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P300 amplitude attenuation in high risk and early onset psychosis youth

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ABSTRACT

Little research has investigated the use of electrophysiological biomarkers in childhood and adolescence to distinguish early onset psychosis and the clinical high risk state. The P300 evoked potential is a robust neurophysiological marker of schizophrenia that is dampened in patients with schizophrenia and, less consistently, in those with affective psychoses and those at clinical high risk for psychosis (CHR). How it may differ between patients with psychotic disorders (PS) and CHR is less studied, especially in youth. The current study compared P300 activity among children and adolescents, aged 5–18 years, at CHR (n = 43), with PS (n = 28), and healthy controls (HC; n = 24). Participants engaged in an auditory event-related potential (ERP) task to elicit a P300 response and completed clinical interviews to verify symptoms and diagnoses. Linear regression analyses revealed a decrease in P300 amplitude with increased severity of psychotic symptoms. PS participants showed a diminished P300 response compared to those at CHR and HC, particularly among adolescents aged 13–18. This response was most evident at centroparietal and parietal locations in the right hemisphere. The findings suggest that high risk and psychotic symptomatology is linked to attenuated parietal P300 activity in youth as young as 13 years. Further exploration of the P300 as a biomarker for psychosis in very young patients could inform tailored, appropriate interventions at early stages of disease progression. Future research should evaluate whether specific phenotypic and genotypic characteristics are differentially associated with neurophysiological biomarkers and whether P300 attenuation in CHR youth can predict later symptom severity.

1. Introduction

The P300 event-related potential (ERP) is a positive deflection in the electroencephalogram observed approximately 300 ms following a stimulus presented during an auditory or visual oddball task. Such tasks require both attention to target stimuli and discrimination of target stimuli from deviant stimuli (Patel and Azzam, 2005; Polich, 1989). P300 amplitude is a robust neurophysiological marker of both recent onset and chronic schizophrenia in adults, irrespective of symptom severity and antipsychotic medication status (Jeon and Polich, 2003; Morstyn et al., 1983; Salisbury et al., 1998; van der Stelt et al., 2005). Little P300 research has been conducted with the 11–18% of patients who present in childhood or adolescence with early onset psychosis (PS) or clinical high risk symptoms (CHR) (Diaz-Caneja et al., 2015). Establishing the validity of neurophysiological markers in youth with PS and CHR symptomatology may improve early identification and treatment of at-risk and ill patients (Gonzalez-Heydrich et al., 2015). Such research is critical given the benefits of early intervention for preventing conversion to psychosis in CHR and worsening of symptoms in PS (Ising et al., 2017).

Numerous reports demonstrate P300 differences between adult high risk and schizophrenia patients versus healthy controls at midline scalp electrode locations Fz, Cz, and Pz (Bramon et al., 2004; Frommann et al., 2008; Jeon and Polich, 2003; Kim et al., 2015). The subcomponents of the P300, the "novelty detection" P3a and the "target detection" P3b, have both been highlighted in schizophrenia research: Studies have shown P3a amplitude reduction in chronic schizophrenia patients (Mathalon et al., 2010) and in clinical high risk as well as first episode adults (del Re et al., 2015; Jahshan et al., 2012; Mondragón-Maya et

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al., 2013). The parietal maximal P3b, or "classic P300" response, is a task-dependent reflection of attentional resources being allocated to a target stimulus (Polich 2007), elicited by an oddball paradigm. The P3b is the commonly studied subcomponent within schizophrenia research (e.g. van Tricht et al., 2010; McCarley et al., 1993; Fusar-Poli et al., 2011; Frodl et al., 2002). Research with CHR children and adolescents as well as schizophrenic adolescents has shown reduced late positive amplitudes at Pz compared to healthy controls in P3b target-detection tasks (Erwin et al., 1986; Friedman et al., 1982; Groom et al., 2008). These reports contribute to a body of evidence supporting a trait marker of dampened P300 response in CHR and PS youth. Whether the P300 response differs between CHR versus PS children and adolescents is unknown. Identifying potential P300 differences between CHR and PS youth may inform our understanding of the neurological underpinnings of psychosis, provide a marker for early identification for at-risk individuals, and offer insight into the development of effective therapies to prevent or halt the progression of psychosis.

Some postulate that P300 amplitude is related to memory operations, as infrequent events have no prior representation in working memory and elicit larger P300 responses than expected or frequent events (Donchin, 1981). The neural processes generating the P300 may depend on the amount of attention allocated to a task, rather than distinctly reflecting memory function, making this component potentially more variable in children than adults (Kilpelainen et al., 1999). Importantly, the P300 amplitude response to auditory stimuli shows a decrease in latency and increase in amplitude from childhood to adolescence (Johnstone et al., 1996; van Dinteren et al., 2014); thus, P300 pattering may differ in youth experiencing psychotic symptoms as compared to adults. Moreover, the neural processes underlying psychosis may differ by age of onset. Psychosis that presents before age 13 is categorized as "very early onset psychosis," or VEOP. Compared to later onset, VEOP is associated with more severe premorbid neurodevelopmental abnormalities; greater frequency of comorbid developmental, speech and language, and educational disabilities; and poorer treatment outcomes (Hafner et al., 1994; Jerrell and McIntyre, 2016). Thus, youth with VEOP may have a different neurophysiological signature than those with later onset. Very limited research has addressed this issue (Gonzalez-Heydrich et al., 2016), yet such differences may suggest unique targets for intervention.

Peak onset of psychotic disorders occurs in adolescence and young adulthood (Kessler et al., 2007); however, neural dysfunction as well as emotional, behavioral, and cognitive difficulties may precede disease onset. Current reliance on diagnostic interviews presents challenges for identifying at-risk children prior to the development of psychosis due to limitations in their ability to reliably capture the subtle intersection of internal symptoms (e.g. hallucinations, delusions) and normal cognitive developmental stages (e.g. imaginary friends, magical thinking) (Courvoisie et al., 2001). Neurophysiological measures may aid in overcoming these diagnostic challenges. Research is needed to determine the utility of the P300 in identifying CHR and PS children and adolescents.

In the current study, we aimed to confirm the limited findings of dampened P300 activation in a sample of CHR and PS children and adolescents relative to healthy controls. We hypothesized that there would be a gradation of P300 activity from healthy controls to CHR to PS in young patients. To our knowledge, this is the first study to test whether P300 activity differs in CHR versus PS in children and adolescents. We conducted an exploratory analysis of differences in patterns of P300 activity between child (5–12 years) versus adolescent participants (13–18 years), as psychosis often presents in adolescence or young adulthood, and we aimed to evaluate whether oft reported P300 dampening would be evident in youth with very early symptom onset as compared to later (adolescent) symptom onset. Finally, we explored possible hemispheric differences in P300 amplitude among clinical groups, given reports of a left temporal deficit in adult schizophrenia, albeit inconsistent (e.g. Ford et al., 2000; Kasai et al., 2002; Ozgurdal et al., 2008; Pfefferbaum et al., 1989).

2. Materials and method

2.1. Participants

Participants identified as clinical high risk (CHR; n = 43), diagnosed with a DSM-IV psychotic disorder (PS; n = 28), and healthy controls (HC; n = 24) between 5 and 18 years of age were enrolled. CHR and PS participants were recruited from the Outpatient Psychiatry Service at Boston Children's Hospital (BCH); the Commonwealth Research Center (CRC); and the Social Neuroscience and Psychopathology Laboratory (SNAP Lab). HC participants were recruited via community advertisements in the Boston area and word of mouth. PS participants met DSM-IV criteria for Schizophrenia (n = 9), Psychotic Disorder NOS (n = 12), Schizoaffective Disorder (n = 5), or Major Depression with psychotic features (n = 2) based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). Diagnosis of CHR was established by the Scale of Prodromal Symptoms (SOPS) embedded within the Structured Interview for Psychosis-Risk Syndromes (SIPS); criteria included intermittent cognitive distortions with an absence of clinical psychosis and reality testing intact. Of these participants, 30% met criteria for Brief Intermittent Psychosis Prodromal Syndrome (BIPS); 70% met criteria for Attenuated Positive Symptom Prodromal Syndrome (APS); and 7% additionally met criteria for Genetic Risk and Deterioration Prodromal Syndrome (GRDS). HC participants could not meet CHR criteria, have a current or past Axis I diagnosis, or any first-, second-, or third-degree biological relatives with a psychotic disorder. Exclusion criteria for all participants included a lifetime diagnosis of substance abuse or dependence, neurological disease, medical illness with cognitive sequelae, sensory impairments, or intellectual disability.

2.2. Procedures and measures

The BCH Institutional Review Board approved all procedures prior to study enrollment. Participants provided assent when able, or consent if the participant was 18 years old, and a parent provided written informed consent. Participants completed demographic questionnaires, clinical interviews, and an auditory ERP paradigm. Clinical interviews were administered using the K-SADS-PL, a validated semi-structured interview used to diagnose DSM-IV psychiatric disorders in youth 18 years and under (Kaufman et al., 2000). Participants were also administered the SIPS/SOPS (McGlashan et al., 2010) to evaluate CHR status and rate symptom severity. If the ERP visit occurred more than one month after the clinical interviews, the SIPS/SOPS were re-administered to confirm clinical group assignment. No participant was reclassified based upon reassessment. Race, ethnicity, date of birth, medical and psychiatric history, medication usage, and school functioning were determined via parent/guardian reports, interviews, and demographic questionnaires.

2.2.1. Auditory ERP paradigm for the P300 component

EEG recordings were collected with an EGI 128-channel Geodesic Net System (Electrical Geodesics Inc., Eugene, OR) while the participant was seated in a quiet room. Auditory stimuli were presented with TDH-49P headphones. All participants watched muted videos during the auditory stimuli in order to help maintain participant composure, and thus compliance, with the EEG task.

In total, 500 frames of stimuli were presented during the task, 15% of which were infrequent or "deviant" stimuli. Frequent and infrequent tones were presented to elicit the differential P300 response, with a ratio of 8 frequent to 1 infrequent tones. The auditory stimuli were 1000 Hz (frequent) and 1500 Hz (infrequent) digitally constructed sinusoidal tone pulses. There was a 500 ms prestimulus baseline, and a random interframe interval of 0–256 ms rendered each subsequent frame unpredictable in terms of whether the tone would be frequent or infrequent as well as the time of delivery. Each tone pulse was 50

Table 1
Participant demographics by clinical group classification.

Variable	Clinical group											
	HC (n = 24)				CHR (n = 43)				PS (n = 27)			
	n	M	SD	%	n	M	SD	%	n	M	SD	%
Age (years)		11.9	3.6			13.0	3.0			12.7	3.2	
Gender (male)	16			66.7	21			51.2	18			64.3
Handedness (left-handed)	4			17	3			7	4			15
Antipsychotic use (CPZ equivalence)	0			0	9	99.9	74.7	20.9	16	85.6	79.2	59.3
Comorbid diagnoses	0			0	30			69.8	22			81.5

Note: HC: healthy control; CHR: clinical high risk; PS: psychosis. CPZ = antipsychotic daily dose converted to equivalent daily chlorpromazine dosage equivalents in mg; percentage reported is percentage of participants within group taking any antipsychotic medication. Antipsychotic medications include: Risperidone (n = 12), Aripiprazole (n = 10), Olanzapine (n = 1), Clozapine (n = 1), Ziprasidone (n = 1). Comorbid diagnoses include Autism Spectrum Disorder, Bipolar Disorder, Attention Deficit/Hyperactivity Disorder, Anxiety disorders, Depression disorders, Panic Disorder, Obsessive Compulsive Disorder, Gender Dysphoria, and Posttraumatic Stress Disorder.

ms in duration bounded by 0.0005-s onset and offset ramps. Sinusoidal tone pulses were adjusted to a Sound Pressure Level (SPL) of 75 dB and presented binaurally on a randomly determined interstimulus interval (Noesis software), varying 2000–3000 ms to avoid rhythm artifact. A trial marker corresponding to stimulus onset was recorded along with the EEG data. Participants were instructed to press a button when the infrequent stimulus occurred, creating an attentional, task-dependent response to elicit a P3b. Task performance and any state changes that were affecting the EEG (i.e. drowsiness, agitation) were monitored by the research staff continuously throughout the paradigm. If necessary, the task was briefly paused, the participant alerted, and the paradigm restarted.

Photogrammetry was performed on 11 photographic images of the original 128-channel EGI net placement to determine true scalp electrode location. The 128 channels were converted to a full 81 channel 10–10 electrode standard data set using three-dimensional spline interpolation. Analyses were based upon common average reference for all channels. Data were collected at 500 Hz and bandpass filtered from 0.53 to 50 Hz with an additional 60 Hz mains filter. ERP epochs were segmented from -500 ms pre-stimulus to 1000 ms post-stimulus. Prior to signal averaging, epochs were visually examined by trained staff for movement and electrode artifact, eyeblink storms, state changes, muscle bursts, and timeout intervals; such epochs were marked for omission from subsequent signal averaging. Automated eyeblink and eye movement artifact removal procedures were then implemented on the entire EEG using BESA 6.0 (Berg and Scherg, 1994).

ERP signals, averaged from infrequent task trials, were low-pass filtered at 8 Hz for all participants to address residual 9-12 Hz activity frequently observed in both pre- and post-stimulus components of individual averaged signals, eliminating spurious contamination. In accordance with previous studies, P300 amplitudes and latencies were identified in each participant as the peak amplitude and associated latency observed across midline electrodes Fz, Cz, and Pz during a window 200-450 ms post-stimulus (Bramon et al., 2004; Jeon and Polich, 2003; Lee et al., 2010; McCarley et al., 1991). For evaluation of hemisphere effects, signal amplitudes in the left/right hemispheres were identified at temporal (T7/T8), centroparietal (CP5/CP6), and parietal (P7/P8) electrode locations at a latency identified by each individual's P300 peak.

Table 2
Means and standard deviations of P300 latency and P300 amplitude at Fz, Cz, Pz.

	HC		CHR		PS	
	M	SD	M	SD	M	SD
Latency (ms)	317	39.2	317	42.5	312	42.5
Amplitude (μV)						
Fz	0.3	2.6	0.5	2.4	−0.003	2.1
Cz	3.1	2.9	2.8	2.5	2.2	1.9
Pz	5.1	3.0	4.9	2.3	3.8	1.9
Maximal midline peak	5.6	2.5	5.4	2.1	4.2	1.4

Note: Analyses were conducted with the maximal midline peak point of activation.

2.3. Data analysis plan

Data were subjected to tests of normality and examined for outliers. Descriptive analyses were conducted. The Freeman-Halton Extension of a Fisher's Exact test assessed group differences on categorical demographic variables (gender, handedness). Analysis of variance (ANOVA) tests evaluated group differences on age and antipsychotic use, with antipsychotic daily doses converted to chlorpromazine equivalence (CPZ; Danivas and Venkatasubramanian, 2013)).

Linear regression modeling tested the association between clinical group and peak P300 amplitude. Peak P300 midline activity was regressed on age, gender, handedness, and antipsychotic CPZ dosage equivalents to account for differences due to demographic variables. All theoretically-based predictor variables were included in analyses and, using the simultaneous evaluation of all predictor variables, coefficients were adjusted properly. An interaction between age and clinical group was included in the model with inclusion of the main effects terms; this interaction was further explored by testing for simple slopes across groups as a function of age. Tests of homogeneity of variance and the presence of heteroscedastic errors were conducted including Levene's test, White's test, the Breusch-Pagan test, and the modified Breusch-Pagan tests. The Freeman-Halton Extension of Fisher's Exact test assessed categorical group demographic differences between children and adolescents, and ANOVA tests assessed differences on point estimates of continuous variables.

To explore asymmetry differences, data were analyzed from left hemisphere electrodes T7, CP5, P7 and right hemisphere electrodes T8, CP6, P8. Electrode sites were chosen in accordance with prior reports of P300 temporal asymmetry in adults (e.g. Strandburg et al., 1990; McCarley et al., 1993) and reports of central and parietal deficits in P300 amplitude (e.g. Morstyn et al., 1983; van Tricht et al., 2010). An ANOVA model, using a within-person factor for left versus right topography and a between-person factor involving participant classification (3 levels), was conducted. Of interest was the presence of a significant interaction, which, when present, was followed by a series of contrasts to identify the location of the interaction.

To anticipate potential biases of the relatively small sample size, all analyses were repeated via bootstrapping (Efron, 1982) to simulate the population distribution and assess possible parameter biases. Results show amount of bias and modified standard errors as per the bootstrap distribution. Bias corrected and accelerated (BCa[1]) 95% confidence intervals were produced using estimated parameters from the bootstrap distribution.

[1] BCa confidence intervals were estimated by taking into account deviations from normality, correcting for bias and skeweness in the distribution of bootstrap estimates (Carpenter and Bithell, 2000).

Table 3
Summary of linear regression analyss for variables predicting P300 amplitude.

Variable	Model 1						Model 2					
	β	Bias	SE B	*t*	Sig.	BCa 95%	β	Bias	SE B	*t*	Sig.	BCa 95%
Clinical group	**−0.770**	**−0.027**	**0.303**	**−2.539**	**0.013**	−1.325–(−0.280)	1.567	0.136	0.924	1.445	0.152	−0.497–3.960
Age (years)	0.086	−0.001	0.067	1.271	0.207	−0.045–0.205	0.457	0.019	0.156	2.562	0.012	0.097–0.836
Gender (male)	−0.599	0.034	0.431	−1.389	0.168	−1.553–0.373	−0.618	0.023	0.433	−0.145	0.147	−1.522–0.342
Handedness (left-handed)	0.834	−0.005	0.663	0.128	0.212	−0.647–2.307	0.830	0.016	0.844	0.127	0.204	−0.937–2.584
Antipsychotic use (CPZ equivalence)	0.001	0.000	0.004	0.018	0.865	−0.008–0.008	0.000	0.000	0.004	0.085	0.932	−0.008–0.008
Clinical group Age	–	–	–	–	–	–	**−0.189**	**−0.010**	**0.071**	**−2.240**	**0.028**	**−0.311–(−0.086)**

Note: Antipsychotic medications include Risperidone (n = 12), Aripiprazole (n = 10), Olanzapine (n = 1), Clozapine (n = 1), and Ziprasidone (n = 1). Predictor variables significantly associated with P300 amplitude are bolded. The increased bias estimate for the clinical group is not interpreted negatively, as it is a qualitative variable and bootstrapping cannot be reliably interpreted. Standard errors and probabilities are based on the Bootstrap distribution. Results in terms of significance were identical using the sample data and those from the bootstrap distribution. 95% Bias-corrected and accelerated confidence intervals are shown. Constant value is not shown for parsimony. Power analysis for the multiple regression model was estimated for identifying significant effects at 80% of the time (i.e., power) resulting from a multiple R-square value of 20%, with 6 predictor variables (Model 2), in relation to a null prediction. Results indicated that n = 88 participants would provide adequate power (Benton & Krishnamoorthy, 2003; Gatsonis & Sampson, 1989). Model 1 with 5 predictors had enhanced power levels for the same configuration (i.e., 83%). Consequently, the present sample suffices for both models.

3. Results

3.1. Descriptive data

Within the PS group, there was a single outlier whose P300 amplitude measurement was four standard deviations from the group mean. With this outlier removed from the data set (PS; n = 27), all clinical groups met tests of normality.

Table 1 depicts the distributions of study variables across clinical groups. Clinical groups did not differ on gender ($p = .317$), handedness ($p = .423$), or age [$F(2,91) = 0.969$, $p = .383$]. As expected, groups differed based on antipsychotic CPZ dosage equivalents [$F(2,91) = 5.029$, $p = .008$], with HC and PS groups differing at $p = .007$. The CHR group did not differ significantly from HC ($p = .379$) or PS ($p = .146$).

3.2. Clinical group differences on P300 amplitude and latency

Means and standard deviations of P300 latency and amplitude along the midline are summarized in Table 2. P300 latency did not differ among clinical groups ($p = .856$) and thus was not explored further. As shown in Table 3, Model 1, of the variables tested via linear regression, only the clinical group classification variable (HC, CHR, PS) significantly predicted P300 amplitude activity ($\beta = -0.770$, $p = .013$). Age, gender, handedness, and antipsychotic use were not significant ($ps > 0.16$).

An ANOVA test revealed a significantly dampened midline P300 amplitude with increasing severity of psychosis spectrum clinical group, from HC to CHR to PS [$F(2,91) = 3.897$, $p = .024$, $\eta^2 = 0.078$]. However, follow-up analyses using Bonferroni post-hoc comparisons revealed the only significant differences were between PS and HC groups ($p = .047$) and between PS and CHR groups ($p = .050$).

3.3. Age-group comparison

In a linear regression including an interaction term between clinical group classification and age (Table 3, Model 2), the interaction was a significant predictor of P300 amplitude ($\beta = -0.189$, $p = .028$; $R^2 = 0.163$). To explore the clinical group by age interaction, an analysis of

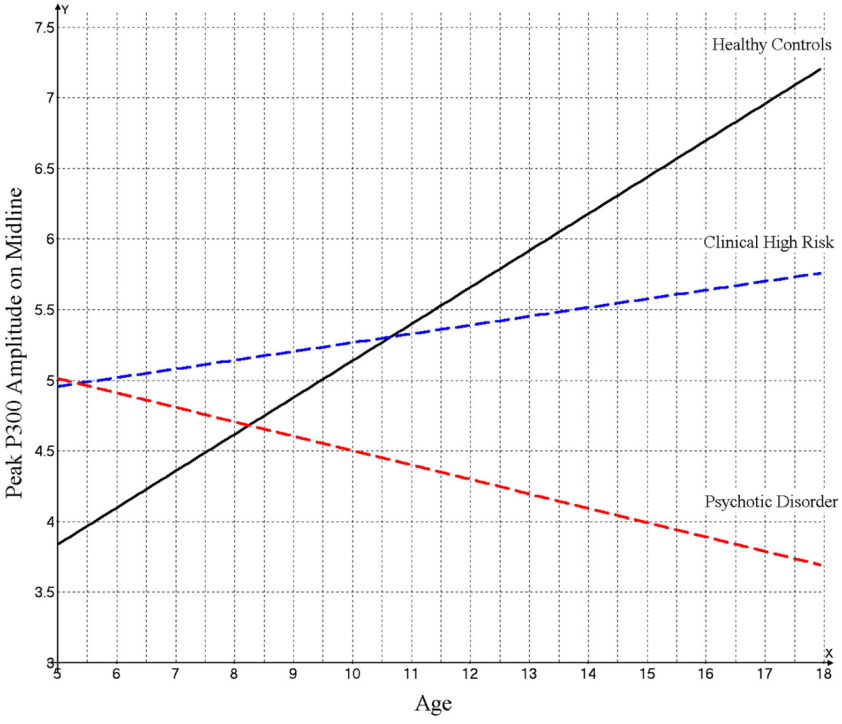

Fig. 1. Analysis of simple slopes testing the interaction between age and clinical group. The figure shows age as a continuous variable to express the slope lines; results are identical using age as a two-group variable, separated into children and adolescents.

Table 4
Participant demographics by child versus adolescent group.

	Child (5–12 years)				Adolescent (13–18 years)			
	HC	CHR	PS	Total	HC	CHR	PS	Total
Analyzed (n)	12	16	12		12	27	15	
Age in years, M (SD)	9.0 (2.4)	9.8 (1.4)	9.6 (1.4)		14.8 (1.4)	15.0 (1.6)	15.1 (1.6)	
Gender (% male)				62.5				53.7
Handedness (% left)				15.0				9.3
Antipsychotic use (% yes)				27.5				24.1

simple slopes was conducted. Tests of homogeneity of variance and the presence of heteroscedastic errors were conducted. Levene's test was non-significant, suggesting equality of groups' error variances [Levene's $F(5) = 1.311$, $p = .267$]. For the assumption of equal error variances across levels of the independent variables, White's test was non-significant, suggesting meeting the assumption of homoscedastic errors [$\chi 2(5) = 7.747$, $p = .171$]. The same result of the tests of error variances were replicated by use of the Breusch-Pagan and the modified Breusch-Pagan tests.

As shown in Fig. 1, there were different simple slopes per clinical classification group. Specifically, there was a significant positive slope for HC ($b = 0.260$, $p = .007$) followed by two non-significant slopes for CHR ($b = 0.062$, $p = .597$), and PS ($b = -0.102$, $p = .159$). An omnibus test of the equality of simple slopes pointed to non-equivalence [Wald test$(2) = 8.992$, $p = .0112$]. This was followed by bivariate comparisons, indicating that there were significant differences between the slopes of the HC and PS groups only ($b = 0.362$, $p = .003$). There were no differences in the slopes between the HC and CHR groups ($b = 0.198$, $p = .190$) or CHR and PS ($b = 0.164$, $p = .232$).

In order to elucidate the results from the simple slopes analysis, namely that P300 differences appear to increase and change as age increases, the sample was stratified into two age groups (child, ages 5–12 and adolescent, ages 13–18). Child and adolescent groups did not differ on gender [$\chi^2(1) = 0.727$, $p = .394$], handedness [$\chi^2(1) = 0.733$,

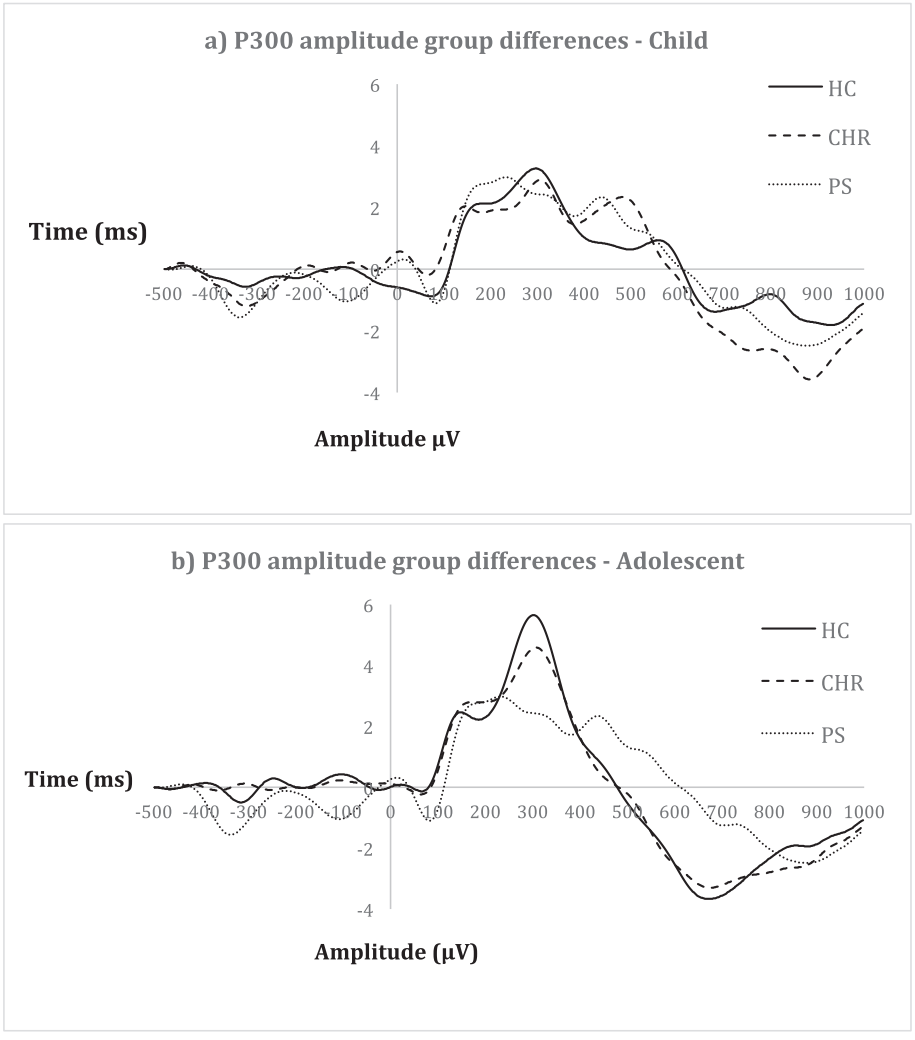

Fig. 2. Age group comparison of P300 amplitudes across clinical groups: a) Clinical group differences within the child group did not reach significance. b) Significant differences emerged in the adolescent group between HC and PS ($p = .029$) and between CHR and PS ($p = .029$). P300 amplitude was evaluated within a window of 200–450 ms post stimulus.

$p = .392$], or antipsychotic use at the time of assessment [$F(1,92) = 0.181$, $p = .671$]. Table 4 provides demographic details of the clinical groups split by age groups.

P300 amplitude by clinical group, separated for children and adolescents, are depicted in Fig. 2a and b. Within the child subgroup, the relationship between clinical group and P300 amplitude suggested in Fig. 2a

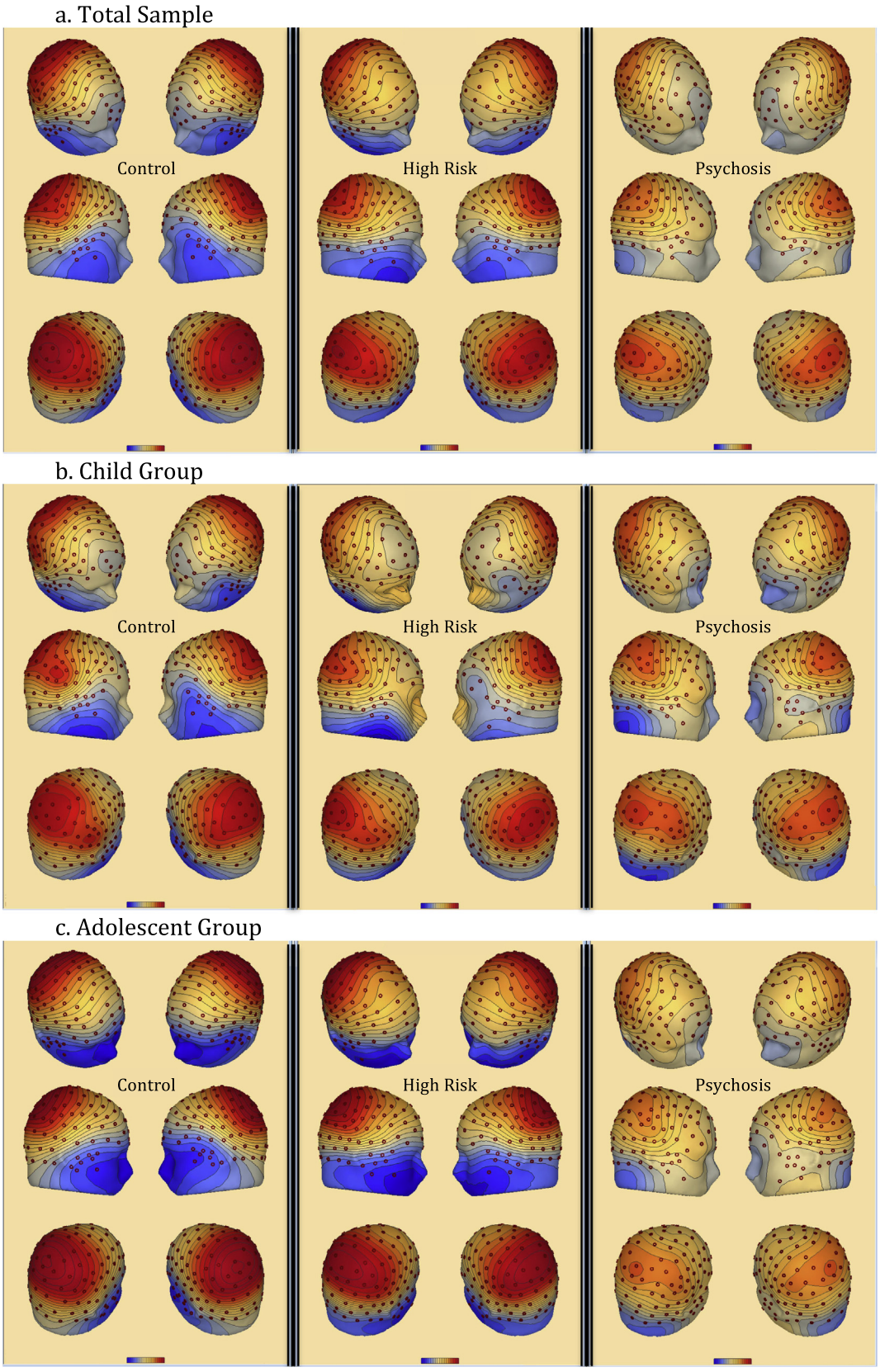

Fig. 3. Topographic maps of P300 activation separated by clinical group in a. the entire youth sample; b. the child group (ages 5–12); and c. the adolescent group (ages 13–17). Significant differences in midline P300 amplitude were found in the adolescent group only, between HC and PS ($p = .029$) and between CHR and PS ($p = .029$).

was not statistically significant [$F(2,37) = 0.203$, $p = .817$], while it was robust and significant within the adolescent group [$F(2,51) = 5.960$, $p = .005$, $\eta^2 = 0.189$]. Subsequent pairwise comparisons found that the PS group showed an attenuated P300 relative to both the CHR (mean difference = 1.71, $p = .029$) and HC (mean difference = −2.51, $p = .029$) groups after Bonferroni correction; the difference between the HC and CHR groups did not reach significance (mean difference = −0.80, $p = .754$).

3.4. Topographic analyses for hemispheric effects

Topographic maps of P300 activity by clinical group are shown in Fig. 3, delineated by a) Total sample, b) Child group, and c) Adolescent group. To test for hemispheric effects, P300 amplitude values at left hemisphere electrodes (T7, CP5, P7) and right hemisphere electrodes (T8, CP6, P7) were examined for child and adolescent groups separately, given that they showed different P300 results overall. Means and standard deviations are displayed by age group in Tables 5a and 5b.

In the child subgroup, there was a significant 3 × 3 interaction for only the right hemisphere models [$F(2, 37) = 3.414$, $p = .044$]. Fig. 4 displays the 3 × 3 models representing left and right topographies and two age groups. Specifically, there was a significant difference between HC and PS groups at P8, with HC having significantly elevated scores [$F(1, 37) = 5.946$, $p = .020$]. In contrast, there were no differences between classification groups in the T8 and CP6 locations.

Among adolescents, results pointed to significant interactions between location and classification for both the left [$F(2, 51) = 4.819$, $p = .012$] and right hemisphere models [$F(2, 51) = 3.955$, $p = .025$]. In the left hemisphere factor model, at the T7 location, there were significant differences between HC and CHR [$F(1, 51) = 6.451$, $p = .014$] and between HC and PS [$F(1, 51) = 6.712$, $p = .012$]. This pattern of differentiation was only evident at T7. For the right hemisphere, there were significant differences in the CP6 location only. Specifically, the PS group had significantly lower mean values compared to both HC [$F(1, 51) = 6.511$, $p = .014$] and CHR [$F(1, 51) = 7.767$, $p = .007$]. Fig. 4 displays the mean P300 amplitudes among the three clinical groups at each scalp location by hemisphere.

4. Discussion

The overall goal of this study was to evaluate P300 activation in a sample of CHR and PS children and adolescents compared to healthy controls (HC). A secondary goal was to examine whether patterns of P300 activation differed among child versus adolescent clinical groups. We found that overall, PS youth differed from CHR and HC groups in their mean P300 amplitude response to auditory stimuli. This was particularly evident in adolescents. Secondary hemispheric analyses revealed dispersed effects at different electrode locations, dependent upon age group and clinical group comparison.

Our hypothesis regarding a gradation of P300 dampening from HC to CHR to PS was only partially supported. While the data showed an association between increasingly severe psychotic spectrum categories and lower average P300 amplitude, post-hoc analyses revealed that the P300 amplitude differed between PS and HC and between PS and CHR, but not HC and CHR. To our knowledge, this study is the first to report significant P300 differences between CHR youth versus those with diagnosed psychosis, extending previous findings of decreased P300 amplitude comparing PS to CHR adults (Bramon et al., 2004; Frommann et al., 2008; Jeon and Polich, 2003; Kim et al., 2015).

Studies in adults with prodromal symptoms of psychosis have found reduced P300 amplitudes compared to healthy controls (Bramon et al., 2008; Frommann et al., 2008; van der Stelt et al., 2005). Additionally, Morimoto et al. (2016) found that CHR adolescents showed a dampened P300 amplitude compared to controls. The lack of a significant difference between HC and CHR participants in the current study possibly reflects clinical heterogeneity in the CHR group, a characteristic widely recognized in studies evaluating this population (Fusar-Poli et al., 2016). In our sample, participants were classified as CHR if they endorsed psychotic-like symptoms without conviction of their basis in reality, or if psychotic symptoms were transient. Symptoms represented in the CHR group of developing children and adolescents may be indicative of a spectrum of mild psychotic symptoms, encompassing a range of severity. A recent study regarding CHR in children and adolescents reported that rates of conversion to psychosis ranged from 17 to 20% at 1-year follow-up and 7–21% at 2-year follow-up (Tor et al., 2017). In adults, the conversion rate at 2-year follow-up is 29% (Fusar-Poli et al., 2012). van Tricht et al. (2010) longitudinally explored P300 abnormalities in young adult ultra high risk patients, finding that reduced P300 amplitude was the best predictor of transition to psychosis. Without longitudinal follow up of these patients, we cannot conclude whether P300 amplitude is a reliable predictor of transition to psychosis among CHR youth; future research should consider whether variability in symptom presentation among child and adolescent CHR participants is associated with differences in P300 activity and whether such neurophysiological markers are predictive of conversion to psychosis in a younger, critically developing population.

We did not find differences in P300 latency between clinical groups, consistent with other reports (e.g. (Frommann et al., 2008; Morimoto et al., 2016). Although some studies have shown increased latency of the P300 in adult schizophrenia patients (O'Donnell et al., 2004; Salisbury et al., 1998), this finding has been attributed to increased age and illness duration, as the course of schizophrenia can be associated with a progressive decline of brain function (Mathalon et al., 2000). Null P300 latency effects in our youth sample are consistent with this hypothesis.

In analyses conducted separately for children and adolescents, only adolescents showed dampened P300 amplitude by clinical group, with pairwise differences emerging between PS and CHR and between PS and HC. Visually, the data show a gradual decline in P300 activation from HC to CHR to PS (Fig. 2b), although the difference between HC and CHR did not reach significance. The fact that our data did not

Table 5a
Topographic analysis – Means and standard deviations of P300 amplitude for children (ages 5–12).

	HC		CHR		PS	
	M	SD	M	SD	M	SD
Left						
T7	1.26	1.50	0.73	1.18	1.23	2.13
CP5	2.79	2.12	2.39	1.14	2.75	2.83
P7	2.43	1.99	2.38	2.14	1.71	2.61
Right						
T8	1.35	1.67	1.38	1.69	2.46	3.70
CP6	3.10	1.57	2.81	1.19	2.52	3.24
P8	3.54	1.81	2.57	2.49	1.26	2.41

Note: Greatest points of P300 activation occurred at the centroparietal scalp electrode locations (CP5, CP6).

Table 5b
Topographic analysis – Means and standard deviations of P300 amplitude for adolescents (ages 13–18).

	HC		CHR		PS	
	M	SD	M	SD	M	SD
Left						
T7	−0.38	1.21	0.88	1.52	1.05	1.39
CP5	2.27	1.99	2.75	1.29	2.09	1.58
P7	1.49	2.22	1.64	1.39	1.22	1.47
Right						
T8	0.53	1.44	0.65	1.78	0.13	1.12
CP6	3.03	2.25	2.86	1.79	1.26	1.29
P8	1.89	1.40	1.70	2.45	0.67	1.21

Note: Greatest points of P300 activation occurred at the centroparietal scalp electrode locations (CP5, CP6).

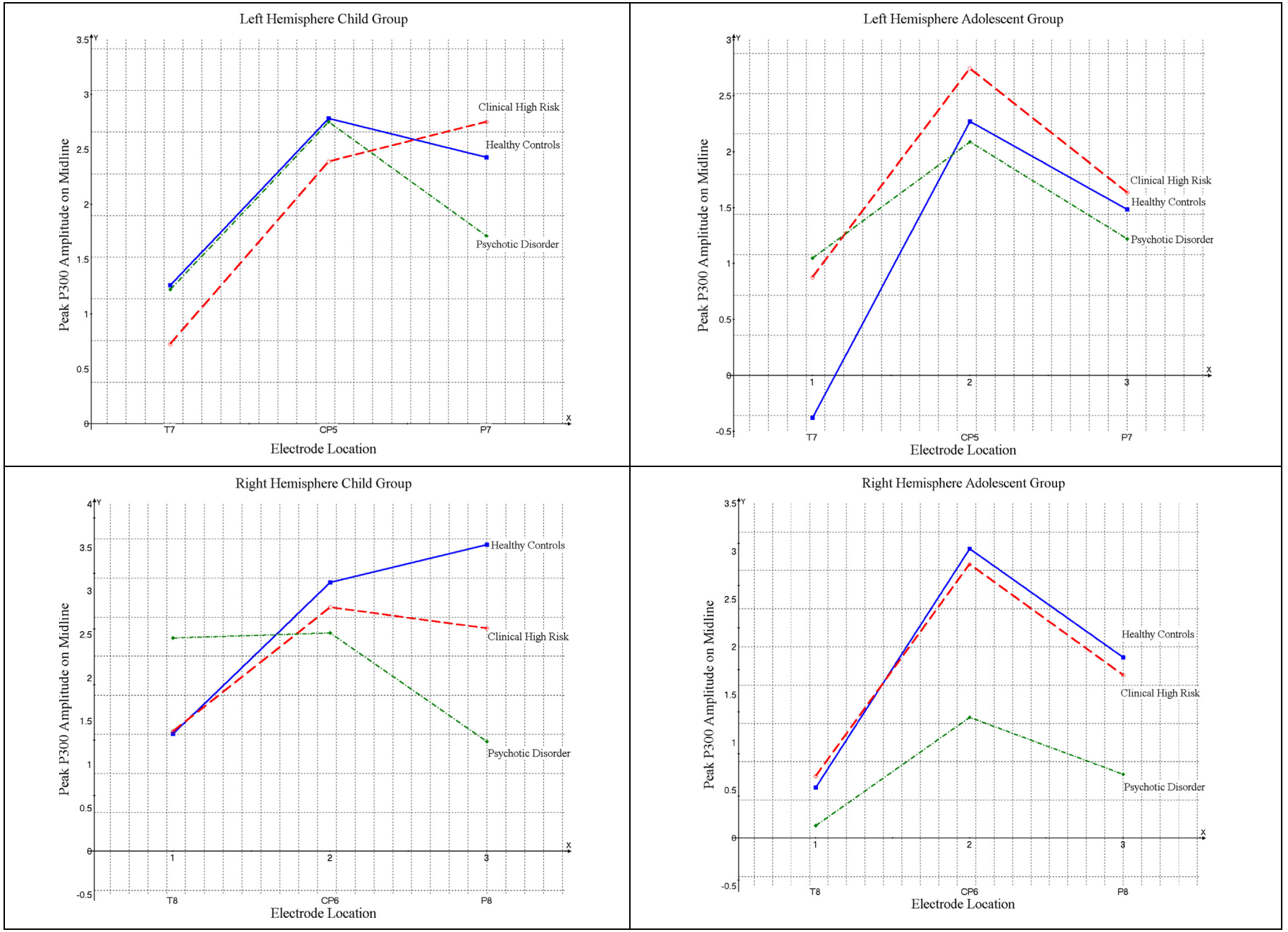

Fig. 4. Topographic analyses of P300, separated by age group and hemisphere. In the child group, there was a significant difference between HC and PS at P8 ($p = .020$). Among adolescents, there were significant differences at T7 between HC and CHR ($p = .014$), as well as between HC and PS ($p = .012$). At CP6, the PS group differed significantly from CHR ($p = .007$) and from HC ($p = .014$).

provide evidence for group differences among children may be because P300 measurement in younger participants is more susceptible to more variable, intermingled component amplitudes as the P300 matures (Polich et al., 1990; van Dinteren et al., 2014). It is also possible that neurologic changes underlying VEOP differ from those underlying adolescent psychosis.

Research has shown the reliability of an attenuated auditory P300 as a putative marker for adult schizophrenia as compared to controls (for reviews, see Jeon and Polich, 2001; Pritchard, 1986). The P300 component is taken to be a neurophysiological index of information processing and representative of higher cognitive brain functions related to memory and attention (Downes et al., 2017; Polich, 1996). In patients with schizophrenia, a dampened P300 could reflect greater thinking disturbances and reduced cognitive resources. Studies using visual stimuli have also demonstrated attenuated P300 responding in youth with psychotic symptoms. For example, Rawdon et al. (2013) assessed P300 responsiveness to a spatial working memory task in adolescents who self-reported psychotic symptoms, particularly auditory hallucinations and delusions, reporting a dampened P300 response compared to controls, consistent with our findings. Among VEOP children with hallucinations, delusions, and thought disorder, Strandburg et al. (1990) found an attenuated P300 amplitude. The results from our child group contrast this finding, potentially reflecting differential involvement of visual and auditory systems by the underlying disease process, or a unique developmental trajectory for the visual P300, whereby prior research has shown a negative association between the strength of the visual P300 and age (Segalowitz et al., 2010; Stige et al., 2007). This contrast could also be due to differences in inclusion criteria for psychotic children in various studies. The current study employed a Research Domain Criteria (RDoC) approach (Insel, 2014), including participants with a range of psychotic disorders. As a group, these studies provide evidence for P300 group differences across auditory- and visually-based tasks in youth on the psychosis spectrum. Our results expand on these findings by showing differences between CHR and PS adolescents, with P300 attenuation greatest in those with psychosis.

This study's topographic results corroborated prior findings (Schreiber et al., 1992; van der Stelt et al., 2005) that the P300 is strongest at parietal locations, namely Pz. P300 amplitudes were largest at centroparietal and parietal electrodes, and PS participants showed a decrease in right hemisphere activation at CP6 and P8 relative to HC and CHR participants. Strandburg et al. (1990) reported dampened left hemisphere activity in schizophrenic children at the earlier P200 neurophysiological marker; in our sample, by separating children and adolescents, we found that PS children showed significantly dampened P300 activity in the right parietal location compared to HC participants. This pattern was also seen in adolescents, suggesting a potential salient marker of altered P300 activity in PS youth. The adolescent subgroup showed a clearer lateralized delineation of P300 dampening at the right hemisphere electrode sites than the child subgroup.

The topographic data revealed differences between CHR versus HC and PS adolescents, with differences between HC and CHR in the left temporal location, and between CHR and PS at the right centroparietal location. Some postulate that structural effects such as asymmetry become more apparent with longer illness duration or chronic psychosis (Renoult et al., 2007; van der Stelt et al., 2005). Those within CHR classification in our sample may encompass enough variance in P300 development, symptom severity, and length of illness to reduce more robust and conclusive group differences in terms of asymmetry. Research in adults with or at risk for schizophrenia and psychosis has evidenced dampened left hemisphere activity, particularly in temporal scalp locations (Frommann et al., 2008; McCarley et al., 1991; Morstyn et al., 1983; Pritchard, 1986) and in first episode adult patients (Salisbury et al., 1998). The current findings, though cross-sectional, considered alongside the extant literature, might suggest an evolving P300 asymmetry with increasing psychosis spectrum category severity. Notably, the research presenting contrary findings or a lack of asymmetry are considerable (e.g. Ford et al., 2000; Iwanami et al., 2002; Ozgurdal et al., 2008; Pfefferbaum et al., 1989), and there is a dearth of P300 asymmetry research in younger populations. The inconclusiveness of these findings emphasizes the need for continued exploration of developing neurophysiological lateralization in children and adolescents experiencing symptoms of psychosis.

This study has several strengths. These results are the first to demonstrate differences in neurophysiological P300 responsiveness between CHR and PS youth as young as 13 years. The data suggest that increased severity of psychotic spectrum clinical category is linked to dampening of P300 activation in parietal areas. Recognizing the P300 as a discernible neurophysiological biomarker may be useful for the creation of tailored, appropriate interventions for affected children and adolescents. Limitations of the current study include a relatively small sample size, particularly when split by clinical group and age, which may have limited power to detect effects. Also, the heterogeneity of symptoms and functioning among the CHR and PS groups likely introduced variance into the analyses. Psychosis was treated as a trait variable in this study, and this hinders the ability to account for current symptom count and or severity in the PS participants, as this could potentially impact ERP characteristics. The current findings suggest that future research on neurophysiological markers, particularly the P300, in CHR and PS youth is worth pursuing. Future research could benefit from further distinguishing CHR and PS groups based on particular psychotic symptoms, comorbid diagnoses, and genetic predisposition to psychotic illness in order to test whether specific phenotypic or genotypic characteristics are differentially associated with P300 activation. Akin to van Tricht et al. (2010), longitudinal follow-up of young cohorts would allow for the corroboration and further exploration of whether P300 activity predicts transition to psychosis during critical developmental periods, changes in symptom severity, or remission in PS individuals.

In summary, the findings presented here suggest that P300 activity may serve as a useful biomarker in evaluating psychosis risk in youth. Research that further explicates the utility of a range of neurophysiological markers in CHR and PS children and adolescents as well as children at risk due to other factors (e.g. genetic high-risk profile, family risk) will contribute to our ability to identify at-risk youth early in the disease process and, ultimately, target interventions that alter disease progression.

Conflict of interests

In the past 2 years, Joseph Gonzalez-Heydrich has received grant support from the Tommy Fuss Fund. In previous years, he served as a consultant to Abbott Laboratories, Pfizer Inc., Johnson & Johnson (Janssen, McNeil Consumer Health), Novartis, Parke-Davis, Glaxo-SmithKline, AstraZeneca, and Seaside Therapeutics; was a speaker for Abbott Laboratories, Pfizer Inc., Novartis, Bristol-Meyers Squibb; and received grant support from Abbott Laboratories, Pfizer Inc., Johnson & Johnson (Janssen, McNeil Consumer Health), and Akzo-Nobel/Organon. He is a founder, equity holder, and head of the scientific advisory board to Neuro'motion Labs, a company that is developing technology based games to enhance the development of emotional regulation and is an inventor on a patent pending for technologies to enhance the development of emotional regulation.

The authors have no further conflicts of interest to disclose.

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