Association Between P300 Responses to Auditory Oddball Stimuli and Clinical Outcomes in the Psychosis Risk Syndrome

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IMPORTANCE In most patients, a prodromal period precedes the onset of schizophrenia. Although clinical criteria for identifying the psychosis risk syndrome (PRS) show promising predictive validity, assessment of neurophysiologic abnormalities in at-risk individuals may improve clinical prediction and clarify the pathogenesis of schizophrenia.

OBJECTIVE To determine whether P300 event-related potential amplitude, which is deficient in schizophrenia, is reduced in the PRS and associated with clinical outcomes.

DESIGN, SETTING, AND PARTICIPANTS Auditory P300 data were collected as part of the multisite, case-control North American Prodrome Longitudinal Study (NAPLS-2) at 8 university-based outpatient programs. Participants included 552 individuals meeting PRS criteria and 236 healthy controls with P300 data. Auditory P300 data of participants at risk who converted to psychosis (n = 73) were compared with those of nonconverters who were followed up for 24 months and continued to be symptomatic (n = 135) or remitted from the PRS (n = 90). Data were collected from May 27, 2009, to September 17, 2014, and were analyzed from December 3, 2015, to May 1, 2019.

MAIN OUTCOMES AND MEASURES Baseline electroencephalography was recorded during an auditory oddball task. Two P300 subcomponents were measured: P3b, elicited by infrequent target stimuli, and P3a, elicited by infrequent nontarget novel stimuli.

RESULTS This study included 788 participants. The PRS group (n = 552) included 236 females (42.8%) (mean [SD] age, 19.21 [4.38] years), and the healthy control group (n = 236) included 111 females (47.0%) (mean [SD] age, 20.44 [4.73] years). Target P3b and novelty P3a amplitudes were reduced in at-risk individuals vs healthy controls (d = 0.37). Target P3b, but not novelty P3a, was significantly reduced in psychosis converters vs nonconverters (d = 0.26), and smaller target P3b amplitude was associated with a shorter time to psychosis onset in at-risk individuals (hazard ratio, 1.45; 95% CI, 1.04-2.00; P = .03). Participants with the PRS who remitted had baseline target P3b amplitudes that were similar to those of healthy controls and greater than those of converters (d = 0.51) and at-risk individuals who remained symptomatic (d = 0.41).

CONCLUSIONS AND RELEVANCE In this study, deficits in P300 amplitude appeared to precede psychosis onset. Target P3b amplitudes, in particular, may be sensitive to clinical outcomes in the PRS, including both conversion to psychosis and clinical remission. Auditory target P3b amplitude shows promise as a putative prognostic biomarker of clinical outcome in the PRS.

Supplemental content

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Psychotic disorders, including schizophrenia, are typically preceded by a prodromal period consisting of attenuated psychotic symptoms and/or a decline in premorbid functioning. Evidence that a shorter duration of psychotic illness before initiation of treatment is associated with better treatment response and clinical outcomes[1,2] has motivated interest in early identification and intervention, leading to the development and validation of clinical diagnostic criteria for the prospective identification of individuals during the prodrome, often referred to as the clinical high risk, ultra-high risk, or psychosis risk syndrome (PRS).[3-5] However, only 15% to 29% of individuals meeting PRS criteria develop psychosis within 2 years.[6-8] Because the PRS is associated with a variety of clinical outcomes ranging from psychosis to remission from the risk state, the justification for early intervention, particularly with antipsychotic medications, remains controversial. Accordingly, if biomarkers that predate psychosis onset are identified that improve the prognostic accuracy of PRS clinical criteria, more aggressive interventions for individuals at greatest risk could be justified. Furthermore, prognosis and treatment planning may benefit from biomarkers associated with clinical remission, potentially facilitating staged treatment algorithms involving less invasive and less intensive treatments for individuals with the PRS who are least likely to transition to psychosis. Furthermore, such biomarkers may help to elucidate the pathophysiologic processes underlying the development of psychosis, potentially guiding development of novel targeted interventions.

Reduced auditory P300 event-related potential (ERP) amplitude is well established in schizophrenia[9-11] and is a primary candidate electrophysiologic biomarker of psychosis. Typically elicited during an oddball target detection task by infrequently presented salient stimuli interspersed among frequent standard stimuli, the P300 is a positive voltage deflection in the stimulus-locked ERP occurring 300 milliseconds after the stimulus.[12] Amplitude of P300 is thought to reflect attentional resource allocation, phasic attentional shifts, working memory updating of stimulus context, stimulus salience, and/or expectancy violation.[13-19] Latency of P300 reflects processing speed or efficiency during stimulus evaluation.[20,21]

Two subcomponents of P300—P3b and P3a—have been identified.[12] The P3b, with a midline parietal maximum, reflects an effortful top-down attentional shift to an infrequent target stimulus requiring a response when detected. Patients with schizophrenia show robust P3b amplitude deficits and latency delays, particularly in the auditory modality.[9,10,22-26] The P3a subcomponent, with a midline frontocentral scalp maximum and a peak latency 25 to 50 milliseconds earlier than P3b, reflects automatic bottom-up orienting of attention to infrequent novel or distractor stimuli requiring no response.[12,27-30] Although fewer studies have examined P3a in schizophrenia, most demonstrate auditory P3a amplitude reductions in response to deviant or novel nontarget sounds.[24,25,31-39] However, other studies have not shown such reductions.[31,40,41]

Both P300 amplitude subcomponents show traitlike reductions in schizophrenia[25,42] but also fluctuate with clinical state.[25,43] Amplitude reductions are present in patients with first-episode schizophrenia and their first-degree relatives, consistent with evidence that P300 amplitude may be a heritable endophenotypic marker of schizophrenia and its genetic risk.[11,44-50] However, P300 amplitude reduction and latency prolongation worsen with longer illness duration,[51,52] which is consistent with its sensitivity to progressive pathophysiologic processes in schizophrenia.

Studies have shown both auditory P3b[53-59] and P3a[34-36,60] amplitude deficits during the PRS, with 2 studies suggesting that auditory P3b is associated with future transition to psychosis and the time to this transition.[54,61] However, it is currently unknown whether auditory P300 abnormalities are related to other clinically relevant outcomes in the PRS, including remission from the syndrome itself. Accordingly, the present study examined target P3b and novelty P3a elicited during an auditory oddball task in individuals with the PRS and healthy controls. In addition to group comparisons, we evaluated whether baseline auditory P3b and P3a were associated with future clinical outcomes. We hypothesized that individuals with the PRS would show reduced P3b and P3a amplitudes, replicating prior research.[34-36,53-60] Consistent with 2 prior PRS studies,[54,61] we also hypothesized that baseline P300 amplitude reductions would be greater in individuals with the PRS who subsequently met psychosis conversion criteria relative to those who did not meet conversion criteria and that greater P300 amplitude deficits would be associated with a shorter time to psychosis onset. In addition, we hypothesized that individuals who achieved remission from the PRS would show less baseline P300 amplitude abnormalities than those who transitioned to full psychosis.

Key Points

Question Is auditory P300 event-related potential amplitude associated with future clinical outcomes among youths with the psychosis risk syndrome?

Findings In this 8-site case-control study of 552 individuals meeting psychosis risk syndrome criteria, greater deficits in baseline P300 amplitude to target, but not novel oddball stimuli were associated with transition to psychosis and the imminence of this transition. Individuals with the psychosis risk syndrome that did not convert to psychosis after 2 years and instead achieved remission from the risk syndrome had normal target P300 amplitudes at baseline.

Meaning The results suggest that P300 is a putative prognostic biomarker of clinical outcomes in the psychosis risk syndrome, including conversion to psychosis and remission from the risk state.

Methods

Participants

The 8-site North American Prodrome Longitudinal Study (NAPLS-2) followed up 764 outpatients meeting PRS criteria and 269 demographically similar healthy control participants aged 12 to 35 years.[62] Of these, 552 PRS and 236 healthy control participants provided usable electroencephalographic (EEG) data collected during an auditory oddball task

(eFigure 1 in the Supplement). The PRS participants met the Criteria of Psychosis-Risk Syndromes based on the Structured Interview for Psychosis-Risk Syndromes,[3,5] and symptoms were rated using the Scale of Psychosis-Risk Symptoms (SOPS). Exclusion criteria included current/lifetime psychotic disorder (including cluster A personality disorders for healthy controls), IQ below 70, or significant central nervous system disorder. The healthy controls could not have a first-degree relative with a psychotic disorder and could not currently be taking antipsychotic medications. Details of recruitment and inclusion and exclusion criteria have been provided.[62] Data were collected from May 27, 2009, to September 17, 2014, and were analyzed from December 3, 2015, to May 1, 2019. The study was approved by the institutional review boards at each site. Adult participants provided written informed consent, and minors provided written assent with parents providing written informed consent. Participants received financial compensation.

The study design called for participants to be followed up for 24 months or until they transitioned to psychosis, undergoing clinical assessments every 6 months. Of the individuals with P300 data, 73 converted to psychosis and met Presence of Psychotic Symptoms criteria[3] (PRS-conversion), and 225 completed 24 months of clinical follow-up but did not convert to psychosis (PRS-nonconversion); study completers and noncompleters did not differ with respect to major demographic or P300 variables (eTable 1 in the Supplement). The PRS-nonconversion participants were further classified by clinical outcome at the 24-month assessment[62] and included symptom remission (PRS-remission, n = 90; no longer meeting Criteria of Psychosis-Risk Syndromes[3]) and syndrome progression and/or symptom persistence (PRS-symptomatic, n = 135; continuing to meet Criteria of Psychosis-Risk Syndromes or experiencing attenuated positive symptoms over the previous 4 weeks).

Oddball Paradigm

The paradigm consisted of frequently presented standard tones (80%), infrequent target tones requiring a button press (10%), and infrequent unique novel distractor sounds that were task irrelevant and required no response (10%). Standards (500 Hz) and targets (1000 Hz) were 50-millisecond pure tones (5-millisecond rise/fall time). Novel sounds were a variety of natural and manmade sounds[63] varying in duration (average, 250 milliseconds) and rise/fall time. The task comprised a fixed pseudorandom sequence of 450 stimuli, with a stimulus onset asynchrony of 1250 milliseconds, divided into 3 blocks. Participants viewed an instructional cartoon and heard prerecorded instructions directing them to press a response key to target tones only, using their preferred hand. Trials with incorrect button presses were excluded from analysis. Following exclusion of 4 PRS participants (1 PRS-conversion) for poor performance (≤50% accuracy), response accuracy was high among the groups (98.7%-99.6%) (eTable 11 in the Supplement).

EEG Acquisition and Preprocessing

Participants sat in front of a computer monitor and wore insert earphones (ER1-A Etymotic; Etymotic Research) for EEG recording during the oddball task. Symptom assessment occurred on a separate day from EEG recording (median [SD], 10.00 [28.13] days).

The EEG recording was digitized at 1024 Hz from a 32-channel (4 sites) or 64-channel (4 sites) electrode cap using a high-impedance recording system (BioSemi ActiveTwo). Reference electrodes were placed on the mastoids. Electrodes placed above and below the right eye and at the outer canthus of each eye recorded the vertical and horizontal electrooculogram to correct for eye movements and blinks. The EEG data were rereferenced offline to averaged mastoid electrodes and high-pass filtered at 0.1 Hz. Data were subjected to fully automated statistical thresholding for EEG artifact rejection,[64] which uses descriptive measures to search for statistical outliers. This approach, which has been applied previously,[65] also included canonical correlation analysis[66,67] for additional denoising (eMethods in the Supplement). Epochs were time locked to auditory stimulus onsets (-1000 to 2000 milliseconds) and baseline corrected (-100 to 0 milliseconds).

Participant ERP averages were calculated separately for standard, target, and novel stimuli and were low-pass filtered at 30 Hz. The standard ERP was subtracted from the target and novel ERPs, yielding difference waveforms where early P300, particularly P3a, was disambiguated from the earlier and often overlapping P200 present in the standard, target, and novel ERPs.[61] P300 was identified as the most positive peak in a 235- to 400-millisecond window following stimulus onset. The P3b peak amplitudes and latencies were chosen from the target minus standard difference wave as the most positive peak at electrode Pz (where P3b is maximum), while P3a peak amplitudes and latencies were identified from the novel minus standard difference wave at electrode Cz (where P3a is maximum). Given prior work demonstrating a slow wave following the target P3b peak[27,68] and its reduced amplitude in schizophrenia,[69] we also assessed the slow wave at electrode Pz by extracting the mean amplitude between 400 and 500 milliseconds.[27] Participants with 30 or more correct target and novel artifact-free ERP trials were included in analysis. The number of artifact-free trials was similar among groups (eTable 11 in the Supplement).

Statistical Analysis

Age- and study site–corrected amplitudes, latencies, and median target reaction times (RTs) were derived for each participant to adjust for effects of normal aging and study site. Values were regressed on age and site in the healthy controls. The resulting regression equations were used to derive age- and study site–specific predicted values that were subtracted from the observed values and divided by the SE of regression, yielding age- and site-corrected *z* scores for all participants reflecting deviations from the values expected for a healthy individual of a given age at that study site. This approach, which has been used previously,[61,70] is preferable to analysis of covariance because it only removes normal aging- and site-specific effects, retaining any pathologic aging effects. Modest age-related P3a and P3b amplitude decreases and latency

increases were evident in healthy controls (eTable 2 in the Supplement), consistent with previous studies.[11]

Group differences in target P3b and novelty P3a amplitude and latency *z* scores were tested using analysis of variance models, with group (PRS, healthy control) or clinical outcome (PRS-conversion, PRS-symptomatic, PRS-remission, or healthy control) as the between-participants factor and stimulus type (novel, target) as the within-participants factor. Planned contrasts compared P300 between the PRS-conversion and PRS-nonconversion groups and among clinical outcomes. The Benjamini-Hochburg false discovery rate procedure[71] was used to account for multiple comparisons (adjusted *P* values are reported). Cohen *d* is reported for group effect sizes. To assess associations between symptom severity and P300, novelty P3a and target P3b amplitude and latency *z* scores were correlated with SOPS symptom scores.

Cox proportional hazards regression was performed to model the association between P300, as well as target RT, and time to psychosis onset among participants with the PRS. The P300 *z* scores for target and novel stimuli were included in a single model to evaluate independent contributions of each to predicting time to psychosis onset. All participants with the PRS were included, with censoring of those who did not convert to psychosis after their last follow-up assessment.

The α level was $P = .05$ with 2-tailed testing, and analyses were conducted with SPSS, version 25 (IBM Corp).

Results

Sample Characteristics

Sample characteristics of the 788 participants are reported in the **Table**. Sex did not differ significantly by group or clinical outcome. Age differed slightly but significantly between healthy control and PRS groups but was comparable among PRS clinical outcomes. The PRS group (n = 552) included 236 females (42.8%) (mean [SD] age, 19.21 [4.38] years), and the healthy control group (n = 236) included 111 females (47.0%) (mean [SD] age, 20.44 [4.73] years).

P300 Amplitude and Latency

Grand average ERP deviant-standard difference waves, scalp topographic maps, and mean amplitude values for each stimulus type are presented in **Figure 1** for PRS and healthy control participants (eTables 3-6 in the Supplement provide means of P300 measures, and eFigures 2-4 in the Supplement provide target, novel, and standard grand average ERP waveforms). Auditory P300 amplitude *z* scores differed by group ($F_{1,786} = 23.31$; $P < .001$) such that participants with the PRS had significantly reduced amplitudes compared with healthy controls ($d = 0.37$). This association did not interact with stimulus type ($F_{1,786} = 0.30$; $P = .58$).

Grand average ERP difference waves, scalp topographic maps, and mean amplitude values by clinical outcome relative to healthy controls are shown in **Figure 2**. Auditory P300 amplitude *z* scores differed by clinical outcome ($F_{3,530} = 8.12$; $P < .001$), but there was also a significant clinical outcome × stimulus type interaction ($F_{3,530} = 2.91$; $P = .03$). Auditory P300 differed by clinical outcome group for both target P3b and novelty P3a amplitude *z* scores examined separately ($F_{3,530} = 10.53$; $P < .001$ and $F_{3,530} = 4.15$; $P = .006$, respectively). For target P3b, follow-up contrasts revealed that PRS-conversion had reduced amplitudes relative to PRS-nonconversion ($P = .048$, $d = 0.26$). Although the PRS-conversion and the PRS-symptomatic groups did not differ significantly from each other ($P = .55$, $d = 0.095$), both groups had smaller amplitudes than the healthy control group ($P < .001$, $d = 0.59$ and $P < .001$, $d = 0.48$, respectively) and the PRS-remission group ($P = .004$, $d = 0.51$ and $P = .005$, $d = 0.41$, respectively). The PRS-remission group did not differ from the healthy control group in target P3b amplitude ($P = .55$, $d = 0.11$).

In contrast, novelty P3a amplitude *z* scores did not differentiate PRS-conversion from PRS-nonconversion ($P = .98$, $d = 0.014$). Although the PRS-symptomatic participants had smaller P3a amplitudes than the healthy controls ($P = .01$, $d = 0.35$), both PRS-conversion and PRS-symptomatic participants did not differ from PRS-remission participants ($P = .90$, $d = 0.036$ and $P = .81$, $d = 0.090$). Relative to healthy controls, the smaller P3a in the PRS-conversion ($P = .11$, $d = 0.29$) and PRS-remission ($P = .11$, $d = 0.24$) groups did not reach significance.

Results were similar to those reported above when analyses were repeated by covarying for symptom severity, target and novel response accuracy, target RT, and artifact-free trial numbers and when based on the subgroup of 429 antipsychotic-free PRS participants (eResults in the Supplement).

Mean slow wave amplitude *z* scores were correlated with target P3b amplitude *z* scores (healthy control: $r = 0.783$, $P < .001$; PRS: $r = 0.795$, $P < .001$). Analysis of slow wave *z* scores yielded the same pattern of results as target P3b amplitude described above (eResults, eFigure 4, and eTables 9 and 10 in the Supplement). Auditory P300 latency did not differ by group or clinical outcome.

Reaction Time and Symptom Correlations

Median target RT did not differ by group ($F_{1,786} = 0.84$; $P = .36$) but differed by clinical outcome ($F_{3,530} = 4.00$; $P = .008$). The PRS-conversion group had slower RTs than the PRS-nonconversion group ($P = .005$, $d = 0.38$), including both the PRS-symptomatic ($P = .03$, $d = 0.33$) and PRS-remission ($P = .005$, $d = 0.45$) groups and healthy control group ($P = .005$, $d = 0.41$) (**Figure 3**; eTable 7 and eTable 8 in the Supplement). There were no significant correlations between target P3b or novelty P3a amplitude or latency *z* scores and SOPS symptoms (all adjusted $P > .20$).

Cox Proportional Hazards Regression Models

Target P3b amplitude *z* scores were significantly associated with time from ERP assessment to psychosis conversion among participants with the PRS (overall model: $\chi^2 = 4.77$, $P = .09$; target P3b: $\text{Wald}_1 = 4.84$, $P = .028$, $\text{Exp}_B = 0.69$; 95% CI, 0.50-0.96; and novelty P3a: $\text{Wald}_1 = 1.59$, $P = .21$, $\text{Exp}_B = 1.18$; 95% CI, 0.91-1.54), indicating that more deficient P3b amplitude was associated with more imminent risk of conversion. Specifically, for each 1-SD unit deficit in target P3b amplitude (controlling for P3a amplitude), there was a 1.45-fold increase in

Table. Demographic and Clinical Characteristics in PRS and Healthy Control Groups

Characteristic	Group, No. (%)			PRS Clinical Outcome Group, No. (%)				
	PRS (n = 552)	Healthy Controls (n = 236)	Statistical Analysis	PRS-Conversion (n = 73)	PRS-Symptomatic (n = 135)	PRS-Remission (n = 90)	Statistical Analysis	Post Hoc Contrast[a]
Sex[b]								
Male	316 (57.2)	125 (53.0)	$\chi^2 = 1.23$; $P = .27$	46 (63.0)	76 (56.3)	45 (50.0)	$\chi^2 = 3.26$; $P = .35$	
Female	236 (42.8)	111 (47.0)		27 (37.0)	59 (43.7)	45 (50.0)		
PRS[b,c]		NA	NA					
APSS	523 (94.7)			70 (95.9)	128 (94.8)	84 (93.3)	$\chi^2 = 0.54$; $P = .77$	
BIPS	16 (2.9)			8 (11.0)	2 (1.5)	1 (1.1)	$\chi^2 = 14.39$; $P < .001$	PRS-conversion>PRS-symptomatic,[d] PRS-remission[d]
GRDS	68 (12.3)			12 (16.4)	14 (10.4)	11 (12.2)	$\chi^2 = 1.62$; $P = .45$	
Current antipsychotic medication[e]	120 (21.7)	0	$\chi^2 = 60.52$; $P < .001$	22 (30.1)	29 (21.5)	16 (17.8)	$\chi^2 = 3.68$; $P = .16$	
Age, mean (SD), y[f,g]	19.21 (4.38)	20.44 (4.73)	$F = 12.38$; $P < .001$	18.49 (3.64)	19.87 (4.63)	18.68 (4.47)	$F = .46$; $P < .001$	Healthy control>PRS-remission,[d] PRS-conversion[d]; PRS-symptomatic>PRS-conversion,[h] PRS-remission
Baseline SOPS ratings, mean (SD)[g,i]								
Positive	11.42 (4.16)	0.90 (1.50)	$F = 1427.94$; $P < .001$	13.19 (4.02)	11.72 (4.09)	9.61 (4.58)	$F = 462.10$; $P < .001$	PRS-conversion>PRS-symptomatic,[d] PRS-remission,[j] healthy control[j]; PRS-symptomatic>PRS-remission,[j] healthy control,[j] PRS-remission>healthy control[j]
Negative	11.49 (6.16)	1.53 (2.47)	$F = 576.59$; $P < 01$	12.27 (6.33)	11.21 (6.59)	11.04 (5.88)	$F = 173.16$; $P < .001$	PRS-conversion, PRS-symptomatic, PRS-remission>healthy control[j]
Disorganization	4.98 (3.06)	0.65 (1.18)	$F = 444.59$; $P < .001$	6.12 (3.97)	5.04 (3.14)	4.19 (2.98)	$F = 133.35$; $P < .001$	PRS-conversion, PRS-symptomatic, PRS-remission>healthy control[j]; PRS-conversion>PRS-symptomatic[d], PRS-remission[j]; PRS-symptomatic>PRS-remission[k]
General	8.77 (4.35)	1.31 (2.12)	$F = 628.39$; $P < .001$	9.53 (4.33)	8.05 (4.26)	7.89 (4.48)	$F = 177.70$; $P < .001$	PRS-conversion, PRS-symptomatic, PRS-remission>healthy control[j]; PRS-conversion>PRS-symptomatic,[d] PRS-remission[d]

Abbreviations: APSS, attenuated positive symptoms syndrome; BIPS, brief intermittent psychotic syndrome; GRDS, genetic risk and deterioration syndrome; NA, not applicable; PRS, psychosis risk syndrome; SOPS, Scale of Psychosis-Risk Symptoms.

[a] PRS clinical outcome group comparisons include healthy controls except for the PRS syndrome and medication, which are compared across PRS groups. False discovery rate correction applied to statistical significance levels are reported.

[b] Analyzed with Pearson χ^2 tests.

[c] PRS Criteria of Psychosis-Risk Syndromes for APSS, BIPS, and GRDS are not mutually exclusive.

[d] $P < .01$.

[e] Some individuals have missing data.

[f] Age range (years): PRS, 12.09 to 36.33; healthy control, 12.09 to 34.50; PRS-conversion, 12.83 to 28.51; PRS-symptomatic, 12.09 to 36.33; and PRS-remission, 12.11 to 31.38.

[g] Analyzed with 1-way analysis of variance.

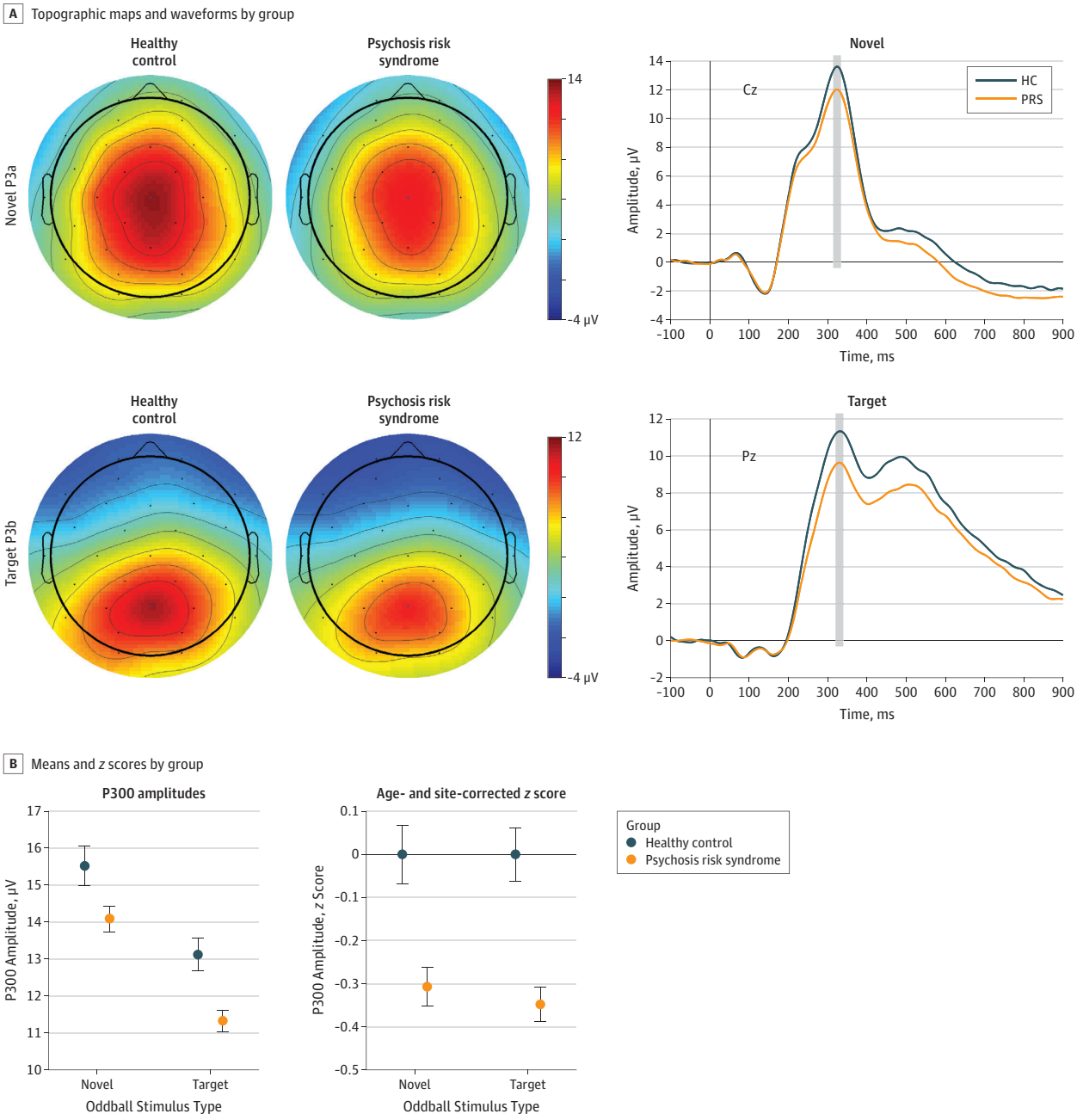
[h] $P < .10$.

[i] SOPS Negative, Disorganization, and General symptom ratings missing for 3 PRS participants (1 PRS-symptomatic).

[j] $P < .001$.

[k] $P < .05$.

Figure 1. P300 Amplitudes by Group



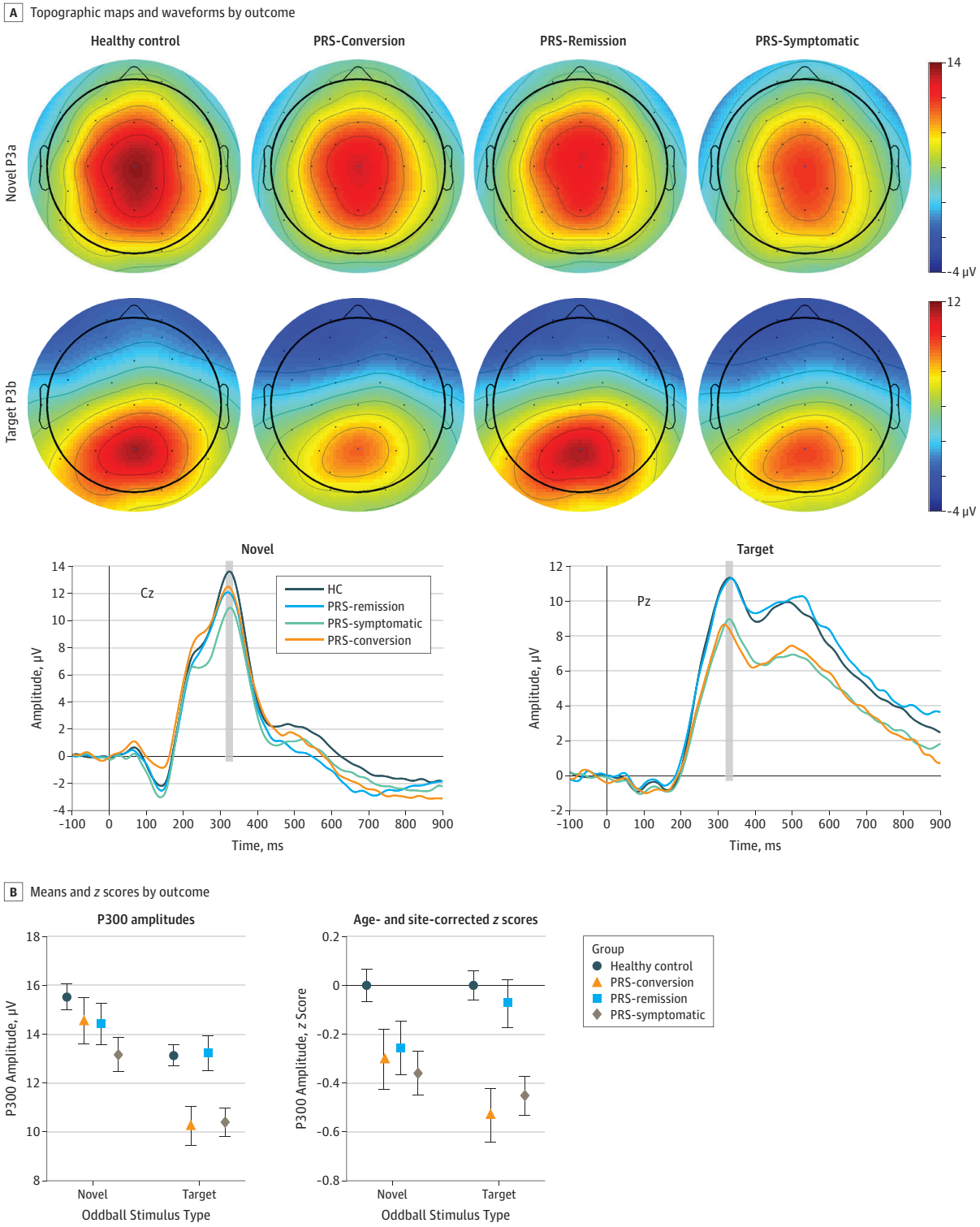
A, On the left, scalp topographic maps depicting mean P300 amplitudes around the mean latency ±10 milliseconds (indicated by gray bars in waveforms) are shown for novel and target stimuli for healthy control (HC) and psychosis risk syndrome (PRS) groups. On the right, difference waveforms for novel stimuli (P3a at electrode Cz) and target stimuli (P3b at electrode Pz) are shown for HC and PRS groups. B, Group means for P300 amplitudes (left) and age- and study site–corrected *z* scores (right). Error bars denote SEs within groups.

risk of conversion to psychosis (hazard ratio, 1.45; 95% CI, 1.04-2.00; P = .03). In addition, slower (ie, more deficient) median target RT *z* scores were associated with more imminent risk of psychosis onset (overall model χ^2 = 8.23, P = .004; median RT: Wald_1 = 8.26, P = .004, Exp_B = 1.31; 95% CI, 1.09-1.58). P300 latency was not associated with time to conversion. Estimated cumulative survival functions for target P3b amplitude and RT *z* scores are presented in **Figure 4**.

Discussion

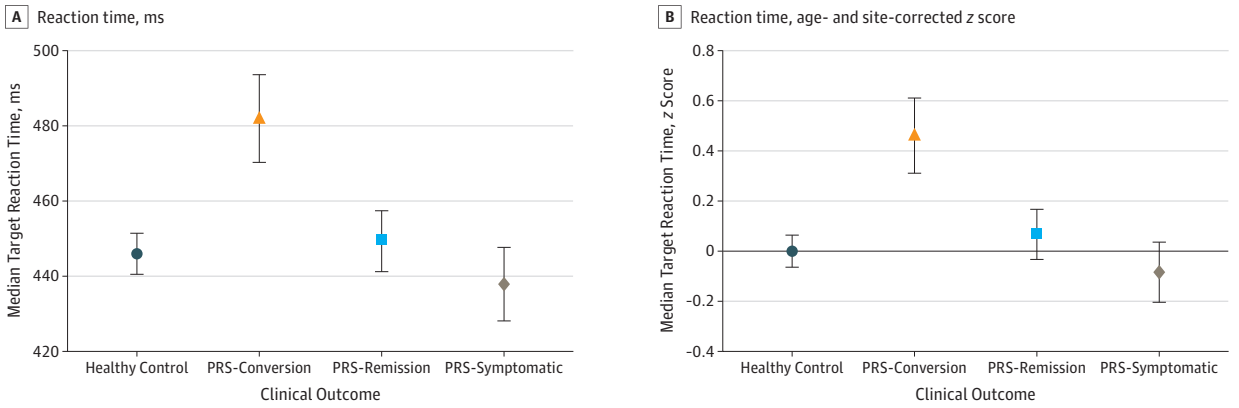
In what we believe to be the largest longitudinal study of the PRS to date, we evaluated whether auditory P300 is deficient during the PRS and is associated with clinical outcomes. In addition to providing further evidence of reduced auditory P300 amplitudes among individuals with the PRS, we found what

Figure 2. P300 Amplitudes by Clinical Outcome



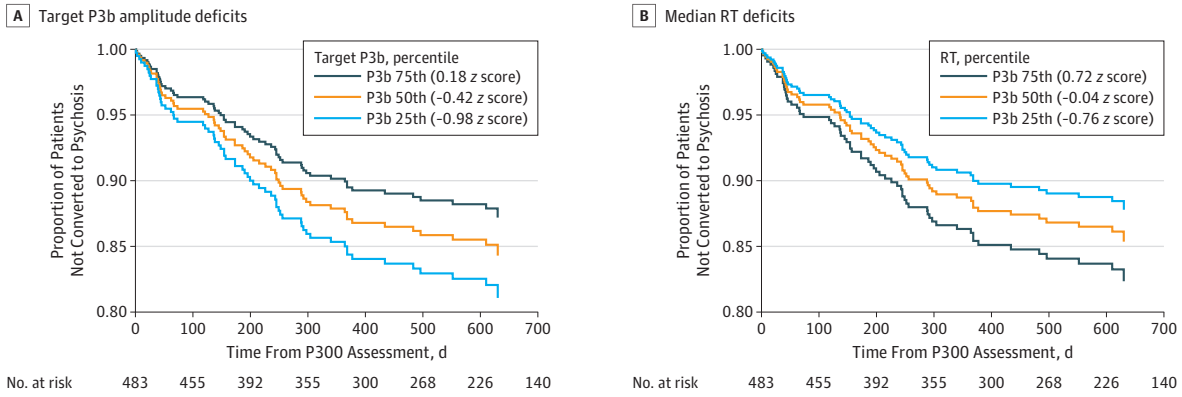
A, At the top of the panel, scalp topographic maps depicting mean P300 amplitudes around the mean latency ±10 milliseconds (indicated by gray bars in waveforms) are shown for novel and target stimuli for healthy control (HC) and psychosis risk syndrome (PRS) conversion, remission, and symptomatic groups. At the bottom of the panel, difference waveforms for novel stimuli (P3a at electrode Cz) and target stimuli (P3b at electrode Pz) are shown for HC, PRS-conversion, PRS-remission, and PRS-symptomatic groups. B, Group means for P300 amplitudes (left) and age- and study site–corrected *z* scores (right). Error bars denote SEs within groups.

Figure 3. Median Target Reaction Time by Clinical Outcome



Group means for median target reaction time (A) and age- and study site-corrected *z* scores (B). Error bars denote SEs within groups. PRS indicates psychosis risk syndrome.

Figure 4. Estimated Survival Functions for Quartiles of P300 Amplitude and Reaction Time in Participants With Psychosis Risk Syndrome (PRS)



A, Greater target P3b amplitude deficits in participants with the PRS are associated with an earlier transition to psychosis. For each SD-unit deficit in target P3b amplitude (controlling for P3a amplitude), there was a 1.45-fold increase in risk of conversion to psychosis. Estimated cumulative survival functions are plotted for the 25th, 50th, and 75th percentiles of target P3b age- and study site–corrected *z* scores at the mean P3a amplitude *z* score (mean = −0.32). B, Greater deficits in median reaction time (RT) to target stimuli in participants with the PRS are associated with an earlier transition to psychosis. For each SD-unit deficit in median target RT (ie, slower RT), there was a 1.31-fold increase in the risk of conversion to full psychosis. Estimated cumulative survival functions are plotted for the 25th, 50th, and 75th percentiles of age- and study site–corrected *z* scores of median RT to target stimuli.

appear to be deficits in target P3b amplitude, but not novelty P3a amplitude, among individuals with the PRS that later converted to psychosis compared with those who did not convert who were followed up for 24 months. Smaller target P3b amplitude and greater reaction time to target stimuli were associated with a shorter time to psychosis onset. Of the individuals with the PRS that did not convert to psychosis, those who achieved symptom remission by 24 months showed greater target P3b amplitudes compared with the individuals with the PRS that converted to psychosis and those who did not convert to psychosis but continued to be symptomatic (eTable 10 in the Supplement). These results suggest that target P3b is sensitive to clinical outcomes in the PRS, including both psychosis progression as well as remission from the at-risk state.

The results described here are consistent with previous reports of reduced auditory P300 among individuals with the PRS[34-36,53-60] and, along with the prior reports that target P3b is associated with later conversion to psychosis,[54,61] suggest that deficient target P3b is a neurophysiologic biomarker of the imminence of psychosis risk. We extended prior research by demonstrating that baseline target P3b amplitudes did not differ significantly between healthy control and PRS nonconverters whose symptoms subsequently remitted, suggesting that intact target P3b indicates a good prognosis.

The P3b and P3a subcomponents of P300 are thought to reflect top-down and bottom-up attention processes, respectively.[12] The fact that target P3b, but not novelty P3a, was associated with clinical outcomes (both conversion and remission) in individuals with the PRS suggests that the integ-

rity of top-down attention to task-relevant stimuli may have a greater relevance for clinical outcomes than the frontal systems underlying the bottom-up orienting of attention to salient distractors. While the automatically elicited novelty P3a showed reduced amplitude in individuals with the PRS as a group, its lack of sensitivity to subsequent clinical outcomes suggests that deficient orienting of attention is a feature of the PRS itself, whereas the effortfully elicited P3b has a greater role in forecasting, and possibly influencing, the likelihood of good vs poor clinical outcomes in individuals with the PRS over time. Moreover, the ability to recruit attentional resources to detect and respond to a task-relevant event may afford some protection against persistence of PRS symptoms and progression to psychosis, suggesting a potential target mechanism for novel treatments aimed at reducing risk.

Target P3b differentiated future clinical outcome groups even after accounting for SOPS symptoms. These findings highlight the potential of biomarkers, such as P300, to augment clinical information in the service of individualized risk stratification to enhance the precision of psychosis risk estimates and suggest that P3b amplitude may play a useful role in efforts to develop clinical staging algorithms that match aggressiveness of treatment with indicators of prognosis.[72-74] For example, initiation of antipsychotic medication and exposure to associated adverse effects may be least justified in individuals with the PRS who have normal P3b amplitudes at baseline given their increased likelihood of remission. As the field moves toward identifying biomarkers for the optimization of individualized care, the potential clinical usefulness of target P3b in guiding treatment warrants further study.

Limitations

This study had several limitations. Although analyses drew from the large NAPLS-2 sample, nearly half of the participants failed to complete the study,[62] preventing their inclusion in clinical outcome analyses. In addition, antipsychotic medications were not controlled; however, analyses repeated in the restricted sample of unmedicated participants demonstrated that antipsychotic medication did not appear to account for group or clinical outcome group differences. The present study did not examine P300 in the visual modality, constraining conclusions to auditory P300. A prior study also demonstrated that visual P3b is associated with conversion to psychosis,[61] and visual P300 outcomes in the NAPLS-2 sample will be examined in a future report.

Conclusions

The present study suggests support for target P3b as a potential prognostic biomarker of clinical outcome in the PRS. The results highlight the potential of P300 as a treatment target for early intervention.

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