Title

Auditory and Visual Oddball Stimulus Processing Deficits in Schizophrenia and the Psychosis Risk Syndrome: Forecasting Psychosis Risk With P300

Journal

Schizophrenia Bulletin, 45(5)

ISSN

0586-7614

Authors

Hamilton, Holly K
Woods, Scott W
Roach, Brian J
et al.

Publication Date

2019-09-11

DOI

10.1093/schbul/sby167

Peer reviewed

Schizophrenia Bulletin vol. 45 no. 5 pp. 1068–1080, 2019
doi:10.1093/schbul/sby167
Advance Access publication 8 December 2018

Auditory and Visual Oddball Stimulus Processing Deficits in Schizophrenia and the Psychosis Risk Syndrome: Forecasting Psychosis Risk With P300

Holly K. Hamilton[1,2,], Scott W. Woods[3], Brian J. Roach[1,4], Katiah Llerena[1,2], Thomas H. McGlashan[3], Vinod H. Srihari[3], Judith M. Ford[1,2], and Daniel H. Mathalon[*,1,2]

[1]Mental Health Service, San Francisco Veterans Affairs Health Care System, San Francisco, CA; [2]Department of Psychiatry, University of California San Francisco, San Francisco, CA; [3]Department of Psychiatry, Yale University, New Haven, CT; [4]Northern California Institute for Research and Education, San Francisco, CA

[*]To whom correspondence should be addressed; 4150 Clement Street, 116D, San Francisco, CA 94121, US; tel: (415) 221-4810x23860, fax: (415) 750-6622, e-mail: daniel.mathalon@ucsf.edu

Identification of neurophysiological abnormalities associated with schizophrenia that predate and predict psychosis onset may improve clinical prediction in the psychosis risk syndrome (PRS) and help elucidate the pathogenesis of schizophrenia. Amplitude reduction of the P300 event-related potential component reflects attention-mediated processing deficits and is among the most replicated biological findings in schizophrenia, making it a candidate biomarker of psychosis risk. The relative extent to which deficits in P300 amplitudes elicited by auditory and visual oddball stimuli precede psychosis onset during the PRS and predict transition to psychosis, however, remains unclear. Forty-three individuals meeting PRS criteria, 19 schizophrenia patients, and 43 healthy control (HC) participants completed baseline electroencephalography recording during separate auditory and visual oddball tasks. Two subcomponents of P300 were measured: P3b, elicited by infrequent target stimuli, and P3a, elicited by infrequent nontarget novel stimuli. Auditory and visual target P3b and novel P3a amplitudes were reduced in PRS and schizophrenia participants relative to HC participants. In addition, baseline auditory and visual target P3b, but not novel P3a, amplitudes were reduced in 15 PRS participants who later converted to psychosis, relative to 18 PRS non-converters who were followed for at least 22 months. Furthermore, target P3b amplitudes predicted time to psychosis onset among PRS participants. These results suggest that P300 amplitude deficits across auditory and visual modalities emerge early in the schizophrenia illness course and precede onset of full psychosis. Moreover, target P3b may represent an important neurophysiological vulnerability marker of the imminence of risk for psychosis.

Key words: clinical high risk/auditory deviance processing/longitudinal/event-related potential/electroencephalography

Introduction

In most patients with schizophrenia (SZ), a prodromal phase is evident from several months to years before the onset of full-blown psychosis that is typically characterized by attenuated psychotic symptoms and deterioration of social and/or occupational functioning. Research on the SZ prodrome, including the development and validation of diagnostic criteria for prospective identification of individuals exhibiting the psychosis risk syndrome (PRS), also referred to as individuals who are at "clinical high risk" for psychosis,[1–7] has increased in recent years for at least 2 reasons. First, a longer duration of psychotic illness (DUP) prior to the initiation of antipsychotic medication is associated with poorer treatment response and clinical outcomes,[8–13] underscoring the potential of early identification and intervention to improve outcomes. Beyond efforts to shorten DUP,[14,15] identifying individuals during the psychosis prodrome might create further opportunities for intervention to improve the illness course or even prevent illness onset.[16] However, recent estimates indicate that only 16%–29%[17–19] of individuals meeting PRS criteria transition to psychosis within 2 years, limiting the justification for early interventions, particularly with antipsychotic medications, and creating a major research imperative to improve PRS criteria by considering biomarkers, setting the stage for more aggressive interventions targeting those individuals at greatest risk.[20] Second, although many neurophysiological indices of neurocognitive dysfunction in SZ have been observed in first-episode patients and are generally assumed to predate psychosis onset, reflecting a genetic vulnerability[21] and/or disrupted neurodevelopment,[22–24] relatively few studies have tested this critical pathophysiological hypothesis.[25] Thus, identification of neurophysiological abnormalities associated

with SZ that predate and predict psychosis onset not only has the potential to improve clinical prediction and targeted early interventions, but also answers fundamental questions about the pathogenesis of SZ.

Amplitude reduction of the P300 event-related potential (ERP) is one of the most replicated biological findings in SZ,[26–28] making it an important candidate electrophysiological marker of psychosis risk. P300, a positive voltage deflection in the stimulus-locked ERP occurring approximately 300 ms poststimulus, is typically elicited during an oddball target detection task in response to infrequent salient stimuli interspersed among frequent "standard" stimuli.[29] Prevailing views consider P300 amplitude to be a neural reflection of phasic attentional shifts,[30] attentional resource allocation,[31–33] working memory updating of stimulus context,[34,35] stimulus salience,[36,37] or stimulus expectancy.[38–40] Its latency reflects processing speed or efficiency during stimulus evaluation[39] independent of motor preparation time.[41,42]

Two subcomponents of P300 have been characterized that depend on the nature of the eliciting stimulus and differ in their neural generators, scalp topography, and latency.[29] The P3b, which has a midline parietal maximum, reflects an effortful "top-down" attentional shift to an infrequent target stimulus requiring a motor response (button press) or updating of memory (running count of stimuli). SZ patients show P3b deficits in both auditory[43–45] and visual[46] modalities, although auditory reductions may be more robust.[26,27,47–49] In contrast, the P3a is elicited by unexpected novel or distractor stimuli, has a frontocentral scalp maximum, and peaks 20–50 ms earlier than P3b. Although P3a reflects automatic "bottom-up" orienting of attention to novel stimuli,[29,50–53] P3a has a direct relationship to behavioral reflections of attentional engagement.[54,55] Relative to P3b, fewer studies have examined P3a in SZ. Most studies, but not all,[56–59] show auditory P3a amplitude reductions in response to deviant or salient sounds.[48,49,59–69] There is also limited evidence supporting visual novel P3a amplitude reductions in SZ.[58,69,70]

Although P300 shows trait-like reductions in SZ,[49,71] auditory P3a and P3b amplitudes also appear sensitive to clinical state fluctuations over time.[49] Evidence of greater auditory P3b deficits in severely ill inpatients relative to moderately ill outpatients also suggests sensitivity to pathophysiological variations that depend on illness severity.[72] Furthermore, P3b amplitudes have been shown to be reduced and delayed in patients with longer illness duration, suggesting that P300 may also be sensitive to progressive pathophysiological processes.[73,74] This is consistent with longitudinal studies showing progressive loss of cortical gray matter volume in SZ,[75] which has also been linked to deficient P300.[76] Taken together, these findings suggest that P300 is related to both pathophysiological and clinical aspects of SZ.

The relative extent to which P3b and P3a amplitudes elicited by auditory and visual oddball stimuli are sensitive to the PRS and predict conversion to psychosis, however, remains unclear. Although several studies have demonstrated P3b amplitude deficits in PRS individuals,[58,77–82] only one study[78] has reported reduced auditory P3b to predict conversion to psychosis, as well as time to conversion, with another study limited by a small number of converters failing to show this effect.[81] Importantly, longitudinal studies may clarify whether amplitude reductions are related to an enhanced vulnerability for psychosis in individuals experiencing attenuated symptoms, or specifically reflect an imminent onset of full psychosis. In addition, although several studies have reported auditory P3a reductions in PRS individuals,[62–64,83] none have examined whether this reduction predicts conversion. Moreover, despite evidence of visual P300 deficits in SZ,[26] all prior PRS studies but one[84] have examined auditory P300, and no studies have directly compared auditory and visual P3a and P3b in the same sample.

Accordingly, this study examined target P3b and novel P3a elicited during separate auditory and visual oddball tasks in PRS individuals, relatively young SZ patients, and healthy controls (HCs). In addition to group comparisons, we evaluated whether baseline auditory and visual P3a and P3b significantly predicted future psychosis onset in PRS individuals who either converted to psychosis (PRS-C) or were followed for at least 22 months without conversion (PRS-NC). We hypothesized that PRS individuals would exhibit reduced P3b and P3a amplitudes in the auditory, and to a lesser extent, visual modalities, and that reductions would be greater in SZ. Furthermore, on the basis of prior P300 SZ and PRS literatures, we predicted that baseline P300 amplitude reductions, particularly auditory P3b deficits, would be greater in PRS-C than PRS-NC individuals, and further, that greater P300 deficits would predict a shorter time to psychosis onset. Given work demonstrating that P3b latency delays are most pronounced later in the course of SZ,[73,74] we hypothesized that P300 latencies would not be affected in our PRS and young SZ groups.

Methods

Participants

Participants included 43 individuals meeting PRS criteria based on the Structured Interview for Psychosis-Risk Syndromes (SIPS),[7,85] 19 young SZ patients diagnosed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV; SCID),[86] and 43 HCs. PRS participants met criteria for at least 1 of the 3 sub-syndromes defined by the Criteria of Psychosis-Risk Syndromes from the SIPS: Attenuated Positive Symptoms Syndrome, Brief Intermittent Psychotic Syndrome, and/or Genetic Risk and Functional Deterioration Syndrome. PRS participants' symptoms were rated using the Scale of Psychosis-Risk Symptoms[1,7] within 1 month of electroencephalography (EEG) recording. Of the PRS participants,

15 converted to psychosis (ie, met *DSM*-IV criteria for a psychotic disorder) within 28 months of EEG assessment (PRS-C). Conversion to psychosis was determined using the SIPS Presence of Psychotic Symptoms criteria or by confirmation of the presence of a psychotic disorder diagnosis by the participant's treating clinician. The SCID was used to determine psychotic disorder diagnosis among PRS-C participants, and included SZ ($n = 7$), schizoaffective disorder ($n = 3$), schizophreniform disorder ($n = 1$), psychotic disorder: not otherwise specified ($n = 2$), and Bipolar I disorder with psychotic features ($n = 2$). Median time to conversion among PRS-C was 7.87 ± 9.00 months. Only PRS participants who were followed for at least 22 months and had not converted to psychosis ($n = 18$) were considered non-converters (PRS-NC), and 10 PRS participants with insufficient clinical follow-up were excluded from analyses examining whether P300 predicted psychosis onset.

Exclusion criteria for HCs included past or current Axis I disorder based on the SCID or having a first-degree relative with a psychotic disorder. Exclusion criteria for all groups included history of significant medical or neurological illness or head injury. The study was approved by the Yale Institutional Review Board. Adult participants provided written informed consent, and minors provided written assent with parents providing written informed consent.

P300 Paradigms

In the auditory oddball task, a pseudorandom series of frequent standard stimuli (500 Hz tone; 80%), and infrequent "target" (1000 Hz tone; 10%) and "novel" (variety of sounds; 10%) stimuli, were presented with a 1.25-second stimulus onset asynchrony (SOA). Tones were 50 ms (5-ms rise/fall time) and 80-dB sound pressure level (SPL) (C scale). Novel sounds[87] ranged between 175 and 250 ms in duration and averaged 80-dB SPL. In the visual oddball task, a pseudorandom series of frequent standard stimuli (small blue circle, white background; 80%), and infrequent target (large blue circle, white background; 10%) and novel (full-screen fractal patterns; 10%) stimuli, were presented for 500 ms with a 1.25-second SOA. During both tasks, participants were instructed to press a response button to target stimuli with their preferred hand and to ignore other stimuli. Each task comprised 3 runs of 150 stimuli (totaling 45 target, 45 novel, and 360 standard stimuli for each modality).

EEG Acquisition and Preprocessing

Participants sat in an acoustically shielded booth in front a computer monitor and wore insert earphones. EEG data were recorded (1000-Hz sampling rate) from 22 scalp sites, band-pass filtered between 0.05 and 100 Hz, and referenced to linked ears. Additional electrodes were placed at the outer canthi of both eyes and above and below the left eye to record eye movements and blinks (vertical and horizontal electrooculogram; VEOG, HEOG). Electrode impedances were less than 10 kOhm. EEG data from 3 midline leads were analyzed (Fz, Cz, Pz). Continuous data were subjected to a 12-Hz low-pass filter and separated into 1024 ms epochs time-locked to stimulus onsets, with a 100-ms pre-stimulus baseline. VEOG and HEOG data were used to correct for eye movements and blinks with a regression-based algorithm.[88] Epochs containing artifacts (exceeding ±100 μV) were rejected.

Difference waveforms were calculated by subtracting the standard ERP from target and novel ERPs separately for each modality. This yielded waveforms where early P300, and particularly P3a, were disambiguated from the overlapping P200. The P3a peak was chosen from the novel difference wave as the most positive peak at Cz, and the average microvolt value within a 30-ms window centered on this peak was extracted for all electrodes. A similar strategy was used for P3b peak extraction from target difference waves at Pz. Auditory P300 was identified as the most positive peak in the 235–400 ms window following stimulus onset, whereas visual P300 was within the 230–500 ms window. P300 peak latencies were measured at Cz for P3a and Pz for P3b.

Statistical Correction for Normal and Pathological Aging Effects

Age-corrected P300 amplitudes, latencies, and median target reaction times (RTs) were derived for each participant to adjust for normal aging effects, allowing direct comparisons of PRS and SZ groups that, necessarily, differed in age. Values were regressed on age in the HC group (age range: 12–35 years). The resulting regression equation was used to derive age-specific predicted values that were subtracted from the observed values and divided by the standard error of regression, yielding age-corrected z-scores for all participants. Age-corrected z-scores reflected deviations, in standard units, from the values expected for a normal healthy individual of a given age. This method, which has been used previously,[89,90] is preferable to analysis of covariance (ANCOVA) because it only removes the effects of normal aging. These effects in the HC group generally showed younger age to be associated with larger P300 amplitudes (particularly for auditory P3a and P3b and visual P3b) and shorter latencies (particularly for novelty P3a across modalities).

Importantly, correlations of age-corrected z-scores with age in the patient groups revealed pathological aging effects, particularly in the PRS group for auditory P3b and visual P3a and P3b, with younger PRS individuals showing greater P300 amplitude deficits for their age than older PRS individuals. Given that the PRS-C group was older than the PRS-NC group (see later), Conversion Outcome analyses of age-corrected z-scores further

included age as a covariate to adjust for these pathological aging effects that would otherwise confound PRS-C vs PRS-NC comparisons. See Supplementary Material for correlations between P300 and age across groups.

Statistical Analysis

P300 amplitude age-corrected z-scores were analyzed in a 4-way mixed model analysis of variance (ANOVA) with Group (HC, PRS, SZ) as a between-subject factor, and within-subject factors of sensory Modality (auditory, visual), Stimulus Type (target, novel), and Lead (Fz, Cz, Pz). P300 latency age-corrected z-scores were analyzed in a 3-way ANOVA with Group, Modality, and Stimulus Type factors. RT age-corrected z-scores were analyzed in a 2-way ANOVA with Group and Modality factors. For reasons described earlier, parallel mixed models assessing Conversion Outcome (PRS-C, PRS-NC) effects on age-corrected z-scores were run as ANCOVAs covarying for age. Greenhouse–Geisser correction was applied when effects violated assumptions of sphericity. The Benjamini and Hochberg procedure[91] was used to account for multiple comparisons, setting the false discovery rate across comparison tests to be $P < .05$. Cohen's d is reported for group effect sizes. Analyses were also repeated with 32 antipsychotic-free PRS participants (11 PRS-C, 15 PRS-NC).

To assess associations between PRS symptom severity and P300 amplitude or latency age-corrected z-scores at baseline, P3a and P3b at maximal leads (Cz and Pz, respectively) for each stimulus type were correlated (Spearman) with SOPS symptom summary scores. Cox regression was performed to model the relationship between P300 amplitude z-scores and time to psychosis onset in PRS participants separately for each stimulus type. In addition, the P300 z-scores for both stimulus types (novel and target stimuli) were included in a single model to evaluate the independent contributions of each when controlling for the other. In all models, age was entered first as a covariate to control for the pathological aging effects on P300 z-scores described earlier.

All PRS participants were included, with censoring of PRS-NC at the time of their last follow-up assessment. Alpha was $P = .05$ for all tests.

Results

Sample Characteristics

The HC, PRS, and SZ groups did not differ in gender or handedness (see table 1 for demographic data). Groups differed in age, and post hoc tests indicated that SZ patients were older than PRS and HC ($P < .001$ and $P = .006$, respectively), and HCs were older than PRS ($P = .007$). As noted earlier, the PRS-C subgroup was also older than the PRS-NC subgroup ($P = .032$). Average parental socioeconomic status (PSES) was also higher in HCs than in PRS and SZ patients ($P = .001$ and $P = .006$, respectively), whereas PRS and SZ did not differ ($P > .05$). Accordingly, Group analyses were repeated using ANCOVA with PSES as a covariate. SOPS negative symptom ratings at the time of EEG testing were greater in PRS-C than in PRS-NC.

P300 Amplitude

ANOVA results are presented in table 2 (see figures 1 and 2). There was a main effect of Group on P300 amplitudes, as well as a significant Group × Lead interaction. Follow-up comparisons demonstrated that at Cz and Pz, but not Fz, P300 amplitudes were greater in HC relative to PRS (Cz: $P = .001$, $d = 0.71$; Pz: $P = .0003$, $d = 0.79$) and SZ (Cz: $P = .006$, $d = 0.85$; Pz: $P = .0002$, $d = 1.16$), whereas amplitudes were comparable between PRS and SZ (Ps $> .05$). All effects involving Group remained unchanged with PSES as a covariate.

The effect of Conversion Outcome on P300 amplitude was assessed in an ANCOVA model covarying for age after confirming that the P300 vs Age regression slopes were not significantly different between PRS-C and PRS-NC (Conversion Outcome × Age: $F(1,29) = 0.26$, $P = .62$). The common slope for Age was significant and interacted with Lead, with stronger Age effects evident at Pz and Cz than at Fz (although the Age effect was significant at each lead). As the analysis was performed on age-corrected z-scores, the Age effects indicated that younger PRS participants were more deficient in P300 amplitude for their age than older PRS participants. Adjusting for these age effects, there was an effect of Conversion Outcome on P300 amplitude z-scores that was qualified by a Conversion Outcome × Stimulus Type interaction. Follow-up tests for each stimulus type revealed a significant effect of Conversion Outcome for target (P3b) but not for novel (P3a) stimuli, indicating greater deficits in PRS-C relative to PRS-NC for target stimuli only ($P = .002$, $d = 0.62$). When SOPS Negative Symptom scores were adjusted for in the ANCOVA model, the Conversion Outcome × Stimulus Type interaction remained significant as did the Conversion Outcome effect on P3b (Ps $< .02$). These effects on P3b also remained significant when adjusting for SOPS Positive Symptom scores (Ps $< .004$), and when adjusting for SOPS Unusual Thought Content (Ps $< .003$) or Suspiciousness (Ps $< .003$) scores, the 2 positive symptoms showing the strongest predictive validity in prior PRS conversion analyses.[18,94]

Results were essentially unchanged when the analyses were based on the subgroup of 32 antipsychotic-free PRS participants.

P300 Latency

There were no effects involving Group or Conversion Outcome on P300 latency (Ps $> .05$).

Table 1. Group Demographic Data

	Schizophrenia (n = 19)		Psychosis Risk Syndrome (n = 43)		Healthy Control (n = 43)			Psychosis Risk Syndrome				
								Converter (n = 15)		Non-converter (n = 18)		
	n	%	n	%	n	%	P	n	%	n	%	P
Gender							.351					.614
Female	4	21.1	16	37.2	17	39.5		6	40	7	38.9	
Male	15	78.9	27	62.8	26	60.5		9	60	11	61.1	
Handedness[a]							.769					.761
Right	16	84.2	29	80.6	36	83.7		10	83.3	12	70.6	
Left	1	5.3	3	8.3	5	11.6		1	8.3	2	11.8	
Ambidextrous	2	10.5	4	11.1	2	4.7		1	8.3	3	17.6	
Antipsychotic type							<.001					.223
Atypical alone	12	63.2	6	14.0				3	20.0	1	5.6	
Typical alone	0	0	2	4.7				1	6.7	0	0	
Both	3	15.8	0	0				0	0	0	0	
None	2	10.5	32	74.4				11	73.3	15	83.3	
Unknown	2	10.5	3	7.0				0	0	2	11.1	
Schizophrenia diagnostic subtype												
Paranoid	11	57.9										
Disorganized	1	5.3										
Undifferentiated	1	5.3										
Catatonic	1	5.3										
Residual	1	5.3										
Schizoaffective	3	15.7										
Schizophreniform	1	5.3										
Psychosis risk syndrome (COPS)[b]												
APSS			43	100				15	100	18	100	
BIPS			1	2.3				1	6.7	0	0	
GRDS			1	2.3				1	6.7	0	0	
	M	SD	M	SD	M	SD	P	M	SD	M	SD	P
Age (years)[c]	23.04	5.47	16.92	3.55	19.55	4.81	<.001	17.47	2.18	15.22	3.30	.032
Parental SES[d]	38.91	10.50	38.15	14.43	28.16	13.29	.001	36.70	13.39	38.79	15.41	.686
SOPS positive symptom total			11.44	4.85				12.47	5.07	10.17	4.30	.168
SOPS negative symptom total			11.42	6.18				14.40	5.05	9.22	6.39	.016
SOPS disorganization symptom total			5.81	3.55				6.73	3.45	4.94	3.39	.144
SOPS general symptom total			8.77	3.83				9.13	3.58	8.22	4.28	.517

Note: Numbers and percentages of participants are reported for gender, handedness, antipsychotic type, schizophrenia diagnostic subtype, and psychosis risk syndrome, and were analyzed using Pearson chi-square tests. Group means (M) and standard deviations (SD) are reported for age, parental socioeconomic status (SES), and Scale of Psychosis-Risk Syndromes (SOPS) Positive, Negative, Disorganized, and General symptom total scores, and were analyzed with one-way ANOVAs. COPS, Criteria of Psychosis-Risk Syndromes; APSS, Attenuated Positive Symptom Syndrome; BIPS, Brief Intermittent Psychotic Syndrome; GRDS, Genetic Risk and Deterioration Syndrome.

[a]The Crovitz and Zener questionnaire[92] was used to measure handedness. Data were unavailable for 7 psychosis risk syndrome participants (3 converters, 1 non-converter).

[b]The COPS for APSS, BIPS, and GRDS are not mutually exclusive.

[c]Age range (years): schizophrenia = 17.1–37.5 years; psychosis risk syndrome = 12.0–26.6 years; healthy control = 12.4–34.8 years.

[d]The Hollingshead 2-factor index of parental socioeconomic status[93] is based on a composite of parental education and occupational status. Lower values signify higher socioeconomic status. Parental socioeconomic status could not be obtained from 2 schizophrenia and 4 psychosis risk syndrome participants (1 non-converter).

Reaction Time

There was a main effect of Group on target RT across modalities ($F(2,102) = 4.13$, $P = .02$), with post hoc tests showing HC to be faster than SZ ($P = .007$) and marginally faster than PRS ($P = .07$). Conversion Outcome groups did not differ on RT ($F(1,30) = 0.09$, $P = .77$), and this lack of effect did not depend on Modality ($F(1,30) = 0.01$, $P = .95$).

Table 2. Diagnostic Group and Conversion Outcome Effects on P300

	Group Effects (HC, PRS, SZ)[a]				PRS Conversion Group Effects (Converter, Non-converter)[b]			
Effect	*df*	*F*	*P*	Follow-up Tests[c]	*df*	*F*	*P*	Follow-up Tests
Group	2, 102	6.52	.002	HC > PRS**, HC > SZ**, PRS = SZ	1, 30	4.34	.046	Non-converter > Converter
Age					1, 30	14.34	.001	Younger age associated with greater P300 amplitude deficit
Stimulus (target, novel)	1, 102	1.57	.213		1, 30	0.96	.334	
Modality (auditory, visual)	1, 102	0.20	.654		1, 30	2.33	.138	
Lead (Fz, Cz, Pz)	2, 204	16.27	<.001		2, 60	6.67	.004	
Group × Stimulus	2, 102	1.08	.344		1, 30	16.57	<.001	
Group effect for targets					1, 30	11.17	.002	Non-converter > Converter
Group effect for novels					1, 30	0.27	.611	
Group × Modality	2, 102	0.19	.828		1, 30	0.21	.648	
Group × Lead	4, 204	4.91	.002		2, 60	0.21	.769	
Group effect at Fz	2, 104	1.16	.318					
Group effect at Cz	2, 104	6.76	.002	HC > PRS**, HC > SZ**, PRS = SZ				
Group effect at Pz	2, 104	10.40	<.001	HC > PRS***, HC > SZ***, PRS = SZ				
Group × Stimulus × Modality	2, 102	1.07	.346		1, 30	2.54	.121	
Group × Stimulus × Lead	4, 204	1.01	.395		2, 60	0.14	.803	
Group × Modality × Lead	4, 204	0.57	.617		2, 60	2.10	.145	
Group × Stimulus × Modality × Lead	4, 204	1.23	.277		2, 62	3.72	.095	

Note: HC, healthy control; PRS, psychosis risk syndrome; SZ, schizophrenia.
[a]Repeated measures ANOVA comparing HC, PRS, and SZ participants across target and novel stimuli using age-corrected P300 z-scores.
[b]Repeated measures ANCOVA comparing converters and non-converters to psychosis, with age as a covariate, across target and novel stimuli using age-corrected P300 z-scores.
[c]Between-group comparisons survived false discovery rate correction for multiple comparisons.
$^{**}P < .01$, $^{***}P < .001$.

Correlations

Target P3b amplitude z-scores, averaged across modality, were associated with SOPS negative symptom scores ($\rho = -0.406$, $P = .007$). There were no relationships between target P3b amplitude z-scores and other symptom domains, nor were there associations between novel P3a amplitude z-scores and any symptom domain. Greater target P3b latency z-scores were also associated with greater disorganization symptom severity ($\rho = 0.343$, $P = .02$), although this association did not survive multiple comparison correction.

Cox Proportional Hazards Models

Cox regression demonstrated that target P3b amplitude z-scores (averaged across modality) and age independently predicted time from ERP assessment to psychosis conversion among PRS participants (overall model: $\chi^2 = 8.33$, $P = .016$; target P3b: Wald(1) = 5.48, $P = .019$, Exp(B) = 0.53; Age: Wald(1) = 6.15, $P = .013$, Exp(B) = 1.24). These effects, each controlling for the other, indicated that more imminent risk of psychosis onset was predicted by greater deficits in target P3b amplitude and older age. The hazard ratio indicated that for each standard deviation unit deficit in target P3b, there was a 1.89-fold increase in psychosis conversion risk. In contrast, novel P3a amplitude z-scores did not predict time to conversion (overall model: $\chi^2 = 2.39$, $P = .30$; novel P3a: Wald(1) = 0.04, $P = .84$, Exp(B) = 0.95; Age: Wald(1) = 2.00, $P = .16$, Exp(B) = 1.12). Controlling for novel P3a amplitude and age, target P3b amplitude z-scores remained a significant predictor (overall model: $\chi^2 = 15.62$, $P = .001$; target P3b: Wald(1) = 10.42, $P = .001$, Exp(B) = 0.29). Latency did not predict time to conversion. The estimated cumulative survival functions for target P3b amplitude z-scores and age are presented in figure 3.

Discussion

This study examined auditory and visual P300, elicited by infrequent target (P3b) and novel (P3a) stimuli, in relatively young SZ patients and PRS individuals. SZ and PRS participants showed auditory and visual P300 amplitude deficits across target and novel stimuli relative to HC. Although P300 amplitudes were generally deficient in PRS, PRS individuals who later converted to psychosis showed a target P3b deficit at baseline relative

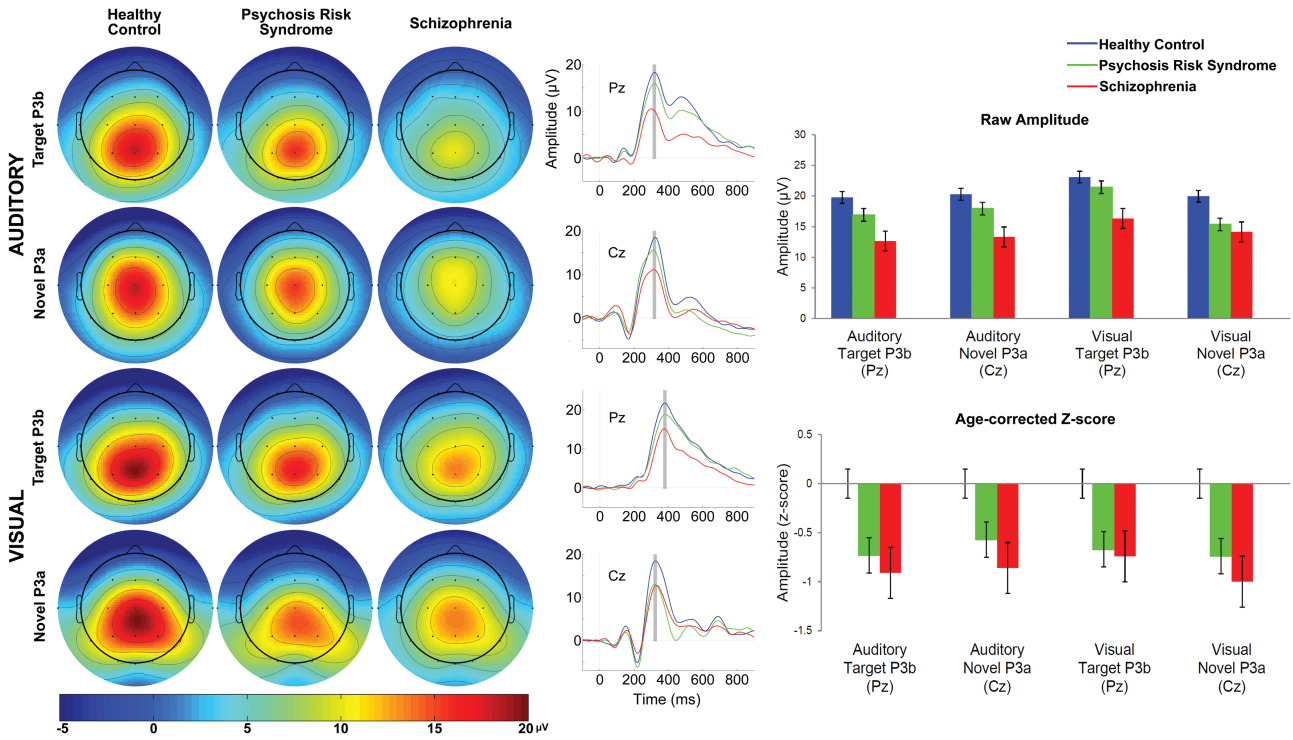

Fig. 1. *Left*: Scalp topography maps, depicting mean P300 amplitudes around the peak latency ±10 ms (indicated by gray bars in waveforms), are shown for novel and target stimuli presented in auditory and visual modalities. *Middle*: Waveforms for novels (P3a at Cz) and targets (P3b at Pz) are shown for healthy control, psychosis risk syndrome, and schizophrenia. *Right*: Column graphs show group means and standard errors for P300 amplitudes (top) and age-corrected z-scores (bottom).

to those who did not convert, whereas no baseline differences in novel P3a between PRS converters and nonconverters were evident, regardless of eliciting modality. Furthermore, smaller amplitudes of target P3b, but not novel P3a, independently predicted shorter time from P300 assessment to psychosis onset among PRS individuals, suggesting that the degree of P3b amplitude deficit is sensitive to the imminence of risk for psychosis.

These results are consistent with previous studies reporting auditory[58,62,64,77–81,83] and visual[84] P300 reductions in the PRS, providing further evidence that P300 abnormalities across both modalities emerge early in the illness and precede the onset of full psychosis. Moreover, findings corroborate one prior report that auditory P3b predicts future conversion,[78] providing strong evidence that target P3b, in particular, may represent an important marker of the imminence of psychosis risk. These findings also suggest that compromise of "top-down" attention allocation processes in the PRS, reflected by deficient P3b, is more strongly associated with future transition to psychosis than "bottom-up" attention orienting processes reflected by P3a.[29] P3a amplitude, which is attenuated in the PRS but unrelated to subsequent conversion, could nonetheless reflect vulnerability to the at-risk state, with the manifestation of psychosis being dependent on other factors that interact with this vulnerability.

We did not find attenuated P300 in the PRS relative to SZ when statistically accounting for normal aging effects on P300, similar to previous studies reporting equivalent P300 amplitude deficits in at-risk subjects and early illness SZ[58,79] and one longitudinal study showing no change in P300 deficits in PRS individuals assessed at baseline and again following conversion to psychosis.[95] This finding is consistent with other evidence that deficient P300 (P3b) amplitude may be a heritable endophenotypic trait marker of SZ and its underlying genetic risk.[28,96–101] However, given that antipsychotic medication status confounds the comparison of PRS individuals with SZ patients and with post-conversion PRS patients, strong conclusions that P300 deficits do not worsen during the transition to psychosis are premature. In particular, prior studies show antipsychotic medication may increase P300 amplitude in SZ patients.[47,102–106] Accordingly, the apparent equivalence of P300 deficits in mostly unmedicated PRS individuals and mostly medicated SZ or post-conversion PRS patients may simply reflect attenuation of the P300 deficit by antipsychotic medication. Moreover, several cross-sectional studies suggest that P300 deficits progressively worsen over the illness course of SZ, over and above the effects of normal aging,[58,73,74,79,107] consistent with a progressive pathophysiological process.

Interestingly, younger PRS participants tended to be more deficient in P300 amplitude for their age than older PRS participants, after adjusting for the effects of normal age-related brain maturation on P300. This suggests that the pathological neurodevelopmental contribution to

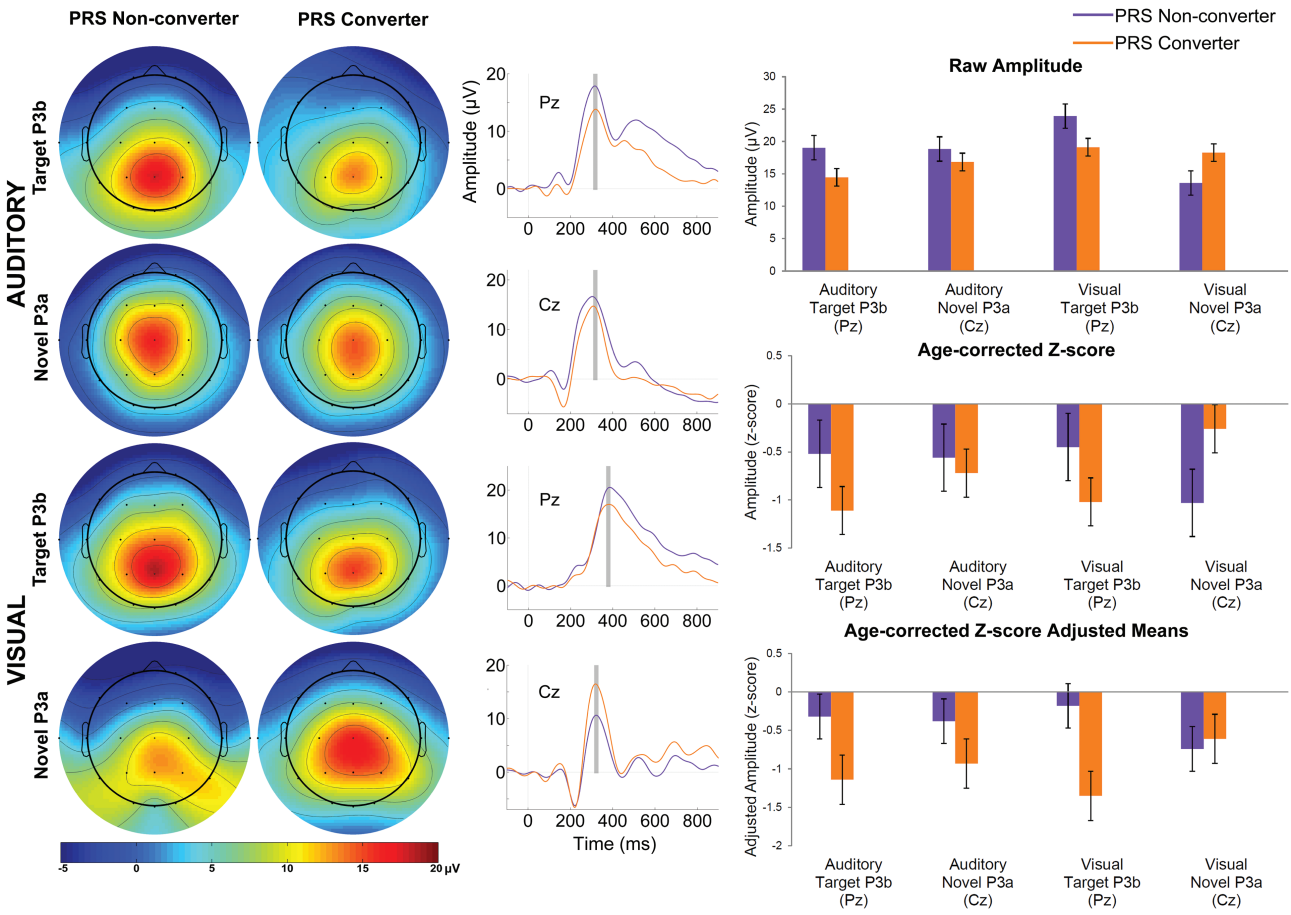

Fig. 2. *Left*: Scalp topography maps, depicting mean P300 amplitudes around the peak latency ± 10 ms (indicated by gray bars in waveforms), are shown for novel and target stimuli presented in auditory and visual modalities. *Middle*: Waveforms for novels (P3a at Cz) and targets (P3b at Pz) are shown for PRS-C and PRS-NC. *Right*: Column graphs show conversion outcome group means and standard errors for P300 amplitudes (top), age-corrected z-scores (middle), and adjusted mean z-scores (bottom), reflecting the ANCOVA adjusting for pathological aging effects. PRS, psychosis risk syndrome.

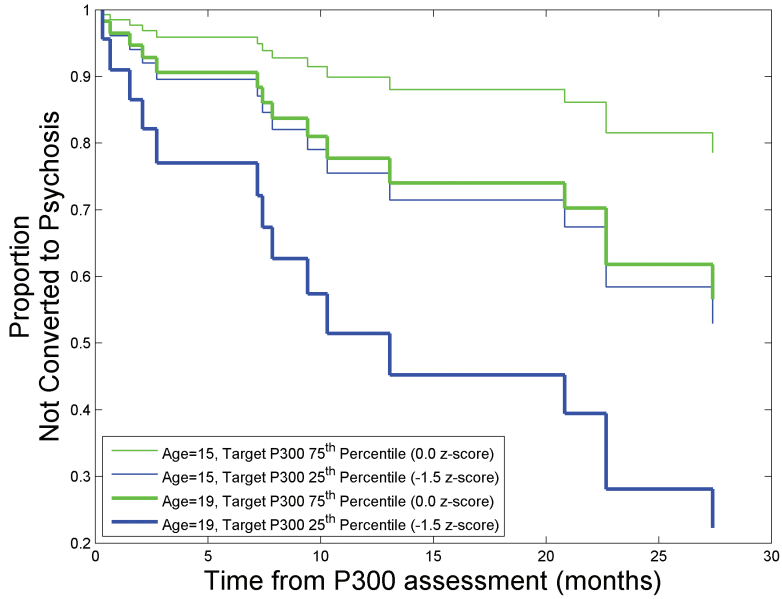

Fig. 3. Greater target P3b deficits and older age in participants meeting psychosis risk syndrome criteria are associated with an earlier transition to psychosis. Estimated cumulative survival functions are plotted for the 25th and 75th percentiles of target P3b age-corrected z-scores and age.

P300 may be more evident in younger PRS individuals before the typical maturational age-related decline in P300 amplitude emerges,[107] attenuating the deficit in older PRS individuals. We did not find evidence of P300 latency abnormalities in our PRS and young SZ groups relative to HC, consistent with prior PRS studies[77,79,84] and other work suggesting that P300 latency prolongation emerges in later illness stages.[73,74] Accordingly, given deficient P300 amplitude but normal P300 latency in PRS and relatively young SZ patients, prior evidence supporting P300 amplitude, but not latency, as a heritable endophenotypic marker of SZ, and possible differential sensitivity of these measures to pathological neurodevelopment during illness pathogenesis and progressive brain changes emerging with illness chronicity, these 2 aspects of P300 likely reflect distinct pathophysiological processes in SZ.

The association between target P3b amplitudes and negative symptom severity is consistent with previous studies of the PRS[78] and SZ.[48,49,108–115] The fact that negative symptoms in PRS individuals were associated with greater deficits in target P3b, but not novel P3a, suggests the possibility that negative symptom–related motivational impairments affect top-down allocation of attention to task-relevant stimuli but do not affect bottom-up orienting of attention to salient distractors. Although some studies have documented relationships between P300 amplitude and positive symptoms in SZ,[113,114,116–119] we did not find evidence of this association in our PRS sample, possibly because the attenuated symptoms that define the PRS are restricted in range relative to the broader symptom severity range present in typical SZ samples. Regardless, the fact that baseline target P3b amplitude differentiated future PRS-C and PRS-NC, even after controlling for positive and negative symptom severity, demonstrates the incremental validity of biomarkers such as P300, over and above clinical data, and underscores their potential to augment clinical information in the service of individualized risk stratification, increasing the precision of psychosis conversion risk estimates. The fact that the degree of P3b amplitude deficit in PRS individuals predicted the imminence of psychosis risk suggests that P3b may have a promising role in efforts to develop a clinical staging algorithm that matches aggressiveness of treatment with imminence of risk.[18,120–123]

This study had several limitations. Antipsychotic medication and dosages were not controlled among participants and confounded the PRS vs SZ group comparison. Importantly, however, analyses repeated in the subgroup of unmedicated PRS participants showed that antipsychotic medication status did not account for PRS or Conversion Outcome effects. Regarding the possible influence of other psychotropic medication such as antidepressants on our P300 findings, this seems unlikely in light of a recent study showing antidepressant medications to have no effect on P300 amplitudes in depressed patients.[124] In addition, 10 PRS participants were lost to follow-up after baseline, preventing their inclusion in conversion analyses. Although target P3b amplitude robustly predicted conversion to psychosis, consistent with one prior study,[78] our PRS sample was relatively small, underscoring the need for replication in larger samples.

In conclusion, this study demonstrates both auditory and visual P300 amplitude reductions in individuals meeting PRS criteria that are similar to the reductions observed in young SZ patients. Moreover, among PRS individuals, the greater the deficit in P3b amplitude for a given individual's age, the more imminent the risk of conversion to psychosis. Future longitudinal studies should extend the follow-up period to track within-patient illness progression and P300 from the prodrome through the early phases of SZ. Furthermore, tracking the clinical course of PRS individuals who do not convert to psychosis would allow further assessment of whether baseline P300 amplitudes predict other clinically important outcomes, such as remission from the PRS.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Funding

National Institute of Mental Health (R01 MH076989, U01 MH082022, K02 MH067967); Brain and Behavior Research Foundation; Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Mental Illness Research and Treatment and Sierra-Pacific Mental Illness Research, Education, and Clinical Center.

Acknowledgments

Dr. Mathalon consults for Boehringer Ingelheim, Alkermes, and Takeda.

References

1. Miller TJ, McGlashan TH, Woods SW, et al. Symptom assessment in schizophrenic prodromal states. *Psychiatr Q.* 1999;70:273–287.
2. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull.* 2003;29:703–715.
3. Häfner H, Maurer K, Ruhrmann S, et al. Early detection and secondary prevention of psychosis: facts and visions. *Eur Arch Psychiatry Clin Neurosci.* 2004;254:117–128.
4. Phillips LJ, Yung AR, McGorry PD. Identification of young people at risk of psychosis: validation of personal assessment and crisis evaluation clinic intake criteria. *Aust N Z J Psychiatry.* 2000;34(suppl):S164–S169.

5. Yung AR, Phillips LJ, McGorry PD, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl.* 1998;172:14–20.
6. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust N Z J Psychiatry.* 2005;39:964–971.
7. McGlashan TH, Walsh BC, Woods SW. *The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-up*. New York, NY: Oxford University Press; 2010.
8. Lieberman JA, Perkins D, Belger A, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry.* 2001;50:884–897.
9. Marshall M, Lewis S, Lockwood A, et al. Association between duration of untreated psychosis and outcome in cohorts of first episode patients: A systematic review. *JAMA Psychiatry.* 2005;62:975–983.
10. Norman RM, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychol Med.* 2001;31:381–400.
11. Woods SW, Miller TJ, McGlashan TH. The "prodromal" patient: both symptomatic and at-risk. *CNS Spectr.* 2001;6:223–232.
12. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry.* 2005;162:1785–1804.
13. Albert N, Melau M, Jensen H, Hastrup LH, Hjorthøj C, Nordentoft M. The effect of duration of untreated psychosis and treatment delay on the outcomes of prolonged early intervention in psychotic disorders. *NPJ Schizophr.* 2017;3:34.
14. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry.* 2016;173:362–372.
15. Hegelstad WT, Larsen TK, Auestad B, et al. Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. *Am J Psychiatry.* 2012;169:374–380.
16. Joa I, Gisselgård J, Brønnick K, McGlashan T, Johannessen JO. Primary prevention of psychosis through interventions in the symptomatic prodromal phase, a pragmatic Norwegian ultra high risk study. *BMC Psychiatry.* 2015;15:89.
17. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry.* 2012;69:220–229.
18. Cannon TD, Yu C, Addington J, et al. An individualized risk calculator for research in prodromal psychosis. *Am J Psychiatry.* 2016;173:980–988.
19. Nelson B, Yuen HP, Wood SJ, et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA Psychiatry.* 2013;70:793–802.
20. Mason O, Startup M, Halpin S, Schall U, Conrad A, Carr V. Risk factors for transition to first episode psychosis among individuals with "at-risk mental states." *Schizophr Res.* 2004;71:227–237.
21. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry.* 2003;160:636–645.
22. Murray RM, O'Callaghan E, Castle DJ, Lewis SW. A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull.* 1992;18:319–332.
23. Waddington JL. Schizophrenia: developmental neuroscience and pathobiology. *Lancet.* 1993;341:531–536.
24. Weinberger DR. On the plausibility of "The neurodevelopmental hypothesis" of schizophrenia. *Neuropsychopharmacology* 1996;14(suppl 3):S1–S11.
25. Bodatsch M, Brockhaus-Dumke A, Klosterkötter J, Ruhrmann S. Forecasting psychosis by event-related potentials-systematic review and specific meta-analysis. *Biol Psychiatry.* 2015;77:951–958.
26. Jeon YW, Polich J. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. *Psychophysiology.* 2003;40:684–701.
27. Ford JM. Schizophrenia: the broken P300 and beyond. *Psychophysiology.* 1999;36:667–682.
28. Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophr Res.* 2004;70:315–329.
29. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* 2007;118:2128–2148.
30. Knight RT. Evoked potential studies of attention capacity in human frontal lobe lesions. In: Levin HS, Eisenberg HM, Benton AL, eds. *Frontal Lobe Function and Dysfunction.* New York, NY: Oxford University Press; 1991:139–153.
31. Isreal JB, Wickens CD, Chesney GL, Donchin E. The event-related brain potential as an index of display-monitoring workload. *Hum Factors.* 1980;22:211–224.
32. Polich J. Habituation of P300 from auditory stimuli. *Psychobiology* 1989;17:19–28.
33. Kramer AF, Strayer DL. Assessing the development of automatic processing: an application of dual-task and event-related brain potential methodologies. *Biol Psychol.* 1988;26:231–267.
34. Donchin E, Coles M. Is the P300 component a manifestation of context updating? (Commentary on Verleger's critique of the context updating model). *Behav Brain Sci.* 1988;11:357–374.
35. Johnson R Jr. A triarchic model of P300 amplitude. *Psychophysiology.* 1986;23:367–384.
36. Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. *Science.* 1965;150:1187–1188.
37. Sutton S, Tueting P, Zubin J, John ER. Information delivery and the sensory evoked potential. *Science.* 1967;155:1436–1439.
38. Donchin E. Presidential address, 1980. Surprise! Surprise? *Psychophysiology.* 1981;18:493–513.
39. Duncan-Johnson CC, Donchin E. On quantifying surprise: the variation of event-related potentials with subjective probability. *Psychophysiology.* 1977;14:456–467.
40. Duncan-Johnson CC, Donchin E. The relation of P300 latency to reaction time as a function of expectancy. *Prog Brain Res.* 1980;54:717–722.
41. Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science.* 1977;197:792–795.
42. McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. *Science.* 1981;221:79–89.
43. Salisbury DF, Shenton ME, Sherwood AR, et al. First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. *Arch Gen Psychiatry.* 1998;55:173–180.
44. 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;113:1754–1763.

45. Demiralp T, Uçok A, Devrim M, Isoglu-Alkaç U, Tecer A, Polich J. N2 and P3 components of event-related potential in first-episode schizophrenic patients: scalp topography, medication, and latency effects. *Psychiatry Res.* 2002;111:167–179.
46. Oribe N, Hirano Y, Kanba S, et al. Progressive reduction of visual P300 amplitude in patients with first-episode schizophrenia: an ERP study. *Schizophr Bull.* 2015;41:460–470.
47. Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A. ERPs in schizophrenia: effects of antipsychotic medication. *Biol Psychiatry.* 1994;36:153–170.
48. Pfefferbaum A, Ford JM, White PM, Roth WT. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. *Arch Gen Psychiatry.* 1989;46:1035–1044.
49. Mathalon DH, Ford JM, Pfefferbaum A. Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. *Biol Psychiatry.* 2000;47:434–449.
50. Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalogr Clin Neurophysiol.* 1975;38:387–401.
51. Comerchero MD, Polich J. P3a, perceptual distinctiveness, and stimulus modality. *Brain Res Cogn Brain Res.* 1998;7:41–48.
52. Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalogr Clin Neurophysiol.* 1975;39:131–143.
53. Goldstein A, Spencer KM, Donchin E. The influence of stimulus deviance and novelty on the P300 and novelty P3. *Psychophysiology.* 2002;39:781–790.
54. Daffner KR, Mesulam MM, Scinto LF, et al. Regulation of attention to novel stimuli by frontal lobes: an event-related potential study. *Neuroreport.* 1998;9:787–791.
55. Daffner KR, Scinto LF, Calvo V, et al. The influence of stimulus deviance on electrophysiologic and behavioral responses to novel events. *J Cogn Neurosci.* 2000;12:393–406.
56. Frodl T, Meisenzahl EM, Müller D, et al. Corpus callosum and P300 in schizophrenia. *Schizophr Res.* 2001;49:107–119.
57. Schall U, Catts SV, Karayanidis F, Ward PB. Auditory event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up. *Int J Neuropsychopharmacol.* 1999;2:83–93.
58. 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;61:237–248.
59. Devrim-Uçok M, Keskin-Ergen HY, Uçok A. Novelty P3 and P3b in first-episode schizophrenia and chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:1426–1434.
60. Merrin EL, Floyd TC. P300 responses to novel auditory stimuli in hospitalized schizophrenic patients. *Biol Psychiatry.* 1994;36:527–542.
61. O'Donnell BF, Ohta H, McCarley RW, et al. The auditory P3a and P3b ERP components in schizophrenia: relationship to frontal and temporal lobe MRI volumes. In: Ogura C, Koga Y, Shimokuchi M, eds. *Recent Advances in Event-Related Brain Potential Research*. Amsterdam, the Netherlands: Elsevier Science B.V.; 1996:30–35.
62. Jahshan C, Cadenhead KS, Rissling AJ, Kirihara K, Braff DL, Light GA. Automatic sensory information processing abnormalities across the illness course of schizophrenia. *Psychol Med.* 2012;42:85–97.
63. Mondragón-Maya A, Solís-Vivanco R, León-Ortiz P, et al. Reduced P3a amplitudes in antipsychotic naïve first-episode psychosis patients and individuals at clinical high-risk for psychosis. *J Psychiatr Res.* 2013;47:755–761.
64. del Re EC, Spencer KM, Oribe N, et al. Clinical high risk and first episode schizophrenia: auditory event-related potentials. *Psychiatry Res.* 2015;231:126–133.
65. Light GA, Swerdlow NR, Thomas ML, et al. Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. *Schizophr Res.* 2015;163:63–72.
66. Ford JM, Roth WT, Menon V, Pfefferbaum A. Failures of automatic and strategic processing in schizophrenia: comparisons of event-related brain potential and startle blink modification. *Schizophr Res.* 1999;37:149–163.
67. Grillon C, Courchesne E, Ameli R, Geyer MA, Braff DL. Increased distractibility in schizophrenic patients. Electrophysiologic and behavioral evidence. *Arch Gen Psychiatry.* 1990;47:171–179.
68. Grillon C, Ameli R, Courchesne E, Braff DL. Effects of task relevance and attention on P3 in schizophrenic patients. *Schizophr Res.* 1991;4:11–21.
69. Mathalon DH, Hoffman RE, Watson TD, Miller RM, Roach BJ, Ford JM. Neurophysiological distinction between schizophrenia and schizoaffective disorder. *Front Hum Neurosci.* 2010;3:70.
70. Bestelmeyer PE. The visual P3a in schizophrenia and bipolar disorder: effects of target and distractor stimuli on the P300. *Psychiatry Res.* 2012;197:140–144.
71. Hamilton HK, Perez VB, Ford JM, Roach BJ, Jaeger J, Mathalon DH. Mismatch negativity but not P300 is associated with functional disability in schizophrenia. *Schizophr Bull.* 2018;44:492–504.
72. Ford JM, Mathalon DH, Marsh L, et al. P300 amplitude is related to clinical state in severely and moderately ill patients with schizophrenia. *Biol Psychiatry.* 1999;46:94–101.
73. Mathalon DH, Ford JM, Rosenbloom M, Pfefferbaum A. P300 reduction and prolongation with illness duration in schizophrenia. *Biol Psychiatry.* 2000;47:413–427.
74. O'Donnell BF, Faux SF, McCarley RW, et al. Increased rate of P300 latency prolongation with age in schizophrenia. Electrophysiological evidence for a neurodegenerative process. *Arch Gen Psychiatry.* 1995;52:544–549.
75. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry.* 2012;2:e190.
76. Ford JM, Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Effects of cortical gray matter, attention, and schizophrenia on P300 amplitude. In: Ogura C, Koga Y, Shimokochi M, eds. *Recent Advances in Event-Related Brain Potential Research: Proceedings of the 11th International conference on Event-Related Potentials (EPIC), Okinawa, Japan, 25–30 June 1995*. Amsterdam, the Netherlands: Elsevier; 1996:916–921.
77. Frommann I, Brinkmeyer J, Ruhrmann S, et al. Auditory P300 in individuals clinically at risk for psychosis. *Int J Psychophysiol.* 2008;70:192–205.

78. van Tricht MJ, Nieman DH, Koelman JH, et al. Reduced parietal P300 amplitude is associated with an increased risk for a first psychotic episode. *Biol Psychiatry.* 2010;68:642–648.
79. Ozgürdal S, Gudlowski Y, Witthaus H, et al. Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia. *Schizophr Res.* 2008;105:272–278.
80. Bramon E, Shaikh M, Broome M, et al. Abnormal P300 in people with high risk of developing psychosis. *Neuroimage.* 2008;41:553–560.
81. Fusar-Poli P, Crossley N, Woolley J, et al. White matter alterations related to P300 abnormalities in individuals at high risk for psychosis: an MRI-EEG study. *J Psychiatry Neurosci.* 2011;36:239–248.
82. Fusar-Poli P, Crossley N, Woolley J, et al. Gray matter alterations related to P300 abnormalities in subjects at high risk for psychosis: longitudinal MRI-EEG study. *Neuroimage.* 2011;55:320–328.
83. Atkinson RJ, Michie PT, Schall U. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. *Biol Psychiatry.* 2012;71:98–104.
84. Lee SY, Namkoong K, Cho HH, Song DH, An SK. Reduced visual P300 amplitudes in individuals at ultra-high risk for psychosis and first-episode schizophrenia. *Neurosci Lett.* 2010;486:156–160.
85. Miller TJ, McGlashan TH, Rosen JL, et al. Prospective diagnosis of the initial prodrome for schizophrenia based on the structured interview for prodromal syndromes: preliminary evidence of interrater reliability and predictive validity. *Am J Psychiatry.* 2002;159:863–865.
86. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Research Version, Patient Edition with Psychotic Screen.* New York, NY: Biometrics Research, New York State Psychiatric Institute; 1997.
87. Friedman D, Simpson G, Hamberger M. Event-related changes in scalp topography to novel and target stimuli. *Psychophysiology* 1993;30:383–396.
88. Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol.* 1983;55:468–484.
89. Pfefferbaum A, Lim KO, Zipursky RB, et al. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcohol Clin Exp Res.* 1992;16:1078–1089.
90. Perez VB, Woods SW, Roach BJ, et al. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. *Biol Psychiatry.* 2014;75:459–469.
91. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol.* 1995;57:289–300.
92. Crovitz HF, Zener K. A group-test for assessing hand- and eye-dominance. *Am J Psychol.* 1962;75:271–276.
93. Hollingshead AB, Redlich FC. *Social Class and Mental Illness: Community study.* Hoboken, NJ: John Wiley & Sons Inc; 1958.
94. Perkins DO, Jeffries CD, Cornblatt BA, et al. Severity of thought disorder predicts psychosis in persons at clinical high-risk. *Schizophr Res.* 2015;169:169–177.
95. van Tricht MJ, Nieman DH, Koelman JH, et al. Auditory ERP components before and after transition to a first psychotic episode. *Biol Psychol.* 2011;87:350–357.
96. Earls HA, Curran T, Mittal V. A meta-analytic review of auditory event-related potential components as endophenotypes for schizophrenia: perspectives from first-degree relatives. *Schizophr Bull.* 2016;42:1504–1516.
97. Bestelmeyer PE, Phillips LH, Crombie C, Benson P, St Clair D. The P300 as a possible endophenotype for schizophrenia and bipolar disorder: evidence from twin and patient studies. *Psychiatry Res.* 2009;169:212–219.
98. van Beijsterveldt CE, van Baal GC. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. *Biol Psychol.* 2002;61:111–138.
99. Malone SM, Vaidyanathan U, Basu S, Miller MB, McGue M, Iacono WG. Heritability and molecular-genetic basis of the P3 event-related brain potential: a genome-wide association study. *Psychophysiology.* 2014;51:1246–1258.
100. Turetsky BI, Dress EM, Braff DL, et al. The utility of P300 as a schizophrenia endophenotype and predictive biomarker: clinical and socio-demographic modulators in COGS-2. *Schizophr Res.* 2015;163:53–62.
101. Hall MH, Rijsdijk F, Picchioni M, et al. Substantial shared genetic influences on schizophrenia and event-related potentials. *Am J Psychiatry.* 2007;164:804–812.
102. Asato N, Hirayau Y, Ofura C, et al. Are event-related potential abnormalities in schizophrenics trait or state dependent? In: Ogura C, Koga Y, Shimokochi M, eds. *Recent Advances in Event-Related Brain Potential Research.* Amsterdam, the Netherlands: Elsevier; 1996:564–567.
103. Coburn KL, Shillcutt SD, Tucker KA, et al. P300 delay and attenuation in schizophrenia: reversal by neuroleptic medication. *Biol Psychiatry.* 1998;44:466–474.
104. Maeda H, Morita K, Kawamura N, Nakazawa Y. Amplitude and area of the auditory P300 recorded with eyes open reflect remission of schizophrenia. *Biol Psychiatry.* 1996;39:743–746.
105. Schall U, Catts SV, Chaturvedi S, et al. The effect of clozapine therapy on frontal lobe dysfunction in schizophrenia: neuropsychology and event-related potential measures. *Int J Neuropsychopharmacol.* 1998;1:19–29.
106. Umbricht D, Javitt D, Novak G, et al. Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol Psychiatry.* 1998;44:716–725.
107. van Dinteren R, Arns M, Jongsma ML, Kessels RP. P300 development across the lifespan: a systematic review and meta-analysis. *PLoS One.* 2014;9:e87347.
108. Perlman G, Foti D, Jackson F, Kotov R, Constantino E, Hajcak G. Clinical significance of auditory target P300 subcomponents in psychosis: differential diagnosis, symptom profiles, and course. *Schizophr Res.* 2015;165:145–151.
109. 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.
110. Eikmeier G, Lodemann E, Zerbin D, Gastpar M. P300, clinical symptoms, and neuropsychological parameters in acute and remitted schizophrenia: a preliminary report. *Biol Psychiatry.* 1992;31:1065–1069.
111. Strik WK, Dierks T, Maurer K. Amplitudes of auditory P300 in remitted and residual schizophrenics: correlations with clinical features. *Neuropsychobiology.* 1993;27:54–60.
112. Maurer K, Dierks T, Strik WK, Frölich L. P3 topography in psychiatry and psychopharmacology. *Brain Topogr.* 1990;3:79–84.

113. Ward PB, Catts SV, Fox AM, Michie PT, McConaghy N. Auditory selective attention and event-related potentials in schizophrenia. *Br J Psychiatry.* 1991;158:534–539.
114. Egan MF, Duncan CC, Suddath RL, Kirch DG, Mirsky AF, Wyatt RJ. Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. *Schizophr Res.* 1994;11:259–271.
115. Ergen M, Marbach S, Brand A, Başar-Eroğlu C, Demiralp T. P3 and delta band responses in visual oddball paradigm in schizophrenia. *Neurosci Lett.* 2008;440:304–308.
116. Juckel G, Müller-Schubert A, Gaebel W, Hegerl U. Residual symptoms and P300 in schizophrenic outpatients. *Psychiatry Res.* 1996;65:23–32.
117. McCarley RW, Faux SF, Shenton ME, Nestor PG, Adams J. Event-related potentials in schizophrenia: their biological and clinical correlates and a new model of schizophrenic pathophysiology. *Schizophr Res.* 1991;4:209–231.
118. Levit RA, Sutton S, Zubin J. Evoked potential correlates of information processing in psychiatric patients. *Psychol Med.* 1973;3:487–494.
119. Roth WT, Pfefferbaum A, Kelly AF, Berger PA, Kopell BS. Auditory event-related potentials in schizophrenia and depression. *Psychiatry Res.* 1981;4:199–212.
120. Mathalon DH. Challenges associated with application of clinical staging models to psychotic disorders. *Biol Psychiatry.* 2011;70:600–601.
121. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry.* 2006;40:616–622.
122. McGorry PD, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust.* 2007;187:S40–S42.
123. Wood SJ, Yung AR, McGorry PD, Pantelis C. Neuroimaging and treatment evidence for clinical staging in psychotic disorders: from the at-risk mental state to chronic schizophrenia. *Biol Psychiatry.* 2011;70:619–625.
124. Zhou L, Wang G, Wang H. Abnormalities of P300 before and after antidepressant treatment in depression: an ERP-sLORETA study. *Neuroreport.* 2018;29:160–168.