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Differing Pattern of Mismatch Negativity Responses in Clinical and Nonclinical Voice Hearers Challenge Predictive Coding Accounts of Psychosis

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ABSTRACT

BACKGROUND: Among people with schizophrenia (PSZ), reduced mismatch negativity (MMN) is conceptualized as evidence of disrupted prediction error signaling that underlies positive symptoms. However, this conceptualization has been challenged by observations that MMN and positive symptoms are often uncorrelated. In the current study, we tested the hypothesis that reduced MMN is associated with the presence of hallucinations and delusions specifically rather than the presence of a psychiatric illness. A second aim was to determine whether the strength of the association with positive symptoms increases for indices that reflect predictions at higher levels of abstraction.

METHODS: Fifty-six PSZ, 34 nonclinical voice hearers, and 48 healthy comparison subjects (HCs) completed 2 MMN paradigms: one with a simple duration deviant type, and one with a higher-level, pattern-violation deviant type. We also measured the repetition positivity, which reflects the formation of auditory memory traces.

RESULTS: We observed that although PSZ exhibited the expected pattern of significantly reduced duration MMN and reduced pattern-violation MMN at the trend level compared with HCs, nonclinical voice hearers exhibited a pattern of duration MMN and pattern-violation MMN amplitude that was statistically similar to that of HCs ($ps > .64$). Similarly, PSZ exhibited a significantly reduced repetition positivity slope compared with HCs in the duration condition and a trend-level reduction compared with HCs in the pattern-violation condition. Nonclinical voice hearers did not differ from either group in repetition positivity slope in either condition.

CONCLUSIONS: These results indicate that the MMN as a prediction error signal does not reflect processes relevant for the manifestation of hallucinations and delusions.

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The predictive coding model of psychosis has become a leading framework for understanding the etiology of symptoms such as hallucinations and delusions. Briefly, this model suggests that a person's beliefs about the world (posterior beliefs) emerge from the integration of prior beliefs with information from external events. A mismatch between expectations and external events produces a prediction error, which is then used to update one's beliefs to ensure more efficient prediction of future events. According to this model, disrupted belief updating is what gives rise to the hallucinations and delusions that are characteristic of schizophrenia (1–3). For example, inappropriate overweighting of prior beliefs relative to incoming sensory information may result in the experience of hearing intelligible words in the presence of ambiguous stimuli, as demonstrated by Alderson-Day *et al.* (4). Indeed, abnormal prediction formation and error signaling among people with schizophrenia (PSZ) has been observed in multiple cognitive domains and sensory modalities, including auditory perception (5–13), visual perception (14–18), sensory and sensorimotor integration (19–24), learning (25–31), and decision making and reasoning (32,33).

An ongoing challenge to this framework is that although PSZ consistently exhibit disruptions in predictive coding compared with healthy comparison subjects (HCs) at the group level, efforts to establish specificity to the presence or severity of positive symptoms have yielded inconsistent findings. One example of these inconsistencies can be found within the mismatch negativity (MMN) literature. The MMN is an event-related potential (ERP) elicited when a simple auditory pattern (e.g., a sequence of identical tones) is infrequently interrupted by a stimulus that deviates along one or more dimensions such as pitch or duration. The magnitude of the resulting mismatch response is thought to reflect capacity for generating prediction errors (34), and the MMN has consequently been conceptualized as a prototypical sensory predictive coding paradigm (35,36). As might be expected, PSZ exhibit robust and reliable reductions in MMN amplitude [see (37) for a meta-analysis], which is consistent with work

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suggesting that aberrant prediction error signaling is a mechanism by which symptoms of psychosis emerge. Despite the conceptual appeal of this hypothesis, the relationship between MMN reduction and symptom severity has been observed inconsistently. Some groups have reported significant correlations between MMN amplitude and hallucinations [e.g., (10,11,38–40)], which have historically been attributable to overly strong priors rather than weak prediction error signaling (3). However, even this association has been observed inconsistently, and several others have found no such relationship, including at least one study with more than 800 PSZ [(41); see (42) for a meta-analysis].

We propose that there are at least 2 possible explanations for this inconsistent, but predominantly null, effect (although see the Discussion for a more complete list of contributing factors). First, it may be that MMN impairment is not reflective of hallucinations or delusions per se but rather is a generalized marker of the structural and functional brain changes that accompany a diagnosis of schizophrenia and the many risk factors associated with it. Alternately, it is possible that hallucinations and delusions are uniquely related to predictive coding phenomena that unfold at higher levels of abstraction, as in complex learning or sensory integration tasks. That is, low-level perceptual prediction errors such as those elicited by a simple MMN paradigm [i.e., those that can be elicited even in the absence of consciousness (43)] may lack sufficient complexity to account for the presence or severity of hallucinations and delusions. To test the first hypothesis, we turned to individuals who experience substantially less disorganization, disability, and distress but nevertheless experience hallucinations and unusual beliefs at a level comparable to that of PSZ (nonclinical voice hearers [NCVHs]). We measured MMN amplitude in a sample of NCVHs and compared them with PSZ and HCs. If the conceptualization of the MMN as a marker of predictive coding abnormalities relevant for developing positive symptoms is supported, it is expected that MMN amplitude in NCVHs would be comparable to that of PSZ, and both would be reduced compared with MMN amplitude in HCs.

To test the second hypothesis, we used 2 MMN paradigms that relied on differing levels of abstraction: one with a lower-level deviant type (duration deviant) and one with a higher-level deviant type (pattern-violation deviant). If the prediction that symptoms are uniquely associated with higher-order predictive processes was supported, we would expect that hallucination and delusion severity would be more strongly associated with prediction errors generated by the pattern-violation deviant (pMMN) than the duration deviant (dMMN). Relatedly, we examined the repetition positivity (RP) effect. The RP is an ERP that is elicited in response to the standard tones and that increases in amplitude with an increasing number of standard stimulus repetitions (44). Therefore, the RP is considered an index of the formation of the auditory memory trace, which permits an individual to establish an auditory environment in which deviant stimulus types can occur (45,46). Within the context of the predictive coding model, Baldeweg (47) and others [e.g., (34)] have suggested that the RP may index higher-order sensory processing that projects prediction signals to lower sensory levels within the hierarchy regarding the expected incoming auditory information. Therefore, we consider the slope of the RP (i.e., the increase in RP amplitude with increasing numbers of standard tones) to reflect this higher-order predictive process. We predicted that, if higher-order prediction formation and error signaling were to exhibit stronger associations with positive symptom severity, the RP slope would be 1) disrupted in both the NCVH and PSZ groups and 2) associated with positive symptom severity.

METHODS AND MATERIALS

Participants

Three groups of participants were included in the current study: 56 individuals who met criteria for schizophrenia or schizoaffective disorder (PSZ), 34 individuals who reported hearing voices but did not meet criteria for a psychiatric illness (NCVHs), and 48 individuals who did not report a history of hearing voices and did not meet criteria for a psychiatric illness (HCs) (Table 1). All PSZ were clinically stable outpatients and did not have any medication changes for at least 4 weeks prior to testing. They were purposefully recruited with varying degrees of symptom severity ranging from hearing no voices during the past week (PSZH−; n = 20) to hearing moderately severe voices during the past week (PSZH+; n = 36), as indicated by a score of 1 (PSZH−) or ≥3 (PSZH+) on the Brief Psychiatric Rating Scale (BPRS) (48) hallucinations item. NCVHs were recruited using advertisements seeking individuals who reported being clairaudient, with the vast majority of this group reporting hearing moderately severe voices over the past week as indicated by a score of ≥3 on the BPRS hallucinations item (n = 29 of 34). NCVHs were otherwise screened using the same inclusion and exclusion criteria as HCs; none of the NCVHs exhibited evidence of functional impairment that is required for a diagnosis of schizophrenia.

The 3 groups were statistically similar on parental education, a proxy measure of socioeconomic status; however, they differed significantly with respect to age, gender, race, and education. Given the known impact of age on estimates of MMN amplitude (49), age was used as a covariate for all electroencephalography (EEG) analyses[1]. Diagnosis was confirmed using the Structured Clinical Interview for DSM-5 (50), as well as a review of medical records and informant reports when appropriate. Chlorpromazine dose equivalents were calculated according to the formula recommended by Andreasen *et al.* (51). All NCVHs were confirmed to be free from a psychotic disorder using the Structured Clinical Interview for DSM-5, denied being prescribed or taking any antipsychotic medication, and reported no first-degree relatives with a diagnosis of a psychotic disorder. HCs were recruited from the surrounding communities via advertisements and had no current psychiatric diagnoses, were not taking psychiatric medications, and reported no first-degree relatives with psychosis. All participants were between the ages of 18 to 67 years and reported no history of neurological injury. All study participants were recruited from the Maryland Psychiatric Research Center, the Connecticut Mental Health Center, and the surrounding Baltimore and New Haven communities. All study procedures were approved by the University of Maryland

[1]The assumption of across groups was met as evidenced by a nonsignificant age × diagnostic group interaction effect in all statistical tests (Fs < 1.80; ps > .18).

Table 1. Demographic, Clinical, and Cognitive Variables

	HCs, n = 48	NCVHs, n = 34	PSZ, n = 56	Statistics
Site, Maryland:Yale	32:16	21:13	44:12	$\chi^2_2 = 3.32$; $p = .19$
Gender, F:M:O	30:18:0	26:8:0	17:39:0	$\chi^2_2 = 20.78$; $p < .001$
Age, Years	37.21 ± 13.30	49.82 ± 10.49	34.43 ± 10.54	$F_{2,135} = 19.83$; $p < .001$
Race, A:AA:C:Other	3:9:30:6	5:2:27:0	4:20:28:4	$\chi^2_6 = 18.01$; $p < .01$
Education, Years	16.30 ± 2.20	15.35 ± 2.50	13.96 ± 1.88	$F_{2,132} = 14.94$; $p < .001$
Parental Education	15.16 ± 3.25	14.15 ± 2.78	14.55 ± 2.50	$F_{2,129} = 1.31$; $p = .28$
CPZ Dose Equivalent, mg/day	–	–	366.19 ± 285.58	–
BPRS Total	1.08 ± 0.11	1.76 ± 0.33	1.76 ± 0.40	$F_{2,127} = 68.67$; $p < .001$
BPRS hallucinations	1.00 ± 0.00	4.47 ± 1.01	3.30 ± 1.89	$F_{2,127} = 67.67$; $p < .001$
BPRS delusions	1.00 ± 0.00	4.47 ± 1.04	2.91 ± 1.60	$F_{2,127} = 82.14$; $p < .001$
BPRS positive	1.01 ± 0.04	3.68 ± 0.59	2.64 ± 1.19	$F_{2,127} = 98.97$; $p < .001$
BPRS negative	1.05 ± 0.24	1.14 ± 0.46	1.71 ± 0.54	$F_{2,127} = 31.78$; $p < .001$
BPRS disorganized	1.02 ± 0.08	1.11 ± 0.24	1.30 ± 0.42	$F_{2,127} = 11.25$; $p < .001$
LSHS Total	8.25 ± 7.22	23.42 ± 8.54	23.29 ± 9.31	$F_{2,128} = 46.29$; $p < .001$
WTAR	115.3 ± 12.15	113.47 ± 9.34	104.76 ± 14.17	$F_{2,131} = 10.22$; $p < .001$
MCCB Processing Speed	55.98 ± 12.97	53.76 ± 8.30	42.20 ± 11.57	$F_{2,130} = 20.57$; $p < .001$
MCCB Working Memory	54.23 ± 8.49	50.00 ± 9.46	44.56 ± 11.95	$F_{2,130} = 10.87$; $p < .001$
MCCB Verbal Learning	48.98 ± 8.02	47.30 ± 8.17	41.85 ± 9.96	$F_{2,130} = 8.54$; $p < .001$

Values are presented as mean ± SD or n.

A, Asian; AA, African American; BPRS, Brief Psychiatric Rating Scale; C, Caucasian; CPZ, chlorpromazine; F, female; HCs, healthy comparison subjects; LSHS, Launay-Slade Hallucinations Scale; M, male; MCCB, MATRICS Consensus Cognitive Battery; NCVHs, nonclinical voice hearers; O, other; PSZ, people with schizophrenia; WTAR, Wechsler Test of Adult Reading.

and Yale University Institutional Review Boards, and informed consent was obtained from all participants.

Neuropsychological and Symptom Measures

To assess the characteristics of participants' experiences with hearing voices, unusual beliefs, and other symptoms associated with schizophrenia, the BPRS (48) and the Launay-Slade Hallucinations Scale (52) were administered. To assess neuropsychological function, the Wechsler Test of Adult Reading (53) and subtests for 3 cognitive domains (processing speed, working memory, and verbal learning) from the MATRICS Consensus Cognitive Battery (54) were used.

MMN Paradigm

Participants completed 2 versions of the MMN paradigm, dMMN and pMMN, in separate blocks recorded during the same session. The order of the blocks was randomly selected for each participant. In both conditions, stimuli consisted of stimulus trains of 6 auditory tones; each stimulus train was separated by 750 ms, and each stimulus within the train was separated by 330 ms. In the dMMN condition, all stimuli were 800 Hz and 58 dB, with a 5-ms rise/fall time. Standard stimulus trains (87.5% of trials) consisted of 6 identical 100-ms tones, whereas deviant stimulus trains (12.5% of trials) were characterized by a 50-ms tone in the fourth position in the stimulus train (Figure 1A). In the pMMN condition, all stimuli were 58 dB and 100 ms in duration, with a 5-ms rise/fall time. Standard stimulus trains (87.5% of trials) consisted of 6 tones alternating between 800 and 1200 Hz, whereas deviant stimulus trains (12.5% of trials) consisted of a repeated 1200-Hz tone in the fourth position in the stimulus train (Figure 1D). Thus, we conceptualize the pMMN as reflecting a higher-level mismatch response compared with the dMMN because detection of a deviant stimulus in this condition requires a prediction about the relationship between tones rather than a simple comparison between 2 tones. Each condition consisted of 800 stimulus trains, with deviant stimulus trains being pseudorandomly distributed within each block of 400 trains. While listening to the auditory stimuli, participants watched a black-and-white silent cartoon to minimize the impact of attentional engagement on MMN amplitude.

EEG Acquisition and Preprocessing

EEG was collected using a 64-channel Brain Products ActiCHamp system at 1 kHz with a cascaded integrator-comb antialiasing filter (half-power cutoff at 499 Hz). All EEG channels were referenced to a single electrode placed on the tip of the nose. Horizontal electrooculogram was recorded by placing 1 electrode on the outer canthi of each eye, and vertical electrooculogram was recorded by placing 1 electrode underneath the left eye. Finally, 1 electrode was placed on each mastoid as an alternative reference. For all EEG analyses, the nose reference was used; however, all effects described below were also observed using a mastoid reference.

Offline data processing was conducted in MATLAB (version 2022a; The MathWorks, Inc.) using EEGLAB (55) and ERPLab (56) toolboxes. Data were first high-pass filtered at 0.05 Hz and underwent visual inspection to identify bad channels for interpolation followed by artifact correction using independent components analysis. Data were then segmented from −100 to 300 ms relative to the onset of the fourth stimulus in all stimulus trains and adjusted to the 100-ms prestimulus period. Epochs containing amplitudes greater than ±200 μV or peak-to-peak amplitudes that exceeded ±150 μV within a 200-ms

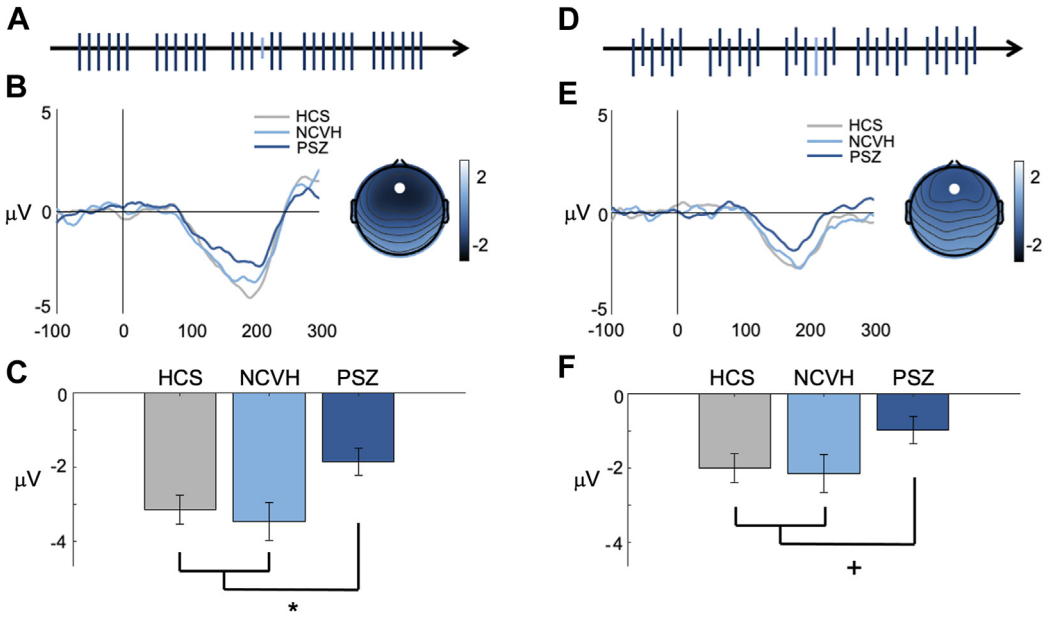

Figure 1. Mismatch negativity (MMN) effect for the duration and repeat conditions. **(A)** Schematic drawing of the duration mismatch condition, with the light blue line representing a duration deviant. **(B)** Event-related potential traces depicting the duration MMN effect, separately by group, at scalp site Fz. **(C)** Age-adjusted duration MMN mean amplitude. **(D)** Schematic drawing of the repeat mismatch condition, with the light blue line representing a deviant repeat stimulus. **(E)** Event-related potential traces depicting the pattern-violation MMN effect, separately by group, at scalp site Fz. **(F)** Age-adjusted pattern-violation MMN mean amplitude. HCS, healthy comparison subject; NCVH, nonclinical voice hearer; PSZ, people with schizophrenia. $^{*}p < .05$, $+p < .10$.

moving window were excluded from analysis. Finally, a visual inspection of the data was conducted to remove any remaining artifacts, and ERPs were created using the remaining artifact-free trials followed by the application of a 30-Hz low-pass filter. HCs, NCVHs, and PSZ retained statistically similar portions of trials in both the dMMN condition (percentage of trials retained = 86.57%, 87.22%, and 86.10%, respectively; $F_{2,137}$ = 0.12; p = .89) and pMMN condition (percentage of trials retained = 85.84%, 88.61%, and 86.69%, respectively; $F_{2,137}$ = 0.85; p = .43).

Both dMMN and pMMN were computed by subtracting the deviant stimulus ERP from the standard stimulus ERP that preceded it. dMMN and pMMN amplitude was then calculated at the mean amplitude of the resulting difference wave between 125 and 225 ms poststimulus. Additionally, the RP was calculated by creating ERP averages from the fourth tone in the second and third standard stimulus trains (RP 2–3), the fourth tone in the fifth and sixth standard stimulus trains (RP 5–6), the fourth tone in the eighth and ninth standard stimulus trains (RP 8–9), and the fourth tone from the 11th to 15th standard stimulus trains (RP 11+), collapsed across the 2 MMN conditions. The amplitude of the RP effect for each of the 4 RP ERPs was calculated as the mean amplitude between 125 and 225 ms poststimulus.

RESULTS

Symptom Ratings and Cognitive Functioning

As shown in Table 1, NCVHs reported a pattern of experiences in which positive symptom ratings were significantly higher than those of PSZ; independent samples t tests revealed that NCVHs endorsed a significantly greater severity of hallucinations (t_{84} = 3.73; $p < .001$) and bizarre beliefs on the BPRS (t_{84} = 5.44; $p < .001$) than PSZ. By contrast, NCVHs exhibited significantly fewer negative and disorganized symptoms than PSZ ($ts_{84} > 2.74$; $ps < .01$). A more comprehensive discussion of the similarities and differences between the experiences reported by the NCVH and PSZ groups is presented in Gold *et al.* (57). Interestingly, NCVHs also exhibited a pattern of cognitive functioning that was significantly higher than that of PSZ ($ts_{85} > 2.22$; $ps < .05$) and comparable to that of HCs with the exception of the working memory domain, in which their performance was significantly poorer than that of HCs (t_{75} = 2.06; p = .02) but still better than that of PSZ (t_{85} = 2.22; p = .01). As expected, HCs endorsed significantly fewer symptoms and exhibited higher cognitive functioning than PSZ on all measures.

Duration and Repeat MMN

Figures 1B and 1E depict the dMMN and pMMN by group, as well as the scalp distribution of the effect. Figures 1C and 1F depict the age-adjusted mean amplitude of the dMMN and pMMN, respectively. A 2 × 3 (condition × group) repeated-measures analysis of covariance with age as a covariate revealed a significant effect of age across all participants ($F_{1,134}$ = 5.73; p = .018), a significant effect of condition ($F_{1,134}$ = 4.41; p = .038) such that pMMN amplitudes were smaller than dMMN amplitudes for all 3 groups ($ps < .05$), and a significant effect of diagnosis ($F_{2,134}$ = 4.98; p = .008). There was no condition × group interaction ($F_{2,134}$ = 0.18; p = .838). Pairwise comparisons revealed that PSZ had significantly reduced dMMN compared with both HCs (p = .017) and

NCVHs (p = .018), whereas HCs and NCVHs did not differ from one another (p = .649). With respect to the pMMN, PSZ once again exhibited the overall pattern of reduced amplitude compared with HCs (p = .055) and NCVHs (p = .077); however, these effects did not rise to the level of statistical significance. HCs and NCVHs were again statistically similar with respect to pMMN amplitude (p = .820).

To expand upon the group effects, PSZ were further subdivided into PSZ who reported experiencing hallucinations during the past week, as evidenced by a BPRS hallucinations score ≥ 3 (PSZH+; n = 20), and PSZ who reported experiencing no hallucinations during the past week, as evidenced by a BPRS hallucinations score of 1 (PSZH−; n = 36). We found that PSZH+ exhibited statistically similar MMN amplitude compared with PSZH− in both the duration (p = .944) and pattern-violation (p = .251) conditions.

Repetition Positivity

Figure 2 depicts the ERP traces for the duration (Figure 2A) and pattern-violation (Figure 2B) conditions, as well as the age-adjusted RP amplitudes across the 3 groups (Figure 2C). A 4 × 2 × 3 (repetition length × condition × group) repeated-measures analysis of covariance with age as a covariate revealed a significant effect of age across all participants ($F_{1,134}$ = 4.37; p = .038), but no significant effect of repetition length ($F_{3,402}$ = 0.39; p = .76), condition ($F_{1,134}$ = 0.86; p = .355), or diagnostic group ($F_{2,134}$ = 0.67; p = .512). However, we did observe a significant repetition length × group ($F_{6,402}$ = 2.54; p = .020) and condition × group interaction ($F_{2,134}$ = 3.41; p = .036).

To further examine the repetition length × group effect, the slope of the RP across all 4 repetition lengths was estimated for each participant, separately for each condition. These slopes were then entered into a 2 × 3 (condition × group) analysis of covariance with age as a covariate. There was no significant effect of age ($F_{1,134}$ = 0.73; p = .396) or condition ($F_{1,134}$ = 0.24; p = .625). There was a significant effect of diagnostic group ($F_{1,134}$ = 3.55; p = .031), with pairwise contrasts revealing that HCs had a significantly larger (more positive) slope than PSZ in the duration condition (0.135 vs. −0.030; p = .028) and a larger slope than NCVHs in the duration condition at a trend level (0.135 vs. −0.035; p = .064). In the pattern-violation condition, both HCs and NCVHs exhibited numerically larger (more positive) slopes than PSZ (0.008 and 0.029 vs. −0.128, respectively); however, these effects did not rise to the level of statistical significance (ps = .059 and .078). When subdividing PSZ into PSZH+ and

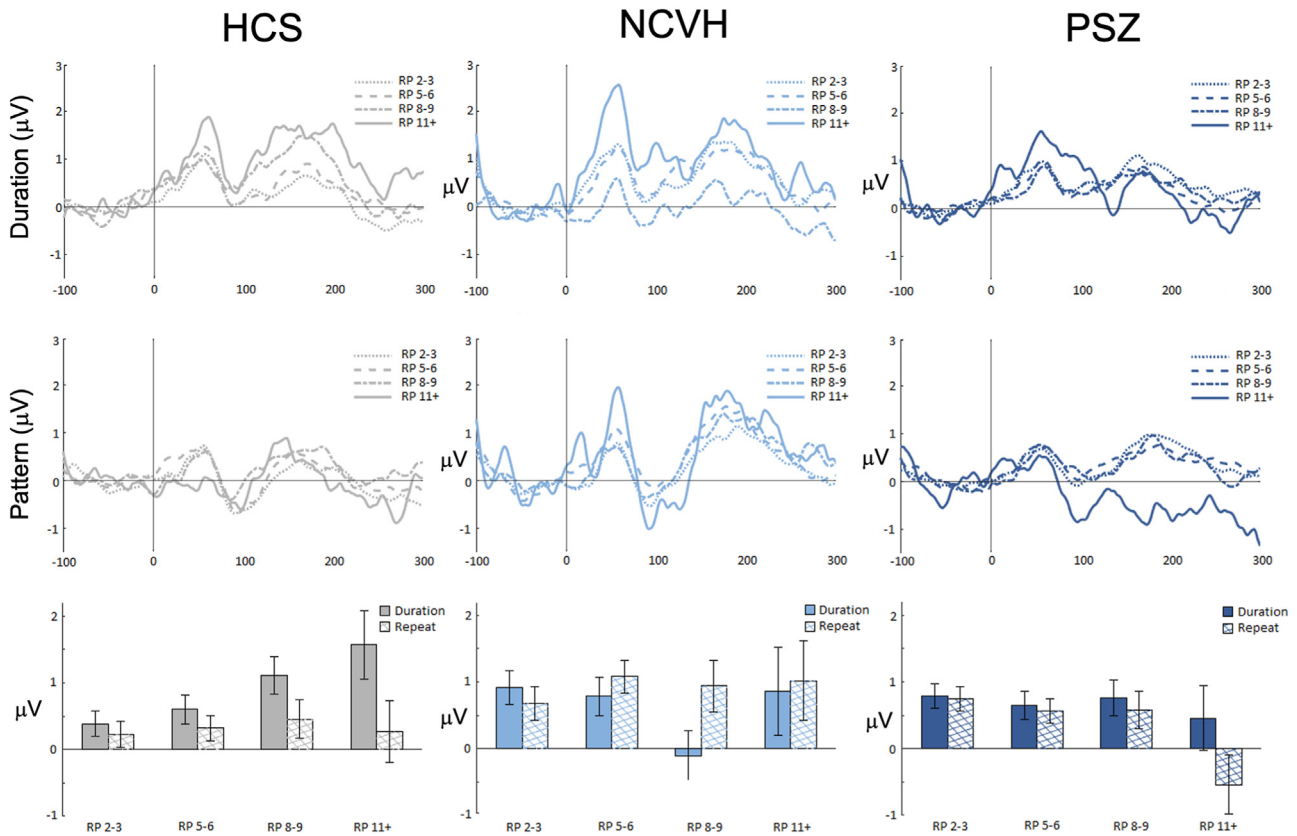

Figure 2. Repetition positivity (RP) effect, collapsed across duration and pattern mismatch negativity conditions. RP measured from the fourth tone of the second to third stimulus trains (RP 2–3), the fourth tone of the fifth to sixth stimulus trains (RP 5–6), the fourth tone of the eighth to ninth stimulus trains (RP 8–9), and the fourth tone of the 11th to 15th stimulus trains (RP 11+) since the last deviant train. HCS, healthy comparison subject; NCVH, nonclinical voice hearer; PSZ, people with schizophrenia.

Table 2. Spearman Correlations Between Symptom Severity, Cognitive Functioning, and Event-Related Potential Measures

	dMMN Amplitude			pMMN Amplitude			Duration RP Slope			Pattern-Violation RP Slope		
	HCs	NCVHs	PSZ	HCs	NCVHs	PSZ	HCs	NCVHs	PSZ	HCs	NCVHs	PSZ
BPRS Hallucinations	–	0.20	0.03	–	0.13	0.16	–	−0.12	−0.05	–	−0.15	0.19
BPRS Delusions	–	0.30	−0.13	–	0.15	0.20	–	−0.06	−0.10	–	−0.12	0.14
BPRS Positive	−0.07	0.18	0.00	−0.04	0.09	0.11	0.22	−0.16	−0.12	−0.07	−0.14	0.18
BPRS Negative	0.26	0.06	0.14	0.22	−0.21	0.01	0.34	−0.07	−0.01	0.02	0.08	0.00
BPRS Disorganized	0.13	0.31	0.07	0.23	−0.09	0.10	0.15	−0.13	−0.12	−0.08	0.14	0.20
LSHS Total	−0.26	−0.16	−0.06	−0.01	0.13	−0.09	0.10	0.22	−0.24	−0.11	0.36	0.14
WTAR	−0.10	−0.28	−0.10	0.04	−0.09	−0.09	−0.22	0.11	0.01	0.11	−0.31	−0.13
MCCB Processing Speed	0.00	0.12	0.13	−0.08	−0.01	0.21	0.05	0.33	0.04	0.24	−0.16	0.05
MCCB Working Memory	−0.10	0.06	0.13	−0.10	−0.08	0.00	−0.03	0.25	−0.00	−0.01	−0.29	−0.12
MCCB Verbal Learning	−0.02	−0.05	0.09	0.14	−0.03	−0.10	0.02	−0.16	−0.12	0.16	−0.42	−0.08

Note that BPRS hallucinations and delusions items were "1" for all HCs, and therefore, no correlation is reported.

BPRS, Brief Psychiatric Rating Scale; dMMN, duration MMN; ERP, event-related potential; HCs, healthy comparison subjects; LSHS, Launay-Slade Hallucinations Scale; MCCB, MATRICS Consensus Cognitive Battery; MMN, mismatch negativity; NCVHs, nonclinical voice hearers; pMMN, pattern-violation MMN; PSZ, people with schizophrenia; RP, repetition positivity; WTAR, Wechsler Test of Adult Reading.

PSZH−, we observed that the 2 patient groups did not differ in slope for the duration condition (p = .633); however, they did differ significantly in the pattern-violation condition such that PSZH− exhibited a higher (i.e., less negative) slope than PSZH+ (−0.055 vs. −0.258, p = .042).

Correlations With Symptom and Cognitive Measures

The correlations between dMMN amplitude, pMMN amplitude, RP slopes for both conditions, and all clinical and cognitive measures are presented in Table 2. No correlations remained significant following false discovery rate (58) correction.

DISCUSSION

The current study was conducted to test the hypothesis that MMN impairment is associated with the presence and/or severity of hallucinations and delusions, irrespective of the presence of a psychotic illness. We also tested the hypothesis that these unusual experiences are more strongly associated with prediction formation and prediction error signaling at higher levels of abstraction as evidenced by pMMN amplitude and RP slope than with dMMN amplitude. Interestingly, we observed that NCVHs exhibited no evidence of impairment in either dMMN or pMMN amplitude. Both NCVH and HC groups exhibited a significantly larger dMMN than PSZ despite participants in the NCVH group reporting significantly greater severity of hallucinations and delusions on average as assessed by the BPRS. These data strongly suggest that the MMN impairment that is so robustly and consistently observed in PSZ (37) reflects a more generalized feature of schizophrenia and/or the multitude of social, genetic, environmental, and cognitive risk factors that accompany the diagnosis rather than a marker of predictive coding that is linked to the expression of hallucinations and delusions specifically.

By contrast, the results from the pMMN and RP analyses were more equivocal. With respect to the pMMN, NCVHs were once again statistically similar to HCs; however, the magnitude of impairment among PSZ compared with these 2 nonclinical groups only reached a trend level. These findings are consistent with those of Avissar *et al.* (59), indicating that more complex MMN paradigms yield smaller group effects among PSZ, and they can be explained by the fact that the pMMN was significantly smaller than the dMMN for all 3 groups. Because PSZ already exhibited an attenuated dMMN, it is unsurprising that the relative decrease in pMMN amplitude was somewhat smaller for patients than for the nonclinical groups, who exhibited a more robust dMMN. A similar pattern of mixed results emerged from the RP analysis: although HCs exhibited steeper RP slopes than PSZ in the duration condition, the strength of the repetition effect was noticeably weaker in the pattern-violation condition, and accordingly, there were no between-group differences that rose to the level of statistical significance. When we tested the prediction that pMMN and RP slopes would exhibit a stronger association with positive symptoms than dMMN, we observed a persuasive null effect; that is, the dMMN, the pMMN, and the RP slopes for either condition did not show any evidence of an association with symptom severity or cognitive functioning, consistent with previous reports (42).

The above observations present a significant but not insurmountable challenge for the predictive coding hypothesis in schizophrenia. That is, the preponderance of the literature has described a null relationship between positive symptoms and MMN amplitude, whereas other predictive coding paradigms have elicited prediction errors that seem to be more consistently associated with symptom severity (14,22). We speculate that prediction formation and prediction error signaling at low levels of abstraction such as those elicited by even higher-order, pattern-violation MMN paradigms are simply not sufficiently complex to show an association with positive symptom severity. It may be true that predictive coding processes such as those that engage sensorimotor integration or decision making are more relevant for the emergence of hallucinations and delusions. One important caveat to this speculative conclusion is that there may be other reasons for the lack of correlation between symptom severity and MMN/RP that cannot be ruled out at this time. For example, the use of antipsychotic medication that consistently attenuates positive symptoms but inconsistently affects MMN amplitude (60) may obscure a true relationship between these variables.

Alternately, the well-known problems associated with unstable estimates of positive symptom severity given the dynamic nature of these experiences may similarly diminish the strength of the correlations, even if a true relationship exists. Another consideration is that the mechanisms that give rise to the emergence of positive symptoms may not be the same mechanisms that contribute to their maintenance once they have already developed. Accordingly, the existence of a true relationship between the predictive coding phenomena indexed by the MMN and positive symptom severity cannot be definitively ruled out at this time.

Finally, there were some limitations to the current study. First, NCVH participants tended to be older and were predominantly female relative to PSZ participants. Given that the MMN amplitude is affected by age, statistical corrections were necessary to account for this key demographic difference. However, we cannot rule out the contribution of gender differences at this time. Second, although we observed a significant RP disruption in PSZ, we note that other groups have observed no evidence of RP impairment in this patient population (10,40). These studies used a "roving standard" MMN paradigm, which Cooper *et al.* (45) have argued may be better suited for eliciting an RP than static standard tones such as those used in the current study. Finally, although NCVHs and currently hallucinating PSZ reported nearly identical intensity of hallucinations and conviction of unusual beliefs, it remains an open question whether these experiences can truly be conceptualized as operating on the same continuum as one another. As described by Gold *et al.* (57), this group of NCVHs had less distress and experienced greater control over their voices and reported significantly less paranoia, passivity, and alterations in self-experience. Thus, although the sensory experience and belief conviction were highly similar across the 2 groups, there were notable differences in the content and emotional experience associated with these symptoms, and the possibility that they emerge via different neural mechanisms cannot be ruled out.

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ARTICLE INFORMATION

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