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Mismatch Negativity But Not P300 Is Associated With Functional Disability in Schizophrenia

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Mismatch negativity (MMN) and P300 event-related potential (ERP) reductions in schizophrenia (SZ) reflect preattentive and attention-mediated auditory processing deficits, respectively. Although both have been linked to cognitive deficits in SZ, their relative contributions to real-world functioning are unclear. We sought to determine the functional significance of disrupted auditory processing in SZ by examining MMN and P300 in typically disabled low-functioning patients and in patients with high levels of independent role functioning. MMN to auditory deviants and P300 to infrequent auditory target and nontarget novel stimuli were assessed in 20 high-functioning SZ patients (HF-SZ), 17 low-functioning patients (LF-SZ), and 35 healthy comparison (HC) subjects. There was a group effect on MMN and P300 amplitudes across stimulus types. MMN was significantly diminished in LF-SZ compared to HF-SZ and HC, and HF-SZ demonstrated comparable MMN to HC. In contrast, P300 was significantly reduced in both LF-SZ and HF-SZ compared to HC. Logistic regression suggested independent sensitivity of MMN to functioning in SZ over and above P300 measures. Neither MMN nor P300 were associated with positive or negative symptom severity. Results replicate MMN and P300 abnormalities in SZ, and also suggest that the neural mechanisms associated with the preattentive detection of auditory deviance are most compromised in patients with functional disability. MMN may index pathophysiological processes that are critical for optimal functioning in SZ.

Key words: auditory information processing/functional outcome/event-related potentials/electroencephalography/psychosis

Introduction

Despite successful treatment of psychotic symptoms, disability in occupational, residential, and social functioning persists for many patients with schizophrenia (SZ). Cognitive dysfunction is a core feature of SZ and a robust predictor of functional outcomes.[1,2] Evidence that antipsychotic medications provide limited benefit for cognitive impairments[3–6] has motivated interest in the development of interventions directly targeting cognition, which is guided by efforts to understand the neural correlates of disrupted cognitive systems in SZ. EEG-based event-related potential (ERP) components are commonly used to characterize the neurophysiological basis of early information processing impairments that may contribute to higher-order cognitive dysfunction and associated functional disability in SZ. In particular, auditory mismatch negativity (MMN) and P300 reductions probe the range of early information processing impairments common in SZ, as they have been linked to cognition and reflect preattentive and early attention-mediated auditory processing deficits, respectively.

MMN is associated with auditory deviance detection and elicited by infrequent deviant stimuli occurring within a series of repeated standard sounds.[7,8] Because deviance detection requires the short-term online formation of a memory trace of preceding stimuli that have been "standard" in the auditory processing stream, MMN is considered to reflect sensory echoic memory.[7,9] MMN has been localized to both auditory cortex and frontal lobes[8] and appears to arise from distinct neural generators within these regions[8,10–14] depending on the deviant sound feature (eg, pitch, duration, intensity).[8,15] Additionally, MMN depends on glutamatergic neurotransmission at NMDA

receptors, based on evidence from pharmacological challenge studies with NMDA receptor antagonists.[16–22] Importantly, MMN is considered to be preattentive, as it is elicited automatically despite engagement in an unrelated primary task and instructions to ignore the simultaneously presented auditory stimuli.[7,23,24] Moreover, MMN is largely unaffected by top-down information processing,[7,25,26] allowing the examination of auditory processing dysfunction in disorders such as SZ without the confounding influence of attentional and motivational deficits that affect performance on higher-order cognitive tasks.[27] MMN amplitude reductions have been consistently observed in SZ[28,29] and are associated with impaired cognition.[30–32] Evidence of reduced MMN amplitudes in individuals at clinical high-risk for psychosis, particularly in those who ultimately transition to full psychosis, suggests that compromised MMN may reflect vulnerability to illness progression.[33–39]

In contrast to MMN, P300 is an attention-dependent ERP following behaviorally relevant infrequent deviant stimuli interspersed among frequent "standard" stimuli during an oddball task.[40] P300 is thought to reflect controlled attentional resource allocation,[40–43] contextual updating of working memory,[44,45] and stimulus salience processing,[46,47] and prefrontal cortex and temporal-parietal junction have been implicated in its generation.[48,49] Two subcomponents of P300 are evident depending on task conditions: P3b and P3a are elicited by infrequent target stimuli and infrequent non-target novel distractor stimuli, respectively.[40,50–53] While P3a reflects bottom-up attention orienting and has a frontocentral scalp maximum,[40,53–56] P3b reflects top-down attentional allocation and is maximal at parietal regions.[40,51,52] Like MMN, auditory P300 amplitude reductions are widely replicated in SZ,[57–59] evident in the clinically high-risk state,[60–63] and associated with cognitive impairments.[64–66]

Given links between early information processing deficits and cognitive impairment in SZ, more recent work has begun to establish relationships between these neurophysiological measures and functional outcomes. Associations between MMN and skills-based measures of psychosocial functioning and clinician-based global assessment of functioning and independent living ratings have been reported by several studies.[32,67–71] Fewer studies have examined the relationship between P300 and functioning, although associations between P3a and psychosocial functioning ratings,[31,70,72] and between P3b and a functioning performance assessment,[66] have been reported. These correlational studies may be limited, however, by a restricted range of functional abilities represented by typically recruited SZ samples. Additionally, common clinician-rated outcome measures confound functional disability with psychiatric symptom severity, capture only a single domain of functioning, or do not account for contextual factors that may influence functional performance.[73] Furthermore, previous work has not examined the relative contributions of MMN and P300 deficits to functional outcomes.

The present study sought to examine whether indices of auditory processing deficits in SZ, including both the preattentive MMN and the later attention-mediated auditory P300, are associated with role functioning in a sample of SZ patients representing a wide range of functional outcomes. To achieve this aim, we prospectively recruited patients with high levels of functioning or more typical poor functioning using a multidimensional measure of functional disability that rates position, performance, and support in several domains.[73] We hypothesized that MMN deficits would be more prominent in lower functioning patients based on prior evidence.[32,67–71] However, given the link between higher-order cognitive dysfunction and functional outcomes in SZ[1,2] and the relatively greater contributions of attention-mediated cognitive processes to P300 relative to MMN, we reasoned that P300 would be at least as sensitive to variation in functional outcomes as MMN. Accordingly, we predicted that patients with greater functional disability would demonstrate reduced MMN and P300 compared to patients with high levels of independent role functioning, and that both MMN and P300 would contribute independently to the prediction of patients' functional status.

Methods

Participants

Thirty-seven individuals with SZ (n = 31) or schizoaffective disorder (n = 6) and 35 healthy comparison subjects (HC) were evaluated via structured interview.[74] Exclusion criteria included history of substance dependence or abuse within the past year, significant medical or neurological illness, or history of head injury with loss of consciousness. Additional exclusion criteria for HC participants included a past or current DSM-IV Axis I disorder or having a first-degree relative with a psychotic disorder. The study was approved by the institutional review boards of Yale University and the University of California, San Francisco, and participants provided written informed consent.

Functional and Clinical Assessment

A clinical psychologist, psychiatrist, or clinically trained research assistant rated SZ patients' level of functional disability using the Multidimensional Scale of Independent Functioning (MSIF).[73] The MSIF assesses role position, support, and performance in work, education, and residential environments over the past month. Based on ratings on each dimension within each environment, global ratings are made on a scale from 1 ("essentially normal role functioning") to 7 ("totally disabled"). SZ patients were classified as high functioning (HF-SZ) if they received global MSIF ratings of 1–3 and generally had normal functioning without or with some support,

or slightly below normal functioning but with minimal support. Patients rated 5–7 were classified as low functioning (LF-SZ) and were significantly disabled and generally unable to function with or without supports. Participants rated as 4 ("moderately disabled") were excluded from participation. Data from 20 HF-SZ and 17 LF-SZ patients were included in the study.

Symptoms were rated using the Scale for the Assessment of Negative Symptoms (SANS)[75] and the Scale for the Assessment of Positive Symptoms (SAPS)[76] within 2 weeks of ERP assessment (mean ± SD = 3.70 ± 4.03 days). Demographically adjusted premorbid intellectual functioning was evaluated using the Wechsler Test of Adult Reading.[77]

MMN Paradigm

MMN was assessed using a multi-deviant paradigm consisting of 4 blocks, approximately 5 min each, with a fixed pseudorandom sequence of 600 tones, presented in counterbalanced order. In 2 blocks, 80% of the stimuli were standard tones (50 ms, 633 Hz), 10% were duration deviant tones (100 ms, 633 Hz), and 10% were pitch deviant tones (50 ms, 1000 Hz). In the other 2 blocks, 90% were standard tones (50 ms, 633 Hz) and 10% were double deviant tones (combined duration and pitch deviant; 100 ms, 1000 Hz). All tones had 5 ms rise/fall times and were presented with a 500 ms stimulus onset asynchrony. Participants were instructed to ignore auditory stimuli and perform a picture-word matching task that required button press responses.[78]

P300 Paradigm

During the oddball task, participants heard a random series of infrequent target tones (8.33%; 1000 Hz, 500 ms), frequent standard stimuli (83.33%; 20 Hz, 30 Hz, or 40 Hz click trains, 500 ms), and infrequent task-irrelevant novel distractor sounds (ie, a variety of natural and man-made sounds[79]; 8.33%; 175—250 ms). Stimuli averaged 80 dB SPL (C weighting) and were presented in 3 blocks with a 1250 ms stimulus onset asynchrony. Participants were asked to press a response key to target tones. Each of the 3 counterbalanced blocks included 15 targets, 15 novels, and 150 standards. In order to maximize signal-to-noise ratio, ERPs to the deviant stimuli were averaged across blocks. Trials with incorrect button presses were excluded from analysis, and there were no group differences in response accuracy, $F(2, 69) = 1.65$, $P = .200$. Time-frequency analyses of the auditory steady state response to click trains are presented separately (Ferri et al., in preparation).

Electroencephalographic Data Acquisition and Preprocessing

Participants sat in an acoustically shielded booth in front of a computer monitor and wore insert earphones (Etymotic Research, Inc.). EEG was recorded at 1000 Hz from 26 scalp electrodes, filtered between 0.05 and 200 Hz, and referenced to the right mastoid (Neuroscan SynAmps, Compumedics Neuroscan). Additional electrodes at the outer canthi of both eyes and above and below the left eye recorded eye movements and blinks (vertical and horizontal electro-oculogram; VEOG, HEOG). All electrode impedances were maintained below 10 kOhm.

EEG data from 9 lead sites were analyzed (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). Continuous data were subjected to a low-pass filter of 30 Hz for MMN and 12 Hz for P300 and re-referenced offline to averaged mastoid electrodes. Data were separated into epochs time-locked to stimulus onset (550 ms with a 50 ms prestimulus baseline for MMN; 1000 ms with a 100 ms prestimulus baseline for P300). VEOG and HEOG data were used to correct for eye movements and blinks with a regression-based algorithm. After baseline correction (−50 to 0 ms for MMN; −100 to 0 ms for P300), epochs containing artifacts (voltages exceeding ±100 μV) were rejected. Separate averages were calculated for all trial types for each participant.

For MMN, standard waves were subtracted from deviant waves, and MMN amplitude was defined as the most negative peak in the difference waves between 90 and 290 ms for each deviant type. P300 was identified as the most positive peak 235—400 ms following stimulus onset. Because P3b and P3a have different topographies, different algorithms were implemented for automated peak-picking (supplementary material).[80,81]

Statistical Analysis

Group differences in MMN and P300 amplitudes were examined at midline electrodes using 3-way repeated-measures ANOVA models with a between-subjects factor of group (HF-SZ, LF-SZ, HC) and within-subjects factors of deviant type (MMN: duration, pitch, double; P300: target, novel) and lead (MMN: frontocentral Fz, Cz; P300: anterior-posterior Fz, Cz, Pz). Secondary analyses were performed at off-midline sites to assess potential hemispheric differences using 4-way group × deviant type × lead × hemisphere (left, right) ANOVAs. Greenhouse-Geisser corrections were applied to within-subjects effects with more than 2 levels, and the Benjamini and Hochberg procedure[82] was used to correct for multiple comparisons. Midline analyses of effects involving the group factor and off-midline analyses showing hemisphere or group × hemisphere effects are described below. Other main effects and repeated-measures ANOVA models examining ERP latency effects are presented in supplementary material.

ERP amplitudes at maximal leads (ie, Fz for MMN, Cz for P3a, Pz for P3b) were used in regression and correlational analyses. To examine independent contributions to functioning, MMN and P300 were entered in hierarchical logistic regression models predicting SZ patient group (ie, LF-SZ vs HF-SZ).

Relationships between ERP amplitudes and SAPS and SANS global subscale scores were examined using Spearman rank-order correlations. An alpha level of $P = .05$, 2-tailed, was used for all statistical tests.

Results

Demographic Differences Between Groups

Demographic data are shown in table 1. Age and gender did not differ between groups. The distribution of handedness differed at a trend level, with LF-SZ having a greater proportion of left-handed participants than HC. HC participants completed more education and had higher predicted IQ scores than both HF-SZ and LF-SZ, whereas the SZ groups did not differ. Average parental socioeconomic status (PSES) was lower in the LF-SZ than HF-SZ and HC, whereas the HF-SZ and HC did not differ. Given these demographic differences, analyses were repeated using analysis of covariance (ANCOVA) with education, PSES, and predicted IQ as covariates.

Table 1. Demographic and Clinical Characteristics

	High Functioning Schizophrenia (n = 20)		Low Functioning Schizophrenia (n = 17)		Healthy Comparison (n = 35)			
	n	%	*n*	%	*n*	%	*P*	Follow-Up Tests
Gender							.789	
Female	4	20.00	5	29.41	8	22.86		
Male	16	80.00	12	70.59	27	77.14		
Handedness[a]							.063	
Right	19	95.00	14	82.35	34	97.14		
Left	0	0.00	3	17.65	1	2.86		
Ambidextrous	1	5.00	0	0.00	0	0.00		
Antipsychotic type							.642	
Atypical alone	17	85.00	15	88.24				
Typical alone	2	10.00	2	11.76				
None	1	5.00	0	0.00				
Diagnostic subtype							.486	
Paranoid	10	50.00	10	58.82				
Undifferentiated	2	10.00	4	23.53				
Residual	3	15.00	1	5.88				
Schizoaffective	4	20.00	2	11.76				
Catatonic	1	5.00	0	0.00				
	M	SD	*M*	SD	*M*	SD	*P*	
Age (years)	32.60	10.64	37.47	7.61	34.57	8.88	.275	
Education (years)	13.55	1.10	12.74	1.73	16.03	2.61	<.001	HF-SZ = LF-SZ, HC > LF-SZ,[e] HC > HF-SZ[e]
Parental SES[b]	31.43	15.07	44.24	16.09	31.96	13.31	.011	HF-SZ > LF-SZ,[d] HC > LF-SZ,[d] HF-SZ = HC
WTAR predicted FSIQ[c]	101.75	5.53	99.29	6.32	107.29	7.06	<.001	HF-SZ = LF-SZ, HC > LF-SZ,[e] HC > HF-SZ[d]
CPZ equivalent dosages	429.10	399.31	665.24	456.47			.102	
Duration of illness (years)	10.26	9.79	14.94	9.26			.151	
MSIF global score	2.10	0.72	5.65	0.49			<.001	
SAPS global total score	5.20	3.14	5.76	3.11			.588	
SANS global total score	4.70	2.66	8.94	4.75			.004	

Note: Numbers and percentages of participants are reported for gender, handedness, antipsychotic type, and diagnostic subtype, and were analyzed using Pearson chi-square tests. Group means (M) and standard deviations (SD) are reported for age, personal years of education, parental socioeconomic status (SES), Wechsler Test of Adult Reading (WTAR) full-scale intelligence quotient (FSIQ), chlorpromazine (CPZ) equivalent dosages, Multidimensional Scale of Independent Functioning (MSIF) global score, and Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) global total scores, and were analyzed with one-way ANOVAs, followed by post hoc false discovery rate (FDR)-corrected tests to further parse group differences.
[a]The Crovitz and Zener questionnaire[83] was used to measure handedness.
[b]The Hollingshead 4-factor index of parental socioeconomic status (SES)[84] is based on a composite of maternal education, paternal education, maternal occupational status, and paternal occupational status. Lower values signify higher socioeconomic status.
[c]Data missing for one healthy comparison participant.
[d]$P < .01$.
[e]$P < .001$.

HF-SZ and LF-SZ did not differ in terms of chlorpromazine (CPZ) equivalent dosages of antipsychotic medications or duration of illness. However, LF-SZ patients experienced greater negative symptom severity than the HF-SZ group, and SZ group comparisons were repeated with SANS global total score as a covariate.

ANOVA of MMN Amplitudes

Grand average difference waves for each deviant type show smaller MMN amplitudes (ie, less negative) in LF-SZ than HF-SZ and HC (figure 1; mean amplitude values are shown in supplementary table S3). The ANOVA of midline MMN amplitudes (table 2) revealed a marginally significant group effect that was qualified by a significant group × frontocentral lead interaction, which indicated variation in the strength of group effects at frontal and central midline leads. Parsing this interaction demonstrated a group effect at Fz, with post hoc tests showing significantly reduced MMN amplitudes in LF-SZ patients compared to both HC (Cohen's $d = .92$) and HF-SZ ($d = .81$), and no difference in MMN between the HF-SZ and HC. The group effect at central leads did not reach statistical significance. This pattern of results was unchanged when years of education, PSES, and IQ were included as covariates, and the difference in MMN between the LF-SZ and HF-SZ groups remained statistically significant after covarying for negative symptom scores.

The ANOVA examining hemisphere effects on MMN demonstrated a similar pattern of group effects, but there were no group × hemisphere interaction effects indicative of hemispheric abnormalities in the SZ patients (supplementary table S1). A main effect of hemisphere was qualified by a frontocentral lead × hemisphere interaction, parsing of which revealed greater MMN amplitudes at right compared to left frontal leads across participants and deviant types.

ANOVA of P300 Amplitudes

Grand average waveforms show reduced novelty P3a and target P3b amplitudes in both patient groups compared to HC (figure 2 and supplementary table S3). The ANOVA of midline P300 amplitudes indicated a significant effect of group, with post hoc tests demonstrating reduced P300 amplitudes in both LF-SZ and HF-SZ compared to HC ($d = .76$ and $d = .75$, respectively; table 3). This main effect was qualified by a group × deviant type × anterior-posterior lead interaction. Parsing this interaction did not reveal an absence of the group effect or a dependence of the group effect on P300 deviant type. Instead, this interaction appeared to capture group variation in the anterior-posterior topography of P3a and P3b (supplementary material). When education, PSES, and IQ were included as covariates, the group and anterior-posterior lead main effects remained statistically significant, while the interaction effects and main effect of deviant type were no longer significant.

The ANOVA examining hemisphere effects on P300 (supplementary table S2) demonstrated a similar pattern of group effects as observed in the midline analysis, with post hoc interrogation of the significant group effect demonstrating P300 amplitude reductions in both HF-SZ and LF-SZ compared to HC. There was not a main effect of hemisphere or a group × hemisphere interaction. Parsing of higher-order interactions involving hemisphere revealed a hemisphere effect in HC participants only and indicated greater target P3b amplitudes at right (C4), relative to left (C3), central leads.

Prediction of Functioning Status

Within patients, larger MMN amplitudes (averaged over deviant types at Fz) were modestly associated with smaller P300 amplitudes (novelty P3a at Cz: $r = .33$, $P = .046$; target P3b at Pz: $r = .37$, $P = .025$). In the first of 2 hierarchical logistic regression models, P3a and P3b amplitudes were entered as a block in step 1 and did not produce a prediction effect ($\chi^2 = 0.61$, $P = .736$), and neither P3a nor P3b produced a predictive increment over and above the other [P3a: Wald(1) = 0.35, $P = .553$, Exp(B) = 1.07; P3b: Wald(1) = 0.58, $P = .447$, Exp(B) = .92]. At step 2, entry of MMN amplitude significantly improved prediction of functional status [$\chi^2 = 8.20$, $P = .004$; P3a: Wald(1) = 0.38, $P = .537$, Exp(B) = 1.09; P3b: Wald(1) = 1.78, $P = .182$, Exp(B) = 0.80; MMN: Wald(1) = 5.77, $P = .016$, Exp(B) = 1.88] such that smaller MMN amplitude was associated with poorer functioning. In the second model, MMN was entered at step 1 and predicted functional status [$\chi^2 = 5.87$, $P = .015$; Wald(1) = 4.52, $P = .034$, Exp(B) = 1.59]. When entered at step 2, P300 failed to improve this prediction [$\chi^2 = 2.95$, $P = .229$; MMN: Wald(1) = 5.77, $P = .016$, Exp(B) = 1.88; P3a: Wald(1) = 0.38, $P = .537$, Exp(B) = 1.09; P3b: Wald(1) = 1.78, $P = .182$, Exp(B) = 0.80]. When MMN was the sole predictor, the results indicated that a one unit decrease in MMN amplitude (ie 1 μV less negative) increased the odds of being LF-SZ by 59%.

Correlations With Symptoms

Neither MMN nor P300 amplitudes were correlated with symptom ratings within LF-SZ or HF-SZ or the combined SZ sample.

Discussion

This study examined the relative contributions of preattentive and attention-dependent auditory processing impairments to functional disability in a sample of SZ patients that ranged considerably in their levels of independent role functioning. As expected, patients with poorer functioning showed MMN deficits compared to

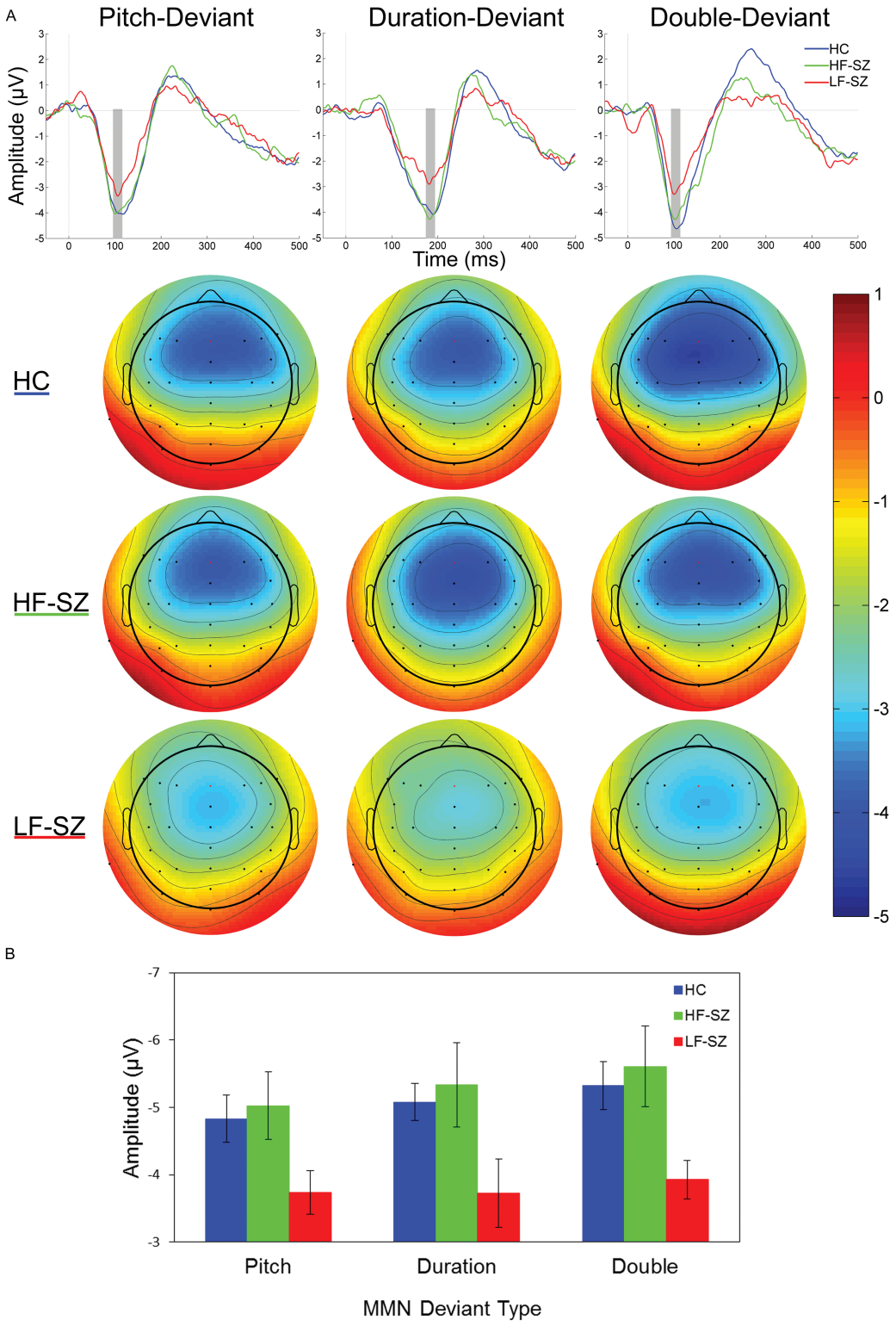

Fig. 1. (A) Mismatch negativity (MMN) difference waveforms, averaged at Fz, for healthy comparison (HC), high-functioning schizophrenia (HF-SZ), and low-functioning schizophrenia (LF-SZ) participants by deviant type. Scalp voltage topography maps, showing group means of MMN amplitudes around the peak latency ±10 ms (indicated by gray bars in waveform plots), are shown for each deviant type. (B) Column graph shows means and standard errors for MMN amplitudes at Fz.

patients with high levels of independent functioning and healthy individuals. These results are consistent with observed correlations between MMN and measures of functional outcome in schizophrenia patients,[32,67–70] and also support findings suggesting that MMN may be most closely associated with work and independent

Table 2. ANOVA of Midline MMN Amplitudes

Effect	df	*F*	*P* Value	Follow-Up Tests[a]
Group	2, 69	3.01	.056	HF-SZ < LF-SZ,[b] HC < LF-SZ,[b] HF-SZ = HC
Deviant type (double, pitch, duration)	2, 138	1.68	.194	
Frontocentral lead (frontal, central)	1, 69	41.66	<.001	Fz < Cz[c]
Group × deviant type	4, 138	0.37	.804	
Group × frontocentral lead	2, 69	5.65	.005	
Group effect in frontal leads	2, 69	4.32	.017	HF-SZ < LF-SZ,[d] HC < LF-SZ,[b] HF-SZ = HC
Group effect in central leads	2, 69	1.66	.197	
Frontocentral lead effect in HC	1, 34	37.68	<.001	Fz < Cz[c]
Frontocentral lead effect in LF-SZ	1, 16	0.54	.474	
Frontocentral lead effect in HF-SZ	1, 19	31.30	<.001	Fz < Cz[c]
Group × deviant type × frontocentral lead	4, 138	1.41	.234	
Deviant type × frontocentral lead	2, 138	2.14	.123	

Note: More negative amplitude indicates larger MMN. ANOVA, analysis of variance; HF-SZ, high-functioning schizophrenia; LF-SZ, low-functioning schizophrenia; HC, healthy comparison.
[a]All follow-up tests of statistically significant effects survived FDR correction for multiple comparisons.
[b]$P < .05$.
[c]$P < .001$.
[d]$P < .01$.

living domains of functioning.[71] Our results also parallel previous findings demonstrating impaired basic tone discrimination in SZ patients residing in long-term care facilities, a setting that typically serves lower functioning patients, relative to outpatient first-episode and chronic patients.[85] Given the lack of MMN reduction in the higher functioning group, we also extend previous reports by showing that patients without functional disability may exhibit normal MMN amplitudes. Furthermore, the absence of a group × deviant type interaction confirms prior work suggesting that the degree of MMN deficit does not significantly depend on the type of auditory deviance[37,67,86–89] (but see Todd et al.[90]).

In contrast to some previous reports,[31,66,70,72] we did not find an association between P300 and role functioning, as novelty P3a and target P3b amplitudes were reduced compared to healthy participants across both SZ groups, regardless of functional status. MMN, but not P300, predicted patients' role functioning status even when covariation between MMN and P300 was statistically controlled. In some respects, this result is surprising, as P300 is thought to reflect higher-order cognitive functions that have been linked to functional outcomes in SZ.[1,2] Moreover, P300 is generated by multiple distributed sources in frontal, temporal, and parietal cortices,[48,91,92] reflecting multi-modal associative and integrative processes that would be expected to support successful management of the complex cognitive and behavioral demands associated with independent functioning. MMN, in contrast, is an automatic response to auditory deviance, requiring no cognitive effort to generate, and is subserved by a relatively limited number of neural generators in auditory and inferior frontal cortex.[8,10–14,24]

Accordingly, P300 would seem to be a more "face valid" indicator of the processes subsuming successful role functioning than MMN. Yet, our results suggest the opposite. One possible explanation is that the cognitive processes giving rise to P300 are subject to multiple influences, including motivation and effort, that may have compensatory or countervailing effects on the attentional and working memory deficits reflected by P300 reduction in SZ. These influences, in turn, may obscure any systematic relationship between P300 and functional outcomes. Processing reflected by MMN, on the other hand, is less susceptible to these influences because it is explicitly assessed with attention directed away from the auditory channel. As such, MMN may provide a more accurate assessment of the basic integrity of brain functioning that transcends its specific function in the auditory system, with MMN deficits reflecting a relatively broad neurophysiological constraint on an individual's capacity for independent functioning. Indeed, recent analyses[93] characterizing pathways from early auditory neurophysiological deficits (including MMN) to poor functional outcomes in SZ indicated that this relationship was mediated by impaired cognition. Moreover, the effects of early auditory processing deficits were not modality-specific, instead contributing to impairments in both auditory and visual neurocognitive domains.

These findings are also consistent with the proposed role of P300 as a trait marker of SZ and reports of robust abnormalities throughout the illness course.[58,94–97] While deficits in MMN seem to be evident in the more typical subgroup of patients with lower levels of role functioning, P300 may have more general sensitivity to SZ irrespective of functioning, and therefore, may hold more promise as a candidate endophenotypic marker of the clinical diagnosis of SZ as currently defined. Although

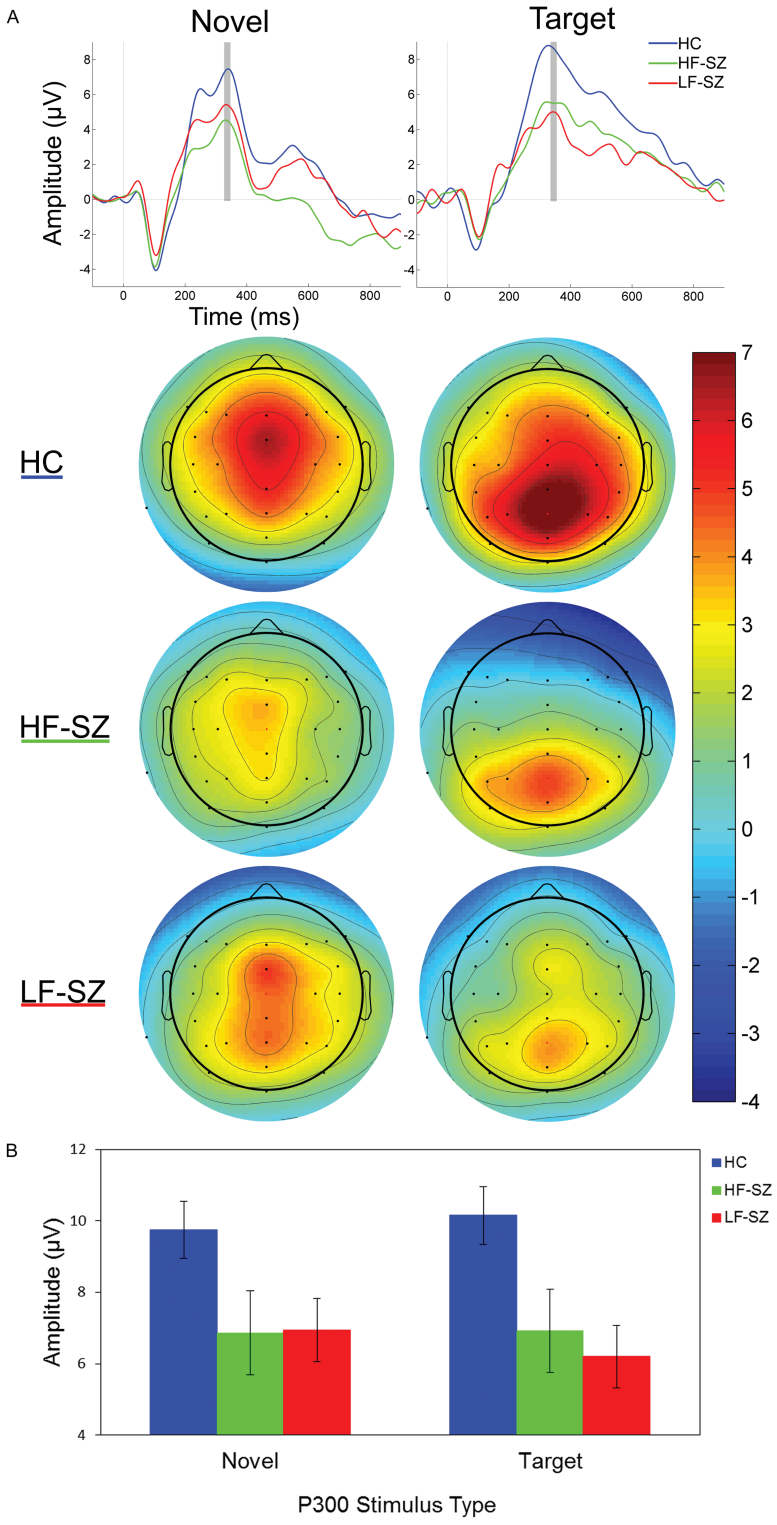

Fig. 2. (A) P300 waveforms, averaged at Cz for novel stimuli (P3a) and Pz for target stimuli (P3b) for healthy comparison (HC), high-functioning schizophrenia (HF-SZ), and low-functioning schizophrenia (LF-SZ) participants. Scalp voltage topography maps, showing group means of P300 amplitudes around the peak latency ±10 ms (indicated by gray bars in waveform plots), are shown for novel and target stimuli. (B) Column graph shows means and standard errors for novelty P3a amplitudes at Cz and target P3b amplitudes at Pz.

P300 varies somewhat with clinical state in SZ,[97] P300 amplitude remains reduced in patients whose symptoms have improved[97–104] and shows trait-like stability when assessed longitudinally.[98,104,105] Given these reports, it is perhaps not surprising that P300 amplitude was reduced even in high functioning patients. In considering possible

Table 3. ANOVA of Midline P300 Amplitudes

Effect	df	*F*	*P* Value	Follow-Up Tests[a]
Group	2, 69	5.18	.008	HC > LF-SZ,[b] HC > HF-SZ,[c] LF-SZ = HF-SZ
Deviant type (novels, targets)	1, 69	23.34	<.001	Novels > targets[d]
Anterior–posterior lead (Fz, Cz, Pz)	2, 138	16.19	<.001	Pz > Cz,[c] Pz > Fz,[d] Cz > Fz[c]
Group × deviant type	2, 69	0.54	.586	
Group × anterior–posterior lead	4, 138	0.30	.835	
Group × deviant type × anterior–posterior lead	4, 138	2.82	.038	
Group × anterior–posterior lead for novels	4, 138	0.23	.878	
Group × anterior–posterior lead for targets	4, 138	1.20	.315	
Group × deviant type at Fz	2, 69	0.86	.429	
Group × deviant type at Cz	2, 69	0.41	.668	
Group × deviant type at Pz	2, 69	2.34	.104	
Deviant type × anterior–posterior lead in HC	2, 68	54.35	<.001	
Deviant type effect at Fz	1, 34	27.10	<.001	Novels > targets[d]
Deviant type effect at Cz	1, 34	13.91	.001	Novels > targets[d]
Deviant type effect at Pz	1, 34	10.46	.003	Targets > novels[c]
Anterior–posterior lead effect for novels	2, 68	2.10	.150	
Anterior–posterior lead effect for targets	2, 68	24.12	<.001	Pz > Cz,[d] Pz > Fz,[d] Cz > Fz[c]
Deviant type × anterior–posterior lead in HF-SZ	2, 38	33.10	<.001	
Deviant type effect at Fz	1, 19	20.29	<.001	Novels > targets[d]
Deviant type effect at Cz	1, 19	15.02	.001	Novels > targets[c]
Deviant type effect at Pz	1, 19	1.01	.327	
Anterior–posterior lead effect for novels	2, 38	0.58	.541	
Anterior–posterior lead effect for targets	2, 38	32.36	<.001	Pz > Cz,[d] Pz > Fz,[d] Cz > Fz[b]
Deviant type × anterior–posterior lead in LF-SZ	2, 32	17.27	<.001	
Deviant type effect at Fz	1, 16	10.02	.006	Novels > targets[c]
Deviant type effect at Cz	1, 16	13.61	.002	Novels > targets[c]
Deviant type effect at Pz	1, 16	0.10	.760	
Anterior–posterior lead effect for novels	2, 32	1.16	.321	
Anterior–posterior lead effect for targets	2, 32	14.29	<.001	Pz > Cz,[b] Pz > Fz,[d] Cz = Fz
Deviant type × anterior–posterior lead	2, 138	84.45	<.001	
Deviant type effect at Fz	1, 71	57.58	<.001	Novels > targets[d]
Deviant type effect at Cz	1, 71	40.93	<.001	Novels > targets[d]
Deviant type effect at Pz	1, 71	7.40	.008	Targets > novels[c]
Anterior–posterior lead effect for novels	2, 142	3.45	.048	Cz > Fz,[b] Cz > Pz,[c] Fz = Pz
Anterior–posterior lead effect for targets	2, 142	60.77	<.001	Pz > Cz,[c] Pz > Fz,[d] Cz > Fz[d]

Note: ANOVA, analysis of variance; HF-SZ, high-functioning schizophrenia; LF-SZ, low-functioning schizophrenia; HC, healthy comparison.
[a]All follow-up tests of statistically significant effects survived FDR correction for multiple comparisons.
[b]$P < .05$.
[c]$P < .01$.
[d]$P < .001$.

reasons for conflicting results with prior work,[31,66,70,72] it is noteworthy that prior studies have used scales requiring a clinician to make broad judgments about functional outcomes or call for patients to respond to hypothetical situations to assess their understanding of what constitutes functionally adaptive behavior. In contrast, our criteria were based on objective indicators of residential, occupational, and educational functioning.[73] Thus, it may be that P300 is sensitive to variation in cognitive responses to hypothetical functional challenges, but has less relevance to patients' actual level of real-world functioning.

Recent meta-analytic reviews have concluded that first-episode SZ patients demonstrate less pronounced MMN deficits than chronic patients,[29,106] and some studies have found normal MMN amplitudes in first-episode patients that subsequently decline over the first 1–2 years of illness,[107,108] consistent with the possibility that MMN tracks disease progression. Although the present sample was comprised primarily of chronic patients, reanalysis after removal of first-episode participants ($n = 4$) maintained similar results, indicating that effects obtained were not due to a predominance of first-episode patients in the high-functioning group. These findings raise the possibility that sampling biases may partially explain inconsistent results, such that first-episode samples may typically have a greater proportion of higher functioning patients than chronic samples.

Similarly, converging evidence showing that MMN deficits predict subsequent conversion to full psychosis in clinically high-risk individuals[37–39] may reflect greater cognitive and functional impairments in those at elevated risk for making this transition.[109–111] Some have also reported

that MMN abnormalities in first-episode patients may be confined to those with lower IQ.[89,112] Inasmuch as low IQ is well-documented in SZ,[113] the mediation of MMN deficits by premorbid IQ or role functioning impairments is best considered a reflection of the functional heterogeneity that is superimposed on the generally poor cognitive and functional trajectory typical of SZ, rather than constituting a confound that needs to be controlled. Regardless, neither years of education nor IQ accounted for group differences in MMN in the present sample, suggesting that intact MMN in patients with successful role functioning reflects more than intellectual ability *per se*. Furthermore, MMN and duration of illness were not correlated, which has also been reported by a recent meta-analysis.[29] Together, these results suggest that MMN may better index functional disability than illness progression, and further suggest that functional status may be important to evaluate in MMN studies examining patients in other stages of illness, including the prodrome. Longitudinal studies will help determine whether MMN changes with functional status, or whether MMN deficits early in the illness reflect trait-like brain dysfunction that compromises later functional outcomes.

Interestingly, we also found that in patients, smaller MMN amplitudes were modestly associated with greater P3a and P3b amplitudes. This association should be interpreted with caution as it may reflect idiosyncrasies within our relatively small samples and therefore needs to be replicated in other larger samples. However, we speculate that the somewhat counterintuitive association observed might reflect the influence of later compensatory attentional strategies to overcome weaknesses in early automatic auditory deviance detection, particularly because the attentional systems reflected by the P3a and P3b are engaged later than the preattentive MMN.

Patients were taking antipsychotic medications when evaluated, which is a limitation of the present study. However, there were no dosage differences between patient groups so medication differences are unlikely to account for the absence of MMN deficits in the high functioning group. This is consistent with studies that failed to demonstrate an effect of antipsychotic medication on MMN.[114–117] Further, evidence of P300 reductions in unmedicated patients[97] and following medication withdrawal,[118] as well as P300 improvement with antipsychotic medications,[59,115–117] suggests that deficits would have been larger across patients if they were medication-free. In addition, although we were able to observe robust effects in a relatively small sample, confirmation of these results in other larger samples will be reassuring.

In conclusion, the present study suggests that MMN deficits, but not P300 deficits, are sensitive to independent role functioning disability in SZ. MMN may index relatively low-level pan-cortical neurophysiological dysfunction (eg, ubiquitous NMDA receptor dysfunction) that extends beyond the auditory cortex and automatic processing of auditory deviance, fundamentally limiting the potential of a patient with SZ to live and work independently.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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