MMN-D) with worse auditory hallucinations ($r = .14$) and disorganization ($r = .14$), frequency MMN (MMN-F) with real-world functioning ($r = .20$) and episodic memory ($r = -.22$), and both components with executive functioning (MMN-D: $r = -.17$; MMN-F: $r = -.15$). Our findings relating MMN reductions with cognitive and real-world functioning replicate earlier research in schizophrenia and extend these relationships to other psychotic disorders. Furthermore, our correlations with MMN-D are consistent with computational modeling research and theoretical proposals that view MMN reduction, cognitive dysfunction, and psychotic symptoms as reflecting underlying predictive coding deficits. However, differences in relationships with MMN-F suggest that additional work is warranted on this topic.

General Scientific Summary

Mismatch negativity (MMN) amplitude has been shown to be diminished in schizophrenia and other psychotic disorders. We show that MMN reductions are associated with worse auditory hallucinations and disorganization, as well as cognitive and real-world functioning, transdiagnostically across psychotic disorders. These findings highlight the importance of MMN in tracking both symptom and functioning related impairment across psychosis-spectrum illnesses. Furthermore, associations with duration MMN are in line with theoretical and computational modeling research that attributes MMN reductions, cognitive dysfunction, and psychotic symptoms to underlying predictive coding deficits, although importantly frequency MMN findings could be argued to contradict a straightforward interpretation within the predictive coding model.

Keywords: schizophrenia, hallucinations, ERPs, mismatch negativity, predictive coding

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It is well-established that mismatch negativity (MMN) amplitude is reduced in schizophrenia (Umbricht & Krljes, 2005) and occasionally seen to be reduced in other psychotic disorders (Erickson, Ruffle, & Gold, 2016). The MMN is an event-related potential (ERP) elicited by the presentation of a deviant stimulus differing in a property such as duration (MMN-D) or frequency (MMN-F) from a more frequently presented standard stimulus (Näätänen, 1995). It is most commonly studied in auditory paradigms, though it can also be elicited in other sensory modalities (Pazo-Alvarez, Cadaveira, & Amenedo, 2003). Although there is considerable evidence linking reduced MMN amplitude to cognitive and real-world functioning in schizophrenia (Erickson et al., 2016; Kim et al., 2014; Light & Braff, 2005; Light et al., 2015; Toyomaki et al., 2008; Wynn, Sugar, Horan, Kern, & Green, 2010), it is unclear whether MMN reduction is associated with specific psychotic symptoms, and if these relationships exist across different psychotic disorders. Here, we use a large, well-characterized cohort of individuals with diverse psychotic disorders as well as never psychotic (NP) individuals to examine MMN relationships with symptoms and functioning in schizophrenia and across psychotic disorders.

Although several theoretical and computational models have linked MMN deficits to psychotic symptom dimensions (Adams, Stephan, Brown, Frith, & Friston, 2013; Wacongne, Changeux, & Dehaene, 2012), empirical studies provide largely null findings. A recent meta-analysis showed that across studies, the MMN bears no significant relationship to either positive or negative symptoms (Erickson et al., 2017). However, a majority of the studies in this meta-analysis examined broadly defined heterogeneous symptoms dimensions, such as total severity of positive symptoms, rather than more narrowly defined symptoms such as hallucinations and delusions which may yield different findings. One large study (from the Consortium on Genetics in Schizophrenia) by Light and colleagues (2015) showed a small but significant correlation between MMN and positive symptoms, $r = .08$, $p < .05$, however, this study also did not examine which specific positive symptoms were driving this association. The few additional studies that show an association between MMN and positive symptoms do so in very circumscribed samples, such as acutely psychotic patients or patients with persistent auditory hallucinations (Fisher et al., 2011; Fisher, Labelle, & Knott, 2008, 2012), nonprodromal adolescents reporting psychotic experiences (Murphy et al., 2013), and ketamine-induced psychosis in healthy individuals (Heekeren et al., 2008; Umbricht, Koller, Vollenweider, & Schmid, 2002).

Overall, it remains unclear to what extent MMN reductions relate to specific psychotic symptom domains across psychosis-spectrum illness. Psychotic symptoms are present not only in schizophrenia but also in other psychotic disorders (American Psychiatric Association, 2013), suggesting that any relationship between MMN amplitude and symptoms may be transdiagnostic. Though some studies have reported diminished MMN in schizophrenia compared to bipolar disorder (Erickson et al., 2016; Kaur et al., 2011), this finding is not consistent (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007) and based predominantly on relatively small sample sizes. Finally, no study to our knowledge has examined the relationship between MMN and psychotic symptoms across the full range of psychotic disorders. In contrast to the scarcity of studies relating MMN deficits to specific psychotic symptoms, there is more research showing associations between

MMN in schizophrenia and poor work/daily functioning, social functioning, and broad cognitive impairment (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Erickson et al., 2016; Javitt, Doneshka, Grochowski, & Ritter, 1995; Kim et al., 2014; Light & Braff, 2005; Light et al., 2015; Toyomaki et al., 2008; Wynn et al., 2010). However, like psychotic symptoms, cognitive and functional impairments are seen across a range of psychotic disorders (Green, 2006; Latalova, Prasko, Diveky, & Velartova, 2011), and their potential transdiagnostic relationships with MMN remain largely unexplored.

Thus, we investigate reduction in MMN-D and MMN-F amplitude as transdiagnostic markers of specific symptom and functioning dimensions in psychotic disorders broadly defined. To accomplish this, we use a large, well-characterized sample of psychosis-spectrum and never-psychotic individuals and a dimensional approach recommended by the National Institute of Mental Health research domain criteria (RDoC) initiative. The goals of the present study are threefold. First, we seek to replicate the expected MMN deficit in schizophrenia and examine to what degree this deficit is present in cases with other psychotic disorders; we hypothesize that MMN-D and MMN-F will be reduced in cases overall compared to NP individuals. Second, we seek to clarify links between these MMN measures and psychotic symptoms. In line with research showing that the predictive coding framework can be used to explain MMN (Baldeweg, 2007; Garrido et al., 2008; Garrido, Kilner, Stephan, & Friston, 2009; Heilbron & Chait, 2018; Stefanics, Heinzle, Horváth, & Stephan, 2018; Wacongne et al., 2012), MMN reduction in schizophrenia (McCleery et al., 2019; Rentzsch, Shen, Jockers-Scherübl, Gallinat, & Neuhaus, 2015; Wacongne, 2016), and psychotic symptoms (Adams et al., 2013; Horga, Schatz, Abi-Dargham, & Peterson, 2014), we hypothesize that reduced MMN-D and MMN-F amplitude will be associated with worse psychotic symptoms and that this relationship will be transdiagnostic in nature. Finally, we examine the relationship of MMN measures with real-world functioning and neurocognitive deficits. Among neurocognitive deficits, we focus on executive functioning, episodic memory, and processing speed, because they tend to be most impaired in schizophrenia (Barch, 2005; Reichenberg et al., 2009). In line with previously discussed literature, we expect that reduction in MMN-D and MMN-F amplitude will be associated with deficits in daily functioning and cognitive abilities across psychotic disorders.

Method

Participants

Study participants were assessed at 20-year follow up of the Suffolk County Mental Health Project (Bromet et al., 2011), an epidemiological study of first-admission psychosis. This sample included cases with a history of schizophrenia and schizoaffective disorder (SZ group; $n = 116$); mood disorder with psychosis (i.e., bipolar disorder and major depressive disorder; MDP group; $n = 75$); and other psychotic disorders (drug-induced psychosis, psychotic disorders not otherwise specified, and other psychoses; OPD group; $n = 25$). These groupings are based on previous research with this sample showing a distinction in course and

severity of SZ versus MDP (Kotov et al., 2013; Reichenberg et al., 2009), and our aim to compare SZ to OPD. Also, 248 NP individuals were recruited from zip codes where cases resided and matched on demographics. Additional information regarding study inclusion is presented in the [online supplemental material](#).

Clinical, Functional, and Neuropsychological Measures

Clinical measures were obtained for each participant concurrent with the MMN task and included the structured clinical interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 2002) as well as scales for the assessment of positive (SAPS; Andreasen, 1984) and negative (SANS; Andreasen, 1989) symptoms, psychosocial functioning as assessed through the Social and Occupational Functioning Assessment Scale (Rybarczyk, 2011), and occupational functioning assessed through consensus ratings of staff psychiatrists (Schwartz et al., 2000). Symptoms were scored into four factor-analytically derived scales: reality distortion, disorganization, avolition, and inexpressivity (Kotov et al., 2016). We also specifically examined auditory hallucinations given their putative link in the predictive coding framework. Although several neuropsychological tests were administered (see the [online supplemental material](#)), we focused analyses on tests of executive functioning (Stroop; Trenerry, Crosson, DeBoe, & Leber, 1989; Trails B; Reitan, 1955), processing speed (Trails A; Reitan, 1955), episodic memory (visual and auditory; indexed by Verbal Paired Associates and Visual Reconstruction components of Wechsler Memory Scale—revised; Wechsler, 1987), and overall academic abilities (as measured by the Wide Range Achievement Test-3; Wilkinson, 1993). Antipsychotic medication status for each participant was determined by asking participants to bring their pill bottles or a list of all medications and dosages. See the [online supplemental material](#) information for further details regarding measures.

Task

Stimuli were a total of 2,458 tones presented every 500 ms at 78 dB with 10-ms rise/fall. Tones consisted of 80% standard tones with a 50-ms duration at 633 Hz and 20% deviant tones, out of which 10% percent deviated in duration (100 ms; MMN-D) and 10% deviated in frequency (1000 Hz; MMN-F) from the standard. Because the MMN is elicited in a preattentive manner, tones were presented in the background while participants completed a picture/word matching task (described in detail by Mathalon, Roach, & Ford, 2010).

Psychophysiological Data Acquisition, Preprocessing, and Analyses

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

Brain Vision Analyzer (Brain Products, Munich, Germany) was used for offline data analyses. Data were referenced to linked

mastoids and a bandpass filter of .1 to 30 Hz was applied. Eyeblinks were removed using ocular correction, and artifacts were rejected trial-wise based on a step of 50 μ V between trials or a 75.0 μ V difference within a trial. ERPs were stimulus-locked to onset of tones, corrected relative to a 200-ms prestimulus baseline, and the MMN was computed as two difference waves: duration deviant minus standard (MMN-D) and frequency deviant minus standard (MMN-F). Duration deviants were quantified at 180–230 ms and frequency deviants at 110–160 ms from tone onset at electrode Fz, based on grand average waveforms. Standard tones were scored separately at the same time windows with respect to deviant type.

Statistical analyses were performed using IBM SPSS Statistics (Version 24.0, IBM, Armonk, NY). Differences between groups in age, gender, race/ethnicity, and use of antipsychotic medication were examined using independent samples *t* tests and chi-square goodness of fit tests. Though MMN-D and MMN-F have been found to be impaired in psychotic disorders (Umbricht & Krljes, 2005), the level of impairment has been shown to differ for the two. Hence, we conducted all analyses separately using MMN-D and MMN-F as dependent variables.

First, to examine MMN amplitude differences between cases and NP, we conducted an analysis of variance (ANOVA) with group (cases vs. NP) as the between-subjects factor and MMN-D/MMN-F as the dependent variable, followed up by an a priori comparison of MMN amplitude across diagnoses (SZ, OPD, MDP) utilizing a one-way ANOVA. Next, we examined whether reductions in MMN amplitude were associated with psychotic symptom dimensions transdiagnostically across cases. To do so, we conducted bivariate correlations of symptom dimensions with MMN-D and MMN-F, in cases only due to a lack of variance in psychotic symptoms in the NP group. Where correlations were significant with either MMN-D or MMN-F, Fishers *r* to *z* was used to examine the significance of differences between correlations with MMN-D versus MMN-F. Symptoms correlating significantly with MMN amplitude in cases were retained for hierarchical regression analyses, with psychotic symptoms, diagnosis, and their interaction predicting MMN-D or MMN-F amplitude. A nonsignificant Symptom \times Diagnosis interaction implied the presence of a transdiagnostic relationship that did not differ by diagnosis (Sheffield et al., 2017). Finally, this hierarchical regression analysis was repeated controlling for demographic variables and medications when diagnostic groups differed on them. We similarly tested hypotheses regarding the transdiagnostic relationship of MMN-D and MMN-F reductions with occupational, social, and neuropsychological functioning across cases. Finally, in instances in which bivariate correlations were significant in both cases and the NP group, similar hierarchical regression analyses were conducted with functioning as the first-level, followed by group (cases vs. NP), and the Group \times Functioning interaction term.

Results

Sample Characteristics

Sample demographics and clinical ratings are presented in [Table 1](#). Groups (cases vs. NP) did not differ in gender but differed in age, race, ethnicity, antipsychotic medication, and severity of symptoms, as well as functional impairment. Diagnostic groups

Table 1
Clinical and Demographic Factors

Factor	Cases						NP		Diagnosis		Group	
	SZ		MDP		OPD							
	<i>n</i> (%)	<i>M</i> (<i>SD</i>)	<i>n</i> (%)	<i>M</i> (<i>SD</i>)	<i>n</i> (%)	<i>M</i> (<i>SD</i>)	<i>n</i> (%)	<i>M</i> (<i>SD</i>)	SZ vs. MDP vs. OPD	Group comparison	Cases vs. NP	Group comparison
Gender	—	—	—	—	—	—	—	—	$\chi^2 = 10.3^{**}$	—	$\chi^2 = .19$	—
Female	43 (37.1)	—	42 (56.0)	—	6 (24.0)	—	110 (44.4)	—	—	—	—	—
Male	72 (62.1)	—	33 (44.0)	—	19 (76.0)	—	138 (55.6)	—	—	—	—	—
Race ^a	—	—	—	—	—	—	—	—	$\chi^2 = 15.1$	—	$t = 3.100^{**}$	—
Asian	4 (3.4)	—	0 (0)	—	1 (4.0)	—	2 (.8)	—	—	—	—	—
African American	13 (11.2)	—	4 (5.3)	—	6 (24.0)	—	14 (5.6)	—	—	—	—	—
White	85 (73.3)	—	66 (88.0)	—	17 (68.0)	—	221 (89.1)	—	—	—	—	—
More than one race	8 (6.9)	—	1 (1.3)	—	0 (0)	—	4 (1.6)	—	—	—	—	—
Other/unknown	6 (5.2)	—	4 (5.3)	—	1 (4.0)	—	7 (2.8)	—	—	—	—	—
Ethnicity	—	—	—	—	—	—	—	—	$\chi^2 = 2.5$	—	$\chi^2 = 4.01^*$	—
Hispanic/Latino	20 (17.2)	—	8 (10.7)	—	2 (8.0)	—	20 (8.1)	—	—	—	—	—
Antipsychotic medication	93 (80.2)	—	27 (36.0)	—	6 (24.0)	—	4 (1.6)	—	$F = 32.3^{***}$	—	$t = 17.40^{***}$	—
Age (years)	—	47.3 (7.9)	—	48.4 (9.0)	—	49.0 (10.9)	—	50.5 (8.8)	$F = .63$	—	—	$t = -3.186^{***}$
Symptoms	—	—	—	—	—	—	—	—	—	—	—	—
Avolition	—	17.5 (8.6)	—	8.4 (7.7)	—	7.8 (7.6)	—	2.9 (3.9)	$F = 33.9^{***}$	—	—	$t = 15.83^{***}$
Inexpressivity	—	10.5 (10.5)	—	2.9 (5.2)	—	3.3 (5.2)	—	.84 (2.6)	$F = 20.0^{***}$	—	—	$t = 10.18^{***}$
Reality distortion	—	7.8 (9.9)	—	.55 (1.7)	—	1.4 (2.5)	—	.08 (.50)	$F = 24.4^{***}$	—	—	$t = 8.6^{***}$
Disorganization	—	6.6 (7.4)	—	2.2 (4.0)	—	4.0 (4.9)	—	.92 (2.4)	$F = 11.8^{***}$	—	—	$t = 8.7^{***}$
Occupational functioning	—	4.2 (1.4)	—	2.8 (5.2)	—	2.8 (2.1)	—	1.9 (1.8)	$F = 18.2^{***}$	—	—	$t = 9.4^{***}$
Psychosocial functioning	—	3.5 (.72)	—	2.2 (1.0)	—	2.1 (1.2)	—	1.1 (.39)	$F = 62.3^{***}$	—	—	$t = 9.5^{***}$

Note. NP = never psychotic; SZ = schizophrenia spectrum; MDP = mood disorder with psychosis; OPD = other psychotic disorders.

^a Because of the small number of individuals identifying as non-White, group differences were examined as White versus other.

* $p < .05$. ** $p < .01$. *** $p < .001$.

(SZ vs. MDP vs. OPD) differed demographically only in gender and antipsychotic medication usage, as well as in symptoms and functioning; across measures, the SZ group showed the most impairment.

Group Differences in MMN Amplitude

Examination of group differences (Figure 1) revealed a significant effect of group on MMN-F, $F(1, 462) = 8.60$, $p = .004$, and MMN-D, $F(1, 46) = 16.114$, $p < .001$, such that cases showed lower amplitude than NP; however, there was no significant dif-

ference among cases by diagnosis—MMN-D: $F(2, 215) = 1.82$, $p = .169$, and MMN-F: $F(2, 215) = .82$, $p = .441$.

Links Between MMN Amplitude, Clinical, and Functioning Measures

More severe disorganization and auditory hallucinations were associated with reduced MMN-D amplitude in cases (Table 2; Figure 2A). These symptoms were not associated with MMN-F and the differences between symptom correlations with MMN-D and MMN-F were significant (hallucinations $p = .015$, disorgani-

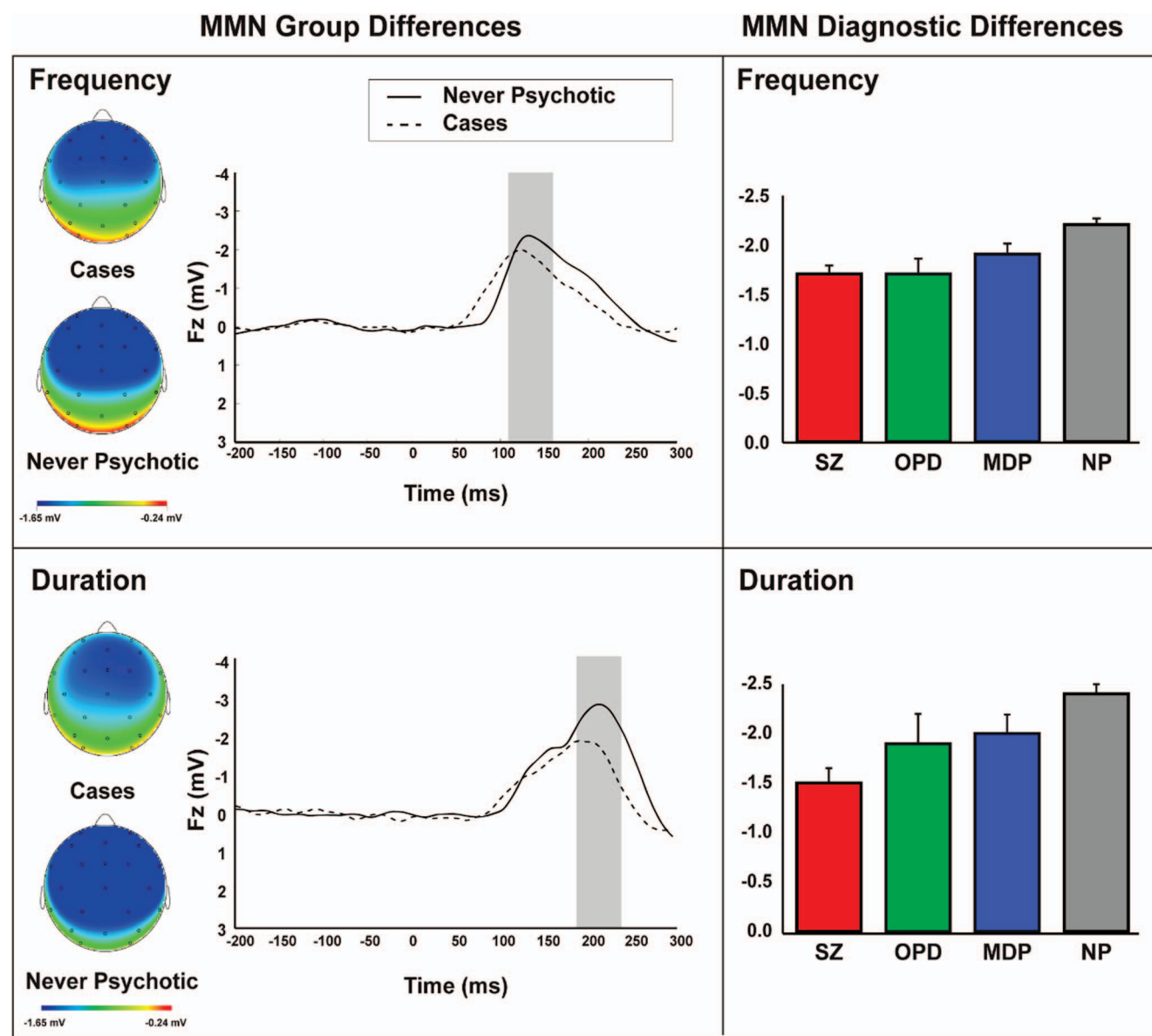


Figure 1. In the top panel, scalp distributions and waveforms depict mismatch negativity (MMN) amplitude in response to frequency deviants in cases versus never psychotic groups (left), whereas bar graphs depict MMN amplitude for each diagnostic group: schizophrenia spectrum (SZ), mood disorder with psychosis (MDP), other psychotic disorders (OPD), and never psychotic (NP). The bottom panel shows corresponding effects for MMN in response to duration deviants. See the online article for the color version of this figure.

Table 2
Clinical Correlations

Variable	Cases		NP	
	Frequency MMN	Duration MMN	Frequency MMN	Duration MMN
Symptoms				
SAPS-P	-.09	.08	—	—
Auditory hallucinations	-.03	.14*	—	—
SAPS-D	.01	.14*	.00	.04
SANS-A	.10	.10	.05	.05
SANS-E	.04	.05	-.02	.06
Real-world functioning				
Occupational functioning	.20*	.10	.01	.07
Social/occupational functioning	-.13	-.12	-.04	-.06
Neuropsychological functioning				
Executive functioning	—	—	—	—
Stroop	-.15*	-.17*	-.21*	-.26*
Trails B	.15*	.15*	.19*	.08
Processing speed	—	—	—	—
Trails A	.12	.03	.14*	.14*
Episodic memory	—	—	—	—
Visual	-.22*	-.11	-.21*	.16*
Auditory	-.15*	-.04	-.14*	-.20*
Cognitive/academic ability	—	—	—	—
WRAT 3	-.16*	-.11	-.07	-.03

Note. NP = never psychotic; MMN = mismatch negativity; SAPS-D = Scale for the Assessment of Positive Symptoms - disorganization subscale; SAPS-P = Scale for the Assessment of Positive Symptoms - psychotic symptom subscale; SANS-A = Scale for the Assessment of Negative Symptoms - avolition subscale; SANS-E = Scale for the Assessment of Negative Symptoms - inexpressivity subscale; WRAT 3 = Wide Range Achievement Test-3. Italicized values survive correction for multiple comparisons, calculated using a false discovery rate of 10% applied to each domain (symptoms, real-world functioning, and neuropsychological functioning) separately for cases and for neighbors.

* $p < .05$.

zation $p = .048$; [Supplement Table S1](#) in the online supplemental material). Hierarchical regression analyses showed that these relationships did not vary by diagnosis as indicated by the nonsignificant Diagnosis \times Symptom interactions ([Table 3](#)). The relationship with disorganized symptoms and auditory hallucinations remained significant and marginally significant, respectively, after controlling for gender and antipsychotic usage ([Supplement Table S3](#) in the online supplemental material).

Worse occupational functioning was associated with reduced MMN-F amplitude ([Table 2](#); [Figure 2B](#)) in cases. Relationships did not vary by diagnosis, as evidenced by the nonsignificant Diagnosis \times Functioning interaction ([Table 4](#)) and remained significant after controlling for gender and antipsychotic usage ([Supplement Table S2](#) in the online supplemental material). Social functioning was marginally associated with MMN-F ($p = .057$) and MMN-D ($p = .085$) amplitude (see [Table 2](#)); however, because this association was not statistically significant regression analyses were not performed.

Worse performance on measures of executive functioning, episodic memory, and processing speed were associated with reduced MMN-F and MMN-D amplitude ([Table 2](#)) in both cases and NP groups. When examined in cases, these relationships did not vary by diagnosis ([Tables 3](#) and [4](#)) and largely remained significant after controlling for gender and antipsychotic medications ([Supplement Tables S2](#) and [S3](#) in the online supplemental material).

These relationships did not vary by group, indicating that they extend to normal populations ([Supplement Table S4](#) in the online supplemental material). In no case did differences between correlations of real-world or neuropsychological functioning and MMN-D versus MMN-F prove to be significant ([Supplement Table S1](#) in the online supplemental material).

Discussion

Though MMN deficits have been linked through theoretical and computational models to symptoms such as hallucinations and delusions ([Adams et al., 2013](#); [Wacongne et al., 2012](#)), there is a relative lack of empirical evidence linking MMN reductions to such dimensions. Using a well-characterized and large cohort that included a variety of psychotic disorders, we examined the hypotheses that MMN-D and MMN-F would be reduced not only in schizophrenia but across diagnoses, and that this reduction in amplitude would be associated with psychotic symptoms and functioning across psychosis-spectrum illness. Our results showed that MMN-D and MMN-F amplitude were reduced in cases overall, and this reduction did not differ by diagnosis. We further observed transdiagnostic associations of MMN-D with symptom domains, MMN-F with functional outcomes, and both MMN components with worse cognitive functioning.

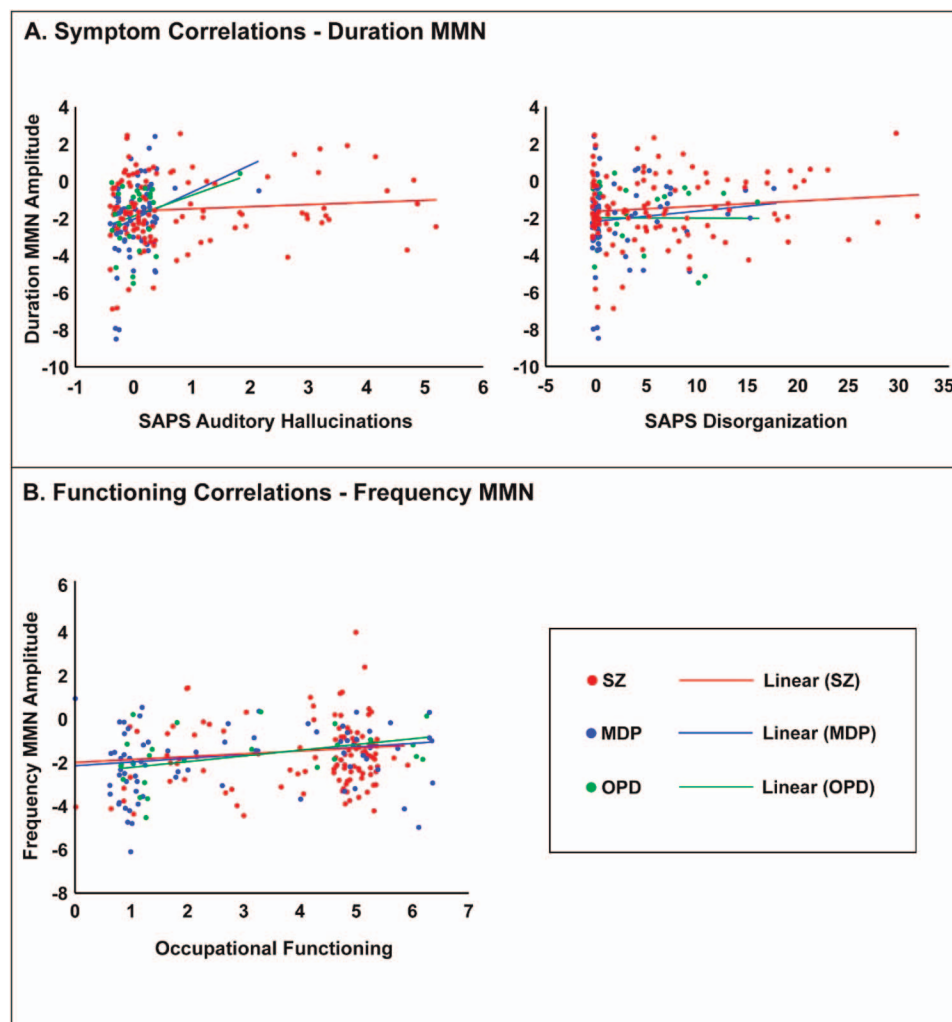


Figure 2. (A) Correlations across cases (different colors for different diagnostic groups) between duration mismatch negativity (MMN-D) and auditory hallucinations (left) and disorganization (right), in which higher scores represent increased frequency/severity. (B) Correlations between frequency mismatch negativity (MMN-F) and occupational functioning. A randomized jitter ($-.4, .4$) was added to each ordinal value on the x-axis for display purposes in order to demonstrate overlapping data points. SAPS = Scale for the Assessment of Positive Symptoms; SZ = schizophrenia spectrum; MDP = mood disorder with psychosis; OPD = other psychotic disorders; NP = never psychotic. See the online article for the color version of this figure.

Our study replicates relationships between MMN reduction and auditory hallucinations seen in acutely psychotic or hallucinating individuals with schizophrenia in a small sample (Fisher et al., 2008, 2011, 2012), as well as MMN-D reduction and positive symptoms more broadly in larger samples (Light et al., 2015). Importantly, our study extends these findings to a more heterogeneous sample transdiagnostically across psychotic disorders. These findings are contrary, at face value, to the lack of association between positive symptoms and MMN amplitude seen in a meta-analysis of previous studies (Erickson et al., 2017). However, it is important to note that this meta-analysis examined relationships with overall psychotic symptom score, rather than specific positive symptoms. Furthermore, this study collapsed across MMN-F and MMN-D components, possibly obscuring the differential relationships that these components bear with symptoms and functioning,

as seen in our sample. Although we expected MMN reductions measured via both MMN components to be related to psychotic symptoms, the presence of a differential relationship may be a reflection of differences in the neuroanatomical substrates that support the generation of these components. MMN-F has been shown to correlate primarily with voxels in core auditory regions, whereas MMN-D has been shown to be related to activation in the somatomotor networks broadly (Lee et al., 2017). Furthermore, MMN-F was found to engage default mode regions, whereas MMN-D is related to activation in attention networks (Lee et al., 2017). Although further research is needed to explore these differences, evidence showing that MMN-D and MMN-F may arise from different cortical processes may provide clues into why we see differential correlations of symptoms and functioning with these two components.

Table 3
Hierarchical Regression—Duration MMN

Model	Predictors	R^2	ΔR^2	p value
Symptoms				
SAPS-D	SAPS-D	.02	.02	.041*
	Diagnosis	.03	.01	.407
	Interaction	.03	.00	.705
Auditory hallucinations	Auditory hallucinations	.02	.02	.039*
	Diagnosis	.03	.01	.448
	Interaction	.04	.01	.371
Cognition				
Trails B	Trails B	.02	.02	.031*
	Diagnosis	.03	.01	.482
	Interaction	.03	.00	.823
Stroop	Stroop	.03	.03	.014*
	Diagnosis	.04	.01	.407
	Interaction	.04	.00	.963

Note. SAPS-D = Scale for the Assessment of Positive Symptoms - disorganization subscale.

* $p < .05$.

The relationship between MMN reduction and symptoms in our sample is in line with previous computational modeling research and the predictive coding framework. Within this framework, the auditory MMN is hypothesized to result from a failure to predict sensory input (i.e., deviant tone) and thereby suppress prediction error (Friston, 2005; Garrido et al., 2009). Specifically, when subsequent events are repeated (e.g., standards in case of the MMN oddball paradigm), there is a suppression of prediction error and the MMN is reduced; however, it appears on the presentation of the unpredicted deviant stimulus (Garrido et al., 2009). Hence, a relative decrease in neural response to deviant auditory stimuli in psychotic disorders may derive from weak prior expectations set by standard stimuli. Although some studies have suggested that hallucinations may arise from strong precision of priors (Powers, Mathys, & Corlett, 2017), studies within this framework also suggest that auditory hallucinations arise from decreased precision of prior expectations and increased precision of sensory information (e.g., inner speech) which shifts the posterior toward the sensory information, resulting in maladaptive inferences (Sterzer et al., 2018). Although this framework provides one among many ways of conceptualizing psychotic symptoms and the MMN, our findings suggest predictive coding dysfunction as a common substrate that does not respect nosological categories.

Interestingly, in the present sample we also found that reduced auditory MMN-D was associated with disorganized symptoms. The predictive coding framework has been used to explain not only perceptual aberrations but also cognitive symptoms such as delusions. Hence, it is possible that the association in the present sample is driven by a common underlying aberrant inferential mechanism that can apply to disorganized thought, language, and behavior. In addition, reduced MMN-D and MMN-F amplitudes were associated with worse cognitive functioning, specifically episodic memory and executive functioning. This is consistent with the notion that a predictive coding framework can explain not only a range of low-level perceptual processes but also high-level cognitive abilities (Spratling, 2016). Computational modeling studies show that predictive coding can simulate several cognitive

functions such as categorization, the impact of context on perception and behavioral control, recall and reasoning regarding conceptual knowledge, and task-switching (Spratling, 2010, 2016).

Interestingly, we find that not all of our cognitive measures are associated with MMN reductions. Although MMN reductions correlated with tasks of executive functioning (Stroop and Trails B) and episodic memory (visual and auditory), they did not correlate with Trails A. It is possible this pattern of relationships is because MMN generation involves a higher level of cognition, rather than processing speed as measured by Trails A. Furthermore, Knowles & colleagues (Knowles, David, & Reichenberg, 2010) showed processing speed abnormalities in psychosis to be moderated by antipsychotic medication dosage, suggesting that these effects may not solely represent deficits underlying the disorder, and in fact may also be impacted by medication usage. This may explain the lack of correlation in the present sample between reduced MMN and scores on measures of cognitive processing speed. Finally, our study showed that MMN-F reductions were associated with worse social and occupation functioning in cases, replicating a large number of previous studies in schizophrenia (Erickson et al., 2016; Kim et al., 2014; Light & Braff, 2005; Light et al., 2015; Toyomaki et al., 2008; Wynn et al., 2010) and extending these findings to the broad spectrum of psychotic illnesses.

Overall, the present study uses a large and well-characterized sample to demonstrate relationships between MMN amplitude reduction and psychotic symptoms. The presence of a large heterogeneous cohort allowed us to examine transdiagnostic effects while also maximizing power to detect smaller effects. These findings are consistent with previously theorized relationships between MMN and symptoms in the predictive coding framework (Adams et al., 2013; Wacongne, 2016). However, it should be noted that the predictive coding framework is one among several

Table 4
Hierarchical Regression—Frequency Mismatch Negativity

Model	Predictors	R^2	ΔR^2	p value
Functioning				
Occupational functioning	Functioning	.04	.04	.004**
	Diagnosis	.04	.00	.696
	Interaction	.04	.00	.595
Cognition				
Auditory EM	Verbal Paired	.02	.02	.03*
	Diagnosis	.03	.00	.781
	Interaction	.05	.02	.084
Visual EM	Visual EM	.05	.05	.002**
	Diagnosis	.05	.00	.812
	Interaction	.06	.01	.312
Trails B	Trails B	.02	.02	.036*
	Diagnosis	.02	.00	.907
	Interaction	.02	.00	.857
Stroop	Stroop	.04	.04	.038*
	Diagnosis	.02	.00	.870
	Interaction	.03	.00	.796
WRAT 3	WRAT 3	.03	.03	.018*
	Diagnosis	.04	.00	.797
	Interaction	.04	.01	.286

Note. EM = episodic memory; WRAT 3 = Wide Range Achievement Test-3.

* $p < .05$. ** $p < .01$.

other theoretical frameworks used to explain MMN. According to the model adjustment hypothesis, the MMN is generated when the current auditory input deviates from a learned regularity or a memory trace of previous standard inputs and captures attention automatically (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001). The alternative adaptation hypothesis posits that the MMN results from a delayed N1 response to standard inputs, attenuated due to similarity with preceding standard inputs, reflecting adaptation of auditory cortex neurons (Jääskeläinen et al., 2004). The predictive coding framework unifies these competing hypotheses by proposing that repetition of standard events leads to suppression of prediction error and the disappearance of the MMN, and that prediction error is generated when there is a mismatch between the predicted and the actual sensory input (Garrido et al., 2009). Furthermore, computational modeling research shows that this framework has been shown to parsimoniously explain both the generation of the MMN and psychotic symptoms (Wacongne, 2016).

Finally, several limitations in our study should be addressed in future research. Though our sample of cases was large in total ($N = 216$), the sizes of our diagnostic groups varied ($SZ = 116$, $MDP = 75$, $OPD = 25$), suggesting a need for future studies with similar sample sizes across groups. It is also important to note that associations with MMN in the present sample are small. This is in line with a substantial literature showing that variability in neuroimaging measures accounts for a small percentage of variance in clinical phenotypes (Patrick et al., 2013; Paulus & Thompson, 2019). Although this small effect size indicates that MMN alone may not be sufficiently strong in making useful single-event predictions, such effects may be consequential in the long-term and may be informative about the etiology of psychotic disorders (Funder & Ozer, 2019; Paulus & Thompson, 2019). It may also be the case that this association is one that represents a specific phenotypic pathway of dysfunction, requiring either large, heterogeneous sample sizes or more targeted recruitment; such as the recruitment of actively hallucinating patients by Fisher and colleagues (Fisher et al., 2008, 2011, 2012). In addition, while predictive coding theory lends preliminary support to the utility of the MMN as an index of prediction error, this theory cannot in its current form explain differences in correlates between MMN-D and MMN-F. Future research should focus on examining these patterns more closely, to provide a more complete understanding of the practical and theoretical significance of this component, as well as the utility of this theoretical framework.

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