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Neural Indicator of Altered Mismatch Detection Predicts Atypical Cognitive-Perceptual Experiences in Psychotic Psychopathology

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Background: **Atypical auditory processing (AAP) in psychotic psychopathology is evident in early (N1), mid-latency (P2/N2/mismatch negativity), and late (P3) neural responses. The influence of attention on AAP, and how temporal stages of AAP are associated with phenomenology of psychotic psychopathology are not well understood.** ***Methods:*** **We used a directed attention oddball task to characterize stages of AAP in psychosis and to examine the influence of selective attention. Ninety patients with schizophrenia (SCZ), 53 patients with bipolar disorder (BP), 90 healthy controls and 72 first-degree relatives of SCZ (SREL) were studied. We used principal components analysis to decompose average-reference 64-channel subject-level ERPs.** ***Results:*** **Altered attentional modulation was evident in SCZ at early (N1 factor) and late (P3 factor) stages of AAP, but not at mid-latency P2 factor. Irrespective of condition, N1 and P3 were reduced in SCZ, which predicted greater psychopathology and schizotypal personality traits. Diminished mid-latency mismatch detection (P2 factor) was evident in SCZ, BP, and SREL and was associated with greater positive symptoms of psychosis as well as self-reported atypical cognitive-perceptual experiences.** ***Conclusions:*** **Attentional modulation of early N1, and later P3 neural responses was atypical in patients, but the degree of attentional modulation did not relate to symptom severity or schizotypal traits. Our findings suggest the link between mid-latency mismatch detection and atypical cognitive/perceptual experiences is not driven by attentional deficits alone and point to the promise of mid-latency mismatch detection as a candidate endophenotype and intervention target.**

Key words: schizophrenia/psychosis/auditory processing/EEG

Introduction

Background

Perceptual anomalies are commonly reported in people with psychosis. Researchers have sought to link such atypical perceptual processes to putative neural mechanisms with the goal of elucidating etiology, developing empirically-based diagnostic systems and establishing targeted interventions. Clarifying the neural mechanisms of altered perception in psychosis has been complicated by selective attention impairments in psychotic psychopathology.[1] Understanding when and how selective attention impacts neural responses is critical for understanding the nature of atypical perceptual processing and the relationship between perception and psychosis.[2] Directed attention oddball listening tasks can address the selective attention confound by explicitly manipulating attention.

Past work has shown that patients with schizophrenia (SCZ) and bipolar disorder (BP) fail to attentionally modulate early auditory processes as measured by the auditory N1 component.[3,4] However, less is known about attentional modulation of mid to late latency neural responses. Moreover, previous work has largely failed to link deficient attentional modulation with symptom severity. To further complicate the matter, schizophrenia has been linked to deficits in passive listening mismatch detection which, in theory, should be independent of selective attention impairment.[5,6] Thus, there is a need to clarify whether deficient attentional modulation is a key driving factor in the phenomenology of psychotic psychopathology.

Certain features of altered auditory processing are thought to be shared across SCZ and their first-degree biological relatives (SREL).[4,7] Previous reports have highlighted a variety of such potential electrophysiological endophenotypes including the N1 component (thought to reflect automatic sensory registration[8,9]), the mismatch negativity (a mid-latency component that modulates between standard and deviant tones during passive listening[5,6]), and the P3 component (a later component that has been linked to a wide range of cognitive processes including context updating and stimulus categorization[10–12]). Despite decades of such investigation, an

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unambiguous electrophysiological endophenotype of schizophrenia remains elusive. This is likely due in part to complications arising from comorbid mental disorders, and questionable reliability and validity of dichotomous DSM-based diagnoses.[13]

Alternatively, it is possible that previously reported endophenotypes of schizophrenia are reflective of a spectrum of psychotic experiences in which patients cluster towards one end of the spectrum, controls cluster toward the other end and first degree relatives of patients cluster somewhere in the middle. Here, we test whether neural aspects of auditory processing differ between DSM-based diagnostic groupings, while also investigating whether individual differences in neural responses relate to self-reported clinical symptom severity and schizotypal traits.

The current analysis uses data collected from over 300 individuals from two independent family studies of psychotic psychopathology to clarify: (*a*) the role of attention on stages of atypical auditory processing in psychosis, and (*b*) the degree to which atypical auditory processing is associated with categorical (i.e. DSM diagnosis) and dimensional (i.e. symptom severity and schizotypal personality traits) measures of psychotic psychopathology. We hypothesized that patient groups and individuals with greater psychotic symptomatology would show blunted N1 irrespective of direction of selective attention and rarity of stimuli, and blunted P3 responses to rare auditory stimuli.

Methods

Participants

Participants were recruited as a part of two separate studies through the Minneapolis VA Medical Center, community mental health programs, and fliers posted throughout the community. Previous publications have reported on subsets of this sample in the context of other experimental paradigms and self-report measures[14–22]; however this is the first report that (*a*) describes directed attention listening in these samples and (*b*) combines data across studies to maximize statistical power. Participants in the psychiatric groups were stable outpatients. Exclusion criteria for patients with schizophrenia, patients with bipolar disorder and healthy controls (CON) included intellectual disability (IQ < 70), drug or alcohol dependence in past 6 months, current or past central nervous system condition, epilepsy, history of electroconvulsive therapy, history of head injury with skull fracture or loss of consciousness longer than 30 min, and age under 18 or over 60. CON were also excluded if they had a history of psychotic disorder, current or past depressive or manic episodes, or family history of depression, mania, or psychotic disorder. First-degree relatives of SCZ were only excluded if they had a general medical condition that made study completion impossible.

Participants' IQ was estimated using the Wechsler Adult Intelligence Scale III (WAIS-III) Vocabulary and Block Design. Psychiatric symptom severity was assessed via the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I[23]), the Brief Psychiatric Rating Scale (BPRS[24]) and the Schizotypal Personality Questionnaire (SPQ[25]). A minimum of two trained raters (advanced doctoral students in clinical psychology, postdoctoral researchers, or licensed doctoral-level psychologists) reached consensus on all diagnoses.

Directed Attention Oddball Listening Task

A directed attention oddball listening task similar to that used by Schreiber and colleagues[26] was administered using Neurobehavioral Systems' Presentation software on a Dell Computer running Windows XP. Tones were presented via headphones at 96dB over a 55dB background of white noise. Four tones of distinct pitch were presented in a pseudorandomized order. Each tone was presented separately (i.e. tones were not played simultaneously) with a duration of 100 ms, 10ms rise/fall time and a jittered intertrial interval of 1200–1500 ms. Participants completed four task blocks with each block consisting of 200 trials.

In the first block, participants were instructed to attend to the left ear and click a mouse with their right index finger when they heard the high tone in their left ear (see figure 1A). This high target tone had a pitch of 2400 Hz and was presented infrequently (10% of all trials). The low tone in the attended ear had a frequency of 1600 Hz and was presented frequently (40% of all trials). In the unattended ear, an infrequent tone (1200 Hz; 10% of all trials) and frequent tone (800 Hz; 40% of all trials) were played. In the second block, the stimuli presentation was identical, but participants were instructed to attend to the right ear instead of the left and to click the mouse when they heard the infrequent 1200 Hz tone in their right ear. For the third and fourth block, the headphones were reversed on the participant's head such that the tones presented to the right ear in blocks 1 and 2 were in the left ear for blocks 3 and 4. Otherwise, stimuli presentation and task instructions were identical for blocks 3 and 4. Further information regarding the task can be found in a previous publication from our group.[4]

EEG Collection/Analyses

For study 1, EEG data were collected using a BioSemi ActiveTwo system with a differential amplifier and a high-density electrode cap. At the beginning of the study, a 64-electrode cap was used, but was upgraded to a 128-electrode cap halfway through the project (see supplemental figure 5 for a comparison of 64 and 128 channel montage amplitudes; we did not observe significant differences). For study 2, EEG data were collected

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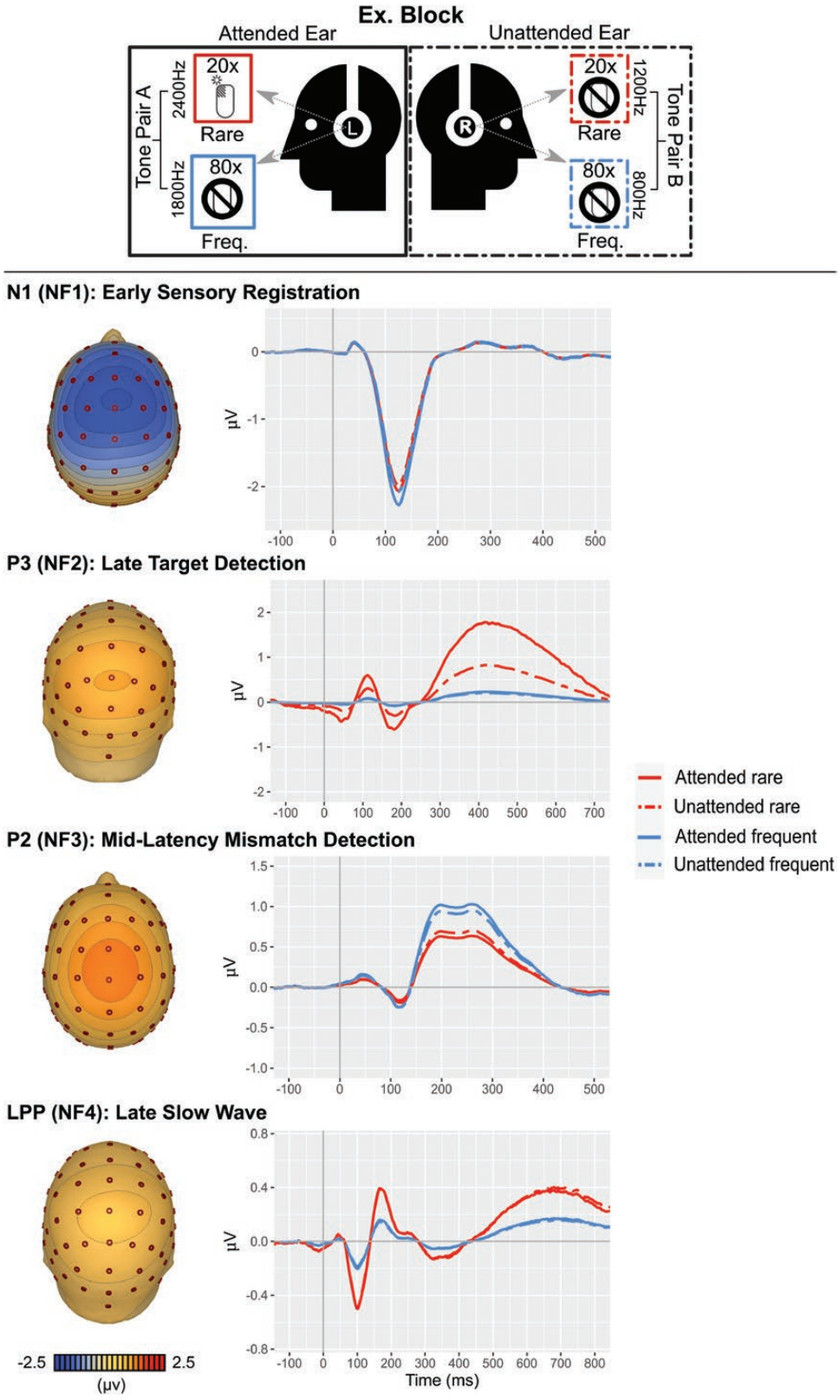

Fig. 1. Neural responses by condition. (Top) An example task block in which the participant is instructed to attend to their left ear and click a mouse upon hearing the higher tone in the attended ear. (Main) Grand average factor topographies and waveforms disaggregated into conditions of interest.

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using a BrainVision actiCHamp EEG system and a 128-electrode cap. BioSemi and Brainvision montages were radially organized centered on Cz, but electrodes were not identically located between systems. During acquisition, the BioSemi data were sampled at 1024 Hz and referenced to ear electrodes while the Brainvision data were sampled at 1000 Hz and referenced to the Cz electrode. Common mode sense (CMS) and driven right leg (DRL) ground electrodes were used for BioSemi recordings while the Fpz electrode served as a ground electrode for Brainvision recordings.

Offline, both sets of data were high-pass filtered at 0.5 Hz and then were resampled to 256 Hz using Matlab's resample function which implements an anti-aliasing lowpass filter that prevents frequencies above the Nyquist frequency (128 Hz in this case) from aliasing during downsampling. Non-neural artifacts were removed using a custom ICA algorithm.[27] Cleaned data were re-referenced to the average head signal.

128-channel BioSemi and Brainvision data were interpolated to a common 64-channel BioSemi montage using the spherical spline approach.[28,29] Subject-level average ERPs were computed for a total of eight conditions (2 attention conditions × 2 oddball conditions × 2 pitch conditions) and baseline corrected using a –150 ms to 0ms baseline period. Only correct trials were included in subject-level average ERPs and individuals were excluded if they had less than 15 (out of 40) correct trials for the higher pitched target tone or the lower pitched target tone. Groups did not differ in number of usable trials per condition (see supplemental table 1; $F(21, 2107) = 1.51$, $P = .163$)

Subject average ERPs were submitted to a covariance matrix based temporal promax-rotated principal components analysis (PCA) using the EPtoolkit.[30] The kappa for the Promax rotation was set at 3. Factor retention was determined based on visual inspection of the eigenvalue scree plot after Promax rotation and the interpretability of resultant factor waveforms. A separate PCA was run for each study to inspect whether similar factors emerged in both studies. Dependent variables were derived by computing the mean of the temporal factor waveforms from 0-900ms pooled across frontal (N1 factor: F1, FZ, F2, FC1, FCz, FC2, and Cz), central (P2 factor: FC1, FCz, FC2, C1, Cz, C2, and CPz) and parietal (P3 & LPP factor: P1, Pz, P2, PO3, PO4, and POz) electrode sites (see figure 1). The choice of time window is arbitrary because the between and within subject effects will be identical irrespective of the time-window chosen (see supplemental figure 6).[31]

Categorical PCA analyses were performed via repeated measures ANOVA (RM-ANOVA) with group (four levels) specified as a between-subject factor, gender as a covariate, and attention (attended vs. unattended tones), oddball (frequent vs rare tones) and pitch (higher vs lower tones) as within-subject factors. Due to substantial amplitude differences between EEG systems, electrophysiological variables were scaled across groups and conditions for each study prior to statistical analysis. All post hoc comparisons were FDR corrected with each component corrected independently and alpha was set at .05. The number of post hoc comparisons assumed per RM-ANOVA depended on the significance of the omnibus test statistics (e.g. a significant main effect of group was followed up with $k(k-1)/2$ comparisons where k = number of groups).

Results

Demographic, Clinical & Behavioral Measures

Participant demographic, clinical and behavioral information is presented in table 1. SCZ reported less education, and were younger than other groups. SCZ exhibited the most psychiatric symptoms (BPRS Total) and schizotypal traits (SPQ Total), with BP second highest and SREL higher than CON. SCZ gender distribution was more male than other groups and the SREL gender distribution was more female than the other groups. Groups did not significantly differ in self-reported hearing loss or handedness. SCZ and BP exhibited fewer hits and slower response times compared to SREL and CON. Target discrimination (signal detection measure d′[32]) was impaired in BP and SCZ compared to SREL, but only BP differed from CON. SCZ and BP exhibited more conservative response patterns (signal detection measure C) than SREL, but BP did not significantly differ from CON while SCZ did.

PCA-derived Neural Factors

Separate temporal PCAs for each study based on subject average ERPs yielded similar neural factors. Tucker's congruence coefficients for the four neural factors (NFs) were 0.949, 0.904, 0.954, and 0.751 respectively.[33] Thus, the first three NFs showed a high degree of similarity between studies. Because the fourth factor was associated with a smaller coefficient, suggesting poor replication between studies, we have relegated analysis of this factor to the supplemental materials.

As presented in figure 1, the first neural factor (NF1) featured topographical and temporal characteristics closely resembling the classical auditory N1 ERP response.[34,35] The second neural factor (NF2) resembled an auditory P3 response[10] with a centroparietal peak around 400 ms that was most potentiated by attended infrequent (i.e. target) tones. The third factor (NF3) featured a positive centro-frontal mid-latency deflection that was most sensitive to stimulus rarity (i.e. oddball) and thus shared key characteristics with the P2 and mismatch negativity (MMN).[5]

Early Sensory Registration: NF1 as N1

Factor waveforms disaggregated by group and interactions of interest are depicted in figure 2 and

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Table 1. Participant Demographic Characteristics and Symptom Ratings

Index	SCZ (n = 90)	BP (n = 53)	CON (n = 90)	SREL (n = 72)	Statistics	Post Hoc Contrasts
Percent female	28%	24%	46%	58%	$\chi^2(3) = 23.27$, $P < .001$	SCZ,BP,CON<SREL
Age	41.48 (11.37)	46.59 (10.34)	46.47 (10.78)	44.11 (10.64)	$F(3, 301) = 4.02$, $P = .008$	SCZ<BP, CON
Estimated IQ(WAIS-III)	98.09 (16.05)	100.7 (12.71)	108.61 (14.75)	107.46 (16.83)	$F(3, 297) = 8.92$, $P < .001$	SCZ, BP<CON, SREL
Education	13.69 (2.02)	14.67 (2.42)	15.2 (1.88)	14.64 (2.04)	$F(3, 300) = 7.72$, $P < .001$	SCZ<BP, CON, SREL
Self-reported hearing	2.2 (0.54)	2.47 (0.82)	2.17 (0.48)	2.25 (0.73)	$F(3, 239) = 2.44$, $P = .065$	N/A
Handedness	4.25 (1.45)	4.5 (1.17)	4.34 (1.37)	4.48 (1.29)	$F(3, 283) = 0.52$, $P = .672$	N/A
Overall symptomatology (BPRS total)	46.09 (12)	37.38 (9.61)	28.26 (4.38)	32.46 (7.75)	$F(3, 289) = 63.23$, $P < .001$	CON<SREL<BP<SCZ
Schizotypal traits (SPQ total)	35.57 (15.65)	22.83 (16.01)	8.85 (7.65)	14.06 (12.94)	$F(3, 260) = 57.59$, $P < .001$	CON<SREL<BP<SCZ
Hits	17.78 (2.4)	17.89 (1.99)	18.8 (1.38)	19.08 (1.11)	$F(3, 301) = 9.84$, $P < .001$	SCZ,BP<CON,SREL
Reaction time	531.77 (99.64)	520.16 (79.95)	466.8 (78.71)	475.88 (77.4)	$F(3, 301) = 10.26$, $P < .001$	SCZ,BP>CON,SREL
Discrimination (d')	4.4 (0.75)	4.14 (0.88)	4.58 (0.69)	4.75 (0.67)	$F(3, 301) = 7.74$, $P < .001$	BP<CON, SRELSCZ<SREL
Bias (c)	0.76 (0.38)	0.65 (0.34)	0.61 (0.26)	0.57 (0.25)	$F(3, 301) = 5.94$, $P < .001$	CON,SREL<SCZ SREL<BP

All data are presented as mean (standard deviation), unless otherwise noted. SCZ = patients with schizophrenia , BP = patients with bipolar disorder, SREL = first degree relatives of SCZ, CON = healthy controls. WAIS-III = Wechsler Adult Intelligence Scale, 3rd edition. BPRS = 24-item brief psychiatric Rating Scale. SPQ = Schizotypal Personality Questionnaire. Self-reported hearing was rated from 0 to 2 (0 = unable to hear, 2 = perfect hearing) in increments of 0.5 for each ear (the values reported above are the sum of right and left ear ratings). Handedness was self-reported on scale of 1–5 where 1 = left dominant, 5 = right dominant . Alpha for all post hoc contrasts was set at 0.05 and P-values were FDR corrected for multiple comparisons when appropriate.

RM-ANOVA results are presented in table 2. For the N1 factor, we observed more negative amplitudes for attended tones (main effect of attention, $F(1, 299) = 18.7$, $P \leq .001$), more negative amplitudes for frequent tones (main effect of oddball, $F(1, 299) = 28.3$, $P \leq .001$), and more negative amplitudes for the higher pitched tone pair (main effect of pitch, $F(1, 299) = 8.27$, $P = .004$). Irrespective of condition, we observed blunted N1 factor amplitudes in patient groups (main effect of group, $F(3, 299) = 5.56$, $P = .001$); however post hoc comparisons only revealed significant differences between SCZ and non-patient groups (FDR corrected Ps <.05). Groups significantly differed in degree of modulation between attended and unattended tones (interaction of group by attention; $F(3, 299) = 3.81$, $P = .010$). CON and SREL significantly modulated this N1 factor while SCZ and BP failed to do so (FDR corrected Ps < .05).

Mid-latency Mismatch Detection: NF3 as P2

The P2 factor was most sensitive to oddball manipulations with more positive amplitudes for frequent tones (main effect of oddball, $F(1, 299) = 71.11$, $P \leq .001$). We also observed slightly more negative amplitudes for unattended compared to attended tones (main effect of attention, $F(1, 299) = 3.97$, $P = .047$), and more negative amplitudes for the higher tones compared to lower tones (main effect of pitch, $F(1, 299) = 4.58$, $P = .033$). Irrespective of condition, we did not observe an effect of group ($F(3, 299) = 1.31$, $P = .271$). Differences between groups were evident with respect to degree of oddball modulation (group by oddball interaction; $F(3, 299) = 11.60$, $P \leq .001$) in which all groups differed from each other except for BP and SCZ (FDR corrected Ps < .05).

Late Target Detection: NF2 as P3

For the P3 factor, we observed more positive amplitudes for attended tones (main effect of attention, $F(1, 299) = 147.27$, $P \leq .001$, more positive amplitudes for rare tones (main effect of oddball, $F(1, 299) = 483.89$, $P \leq .001$), and more positive amplitudes for the higher pitched tone pair (main effect of pitch, $F(1, 299) = 5.78$, $P = .017$). We observed significant differences in P3 factor amplitude between groups (main effect of group, $F(3, 299) = 5.55$,

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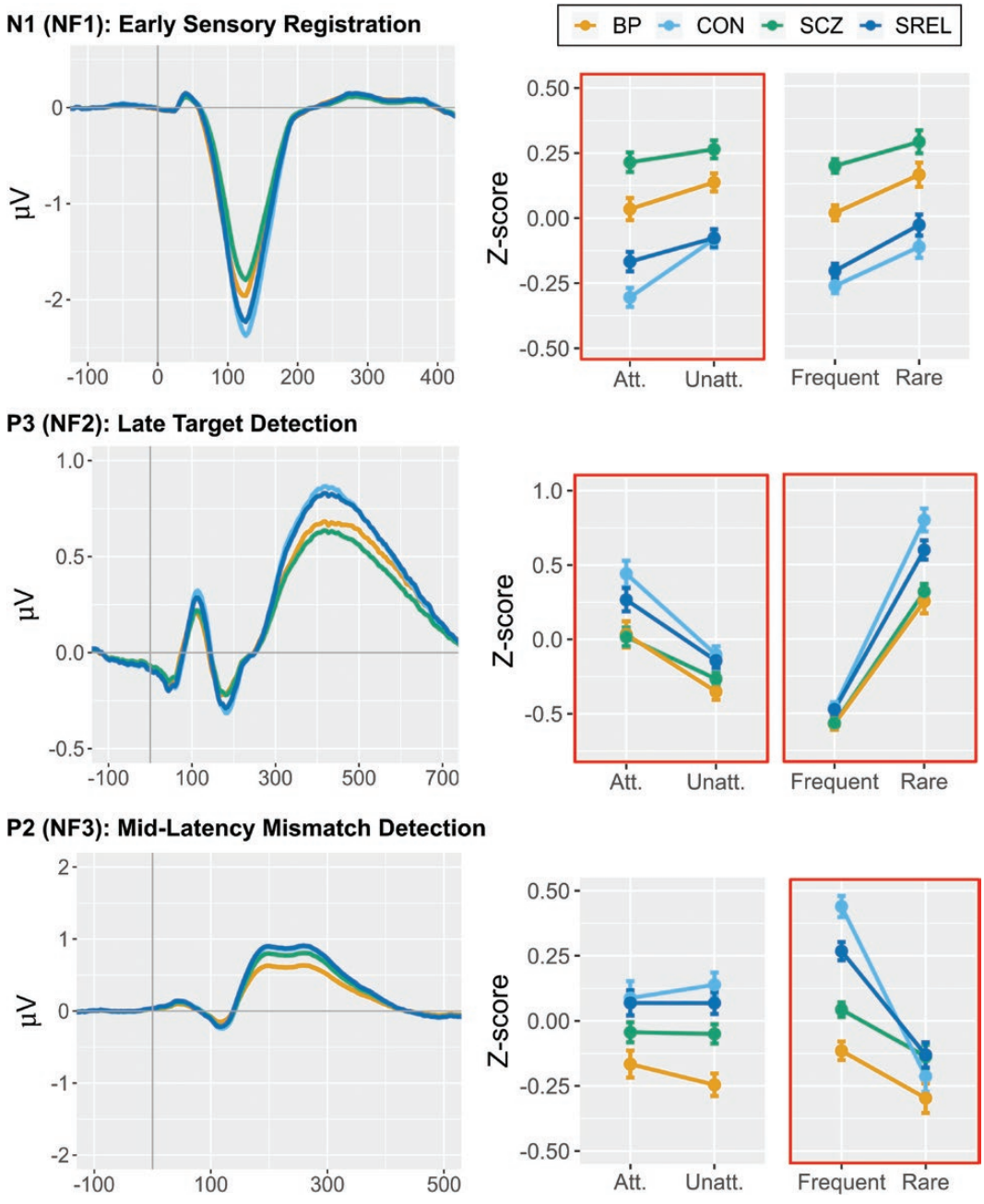

Fig. 2. Group differences in neural responses. (Column 1) Grand average factor waveforms by group. (Column 2) Group means for attended and unattended tones. (Column 3) Group means for rare and frequent tones. Borders indicate a significant interaction of group by condition. Error bars are within subjects standard error of the mean with a Morey correction factor.[36]

P = .001) with SCZ and BP exhibiting blunted amplitudes as compared to CON (FDR corrected Ps < .05). Groups differentially modulated P3 factor amplitude between attentional conditions (interaction of group by attention, $F(3, 299) = 3.71$, P = .012) with SCZ modulating less than CON (FDR corrected P = .009). Groups also differentially modulated P3 factor amplitude between frequent and rare tones (interaction of group by oddball, $F(3, 299) = 5.30$, P = .001) with SCZ and BP modulating less than CON (FDR corrected Ps <.05).

Association of Neural Factors with Symptomatology and Task Performance

To map neural responses during auditory processing onto symptomatology, we computed composite scores (i.e. averaged across conditions), attended-unattended difference scores and frequent-rare difference scores for the N1, P2, and P3 factors. We then calculated Pearson correlations between these indices and BPRS total, BPRS positive, SPQ total and SPQ cognitive-perceptual scores. We also correlated neural indices with average

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Table 2. Summary of Categorical Results

Neural Factors	Attention	Rarity	Group	Attention × Group	Rarity × Group
N1 (NF1): early sensory Registration	***	***	** {SCZ < CON, SREL}	* {SCZ < CON}	–
P3 (NF2): late target detection	***	***	** {SCZ,BP < CON}	*{SCZ < CON}	**{SCZ,BP < CON}
P2 (NF3): mid-latency mismatch detection	*	***	–	–	*** {SCZ,BP < SREL < CON}
LPP (NF4): late slow wave	–	***	* {SCZ < CON}	–	–

*P < .05.
**P < .01.
***P < .001.
{} = Significant post hoc group comparisons.

number of hits and response time. To control for Type-1 error, we FDR corrected all 54 P-values (9 neural measures × (4 clinical measures + 2 behavioral measures)). The results of this mass univariate analysis can be found in figure 3.

Blunted N1 and P3 composite scores significantly predicted higher BPRS total, SPQ total and SPQ cognitive-perceptual scores irrespective of task manipulations. N1 composite scores also significantly predicted response times with less negative scores predicting greater response times. N1, P2, and P3 attended-unattended difference scores did not significantly correlate with any self-report measures after correction for multiple comparisons. Reduced P2 frequent-rare difference scores were associated with greater BPRS total, BPRS positive, SPQ total, and SPQ cognitive-perceptual scores (see figure 3). Both P2 and P3 frequent-rare difference scores were associated with number of hits and response latency though in opposing directions: more positive P2 frequent-rare difference scores predicted more hits and smaller response times while more negative P3 frequent-rare difference scores predicted more hits and smaller response times.

Discussion

We isolated neural responses elicited during directed attention oddball listening that were replicated across two independent samples of people with schizophrenia, people with bipolar disorder, first-degree relatives of people with schizophrenia and healthy controls. Irrespective of group, all neural responses were affected by selective attention, however only N1 and P3 factors were associated with differential attentional modulation by group. P2 responses, on the other hand, were not associated with differential attentional modulation between groups suggesting that mid-latency mismatch detection deficits evident in SCZ, BP, and SREL are not driven by selective attention deficits.

Role of Attention in Atypical Auditory Processing

Consistent with previous literature, both N1 and P3 were associated with differential attentional modulation as a function of group; however, attended-unattended difference scores for the N1 and P3 factor did not significantly predict symptom severity or schizotypal traits (FDR corrected Ps >.05). Thus, our results replicate previous findings of reduced attentional modulation of N1 and P3 in SCZ compared to CON, but these reductions do not strongly map onto downstream clinical outcomes.

Consistent with other studies of mid-latency mismatch detection, the mid-latency P2 component was less sensitive to attentional manipulations and groups did not differ in degree of attentional modulation. Furthermore, we did not observe an association between P2 attended-unattended difference scores and clinical measures. Given the reduced influence of attention and the spatiotemporal characteristics of the neural response, we hypothesize that this P2 response reflects a similar automatic process as the passively elicited mismatch negativity and is more robust than N1 and P3 to selective attention deficits.

Mid-latency Mismatch Detection Predicts Psychotic Symptomatology

SCZ, BP, and SREL exhibited altered mid-latency mismatch detection as evidenced by reduced oddball modulation of the P2 factor. Furthermore, weakened mid-latency mismatch detection predicted positive schizophrenia symptoms and unusual cognitive-perceptual experiences. Recent work has demonstrated that reduced mismatch detection is likely reflective of disrupted thalamocortical and corticocortical connectivity with inferior frontal cortex playing a crucial role in MMN generation.[37,38] Moreover, neural markers of mismatch detection have been shown to be responsive to neuromodulatory treatments such as TMS and tDCS/tACS[39,40]; Thus, the currently reported symptom correlations along with findings from other groups[41] suggest that mid-latency mismatch

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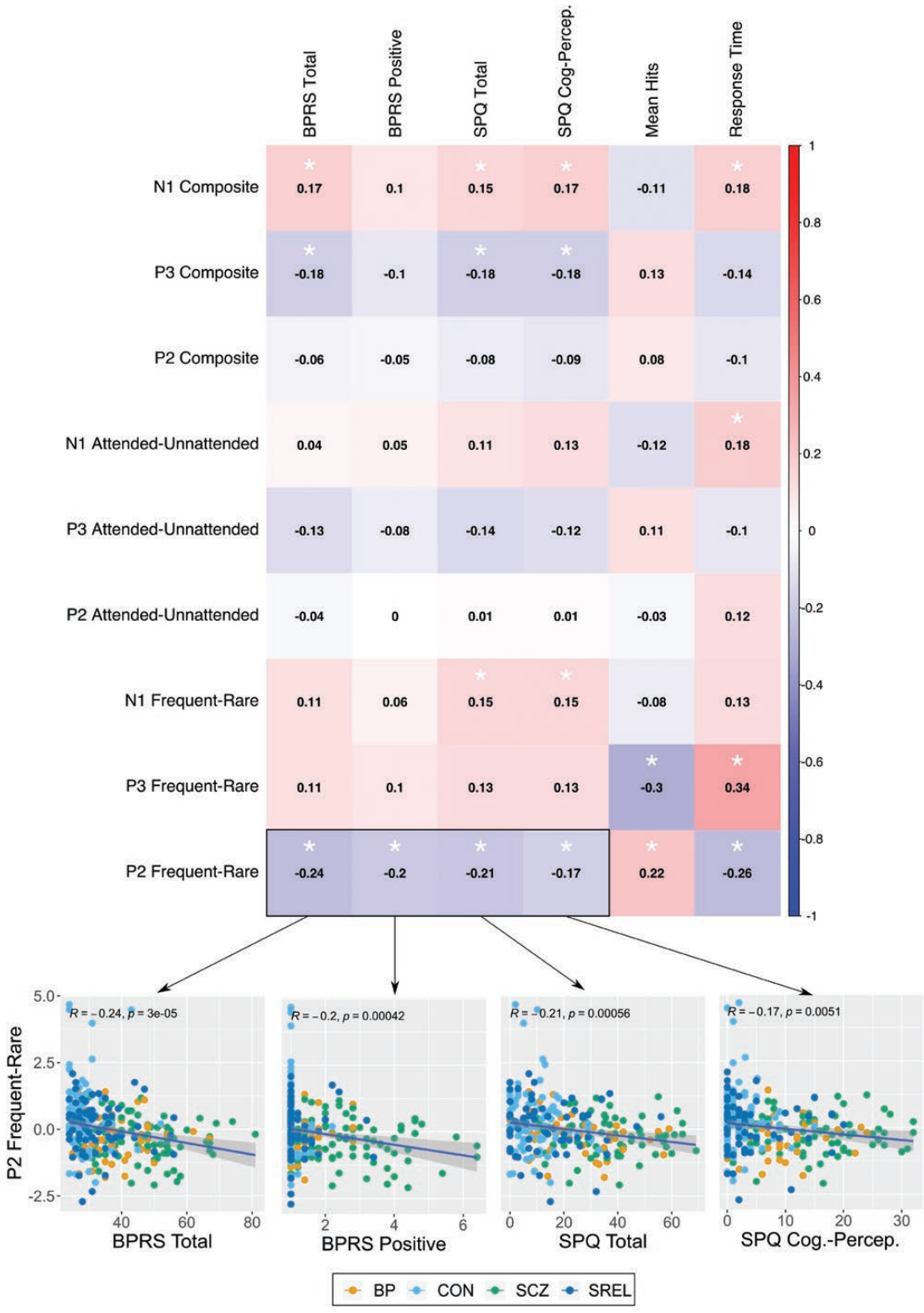

Fig. 3. Neural responses, symptoms and behavior. (Top) Correlation matrix with white asterisks indicating FDR corrected $P < .05$ and black numbers indicating Pearson's correlation coefficient. (Bottom) Scatterplots of P2 frequent-rare scores with symptom severity scores.

detection may be a promising intervention target. It should be noted that our paradigm differed from a classical MMN paradigm due to the manipulation of attention and the active response requirement and thus further work is needed to clarify the relationship between the mismatch neural activity reported here and the MMN. Furthermore, the reported R^2 values for the relationship between mid-latency mismatch detection and clinical

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outcomes are modest. This is likely due to measurement error and the fact that our experimental task does not capture naturalistic, real world sensory experiences which may be more relevant to clinical outcomes.

N1 and P3 as Endophenotypes of Schizophrenia?

Our results align with previous findings of generally blunted N1 in first-hospitalized and chronic schizophrenia patients.[8] Although auditory N1 has been proposed as an endophenotype specific to schizophrenia,[4,7] we found that SREL N1 responses did not significantly differ from CON and *did* significantly differ from SCZ. Thus our results do not support N1 as a schizophrenia endophenotype. Reduced N1 responses did correlate with BPRS and SPQ total scores which is consistent with a dimensional view of psychosis in which greater psychiatric symptom severity and schizotypal personality traits are associated with general blunting of early auditory evoked neural responses irrespective of diagnostic group or genetic liability.

The P3 component has also been proposed as an endophenotype for schizophrenia.[11] P3 oddball modulation was reduced in SCZ and BP, but not in SREL compared to controls. This is in contrast to previous findings from our group[4] and other research groups[42] in which no differences were found between diagnostic groups in oddball P3 generation, but does agree with other reports.[43,44] It should be noted that we implemented a high-pass filter of 0.5 Hz which allowed for better separation of neural and artifactual signals, but has been shown to attenuate the amplitude of late ERP components.[45] This is unlikely to confound statistical inferences reported here because amplitudes will be attenuated across all groups and conditions, but is nevertheless important to consider when interpreting P3 amplitudes.

Only atypical mid-latency mismatch detection was shared between SCZ and SREL suggesting the P2 factor may be a promising potential endophenotype of psychosis. It should be noted, however, that we did not assess for mild traumatic brain injury (concussion) which has been linked to AAP.[46] Additionally, because SREL are a valuable population and our goal was to maximally sample individuals with heightened genetic liability for psychotic psychopathology, exclusion criteria were less restrictive compared to other groups. Thus, it is possible that conditions that led to exclusion in other groups were present in SREL which may have influenced findings. To partially address this, we have provided a supplemental table (supplemental table 4) that details serious medical conditions in SREL.

Conclusion

We sought to clarify the role of altered selective attention in AAP in psychosis and the degree to which stages of AAP are associated with categorical and dimensional measures of psychotic psychopathology. Diminished modulation of mid-latency mismatch detection was associated with positive symptoms of schizophrenia and cognitive-perceptual schizotypal traits. Early sensory registration and later target detection reflected in the N1 and P3 response, respectively, was impaired in schizophrenia and associated with greater overall symptomatology. Attentional modulation of early, and late neural responses was atypical in patients, but did not relate to clinical phenomenology. Our findings suggest a link between mid-latency mismatch detection and atypical cognitive/perceptual experiences that are likely not the result of attentional deficits and point to the promise of mid-latency mismatch detection as a candidate endophenotype and intervention target.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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References

1. Gold JM, Robinson B, Leonard CJ, et al. Selective attention, working memory, and executive function as potential independent sources of cognitive dysfunction in Schizophrenia. *Schizophr Bull.* 2018;44(6):1227–1234.
2. Mathalon DH, Heinks T, Ford JM. Selective attention in schizophrenia: sparing and loss of executive control. *Am J Psychiatry.* 2004;161(5):872–881.
3. Ren X, Fribance SN, Coffman BA, Salisbury DF. Deficits in attentional modulation of auditory N100 in first-episode schizophrenia. *Eur J Neurosci.* 2021;53(8):2629–2638.
4. Force RB, Venables NC, Sponheim SR. An auditory processing abnormality specific to liability for schizophrenia. *Schizophr Res.* 2008;103(1-3):298–310.
5. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res.* 2005;76(1):1–23.
6. Jessen F, Fries T, Kucharski C, et al. Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. *Neurosci Lett.* 2001;309(3):185–188.

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7. Foxe JJ, Yeap S, Snyder AC, Kelly SP, Thakore JH, Molholm S. The N1 auditory evoked potential component as an endophenotype for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives, first-episode, and chronic schizophrenia patients. *Eur Arch Psychiatry Clin Neurosci.* 2011;261(5):331–339.
8. Salisbury DF, Collins KC, McCarley RW. Reductions in the N1 and P2 auditory event-related potentials in first-hospitalized and chronic schizophrenia. *Schizophr Bull.* 2010;36(5):991–1000.
9. Brown KJ, Gonsalvez CJ, Harris AW, Williams LM, Gordon E. Target and non-target ERP disturbances in first episode vs. chronic schizophrenia. *Clin Neurophysiol.* 2002;113(11):1754–1763.
10. Blackwood DH, Whalley LJ, Christie JE, Blackburn IM, St Clair DM, McInnes A. Changes in auditory P3 event-related potential in schizophrenia and depression. *Br J Psychiatry.* 1987;150:154–160.
11. Bramon E, McDonald C, Croft RJ, et al. Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study. *Neuroimage.* 2005;27(4):960–968.
12. Polich J. Task difficulty, probability, and inter-stimulus interval as determinants of P300 from auditory stimuli. *Electroencephalogr Clin Neurophysiol.* 1987;68(4):311–320.
13. Markon KE, Chmielewski M, Miller CJ. The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. *Psychol Bull.* 2011;137(5):856–879.
14. Pokorny VJ, Lano TJ, Schallmo M-P, Olman CA, Sponheim SR. Reduced influence of perceptual context in schizophrenia: behavioral and neurophysiological evidence. *Psychol Med*. 2019;51(5):1–9.
15. Pokorny VJ, Espensen-Sturges TD, Burton PC, Sponheim SR, Olman CA. Aberrant cortical connectivity during ambiguous object recognition is associated with Schizophrenia. *Biol Psychiatry*. 2020. doi:10.1016/j.bpsc.2020.09.018.
16. Longenecker JM, Krueger RF, Sponheim SR. Personality traits across the psychosis spectrum: a hierarchical taxonomy of psychopathology conceptualization of clinical symptomatology. *Personal Ment Health.* 2020;14(1):88–105.
17. Olman CA, Espensen-Sturges T, Muscanto I, et al. Fragmented ambiguous objects: stimuli with stable low-level features for object recognition tasks. *PLoS One.* 2019;14(4):e0215306.
18. Schallmo MP, Sponheim SR, Olman CA. Abnormal contextual modulation of visual contour detection in patients with schizophrenia. *PLoS One.* 2013;8(6):e68090.
19. Klein SD, Shekels LL, McGuire KA, Sponheim SR. Neural anomalies during vigilance in schizophrenia: diagnostic specificity and genetic associations. *Neuroimage Clin.* 2020;28:102414.
20. Van Voorhis AC, Kent JS, Kang SS, Goghari VM, MacDonald AW 3rd, Sponheim SR. Abnormal neural functions associated with motor inhibition deficits in schizophrenia and bipolar disorder. *Hum Brain Mapp.* 2019;40(18):5397–5411.
21. Kang SS, MacDonald AW, Sponheim SR. Dysfunctional neural processes underlying context processing deficits in Schizophrenia. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2019;4(7):644–654.
22. Lynn PA, Kang SS, Sponheim SR. Impaired retrieval processes evident during visual working memory in schizophrenia. *Schizophr Res Cogn.* 2016;5:47–55.
23. First MB, Spitzer RL, Gibbon M, Williams JBW, Others. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. SCID-I/P New York, NY; 2002.
24. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 1962;10(3):799–812.
25. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull.* 1991;17(4):555–564.
26. Schreiber H, Stolz-Born G, Kornhuber HH, Born J. Event-related potential correlates of impaired selective attention in children at high risk for schizophrenia. *Biol Psychiatry.* 1992;32(8):634–651.
27. Kang SS, Sponheim SR, Lim KO. Interoception underlies the therapeutic effects of mindfulness meditation for post-traumatic stress disorder: a randomized clinical trial. *arXiv [q-bioNC]*. 2020. http://arxiv.org/abs/2010.06078.
28. Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. *Electroencephalogr Clin Neurophysiol.* 1989;72(2):184–187.
29. Kang SS, Lano TJ, Sponheim SR. Distortions in EEG interregional phase synchrony by spherical spline interpolation: causes and remedies. *Neuropsychiatric Electrophysiol*. 2015;1(1):9.
30. Dien J. The ERP PCA Toolkit: an open source program for advanced statistical analysis of event-related potential data. *J Neurosci Methods.* 2010;187(1):138–145.
31. Dien J. Applying principal components analysis to event-related potentials: a tutorial. *Dev Neuropsychol.* 2012;37(6):497–517.
32. Stanislaw H, Todorov N. Calculation of signal detection theory measures. *Behav Res Methods Instrum Comput.* 1999;31(1):137–149.
33. Lorenzo-Seva U, ten Berge JMF. Tucker's congruence coefficient as a meaningful index of factor similarity. *Methodology*. 2006;2(2):57–64.
34. Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology.* 1987;24(4):375–425.
35. Tomé D, Barbosa F, Nowak K, Marques-Teixeira J. The development of the N1 and N2 components in auditory oddball paradigms: a systematic review with narrative analysis and suggested normative values. *J Neural Transm (Vienna).* 2015;122(3):375–391.
36. Morey RD. Confidence intervals from normalized data: a correction to Cousineau (2005). *TQMP*. 2008;4(2):61–64.
37. Lee M, Sehatpour P, Hoptman MJ, et al. Neural mechanisms of mismatch negativity dysfunction in schizophrenia. *Mol Psychiatry.* 2017;22(11):1585–1593.
38. Lui TK, Shum YH, Xiao XZ, et al. The critical role of the inferior frontal cortex in establishing a prediction model for generating subsequent mismatch negativity (MMN): a TMS-EEG study. *Brain Stimul.* 2021;14(1):161–169.
39. Oshima H, Shiga T, Niwa SI, Enomoto H, Ugawa Y, Yabe H. Alteration of duration mismatch negativity induced by transcranial magnetic stimulation over the Left Parietal Lobe. *Clin EEG Neurosci.* 2017;48(1):11–19.
40. Chen JC, Hämmerer D, Strigaro G, et al. Domain-specific suppression of auditory mismatch negativity with transcranial direct current stimulation. *Clin Neurophysiol.* 2014;125(3):585–592.

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41. Wynn JK, Sugar C, Horan WP, Kern R, Green MF. Mismatch negativity, social cognition, and functioning in schizophrenia patients. *Biol Psychiatry.* 2010;67(10):940–947.
42. Kayser J, Bruder GE, Tenke CE, Stuart BK, Amador XF, Gorman JM. Event-related brain potentials (ERPs) in schizophrenia for tonal and phonetic oddball tasks. *Biol Psychiatry.* 2001;49(10):832–847.
43. van der Stelt O, Frye J, Lieberman JA, Belger A. Impaired P3 generation reflects high-level and progressive neurocognitive dysfunction in schizophrenia. *Arch Gen Psychiatry.* 2004;61(3):237–248.
44. Roth WT, Pfefferbaum A, Horvath TB, Berger PA, Kopell BS. P3 reduction in auditory evoked potentials of schizophrenics. *Electroencephalogr Clin Neurophysiol.* 1980;49(5–6): 497–505.
45. Tanner D, Morgan-Short K, Luck SJ. How inappropriate high-pass filters can produce artifactual effects and incorrect conclusions in ERP studies of language and cognition. *Psychophysiology.* 2015;52(8):997–1009.
46. Washnik NJ, Anjum J, Lundgren K, Phillips S. A review of the role of auditory evoked potentials in mild traumatic brain injury assessment. *Trends Hear.* 2019;23:2331216519840094.

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