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The utility of P300 as a schizophrenia endophenotype and predictive biomarker: Clinical and socio-demographic modulators in COGS-2

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ABSTRACT

Reduced auditory P300 amplitude is a robust schizophrenia deficit exhibiting the qualities of a viable genetic endophenotype. These include heritability, test–retest reliability, and trait-like stability. Recent evidence suggests that P300 may also serve as a predictive biomarker for transition to psychosis during the schizophrenia prodrome. Historically, the utility of the P300 has been limited by its clinical nonspecificity, cross-site measurement variability, and required EEG expertise. The Consortium on the Genetics of Schizophrenia (COGS-2) study provided an opportunity to examine the consistency of the measure across multiple sites with varying degrees of EEG experience, and to identify important modulating factors that contribute to measurement variability. Auditory P300 was acquired from 649 controls and 587 patients at 5 sites. An overall patient deficit was observed with effect size 0.62. Each site independently observed a significant patient deficit, but site differences also existed. In patients, site differences reflected clinical differences in positive symptomatology and functional capacity. In controls, site differences reflected differences in racial stratification, smoking and substance use history. These factors differentially suppressed the P300 response, but only in control subjects. This led to an attenuated patient-control difference among smokers and among African Americans with history of substance use. These findings indicate that the P300 can be adequately assessed quantitatively, across sites, without substantial EEG expertise. Measurements are suitable for both genetic endophenotype analyses and studies of psychosis risk and conversion. However, careful attention must be given to selection of appropriate comparison samples to avoid misleading false negative results.

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1. Introduction

Underlying its clinical symptomatology, schizophrenia is characterized by a disturbance in the regulated processing of environmental information (Venables, 1964). Especially notable are impairments in identifying and responding to stimuli that are either salient or novel.

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The P300 event-related potential (ERP) is a physiological index of the cognitive processes elicited by such task-relevant or novel deviant stimuli (Regan, 1989). Generators of the P300 are widely distributed across both cortex and subcortex. However, the scalp-recorded P300 response to an auditory target stimulus – also referred to as P3b to differentiate it from the P3a orienting response to novelty (Light et al., 2015–in this issue; Polich, 2007; Squires et al., 1975) – arises primarily from inferior parietal and supramarginal cortical regions (Linden, 2005; Smith et al., 1990). Reduced amplitude of this response is one of the most robust physiological abnormalities associated with schizophrenia, being replicated across hundreds of studies with a relatively large (>0.80) effect size (Bramon et al., 2004; Jeon and Polich, 2003). Although P300 amplitude varies to a certain extent with fluctuations in clinical symptomatology (Mathalon et al., 2000), it also exhibits characteristics of a trait-like disease marker. The measure has relatively high test–retest reliability (Fabiani et al., 1986; Mathalon et al., 2000; Segalowitz and Barnes, 1993; Turetsky et al., 1998b), and the patient deficit persists regardless of the level of acute symptomatology or psychotropic medication (Duncan et al., 1987; Ford et al., 1994; Mathalon et al., 2000; Turetsky et al., 1998b). There is also strong evidence implicating a genetic contribution to P300 amplitude in both healthy subjects (O'Connor et al., 1994; Polich and Burns, 1987) and patients (Frangou et al., 1997; Turetsky et al., 2000). Thus, P300 amplitude meets the essential criteria for a schizophrenia endophenotype (Braff et al., 2007; Gottesman and Gould, 2003; Turetsky et al., 2007).

Historically, an impediment to the utility of the P300 as a schizophrenia biomarker has been its lack of specificity. P300 is disrupted in a variety of neuropsychiatric disorders associated with cognitive impairment. These include, among others, Alzheimer's disease (Polich et al., 1990), alcoholism (Hesselbrock et al., 2001) and affective illness (Gangadhar et al., 1993; Salisbury et al., 1999). Additionally, the P300 response is influenced by a variety of factors, independent of clinical diagnosis. Most notable among these are age and sex; P300 amplitude is smaller, overall, in men (Turetsky et al., 1998a) and exhibits both reduced amplitude and prolonged latency in the elderly (Knight, 1987; Patterson et al., 1988). It is also altered by both the acute and chronic administration of various psychoactive substances. P300 amplitude is smaller in active smokers compared to nonsmokers, and this decrement reflects both the current number of cigarettes smoked per day and the number of years of continuous smoking (Hedges and Bennett, 2014). It is similarly reduced following acute administration of marijuana (Hart et al., 2010), alcohol (Wall and Ehlers, 1995), and cocaine (Herning et al., 1985), and among chronic users of these substances (Campanella et al., 2014). In contrast, the effect of antipsychotic medications, among schizophrenia patients, appears to be relatively inconsequential (Bramon et al., 2004). Another potentially important factor that has only rarely been considered is race or ethnicity, and the little evidence that exists concerning this has been inconclusive (Ehlers et al., 1998; Lewis et al., 2008). Given the frequent co-occurrence of schizophrenia with other co-morbid neuropsychiatric and substance use disorders, as well as the differences in smoking prevalence and racial stratification that is often found in schizophrenia patient vs. healthy control samples, a comprehensive understanding of the impact of such modulating factors is critical to enhancing the utility of P300 as a disease-specific schizophrenia biomarker.

Recently, with the advent of studies of the schizophrenia prodrome, the importance of the P300 as a putative biomarker has taken on added significance. There is now substantial evidence that P300 amplitude is reduced in “high-risk” individuals with prodromal symptoms, prior to illness onset (Bramon et al., 2008; Frommann et al., 2008; Özgürdal et al., 2008; van der Stelt et al., 2005). Importantly, within a high-risk cohort, P300 appears to be a sensitive predictor of which individuals will, in fact, transition to frank psychosis. Moreover, the degree of impairment indicates the proximity of illness onset (Nieman et al., 2013; van Tricht et al., 2010). The greater the magnitude of the amplitude reduction, the more likely that psychosis onset is imminent.

P300 amplitude assessment may, therefore, play an important part in the clinical evaluation of at-risk individuals. However P300 studies have thus far been confined primarily to academic neurophysiology laboratories, and data analyses have been limited primarily to between-group comparisons of measures acquired in one laboratory under identical conditions. It is thus unclear whether specific values obtained in one experimental setting can be compared or co-mingled with values obtained in another setting under less-than-identical conditions. The ability to aggregate quantitative data across multiple sites is critical to the strategy employed by the Consortium on the Genetics of Schizophrenia (COGS-2) to identify the genetic substrates of disease endophenotypes. It is also critical to the utility of this measure as a specific predictive biomarker of impending psychosis.

The purpose of the current analysis was therefore, first, to determine if a standardized P300 data acquisition system could be successfully deployed to multiple settings without on-site electrophysiology expertise. We assessed the overall usability of the ERP data and the ability to detect known schizophrenia deficits. We also considered the consistency of measurements across five COGS-2 sites, and examined various socio-demographic modulating factors (age, sex, race, smoking, medications) that can contribute to measurement variability. As noted, a careful understanding of the quantitative impact of these modulating factors is an important prerequisite to any interpretation of a specific set of measurements.

2. Materials and methods

2.1. Participants

Healthy control subjects (HCS) and schizophrenia patients (SZ) were enrolled in the COGS-2 endophenotype study at 5 sites, as detailed in the introductory article of this Special Issue (Swerdlow et al., 2015–in this issue). Briefly, all participants were assessed using a modified version of the Structured Clinical Interview for DSM-IV-TR (SCID), Modules A–E (First et al., 2007). All patients met criteria for either SZ or schizoaffective disorder, depressed subtype. HCS were excluded for any history of a psychotic disorder in either themselves or a 1st-degree relative, a current Axis I mood disorder, a Cluster A Axis II disorder, or current psychoactive medication use. Subjects were also excluded for any medical or neurological condition that could interfere with endophenotype assessment, history of substance abuse in the past month or substance dependence in the past 6 months, or a positive toxicology screen at the time of testing. Clinical and demographic characteristics of the P300 sample are presented, by site, in Table 1. Specific past substance related diagnoses are detailed in Table 2. Adjunctive psychoactive medications used by patients are listed in Table 3. In addition to the Structured Clinical Interview and the various endophenotype measures, all subjects were assessed with the Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) and the Global Assessment of Functioning Scale (GAF) (Hall, 1995). Patients were further assessed with two measures of functional capacity: the 15-item clinician rated Scale of Functioning (Rapaport et al., 1996), and the UCSD Performance-based Skills Assessment-Brief (UPSA-B) (Mausbach et al., 2011), which directly assesses an individual's capacity in multiple domains of everyday functioning through the use of props and standardized skill performance tests.

There were significant group differences in age (SZ older than HCS), sex (more male SZ) and racial composition (more African-American SZ). There were also significant site differences for each of these measures, and group × site interactions for age and sex. As expected, patients and controls differed on education, GAF, and MMSE scores. There were also significant main effects of site and group × site interactions for both GAF and MMSE. Site differences were also evident for rates of past substance use, major depressive disorder, and nicotine use. Among patients, site differences were observed for duration of illness, age of onset, and current symptomatology (SAPS and SANS

Table 1
Patient sample composition.

Test site	1 — UCSD	2 — UCLA	3 — MSSM	4 — PENN	5 — UW
Subjects (N)	144	150	42	133	118
Age (yrs ± sd)[abc]	45 ± 11	48 ± 11	45 ± 10	43 ± 11	47 ± 11
Sex (% male)[abc]	76	73	52	68	77
Race (%)[ac]					
Caucasian	53	45	45	33	55
African-Amer.	15	35	48	60	22
Asian	4	7	0	2	5
Pacific Islander	2	1	0	0	3
Native American	3	0	0	1	1
Mixed	22	11	5	4	14
Not reported	0	0	2	0	0
Education (yrs ± sd)[ac]	12.4 ± 1.9	13.0 ± 1.9	11.7 ± 2.3	12.6 ± 2.4	13.3 ± 1.9
GAF Score (±sd)[abc]	40.9 ± 5.5	45.5 ± 9.5	51.3 ± 9.5	44.3 ± 9.5	40.4 ± 4.1
MMSE (±sd)[abc]	32.0 ± 2.9	31.5 ± 3.0	30.7 ± 3.1	31.3 ± 3.3	32.2 ± 2.3
Past mood disorder (%)[ab]	28	35	17	46	37
Past substance use Dx (%)[abc]	56	46	19	50	47
Smoking history (%)[abc]					
Never	28	38	38	50	62
Past	19	7	2	1	0
Current	53	55	60	50	38
Illness duration[b]	22.0 ± 10.6	25.5 ± 12.2	21.9 ± 10.3	21.5 ± 12.1	23.1 ± 12.1
Age of onset[b]	23.0 ± 7.3	22.3 ± 8.2	23.3 ± 5.7	21.4 ± 5.9	23.7 ± 7.8
Antipsychotic medication					
Atypical only (%)	67	79	67	68	69
Typical only (%)	5	6	17	10	7
Atypical + typical (%)	16	7	9	12	8
No antipsychotic (%)	6	5	2	5	6
Unknown (%)	6	3	5	5	9
CPZ equivs (mgs ± sd)[b]	1037 ± 1423	709 ± 1017	927 ± 1205	641 ± 834	642 ± 972
Adjunctive medications (%)[b]	74	62	50	60	71
SAPS global (±sd)[b]	7.5 ± 3.9	6.2 ± 4.1	4.7 ± 3.0	7.3 ± 4.1	6.5 ± 3.6
SANS global (±sd)[b]	15.6 ± 4.2	9.2 ± 4.4	4.2 ± 4.1	9.8 ± 3.7	12.8 ± 3.5
Scale of function (±sd)[b]	46.5 ± 5.6	48.6 ± 6.0	48.1 ± 5.1	48.4 ± 5.4	43.4 ± 4.6
Control sample composition					
Subjects (N)	135	175	66	131	142
Age (yrs ± sd)[abc]	39 ± 13	46 ± 8	36 ± 12	32 ± 12	37 ± 14
Sex (% male)[abc]	44	61	48	47	54
Race (%)[ac]					
Caucasian	53	64	45	57	73
African-Amer.	12	23	36	31	8
Asian	12	6	14	5	6
Pacific Islander	2	1	0	0	2
Native American	1	0	0	0	0
Mixed	20	6	5	8	12
Not reported	0	0	0	0	0
Education (yrs ± sd)[ac]	15.0 ± 2.1	14.7 ± 1.7	15.2 ± 2.4	15.1 ± 2.2	15.1 ± 2.5
GAF score (±sd)[abc]	90.6 ± 7.1	81.9 ± 7.9	90.5 ± 6.8	87.5 ± 6.1	82.7 ± 6.3
MMSE (±sd)[abc]	33.6 ± 1.6	33.3 ± 1.8	34.1 ± 1.5	33.6 ± 2.0	33.8 ± 1.3
Past mood disorder (%)[ab]	3	4	2	15	15
Past substance use Dx (%)[abc]	8	18	2	15	21
Smoking history (%)[abc]					
Never	80	83	86	93	89
Past	11	3	0	0	0
Current	9	14	14	7	11

GAF: Global Assessment of Function Scale.
MMSE: Mini-Mental Status Examination.
CPZ Equivs: Chlorpromazine Equivalent Dosage.
SAPS Global: Scale for Assessment of Positive Symptoms Global Items Sum.
SANS Global: Scale for Assessment of Negative Symptoms Global Items Sum.
[a] Significant group difference.
[b] Significant site difference.
[c] Significant group × site interaction.

rating scales). This variability indicates that different sites drew their samples from different socio-demographic and clinical pools.

2.2. Procedure

The auditory P300 was conducted as the last task of the COGS-2 battery, following completion of the Mismatch Negativity (MMN) experiment described by Light et al. (2015–in this issue). A San Diego Instruments 2-channel ERP-LAB system with a pre-set P300 module was used for stimulus presentation and EEG recording. One channel recorded EEG activity at the vertex (Cz) referenced to the left mastoid process (full scale setting 0.1, bandpass filter settings 0.5–100 Hz). A second channel recorded eye movement (EOG) activity from electrodes placed mid superior and lateral to the right orbit (full scale setting 0.25, bandpass filter settings 0.5–100 Hz). A ground electrode was placed on the right mastoid. All electrode impedances were below 5 kΩ. The Cz electrode location represented a compromise between the preferred electrode placements for MMN (Fz) and P300 (Pz) recordings, given the

Table 2
Substance use diagnoses.

Test Site	1 — UCSD		2 — UCLA		3 — MSSM		4 — PENN		5 — UW	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Substance Abuse										
Alcohol	6	6	8	10	5	0	9	8	10	9
Opioid	1	0	2	1	0	0	1	0	3	1
Anxiolytic/Sed-Hypn.	0	0	1	1	0	0	1	0	0	0
Cocaine	2	0	3	1	3	0	4	0	4	0
Cannabis	9	2	10	4	3	0	12	2	19	7
Amphetamine	3	0	1	0	0	0	2	0	2	0
Hallucinogen	1	0	2	1	0	0	1	0	1	1
Phencyclidine	1	0	2	1	0	0	0	0	0	0
Substance Dependence										
Alcohol	28	2	18	4	17	2	23	3	24	6
Opioid	4	0	2	0	0	0	1	1	2	1
Anxiolytic/Sed-Hypn.	1	0	1	0	0	0	2	0	0	0
Cocaine	9	1	21	2	3	0	14	1	15	2
Cannabis	18	0	18	3	3	0	16	2	9	4
Amphetamine	18	1	3	1	0	0	2	0	2	1
Hallucinogen	1	0	2	0	0	0	0	0	0	0
Phencyclidine	2	0	2	0	0	0	0	0	0	0
Polysubstance	6	0	1	0	0	0	5	0	3	1

Entries represent % of total patient or control sample at each site having a specific past diagnosis.
Subjects with different diagnoses at different points in time are included in more than one cell.

limitations of the 2-channel recording system and the need to dedicate one of these to the EOG.

Subjects were seated in front of a computer monitor and directed to fixate their gaze on the center screen. A hearing test was conducted to ensure >40 dB hearing threshold bilaterally at 1000 Hz. Subjects were instructed to press the button on a hand-held counter whenever they heard a 1500 Hz target tone amid a stream of 1000 Hz tones. They were given a brief practice period to ensure initial task comprehension and compliance. Unfortunately, the experimental hardware did not allow further real-time monitoring of button-press responses over the course of the experiment. Subjects were then presented a series of 400 tones, including 62 random targets. The ERP system digitally sampled the EEG at 1000 Hz and wrote 1400 ms of data for each stimulus trial, beginning at 100 ms prior to stimulus onset. At the conclusion of the experiment, the number of button presses was recorded from the counter.

2.3. Electrophysiology data processing

Raw EEG data from all 5 COGS-2 sites were uploaded to a centralized database. Quality assurance data review and analysis was then conducted by a single investigator who was blind to all demographic and diagnostic information. EEG data were processed using Brain Vision Analyzer 1.5 (Brain Products GmbH). Data were digitally filtered between 0.1 and 30 Hz (24 dB/oct) and eye movement artifact was removed using an automated algorithm (Gratton et al., 1983). Intervals with additional EEG artifact (activity exceeding +/−75 μV) were excluded from further analysis. Remaining trials were then sorted and combined to form separate average ERP waveforms for the target and frequent tone conditions. These were baseline corrected relative to the 100 ms pre-stim interval and visually inspected to determine the presence or absence of reliably identifiable ERP components. A highly conservative, stringent, approach to data inclusion was employed. Data without an unambiguous N100/P200 response to the frequent tone, or a reliably identifiable P300 response to the target (as agreed by two investigators) were excluded. Subjects were also excluded if their target count deviated by more than 20 from the actual number of 62, regardless of the quality of EEG data, since appropriate task engagement could not be documented. For the remaining subjects, P300 amplitude and latency were measured from the peak target response between 250 and 400 ms. (See Fig. 1).

Table 3
Patient adjunctive medication usage.

Test Site	1 — UCSD	2 — UCLA	3 — MSSM	4 — PENN	5 — UW
Antidepressant	52	37	21	40	49
Benzodiazepine	16	9	7	20	27
Anticholinergic	29	17	7	16	24
Mood stabilizer	22	27	19	12	20
Stimulant	0	1	0	0	0
Opiate	4	4	0	0	6
Steroid	0	0	0	0	1
Other	1	1	0	0	3

Entries represent % of total patient sample at each site.
Individual subjects using more than one medication are included in more than one cell.

2.4. Statistical analysis

P300 amplitude and latency differences were analyzed in two separate general linear models (GLM), with diagnosis, sex and test site as categorical factors and age as a continuous predictor. Significant main effects and interactions were parsed with post-hoc paired contrasts. The effects of various modulating factors (e.g., race, substance use, mood diagnosis, cognitive measures) were then initially assessed by adding these individually as separate additional factors to the original model. To rule out potential false positive results from multiple tests of different modulators, all significant modulating variables ($p < 0.01$) were then included in one omnibus regression model to evaluate the collective and individual residual effects of these multiple factors. Associations between P300 and clinical factors, in the patient sample, were examined via Pearson correlation coefficients, with a significance threshold of $p < 0.01$.

3. Results

3.1. Data quality and final sample composition

P300 data were uploaded to the COGS-2 database for 1677 subjects (789 HCS, 888 SZ). Of these, 1538 (752 HCS, 786 SZ) were deemed to have complete electrophysiological recordings of sufficient quality to unambiguously identify the obligate N100/P200 response to the frequent stimulus. From these, 119 (37 HCS, 82 SZ) were excluded because they failed to demonstrate adequate task engagement (incorrect target count). An additional 183 subjects (66 HCS, 117 SZ)

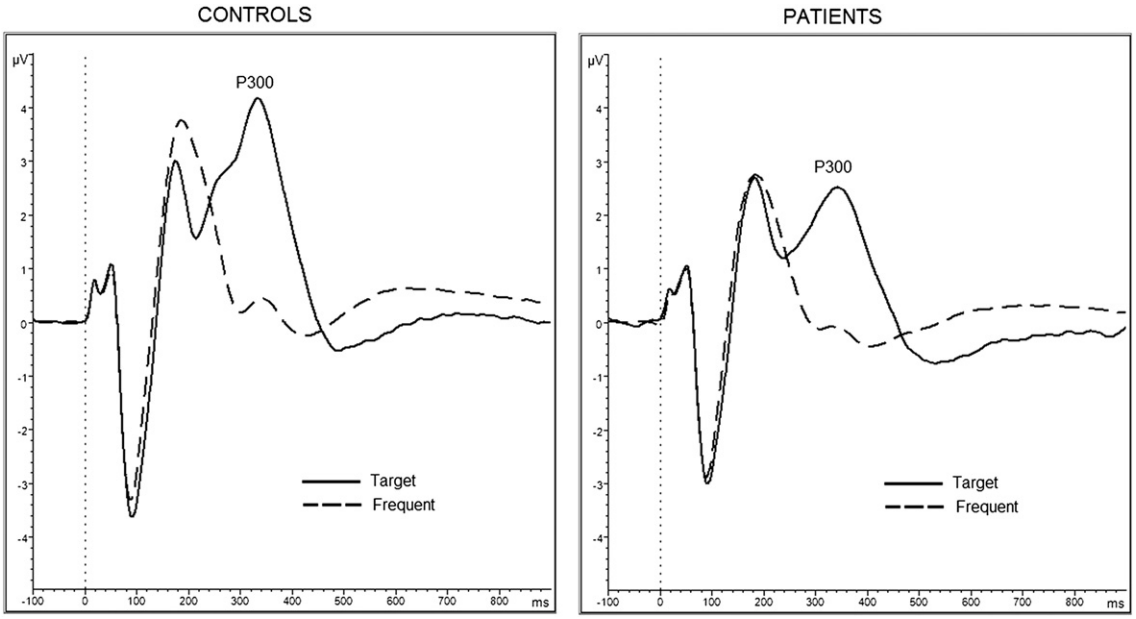

Fig. 1. Grand average waveforms showing evoked potential responses to frequent and target tones for control subjects (left) and schizophrenia patients (right). The P300 component elicited by the target tone is easily identified and shows a clear patient-control difference.

were deemed to not have an identifiable P300 response. The final sample was thus 1236 (649 HCS, 587 SZ). At each stage, the loss of data was significantly greater for patients. Relative data loss also differed significantly across sites, ranging from 13% to 29% for subjects with acceptable N100/P200 auditory evoked potential responses but invalid or unreliable P300s [$X^2(4) = 35.3$, $p < 0.0001$]. On-site electrophysiology expertise, however, provided no advantage. At the two sites (1 and 4) with experienced electrophysiology investigators, this data loss parameter was 23.7%; at the three sites without prior experience, the data loss was 16.1%.

3.2. P300 evoked potential response

GLM analysis of P300 amplitude revealed significant main effects for diagnosis, age and site, with no significant interactions. Consistent with previous literature, patients [$F(1,1215) = 54.56$, $p < 0.000001$] and older subjects [$F(1,1215) = 18.56$, $p < 0.0001$] both had robust P300 amplitude reductions. The overall effect size for diagnosis was 0.62 (Cohen's *d*). Despite previous reports of sex differences in P300 (Turetsky et al., 1998a), no effect of sex was seen [$F(1,1215) = 0.07$, $p = 0.79$]. The effect of test site [$F(4,1215) = 6.54$, $p < 0.0001$] remained significant, in separate analysis, for both controls ($p < 0.001$) and patients ($p < 0.01$). However, despite this variability across sites, each site independently observed a statistically significant diagnostic difference, with site-specific effect sizes ranging from 0.36 to 0.94. Notably, the two sites with greater electrophysiology expertise did not observe more robust patient-control differences (Fig. 2).

A parallel analysis for P300 latency revealed significant effects of age [$F(1,1215) = 28.28$, $p < 0.000001$] and site [$F(4,1215) = 3.53$, $p < 0.01$], but no effect of diagnosis [$F(1,1215) = 2.78$, $p = 0.10$] or sex [$F(1,1215) = 0.82$, $p = 0.36$]. P300 latency was prolonged with increasing age but this effect was similar for patients and controls across sites, with no significant interactions. Given the absence of a diagnosis effect, no further analysis of P300 latency was conducted.

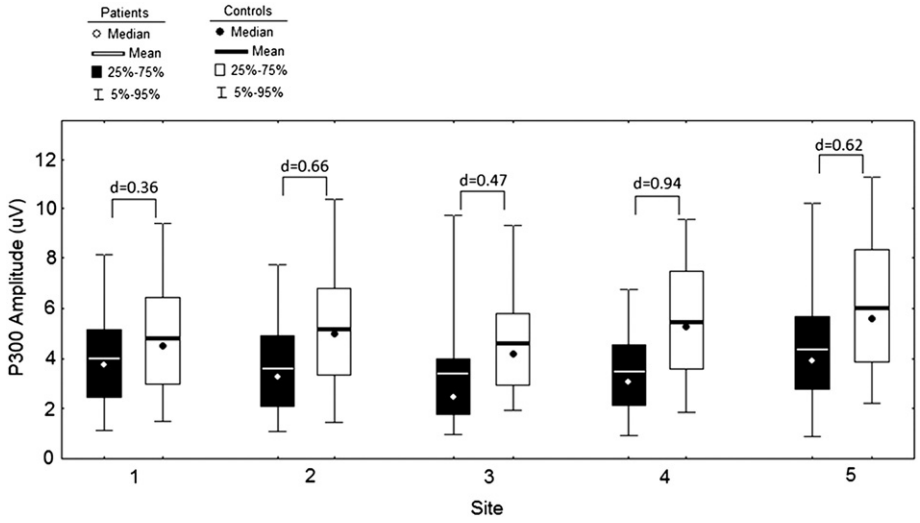

Fig. 2. P300 amplitude distributions for schizophrenia patients and control subjects at each of the five test sites. Effect size at each site is presented as Cohen's *d*. Site 1 and site 4 are those with expertise in electrophysiology.

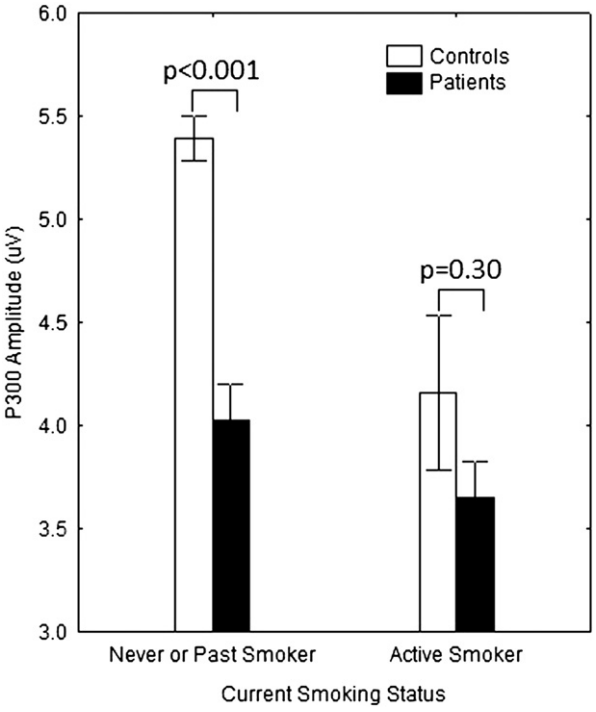

Fig. 3. P300 amplitude (mean ± standard error) for schizophrenia patients and control subjects, separated according to current smoking status. Patient-control differences are only observed within the non-smoking sample. Smoking differentially reduced P300 responses in control subjects, which eliminated the patient-control difference.

3.2.1. Modulating factors

We examined the effects of several potential modulating variables, to determine how they independently influenced P300 amplitude and whether they contributed to observed site differences. Each variable was added as a single additional factor to the original multi-factorial model. MMSE score [$F(1,1139) = 4.79$. $p < 0.05$] was positively associated with P300 amplitude independent of diagnosis, but had no impact on observed site differences. Other measures of cognitive and functional status – GAF score and education – were not significant predictors of P300. Smoking, however, was found to be a robust modulator of P300 amplitude [$F(1,1195) = 10.34$, $p < 0.01$]. Although the interaction between smoking and diagnosis was not significant [$F(1,1195) = 2.44$, $p = 0.12$], separate within-group analyses of smokers and nonsmokers revealed a significant patient-control difference only among nonsmokers [$F(1,1195) = 29.69$, $p < 0.00001$]. Smoking differentially reduced P300 amplitude in healthy control subjects while having little effect in patients (Fig. 3), which eliminated all diagnostic differences [$F(1,1195) = 1.09$, $p = 0.30$]. However, site differences remained robust even after controlling for smoking status. It should be noted, though, that only 70 control subjects (11%) were classified as smokers, compared to 50% of patients.

The observed site differences appeared to primarily reflect racial stratification differences. Inclusion of race as an additional predictor produced a significant race effect [$F(2,1175) = 16.29$, $p < 0.000001$], which eliminated the site effect while leaving the effects of both diagnosis [$F(1,1175) = 20.64$, $p < 0.00001$] and age [$F(1,1175) = 15.56$, $p < 0.0001$] intact. P300 amplitude was lower, overall, in the African American sample (3.68 ± 2.07) than in either the Caucasian (5.08 ± 2.65) or "Other/Mixed" (4.67 ± 2.61) racial groupings. There was a clear trend towards an interaction of race × diagnosis, but it did not reach statistical significance [$F(2,1175) = 2.85$, $p = .06$]. In separate analyses, significant patient-control differences were observed within each racial subgroup, although the effect size was noticeably smaller within the African American sample (Fig. 4).

The differential impact of race on the association between schizophrenia and P300 was manifested primarily as an amplitude reduction among African American controls, rather than patients. Further consideration of potential modulating variables revealed that this apparent racial difference was due, in part, to the differential impact across the racial groupings of prior substance use disorders. When the sample was restricted to subjects with no history of substance use, the interaction of race × diagnosis was insignificant [$F(2,857) = 1.56$, $p = 0.21$] and the magnitude of the patient-control difference was similar across racial categories (Fig. 5, left). However, among those with a past history of substance abuse or dependence, there was a significant race × diagnosis interaction [$F(2,367) = 6.77$, $p < 0.001$]. As illustrated (Fig. 5, right), P300 responses of otherwise-healthy African American controls were indistinguishable from those of African American schizophrenia patients. Comparable attenuating effects of past substance use were not observed for the Caucasian or Other/Mixed control samples. (Note: although the control-patient comparison in the Other/Mixed + substance use subgroup was not statistically significant, this reflected the fact that there were only 6 control

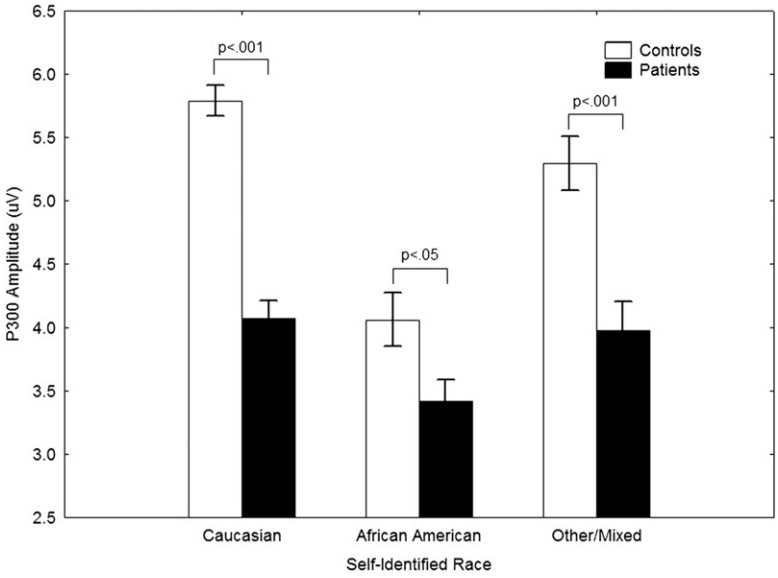

Fig. 4. P300 amplitude (mean ± standard error) for schizophrenia patients and control subjects, separated according to self-identified racial classification. Significant patient-control differences are observed within each racial grouping. However, diagnostic group differences are less robust among African Americans.

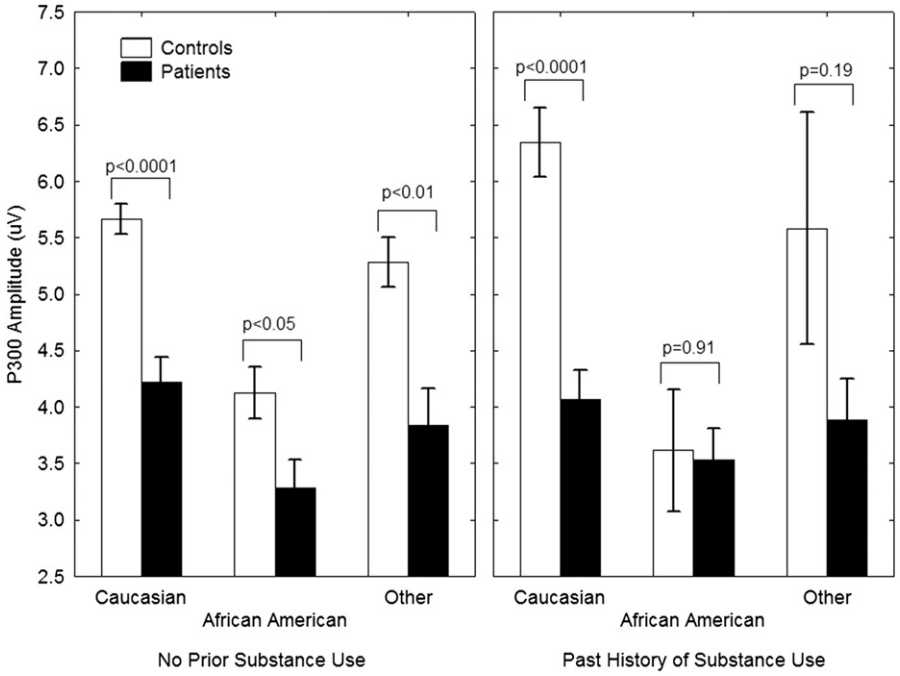

Fig. 5. P300 amplitude (mean ± standard error) for schizophrenia patients and control subjects, broken down by self-identified racial classification among those with (right) and those without (left) a prior history of substance use disorders. Among African Americans, prior substance use attenuated control subjects' P300 responses and eliminated the patient-control difference.

subjects in this subgroup, rather than the impact of substance use). Importantly, prior substance use appeared to have no impact on P300 responses within the patient sample. A past history of mood disorder had no observable effect on P300 in either patients or controls.

An omnibus multiple regression model examined the residual effects of these modulators while adjusting for the presence of other significant modulators. Independent variables included diagnosis, race, smoking, substance use, the 2-way interactions with either diagnosis or race, and 3-way interactions with both diagnosis and race. Age was included as an additional predictor. The model explained 15.5% of P300 variance. Significant main effects remained for each independent variable (Table 4). The only significant interaction was diagnosis × substance use. The 3-way interaction of diagnosis × African American race × substance use just missed significance threshold.

3.2.2. Clinical factors

Within the patient sample, we also explored the effects of several different indices of illness severity. P300 amplitude was positively associated with patients' cognitive status as indexed by the MMSE ($r = 0.13$, $p < 0.01$), and with real-life functional capacity as indexed by the UPSA-B ($r = 0.11$, $p < 0.01$). It was also inversely associated with the total SAPS global ratings of positive symptomatology ($r = -0.11$, $p < 0.01$). P300 was unrelated to other indicators of either

Table 4
Composite regression model.

	Regression parameter	Standard error	−95.00% confidence limit	+95.00% confidence limit	t	p
Intercept	6.56054	0.258635	6.05312	7.067957	25.36603	0.000000
Diagnosis	−1.26510	0.271908	−1.79856	−0.731641	−4.65269	0.000004
Age	−0.02106	0.005701	−0.03224	−0.009872	−3.69357	0.000231
Race:AA	−1.44469	0.271937	−1.97821	−0.911176	−5.31260	0.000000
Race:Mixed	−0.54668	0.262748	−1.06217	−0.031185	−2.08060	0.037679
Smoking	−0.92496	0.394829	−1.69958	−0.150335	−2.34268	0.019306
Substances	0.89175	0.328165	0.24792	1.535586	2.71740	0.006673
Dx × Race:AA	0.58481	0.451171	−0.30035	1.469971	1.29621	0.195148
Dx × Race:Mixed	0.13794	0.492115	−0.82755	1.103427	0.28030	0.779295
Dx × smoking	0.40892	0.491026	−0.55443	1.372270	0.83279	0.405129
Dx × substances	−0.88882	0.438312	−1.74875	−0.028891	−2.02783	0.042795
Race:AA × substances	−1.05947	0.676583	−2.38687	0.267931	−1.56591	0.117630
Race:AA × smoking	0.01508	0.719475	−1.39647	1.426624	0.02095	0.983287
Race:Mixed × substances	−0.28370	1.048818	−2.34139	1.773990	−0.27050	0.786824
Race:Mixed × smoking	0.49181	1.072009	−1.61138	2.595002	0.45877	0.646478
Dx × AA × substances	1.48620	0.818152	−0.11895	3.091344	1.81653	0.069535
Dx × AA × smoking	0.07123	0.856074	−1.60832	1.750770	0.08320	0.933706
Dx × Mixed × Substances	0.78233	1.183324	−1.53925	3.103909	0.66113	0.508655
Dx × Mixed × smoking	−0.49866	1.203665	−2.86015	1.862825	−0.41429	0.678736

Dx/diagnosis: 1 = schizophrenia, 0 = control.
Race:AA: 1 = African American, 0 = Caucasian or Mixed/Other.
Race:Mixed: 1 = Mixed/Other race, 0 = Caucasian or African American.
Substances: 1 = past history of substance abuse or dependence, 0 = no past history.
Smoking: 1 = current smoker, 0 is past or non smoker.

illness severity or chronicity, including age of onset, illness duration, number of inpatient hospitalizations, negative symptom ratings and GAF score. It was also unrelated to medication usage, assessed either by daily dosage (chlorpromazine equivalents, $r = -0.03$, $p = 0.42$) or by categorical distinctions between typical vs. atypical antipsychotic treatment. Importantly, differences in positive symptomatology completely accounted for the observed effects of both site and race on P300 amplitude within the patient sample. In an analysis restricted to patients, neither of these factors was significant if SAPS scores were included in the model [site:$F(4,551) = 2.09$, $p = 0.08$; race:$F(2,551 = 2.76$, $p = 0.07$]. Conversely, though, the SAPS score remained a significant predictor [$F(1,551) = 7.84$, $p < 0.01$].

4. Discussion

The principal aim of this analysis was to determine the feasibility of acquiring comparable P300 data across multiple testing sites, both with and without specific ERP expertise, and to examine the clinical and socio-demographic factors that modulated the measurements across sites. Comparability across sites is a necessary predeterminant of the measure's utility as an endophenotypic biomarker. To that end, the results are both very encouraging and somewhat cautionary. Across sites, 92% of subjects yielded technically acceptable EEG recordings with identifiable auditory evoked potential waveforms. Additional data loss, beyond this, resulted from 1) our failure to monitor subjects' behavioral responses on-line in real time (compounded by the fact that subjects sometimes accidently pressed the reset button on the hand-held counters), and 2) our conservative strategy of rejecting any data lacking a reliable visibly identifiable P300 component. Many studies use an automated algorithm to measure P300 amplitude regardless of waveform appearance. Such an approach would have increased our final data yield from 74% to 85%. Given this overall yield, the fact that data quality did not differ between sites with or without prior electrophysiology experience, and the fact that the schizophrenia P300 deficit was replicated at each site, this study clearly demonstrates the feasibility of implementing large-scale ERP studies across diverse settings.

The overall case-control effect size that we observed, 0.62, was somewhat lower than that reported in meta-analyses (Bramon et al., 2004; Jeon and Polich, 2003). Since the patient sample was older than the control sample and age significantly affected P300, the patient-control difference was attenuated somewhat by inclusion of age as a covariate. The effect size was almost certainly also lowered by our conservative data strategy, which likely excluded a number of subjects – primarily patients – with negligible but real P300 responses. This moderately large effect is, nevertheless, well within the expected distribution of published studies. Although we observed a significant difference across test sites, this did not reflect differences in data quality, methodology, or experimental rigor. Rather it reflected differences in the stratification of the samples across sites, as this relates to clinical and socio-demographic confounds or modifiers.

In patients, site differences were entirely explained by differences in the level of positive symptomatology. Although the P300 deficit is traditionally thought of as being immune to changes in patients' clinical status (Duncan et al., 1987), it should probably be considered as more of a relatively stable deficit. It clearly does not normalize with treatment, even when symptoms dramatically improve. However, it still exhibits modulation over time in association with positive symptoms (Mathalon et al., 2000; Turetsky et al., 1998b). Indeed, it is this ability to reflect increasing positive symptomatology that underlies the emerging utility of P300 as a predictive biomarker for imminent prodromal conversion to psychosis (Nieman et al., 2013). Except for MMSE and UPSA-B, global indices of cognitive ability and real-world functional capacity, no other clinical measures were associated with P300, indicating that the association with positive symptoms is relatively specific. Since these patients were all clinically stable outpatients on stable medication regiments, differences in positive symptomatology presumably reflected relatively stable trait-like differences on this dimension of illness severity. P300 may therefore be an endophenotype that is especially informative regarding the genetic basis of positive symptoms.

The associations with MMSE and UPSA-B highlight the utility of the P300 as a sensitive physiological index of differences in brain function, even within a relatively homogeneous clinical sample. The magnitude of the P300 response has long been considered a broad indicator of "cognitive fitness" and, more specifically, of the ability to appropriately process and respond to task-salient environmental inputs — i.e., to correctly detect a signal within noise. It is thought to require intact attentional and working memory capacities (Donchin et al., 1984), and to reflect complex neural processes of temporal and spatial integration across multiple brain regions (Kügler et al., 1993; Picton, 1992). It is not surprising, therefore, that the P300 would correlate with other measures of cognitive and functional capacity. A similar association between P300 amplitude and MMSE has been reported previously in chronic Alzheimer's disease patients (Pokryszko-Dragan et al., 2003) and, acutely, in uremic patients undergoing dialysis (Tilki et al., 2004), where the two measures showed a correlated improvement, as well, following treatment. There have been no prior studies reporting a relationship between P300 and specific measures of functional capacity, including UPSA-B, either in schizophrenia patients or other clinical samples. However, this association is entirely consistent with the relationship between P300 and cognition. Prior studies examining the relationship between neurocognitive and functional deficits have routinely found that cognitive ability, specifically working memory, is the strongest predictor of schizophrenia patients' real-world functional capacity (Holshausen et al., 2014; Vesterager et al., 2012). Indeed, in our own data, we observed a similar robust correlation ($r = 0.43$, $p < 0.001$) between MMSE and UPSA-B.

These associations support the utility of P300 amplitude as a potential biomarker for predictive risk and treatment studies. However, they also emphasize the relatively non-specific nature of the measure. This was evident, as well, in the control sample data. In these otherwise healthy subjects, P300 amplitude was affected by smoking, race and, as one mediator of the race effect, prior history of substance abuse or dependence. Previous studies have shown that nicotine reduces P300 (Anokhin et al., 2000; Mobascher et al., 2010; Polich and Ochoa, 2004), yet – despite the well-known propensity of schizophrenia patients to smoke – there has been virtually no consideration of the effect of smoking on the auditory P300 in patients. We observed no parallel effect of nicotine in patients, presumably because their ERPs were already suppressed. This is consistent with a recent small study of healthy subjects administered with intravenous ketamine. Ketamine induced schizophrenia-like symptoms and attenuated the auditory target P300 response, but this was unaffected by co-administration of nicotine vs. placebo (Mathalon et al., 2014). Similarly, reduced P300 has been associated with the use of stimulants (Zhang et al., 2012), opioids (Singh et al., 2009) and cannabis (D'Souza et al., 2012). Yet, again, we saw no effect of prior substance use on P300 in the schizophrenia patients. This mirrors what was recently reported in a study examining the effects of cannabis in prodromal subjects considered to be at ultra-high risk for developing psychosis. In this sample, those with a history of cannabis use were indistinguishable from those without. However, among the otherwise-healthy controls, those who used cannabis had reduced P300 responses that were indistinguishable from those of the prodromal sample (van Tricht et al., 2013).

The impact of substance abuse on the African-American sample may reflect differences in the specific character and/or quantity of substance use within the different racial groupings, which are not captured by a simple dichotomous categorization. Similarly, the residual effects of race, independent of past substance use, could reflect the impact of other psychosocial stressors in the different racial communities. Unfortunately, we have no objective measures of either of stressful life events or physiological markers of stress to test this hypothesis.

The fact that modulating factors such as nicotine and substance abuse can differential affect controls, but not patients, raises an important cautionary note about how to interpret study results, potential false negative findings, and what constitutes the best comparison sample for genetic or biomarker studies. A common recommended strategy is to recruit control subjects who are similar to the clinical sample on various modulating factors and co-morbid conditions. The results of this study would seem to temper that recommendation, at least for P300. It suggests that, in matching the samples, individual and group differences may be attenuated for reasons other than psychosis. Consequently, genetic associations with the endophenotype may be obscured and the ability of the measure to predict transition to psychosis may be weakened. This is an issue that clearly requires careful consideration in future analyses. However, the broad utility of P300 as a robust marker for large multi-site studies is confirmed, along with important associations with both positive symptoms and decreased cognitive and functional capacity.

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Contributors

BIT conducted quality assurance on all EEG data, performed the initial statistical analyses and wrote the initial draft of the manuscript. EMD conducted quality assurance on all EEG data, processed the EEG data and wrote draft sections of the manuscript. GL and BIT implemented the multi-site EEG hardware and software and conducted annual EEG training. All other authors contributed substantially to study design, data acquisition and/or quality assurance. All authors reviewed and approved the final version of the manuscript.

Conflict of interest

Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen.

Dr. Lazzeroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Nuechterlein has received unrelated research support from Janssen Scientific Affairs, Genentech, and Brain Plasticity, Inc., and has consulted to Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd. All other authors declare that they have no conflict of interest.

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