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Pitch and Duration Mismatch Negativity and Premorbid Intellect in the First Hospitalized Schizophrenia Spectrum

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Mismatch negativity (MMN) is a robustly abnormal brainwave in chronically ill schizophrenia that has generated interest as a disease presence biomarker. Reports of MMN reduction in first-episode schizophrenia have been equivocal, raising uncertainty about its reduction at first psychotic break. Here we tested 29 schizophrenia-spectrum participants under 1 year from their first hospitalization for psychosis and 40 age-, gender-, parental socioeconomic status-, and Wechsler Adult Intelligence Scales III Information-matched healthy controls on both pitch and duration MMN. Participants performed a visual checkerboard tracking task while standard (1 kHz, 50 ms, 80%), pitch-deviant (1.2 kHz, 50 ms, 10%) and duration-deviant (1 kHz, 100 ms, 10%) tones were presented over headphones (75 dB) and EEG was recorded. Independent component analysis was used to remove eye movements and visual stimulus processing activity. Groups did not differ in pitch MMN or duration MMN amplitudes. Smaller pitch and duration MMN amplitudes were associated with lower estimates of premorbid intellect in all participants and independently with greater positive symptoms in first hospitalized schizophrenia. Overall MMN reduction was not present in these relatively high functioning individuals at the first episode of schizophrenia, and therefore is not a good disease presence biomarker for this sample. Future research is warranted to determine the degree of MMN reduction at the first episode of psychosis across a greater range of cognitive impairment, the utility of MMN as an indicator of risk or diagnosis, and its role for understanding pathophysiological mechanisms in emerging psychosis.

Key words: biomarker/psychosis/first episode/sensory memory/IQ matching

Introduction

Mismatch negativity (MMN) is a small negative EEG deflection elicited outside the focus of attention for changes in stimuli from past patterns. Typically it is elicited by rare sounds differing physically (pitch, duration, loudness, location, etc.) from repeated standard tones. Whether MMN reflects an active comparison of current events with past events,[1] a prediction of what should occur,[2] or increased sensory responses to rare deviants than to repeated sensory adapted stimuli[3] is hotly debated, but not germane to its clinical utility as a possible schizophrenia biomarker. MMN has attracted interest as a biomarker because it is highly abnormal in chronically ill schizophrenia, with effect sizes (Cohen's *d*) near 1,[4] is relatively easy and inexpensive to measure, and passively acquired.

A biomarker can be used for risk prediction and for screening, diagnosis, or tracking disease progression.[5] When used for diagnosis, the putative biomarker should be present in those afflicted, and thus if MMN is a disease presence biomarker, it must obligatorily be reduced at first hospitalization for schizophrenia. The findings in the first episode of schizophrenia literature, however, are equivocal. It is important to note that we are solely dealing with individuals who have experienced psychosis. We make no claim about the MMN prior to psychosis onset and its putative role as a potential screening biomarker. Our question is whether MMN is reduced at the known

first episode of psychosis and to what characteristics it might be related.

Here we review pitch and duration MMN findings in the entire first-episode schizophrenia-spectrum and first-episode psychosis (mixed schizophrenia-spectrum and affective-spectrum) literature. In studies that examined only schizophrenia-spectrum psychosis participants within 1 year of their first episode or first hospitalization (table 1), no study reported reduced pitch MMN, with the largest effect a trend-level finding of a small effect size (d = 0.34).[17] In studies of mixed first-episode psychosis under 1 year from hospitalization (table 2), there was no evidence of pitch MMN reduction. Based on all extant studies, pitch MMN reduction does not appear suitable as a diagnostic biomarker at first episode.

The results for duration MMN reduction are variable. Among studies that examined only schizophrenia-spectrum psychosis participants within 1 year of their first episode or first hospitalization (table 1), most showed reduction. However, effect sizes ranged from negative (d = −0.42, patients showing a larger MMN than controls) to large (d = 1.47, a deficit larger than in long-term schizophrenia). An important clue to what might be at least partially driving the variability in duration MMN findings was provided by a follow-up analysis by Umbricht et al.[9] Although no duration MMN reduction was observed in the entire group of first-episode schizophrenia (FESz) subjects, patients who had not attended college had smaller MMNs than controls and first break patients that did. This suggests that academic achievement and, by inference, premorbid intelligence quotient (IQ) might be important variables associated with the equivocal duration MMN findings. In studies of the early course of the schizophrenia spectrum (including subjects >1 y postbreak), large effects were reported (table 1). In studies of mixed first-episode psychosis under 1 year from hospitalization (table 2), 2 reported duration MMN reduction, but did not control for IQ or education, while the one that did[25] reported no significant duration MMN reduction at Fz. In summary, there is some evidence for duration MMN reductions at the first break of schizophrenia, but results are equivocal, and may be related to intellectual deficits.

It is unclear whether MMN reflects disease presence (risk, screening, and diagnosis) or progression (pathology subsequent to psychosis onset). The 3 studies with a longitudinal component show no significant reduction at first episode, with MMN deficits developing shortly thereafter. Salisbury et al[10] replicated no reduction of pitch-deviant MMN at first hospitalization in 20 first hospitalized schizophrenia participants partially overlapping with Salisbury et al[6]; but patients with the most impaired MMN had the greatest gray matter loss in left auditory cortex (Heschl's gyrus). Pitch MMN showed significant reductions at follow-up ~1.5 years later, associated with progressive left auditory cortex gray matter volume loss. All comparisons were made between groups matched for estimated premorbid IQ. Devrim-Üçok et al[11] reported no significant reductions in pitch MMN in 30 FESz participants (d = 0.0), although they saw MMN reductions in the postacute phase 1–9 months later (d = 0.43). Premorbid IQ was not reported, but groups were matched for years of education. Kaur et al[25] studied 15 affective-spectrum and 12 schizophrenia-spectrum subjects. When this mixed first-episode psychosis group and healthy controls were matched for cognitive functioning, no significant MMN reductions at first episode were found at Fz, and progressive MMN reductions with course were detected. Consistent with possible progressive MMN decline in the immediate postbreak period, largest effect sizes for MMN reduction were observed in samples including patients over 1 year from first psychosis (table 1).

MMN reduction at first episode is associated with poor educational achievement[9] and loss of cortical gray matter in auditory cortex.[10] These data suggest that, although the group mean of MMN may be normal, there are likely certain FESz subjects with reduced MMNs, auditory cortex gray matter loss, and poor functioning and achievement. (Parenthetically, chronic schizophrenia patients that did not finish high school show the greatest MMN impairments, particularly for duration MMN[26]; see their figure 4.) It is imperative to determine whether MMN is sensitive to psychosis presence or rather tracks progressive perionset brain gray matter loss. The purpose of this study was to examine pitch and duration MMN in a new sample of first-episode schizophrenia-spectrum patients and healthy controls to assess whether MMN was reduced in first-episode patients and showed associations with specific symptoms and estimates of premorbid intellect.

Methods

Subjects

Subjects had no history of a learning disability, including dyslexia, special education, childhood treatment for attention deficit disorder/attention deficit hyperactivity disorder, any infectious or neurological disease affecting the central nervous system, any loss of consciousness >20 minutes and/or traumatic brain injury with sequelae, electroconvulsive therapy, drug or alcohol detox or dependence within the last 5 years, intravenous drug abuse ever, or seizure disorder. Subjects had a minimum 9th grade education and an estimated IQ >85 as ascertained from chart notes. All subjects had normal hearing as assessed with audiometry, defined as within 30 dB nHL, no more than 15 dB difference between ears at 500, 1000, and 1500 Hz.

Patients were recruited from consecutive inpatient admissions at McLean Hospital less than 1 year from their first inpatient admission for psychosis (the mean since

Table 1. Summary of First-Episode Schizophrenia-Spectrum MMN Studies

Study	Time of Testing	*N* (SzS/HC)	Pitch MMN Reduction	Duration MMN Reduction	IQ or Education Controlled	Effect Size at Fz/Fcz (Cohen's *d*)	
						Pitch	Dur.
Tested < 1-y FH							
Salisbury et al[6,a]	<1-y FH	21/27	N		Y	0.09	
Oknina et al[7]	At FH	25/14	N		Y		
Oades et al[8,b]	At FH	28/22		Y	N		1.0
Umbricht et al[9,c]	<6-mo FH	26/39	N	N	N	0.33	0.25
(College subsample)[c]	<6-mo FH	12/39	N	N	Y	−0.10	−0.42
(No college subsample)[c]	<6-mo FH	14/39	Y	Y	N	0.67	0.96
Salisbury et al[10,a]	<6-mo FH	20/32	N		Y	−0.008	
Devrim-Üçok et al[11]	At FH	30/34	N		Y	0.0	
Magno et al[12]	<3-mo FH	12/27	N	N	U	−0.36	−0.24
Kaur et al[13,d]	<1-y FE	18/18		Y	N		1.47
Bodatsch et al[14]	At FE	33/67	N	Y	U	0.11	0.45
Hsieh et al[15]	<1-y FE	32/56		Y	N		0.50
Mondragón-Maya et al[16,f]	At FH	20/23	N		Y	0.17	
Nagai et al[17]	<1-y FE	20/22	T	Y	Y	0.34	0.80
Tested < 2-y FH							
Kaur et al[18,d]	First or second episode	20/20		Y	N		1.40
Higuchi et al[19,e]	<2-y FH	20/20		Y	U		1.60
Higuchi et al[20,e]	<2-y FH	19/19		Y	U		1.20
Solís-Vivanco et al[21,f]	<2-y FH	20/23		Y	Y		1.14

Note: FE, first episode; FH, first hospitalization; HC, healthy controls; IQ, intelligence quotient; MMN, mismatch negativity; SzS, schizophrenia spectrum; Y, yes; N, no; T, trend level; U, unreported. Effect sizes: pitch, pitch MMN (left side); dur., duration MMN (right side). Negative values indicate patient samples had *larger* responses than healthy subjects.

[a–e]Studies with matching superscripts present data from overlapping samples. Caution should be used to avoid "double weighting" effect sizes.

[c]Umbricht et al performed secondary analyses based on whether FHSz had or had not attended college. Note the strong effect on group differences.

[f]Subject overlap between studies is unclear.

Table 2. Summary of First-Episode Mixed Psychosis Spectrum MMN Studies

Study	Time of Testing	*N* (SzS/APS/HC)	Pitch MMN Reduction	Duration MMN Reduction	IQ or Education Controlled	Effect Size at Fz/Fcz (Cohen's *d*)	
Tested < 1-y FH						Pitch	Dur.
Valkonen-Korhonen et al[22]	<1-y FH	21/4/19	N		Y	0.05	
Hermens et al[23,a]	<1-y FE	9/8/17		Y	N		0.86
Atkinson et al[24,b]	At FE	U 10/20		Y	N	Short	1.00
						Long	1.52
Kaur et al[25,a]	U	27/33/30		N	Y	0.39	

Note: Abbreviations are explained in the first footnote to table 1. APS, affective psychosis spectrum.
[a]Subject overlap between matching superscripts.
[b]Diagnostic breakdown unknown, all psychotic subjects included. Both short- and long-duration deviants were tested.

first hospitalization was 9.6 [14.5] wk, the median was 2.9 wk). All patients received a research diagnosis based on the Structured Clinical Interview for the Diagnostic and Statistical Manual (SCID)—Patient edition and/or chart review. The first hospitalized schizophrenia-spectrum group (FHSz, n = 29) included schizophrenia (17 paranoid, 1 disorganized, 2 undifferentiated), schizophreniform disorder (2), delusional disorder (1), and schizoaffective disorder (depressed subtype 1, bipolar subtype 5). Fourteen FHSz received >6 months follow-up diagnoses. Two FHSz were unmedicated. The remaining FHSz were on antipsychotic medications (the mean lifetime exposure to antipsychotic medications was 9.5 [14.5] wk, the median was 2.7 wk). Psychiatrically healthy control subjects (HC, n = 40) were recruited from newspaper advertisements, and screened using the SCID Non-Patient Edition P and SCID II. No HC reported an Axis I psychiatric disorder in a first-degree relative. The McLean Hospital IRB approved this study. After complete description of the study, written informed consent was obtained. Subjects were paid $15/h for their participation. All participants performed the Information, Vocabulary, Digit Span, and Digit Symbol Subtests of the Weschsler Adult Intelligence Scales—3rd Edition (WAIS III), and the Mini-Mental State Examination (MMSE). Patient symptoms were rated on the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS).

Procedure

Subjects were presented binaural tone pips. Standard tones (1 kHz, 75 dB, 50 ms duration, 10 ms rise/fall) were presented on 80% of trials. Pitch-deviant tones (1.2 kHz, 75 dB, 50 ms duration, 10 ms rise/fall) and duration deviants (1 kHz, 75 dB, 100 ms duration, 10 ms rise/fall) were presented on 10% of trials each. Tones were presented with a 300 ms stimulus onset asynchrony while subjects performed a visual task. Subjects sat 1 m from a monitor on which was displayed a checkerboard with green and red squares, and instructed to ignore the tones, pay attention to the checkerboard, and make a right index finger keypad response to checkerboard color reversals (asynchronous, range: 430–1500 ms). Tracking performance was monitored, and subjects were encouraged to maintain the task.

EEG Recording

EEG activity was recorded from 60 scalp sites and the nose tip using a 64-channel cap (custom designed ElectroCap International sintered Ag–AgCl caps using the 10–10 system). Activity was recorded continuously using SynAmps and Scan Acquire (Neuroscan/Compumedics USA). The right mastoid served as the recording reference, except for 2 bipolar electro-oculogram channels. Two electrodes medial to the right eye, one above and one below, monitored vertical eye movements and blinks. Electrodes at the outer canthi of the eyes monitored horizontal eye movements. The forehead served as ground. Electrode impedances were below 5 kOhms. The EEG bandpass was 0.10 (6 dB/octave roll-off) to 100 Hz (24 dB/octave roll-off). EEG was digitized at 500 Hz.

EEG Preprocessing

EEG data were preprocessed using custom MATLAB scripts utilizing the extended infomax independent component analysis (ICA) algorithm[27] in EEGLAB.[28] EEG data were bandpassed (0.2–100 Hz), notch filtered (58–62 Hz), and segmented into 800 ms epochs centered on auditory stimulus onset. Bad channels and epochs containing unique nonstereotyped artifacts were removed. The ICA components capturing stereotyped artifacts were excluded.[29,30] ICA was also employed to remove residual checkerboard visual activity. Segments containing artifacts were eliminated (±50 μV).

MMN Processing

Data was re-referenced to the nose tip. Standard, pitch-deviant, and duration-deviant waveforms were

constructed by averaging reprojected EEG epochs (−50 to 350 ms relative to tone onset). MMN was visualized by subtraction of the standard waveform from the deviant waveform. Pitch MMN was measured over 120–220 ms. Duration-deviant MMN was measured over 170–270. These intervals were based on the grand-averaged morphology, and captured the entire MMN ERP and the mastoid and frontal peaks well.[6,31] MMNs were subjected to current source density (CSD) analysis to show source–sink topography. Interpolation was done using spherical splines, with the order of splines set to 4, the maximum degree of Legendre polynomials set to 10, and a default lambda of 1e-5.

Statistical Analyses

Demographics and basic cognitive measures were compared between groups with *t* tests and chi-squared analyses where appropriate. Pitch MMN and duration MMN were analyzed in 2 ways. First, to maximize the probability of finding a significant difference, a *t* test between groups at Fz was conducted. Second, a regional analysis of left and right frontocentral sites was performed (F1/2, FC1/2, and C1/2). Correlations between MMNs at Fz and basic cognitive measures and symptoms were conducted using Pearson's *r*. Results were considered significant at $P \leq .05$.

Results

Groups were matched for age, gender, handedness, parental socioeconomic status (SES), and WAIS III Information scaled scores. (Five patients refused to complete neuropsychological testing.) Consistent with their illness, patients has significantly lower SES and scored significantly lower on the MMSE and WAIS III Digit Span and Digit Symbol, with trend-level impairment on Vocabulary (table 3). Note that WAIS III Information and Vocabulary were above average in FHSz, whereas working memory subtests of Digit Span and Symbol-Digit were below average (mean WAIS scaled scores are 10, SD is 3). Clinical measures are presented in table 4. Amplitudes at each site tested and mastoids are presented in table 5.

Pitch MMN

Both groups showed MMN to pitch deviants with frontocentral voltage topography and CSD topography consistent with bilateral temporal generators (figure 1). Groups did not differ in pitch MMN at Fz (table 5). FHSz were slightly *larger* than HC (small effect size, $d = -0.10$). Frontocentral analysis likewise revealed no significant group differences ($F_{1,67} = 0.25$, $P = .62$, partial $\eta^2 = 0.004$).

Duration MMN

Both groups showed MMN to duration deviants with frontocentral voltage topography and CSD topography consistent with bilateral temporal generators (figure 2), albeit of a slightly different orientation that pitch MMN (figure 1). Groups did not differ in duration MMN at Fz (table 5). FHSz were slightly smaller than HC (small effect size, $d = 0.11$). Frontocentral analysis likewise revealed no significant group differences ($F_{1,67} = 0.38$, $P = .54$, partial $\eta^2 = 0.006$).

Table 3. Demographics and Cognitive Measures

	FHSz	HC	Statistics
Group size	29	40	
Age	25.0 (8.6)	24.9 (7.4)	$t_{67} = 0.06$, $P = .95$
Gender	20M/9F	29M/11F	$\chi^2 = 0.17$, $P = .68$
Handedness	0.60 (0.51)	0.76 (0.30)	$t_{62} = 1.58$, $P = .16$
SES	3.3 (1.4)	1.9 (0.6)	$t_{65} = 5.31$, ***P* < .001**
PSES	1.5 (0.8)	1.7 (0.9)	$t_{62} = 0.75$, $P = .46$
Education (y)	13.1 (2.0)	15.0 (1.4)	$t_{65} = 4.50$, ***P* < .001**
MMSE	28.5 (1.4)	29.4 (0.7)	$t_{62} = 3.21$, ***P* = .002**
WAIS Information	12.7 (2.5)	13.1 (2.2)	$t_{62} = 0.77$, $P = .44$
WAIS Vocabulary	13.0 (3.0)	14.3 (2.8)	$t_{62} = 1.77$, $P = .08$
WAIS Digit Span	9.6 (2.2)	12.4 (2.3)	$t_{62} = 4.81$, ***P* < .001**
WAIS Digit Symbol[a]	7.5 (2.3)	11.5 (2.7)	$t_{61} = 6.09$, ***P* < .001**

Note: Values are mean (SD) unless otherwise indicated. WAIS scaled scores. Significant differences between groups are highlighted in bold. PSES, parental socioeconomic status; FHSz, first hospitalized schizophrenia; HC, healthy controls; MMSE, Mini-Mental State Examination; SES, socioeconomic status; WAIS, Weschsler Adult Intelligence Scales.
[a]WAIS Digit Symbol data was lost for 1 HC. Variations in *df* reflect missing values.

Table 4. Clinical Measures

PANSS Total	78.3 (16.3)
PANSS Positive	19.7 (4.4)
PANSS Negative	17.9 (7.6)
PANSS Composite	1.8 (9.1)
PANSS Thought Disturbance	10.7 (3.7)
PANSS Paranoia/Belligerence	8.1 (3.0)
PANSS General	36.5 (8.4)
PANSS Anergia	10.6 (4.0)
PANSS Activation	4.8 (1.3)
PANSS Depression	10.3 (4.0)
SAPS	8.7 (4.2)
SANS	9.8 (4.2)
Medication (CPZ equivalents)	267.1 (170.3)

Note: Values are mean (SD). CPZ, chlorpromazine; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

Cognitive and Clinical Correlations

Among all subjects, there was a significant association between WAIS Information scaled score and both pitch ($r = -.31$, $P = .012$) and duration MMN at Fz ($r = -.31$, $P = .014$, figure 3). The more negative (larger) the MMN, the more positive (greater) the Information scaled score. In patients, significant associations were observed between

pitch and duration MMN at Fz and PANSS and SAPS positive symptom factors, and the PANSS Paranoia/Belligerence factor (see *r* values in figure 4), where more severe symptoms were associated with smaller MMNs. These associations remained after controlling for premorbid intellect.

Sampling Simulation and Premorbid IQ Effects

To determine whether unmatched premorbid IQ could affect the findings, we performed a median split for WAIS III Information scaled scores in each group (median = 13 for both groups) and compared the lower FESz to the higher HC. WAIS Info was significantly reduced (FHSz: 10.5 [2.2], HC: 15.1 [0.7], $t_{25} = 7.8$, $P < .001$). Pitch MMN was not significantly reduced at Fz (FHSz: −1.0 [2.1], HC: −2.0 [1.0], $t_{25} = 1.6$, $P = .118$), but duration MMN was (FHSz: −1.6 [1.1], HC: −3.1 [1.7], $t_{25} = 2.6$, $P < .016$).

Table 5. MMN Amplitudes

Site	FHS	HC	*t* Test	Effect Size (*d*)
Pitch				
F1	−1.8 (2.2)	−1.6 (1.7)	$t_{67} = 0.53$, $P = .60$	−0.10
Fz	−1.9 (2.2)	−1.7 (1.7)	$t_{67} = 0.42$, $P = .68$	−0.10
F2	−1.8 (2.2)	−1.7 (1.7)	$t_{67} = 0.37$, $P = .71$	−0.05
FC1	−2.0 (2.4)	−1.7 (1.8)	$t_{67} = 0.57$, $P = .57$	−0.14
FC2	−1.9 (2.3)	−1.7 (1.9)	$t_{67} = 0.38$, $P = .71$	−0.09
C1	−1.8 (2.3)	−1.5 (1.7)	$t_{67} = 0.74$, $P = .46$	−0.15
Cz	−1.9 (2.3)	−1.7 (1.8)	$t_{67} = 0.42$, $P = .67$	−0.10
C2	−1.9 (2.3)	−1.7 (1.9)	$t_{67} = 0.40$, $P = .69$	−0.09
M1	0.8 (1.3)	1.2 (1.2)	$t_{67} = 1.34$, $P = .19$	0.32
M2	0.8 (1.6)	1.2 (1.2)	$t_{67} = 1.19$, $P = .24$	0.28
Duration				
F1	−2.1 (1.9)	−2.3 (1.7)	$t_{67} = 0.54$, $P = .59$	0.11
Fz	−2.2 (1.9)	−2.4 (1.7)	$t_{67} = 0.46$, $P = .65$	0.11
F2	−2.3 (1.9)	−2.4 (1.7)	$t_{67} = 0.33$, $P = .75$	0.06
FC1	−2.3 (1.9)	−2.6 (1.9)	$t_{67} = 0.64$, $P = .52$	0.16
FC2	−2.3 (2.0)	−2.6 (1.8)	$t_{67} = 0.64$, $P = .53$	0.16
C1	−2.0 (2.0)	−2.3 (1.9)	$t_{67} = 0.62$, $P = .54$	0.15
Cz	−2.1 (2.0)	−2.6 (1.9)	$t_{67} = 0.88$, $P = .38$	0.26
C2	−2.2 (2.0)	−2.6 (1.9)	$t_{67} = 0.83$, $P = .41$	0.21
M1	1.2 (1.0)	1.1 (1.5)	$t_{67} = 0.32$, $P = .75$	−0.08
M2	1.3 (1.2)	1.2 (1.8)	$t_{67} = 0.20$, $P = .84$	−0.07

Note: Values are mean μV (SD). FHS, first hospitalized schizophrenia; HC, healthy control; MMN, mismatch negativity.

Discussion

Neither pitch MMN nor duration MMN were reduced in FHSz within 1 year of first hospitalization (most within 3 wk), when matched for estimated premorbid IQ with HC. Despite significant symptoms and cognitive impairment in Digit Span and Digit Symbol performance, MMN remained within normal limits in this above-average sample. Pitch and duration MMN were smallest in FHSz showing the greatest positive symptoms and paranoia. Hence, the underlying pathology related to symptom severity is reflected in pathophysiology of MMN generators. However, in this group overall, FHSz MMN distributions overlapped HC; no patient was smaller (more positive) than the worst HC (figure 3).

The association between premorbid intellect and MMN amplitude may provide an explanation for inconsistent findings of reduced duration MMN in FESz; our median split simulation, where FHSz had a 4.4 point reduction in WAIS Information scaled scores, showed reduced duration but not pitch MMN, similar to the existing aggregate MMN findings (table 1). This begs the question of upon what measure(s) to match groups. Educational achievement, social and occupational functioning, and cognitive functioning are all affected by the disease, leading to the so-called "matching fallacy."[32] Cognitive deficit remains a strong and perhaps the best predictor of functional outcome,[33–36] even at first hospitalization.[37] If the disease

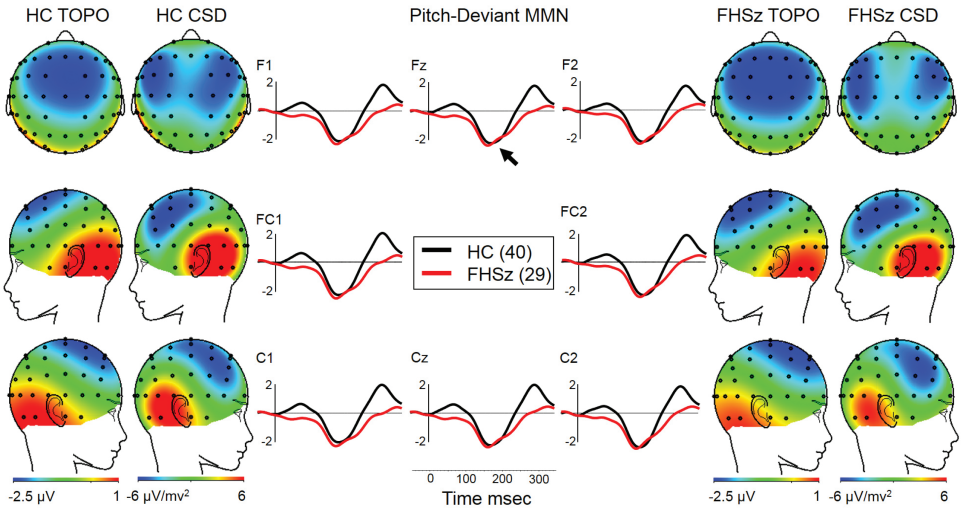

Fig. 1. Pitch-deviant MMN (arrow at Fz in middle panel). Voltage topography is highly similar in both groups (HC TOPO and FHSz TOPO) and CSD maps are consistent in both groups with bilateral temporal lobe generators. CSD, current source density; FHSz, first hospitalized schizophrenia; HC, healthy controls; MMN, mismatch negativity; TOPO, topography.

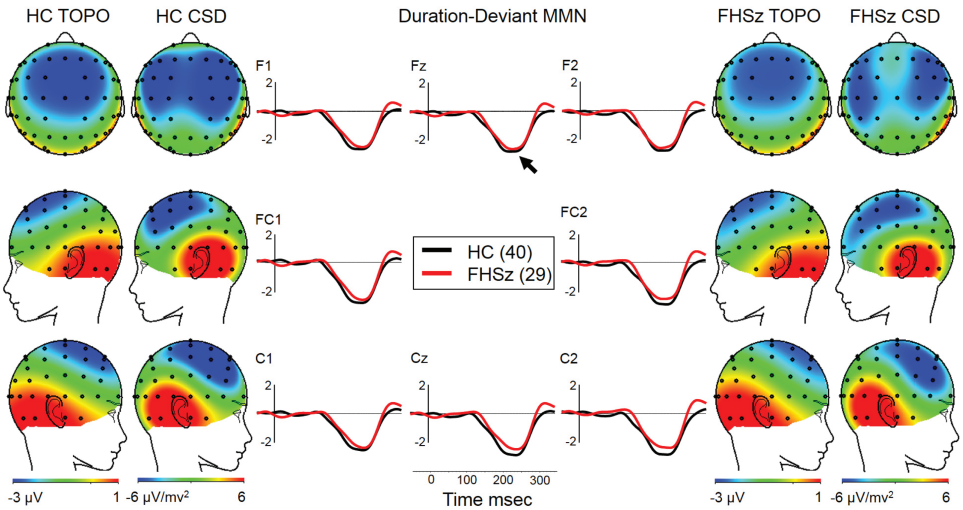

Fig. 2. Duration-deviant MMN (arrow at Fz in middle panel). Voltage topography is highly similar in both groups (HC TOPO and FHSz TOPO) and CSD maps are consistent in both groups with bilateral temporal lobe generators. CSD, current source density; FHSz, first hospitalized schizophrenia; HC, healthy controls; MMN, mismatch negativity; TOPO, topography.

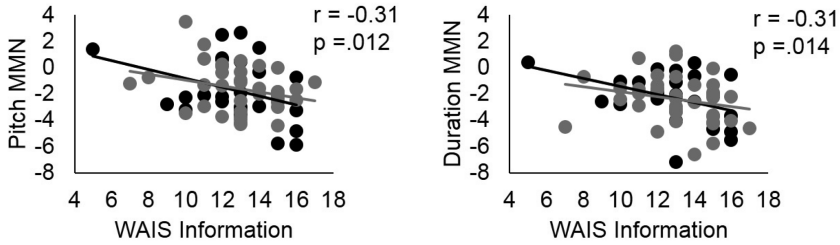

Fig. 3. Correlations between pitch-deviant and duration-deviant MMN at Fz and WAIS III Information scaled score in all participants. Black: first hospitalized schizophrenia; gray: healthy controls. MMN, mismatch negativity; WAIS III, Weschsler Adult Intelligence Scales—3rd Edition.

affects cognition, but cognition is associated independently with the measure of interest, it is difficult to "unconfound" cognition and disease effects.

Not to match subjects groups on some estimate of premorbid IQ risks ascribing differences to the disease process better accounted for by a priori intellectual differences. Showing that intellectually impaired FESz show smaller MMN does not necessarily imply that MMN is specifically reduced in FESz (see study by Chapman and Chapman[38]). Research has identified so-called "hold" variables that are more resistant to schizophrenia,[39–42] typically including WAIS Information and Vocabulary subtests and the Wide Range Achievement Test (WRAT) reading and spelling subtests. Typically, tests of semantic or "crystallized" knowledge serve as "hold" variables, while tests of executive function, working memory, or "fluid" intelligence are highly impaired. For example, in our sample where WAIS Information was matched, robust deficits were observed in WAIS Digit Span and Digit Symbol measures (table 3). To the extent that WAIS Information scaled scores are relatively resistant to schizophrenia, they are useful for avoiding ascribing deficits specifically to the disease better accounted for by premorbid intellectual differences.

On the other hand, it is not clear that "hold" tests are impervious to psychosis. Deficits in WAIS Information and Vocabulary (~2 scaled points) have been reported in first-episode samples.[43,44] Matching for WAIS Information may *underestimate* premorbid intellectual function in FHSz. To closely approximate the smaller decline in WAIS Information observed in epidemiologic studies, we compared 15 FHSz (WAIS Info: 11.3 [2.2]) to 15 HC (WAIS Info: 14.5 [1.3], $t_{28} = 4.8$, $P < .001$). Neither pitch ($t_{28} = 0.18$, $P = .53$) nor duration MMN ($t_{28} = 1.2$, $P = .26$) were reduced. These simulation data suggest that even in these high normal FHSz, extreme differences in premorbid IQ may influence finding reduced MMN, while differences closer to the population norm do not reveal MMN reductions.

If WAIS Information was independently affected by the disease, then the correlation with MMN in FHSz should be greater than in HC (due to additive or multiplicative effects of disease on the IQ-MMN association). There was no significant difference between the correlation in FHSz and HC for pitch (Fisher's $z = 0.242$, $P \approx .80$) or duration MMN (Fisher's $z = 0.696$, $P \approx .48$). Still it is likely that some effects of disease are removed when matching for estimates of premorbid IQ, and the field needs to develop procedures to disentangle the confound.

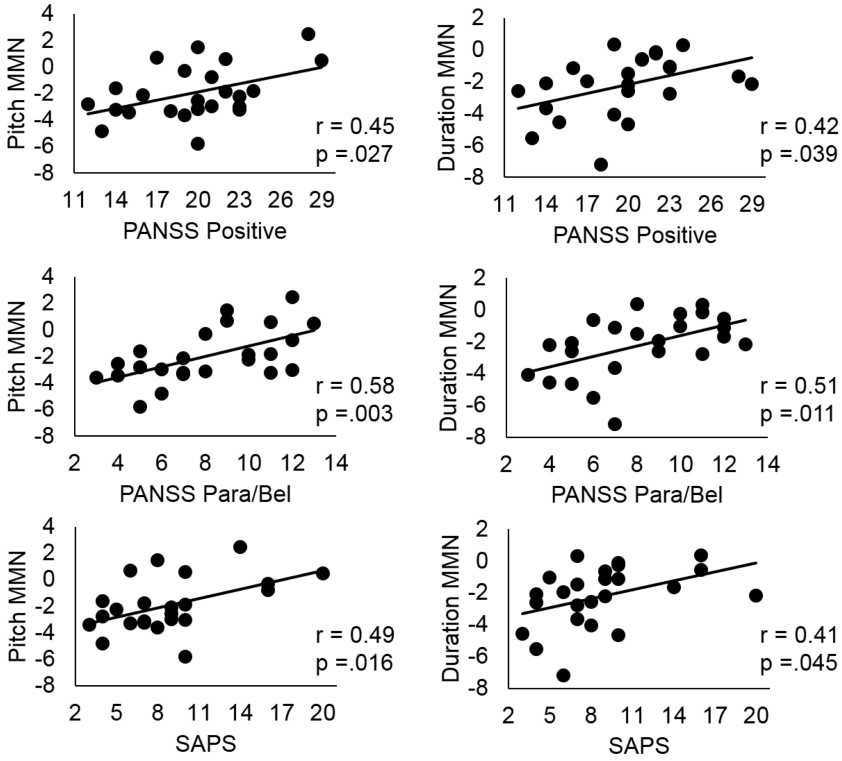

Fig. 4. Correlations between reduced pitch-deviant MMN and duration-deviant MMN at Fz and positive symptoms at first hospitalization, particularly for paranoia. MMN, mismatch negativity; PANSS Para/Bel, Positive and Negative Syndrome Scale Paranoia/Belligerence Factor; SAPS, Scale for the Assessment of Positive Symptoms.

Researchers are faced with a difficult choice. While matching for full-scale IQ or for years of education may be erroneously selecting for higher premorbid IQ in patients (perpetuating a "matching fallacy"),[45] group differences in overall premorbid IQ independent from disease may spuriously select for group differences in the dependent variable. Here IQ accounted for approximately 10–16% of the MMN variance (r^2; pitch, duration, respectively) with positive symptoms accounting for an additional 13–46% of the variance. While MMN pathophysiology should provide clues about underlying pathology reflected in positive symptoms at first break, in this relatively high functioning sample of FHSZ it was not useful for diagnosis. Association with premorbid intellect cannot account for all reported differences, yet may be a major cause of equivocal results. Future research is warranted to determine the degree of MMN reduction at the first episode of psychosis across a greater range of cognitive impairment, the utility of MMN as an indicator of risk or diagnosis, and its role for understanding pathophysiological mechanisms in emerging psychosis.

Inspection of table 1 of every MMN study within a year of first psychosis shows little effect for pitch MMN, and a small to medium effect for duration MMN. We hypothesize that in FHSz without marked intellectual decline MMN deficits with a large effect size emerge very shortly after the onset of psychosis.[10,11,25] The first-episode subgroup that showed MMN reductions in Umbricht et al[9] may have been suffering from longer untreated psychosis and more progressive cortical gray matter loss in auditory cortex.[10,42,46] Belger and colleagues[47,48] have presented evidence suggesting MMN tracks progressive deficits early in disease course. While these data suggest that MMN is a biomarker well suited to track disease progression, further longitudinal studies must be conducted to replicate and expand the extant data.

In particular, research must be undertaken to assess the relationship between accurate measure of psychosis onset and MMN reductions; the lack is a weakness of the current study. It is also a limitation that half of the subjects did not return for diagnostic follow-up, an issue which plagues most first-episode studies. It is possible that the patients studied here express greater intelligence or neurocognitive robustness than the norm, representing only a subgroup of the larger FHSz population. Larger samples with a wider range of premorbid intellect are needed. We make no claim regarding the use of MMN as a screening tool for incipient psychosis. We have no data on such cases, and will not argue beyond our data. It is entirely possible that intensive treatment at first inpatient hospitalization may improve the MMN for the short term, or that compensatory cortical gain mechanisms at first psychosis may increase MMN within a prodromal context of reduction. Only long-term longitudinal studies of at-risk individuals comprising converters and nonconverters can answer such questions.

Consistent with prior studies, reduced MMN correlated with increased positive symptoms. Fisher and colleagues[49,50] showed correlations between MMN and the severity of the specific positive symptom of auditory verbal hallucinations (AVH). Our data pointed to a more general relationship of MMN and positive symptoms, as well as with paranoia. These data suggest that the symptom profile at first hospitalization for schizophrenia may be weighted toward paranoia and delusions, and more stable associations between MMN and AVH may develop with disease course. Here the associations between MMN and positive symptoms remained when partialing out the contribution of premorbid intellect. Thus MMN is likely to provide valuable information regarding cortical mechanisms underlying positive symptoms.

In summary, we saw no pitch or duration MMN reductions in FHSz that were matched with HC on WAIS Information, used as a proxy estimate of premorbid IQ. However, for both groups, reduced MMN correlated with lower WAIS information subtest scores. In addition, for patients, smaller MMNs correlated with positive symptom severity, independent of premorbid IQ estimate. Premorbid intellectual functioning may be a confounding variable at least partially underlying the equivocal reports of duration MMN reduction at first schizophrenic break, as some studies accounted for it but others did not. Carefully controlled longitudinal studies are warranted to determine precisely what contribution MMN can make to risk assessment, screening, and diagnosis.

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