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Can P300 distinguish among schizophrenia, schizoaffective and bipolar I disorders? An ERP study of response inhibition

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ABSTRACT

Research utilizing visual event-related brain potentials (ERPs) has demonstrated that reduced P300 amplitude and prolonged latency may qualify as a biological marker (biomarker) for schizophrenia (SZ). We examined P300 characteristics in response inhibition among three putatively distinct psychopathology groups including schizophrenia (SZ), bipolar I disorder (BD) and schizoaffective disorder (SA) in comparison with healthy controls (CT) to determine their electrophysiological distinctiveness. In two separate studies, deficits in response inhibition indexed by the P300 component were investigated using a lateralized Go/NoGo task. We hypothesized that deficits in response inhibition would be present and distinctive among the groups. In both studies, SZ showed response inhibition deficits as measured by P300 when stimuli were presented to the right visual field. In Study 2, delayed cognitive stimulus evaluation was observed in BD as indexed by prolonged P300 latency for NoGo trials. Six selected NoGo P300 variables out of thirty six NoGo P300 variables (18 amplitude, 18 latency) correctly classified SZ (79%), SA (64%) in Study 1 and seven variables selected in Study 2 classified CT (80%), and SZ (61%), BD (67%) and CT (68%) with the accuracy higher than chance level (33%). The findings suggest that distinct P300 features in response inhibition may be biomarkers with the capacity to distinguish BD and SZ, although SA was not clearly distinguishable from SZ and CT.

1. Introduction

The identification of biomarkers in mental illness is a critical step towards developing a reliable and valid psychiatric classification system, predicting disease risk, course, and therapeutic responses (Goodman, 2009). Arguably one of the most contentious areas of debate centers in the development of an accurate classification for psychotic and mood syndromes. Historically, whether schizoaffective disorder (SA) should be a separate diagnosis from schizophrenia (SZ) and mood disorders (Evans et al., 1999; Lake and Hurwitz, 2007; Cheniaux et al., 2008) has been a specific and unresolved controversy. Further, the "Neo-Kraepelinian" dichotomous categorization of SZ and bipolar disorder (BD) reflected in the DSM-IV has been challenged by suggestions that these groupings share common features including multiple genetic susceptibilities (Maier et al., 1999; Blackwood et al., 2001; Berrettini, 2003; Mortensen et al, 2003), similar lifetime risk, stress vulnerability, and suicidal risk (Berrettini, 2003; Murray et al., 2004). Identifying a biomarker that can reliably differentiate these diagnostic categories would help clarify the nature of psychotic and mood disorders.

In this report, we present our evaluation of P300, an event-related brain potential (ERP) component, in the context of response inhibition as a potential biomarker to differentiate SZ, BD and SA. We focused on P300 because reduced and/or delayed P300 has been a robust observation in individuals with SZ (Ford, 1999; Hall et al., 2007a; Groom et al., 2008; Bestelmeyer et al., 2009; Ford et al., 2010; Luck et al., 2010; Rissling et al., 2010) and their first-degree relatives (Anokhin et al., 2004; Sponheim et al., 2006; Groom et al., 2008). There is also some evidence of delayed (Schulze et al., 2008) and reduced P300 (Hall et al., 2007a) in BD. While several studies have documented P300 deficits in pairs of these 3 disorders (e.g., delayed latency in SZ and SA, Mathalon et al., 2009; reduced/delayed in SZ and BD, Bestelmeyer et al., 2009; Salisbury et al., 1999; Muir et al., 1991; O'Donnell et al., 2004), the utility of P300 deficits to distinguish SZ, BD, and SA remains to be investigated.

Since many P300 deficits in SZ were observed in NoGo trials of Go/NoGo paradigms (Weisbrod et al., 1997; Kiefer et al., 1998; Kiehl et al., 2000; Weisbrod et al., 2000; Ford et al., 2004), P300 elicited in the context of response inhibition may be a particularly useful index in

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this line of investigation. In fact, some prominent clinical features of psychotic and manic disorders, including disorganized speech, difficulty with goal-directed behaviors, or impulsivity and related risk behaviors (e.g. suicidal attempts, substance abuse; Christodoulou et al., 2006; Enticott et al., 2008), reflect problems in frontal lobe integrity, which may be readily indexed by the NoGo P300, or P3a, responses (Polich, 2007). A related issue that remains to be addressed concerns the lateralization of response inhibition deficits. While some reported left-lateralized response inhibition deficits in SZ (Weisbrod et al., 1997, 2000; Rubia et al., 2001), others reported that the problems occurred in the right hemisphere (Aron et al., 2004; Bellgrove et al., 2006; Kaladjian et al., 2007). Therefore, including the variable of lateralization may further clarify the hemispheric specificity of the response deficits in SZ and improve the utility of NoGo P300 as a diagnostic tool.

In the following two studies, we tested the diagnostic utility of the P300 component elicited in a Go/NoGo paradigm for SZ, SA, and BD. In order to encourage differential hemisphere-specific processing, a Go/NoGo task with lateralized stimulus presentation was used (see Section 2.1.2 for detail). Specifically, we investigated whether P300 characteristics of response inhibition can differentiate SZ from BD, SA, and healthy controls (CT) by examining the group classification accuracy based on Sparse Logistic Regression (SLR; see Section 2.1.5 for detail). We hypothesized that: (1-a) P300 for NoGo trials would be reduced and/or delayed among SZ compared to other diagnostic groups over the fronto-central sites, which would be modulated by stimulus location (right or left visual field). Such deficits in SZ would not be observed for Go trials. (1-b) BD and SA would demonstrate less response inhibition-related P300 deficits than SZ. We also explored whether and to what extent NoGo P300 variables would be able to classify different diagnostic groups.

2. Study 1

2.1. Methods

2.1.1. Participants

Fourteen patients diagnosed with SZ, eleven patients diagnosed with SA, and fifteen CT without any DSM-IV Axis I disorder participated in this study. The Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-I/P) was administered by a doctoral-level clinical psychologist or graduate student (First et al., 1996). All participants' primary language was English and their vision was normal or corrected-to-normal. All participants in this study were right-handed. The three groups did not differ in age and education. The SZ group was male dominant, while the SA and CT groups were female dominant. Patient groups did not differ in symptom severity, age of onset and length of illness (Table 1).

2.1.2. Materials and procedure

Participants' electroencephalograms (EEGs) were recorded while they completed a modified version of a visual Go/NoGo task (Eimer, 1993). Two letters (M and W), subtending 1° each, were presented at the center of either a right or left square. M and W were designated as the Go and NoGo targets respectively. The participants were instructed to press the right or left button when the Go stimulus was presented on the right or left side respectively and to withhold response when the NoGo stimulus was presented on either side. In order to direct participant's spatial attention to either side of visual hemi-fields (Eimer, 1993), each trial included an arrow as a pre-cue (200 ms) indicating which side of the screen the stimulus would be presented, followed by an inter-stimulus interval (700 ms), and the target (M or W, 150 ms). The validity of pre-cue was 100%. The interval between letter offset and the onset of the next arrow was 1750 ms. The task consisted of 240 trials, presented in four separate blocks of 60 trials each; 70% were Go trials and 30% were NoGo trials.

2.1.3. Physiological recording

EEG was recorded from ten scalp sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, and Oz) using tin electrodes arranged on an elastic cap (Electro Cap International, Inc., Eaton OH) according to the International 10–20 System and James Long EEG Research System. Electrooculograms (EOG) were recorded using tin electrodes placed on the outer horizontal and supraorbital/infraorbital (vertical) positions of the left eye. EEG was referenced to the left mastoid (M1) and algebraically re-referenced to the averaged mastoids (M1, M2) off-line. Impedance for all electrodes was checked prior to the presentation of stimuli and kept below 10 kΩ. During data acquisition, a high-pass filter of 0.01 Hz and a low-pass filter of 30 Hz were applied. Signals were digitally sampled at 512 Hz during recording.

2.1.4. ERP pre-processing

Analysis of the physiological data included only correct trials. Data were processed with software developed by James Long Company. ERPs from 9 electrode sites were analyzed (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4). The EEG data were downsampled to 225 Hz and digitally filtered using a 30 Hz low-pass filter. Artifacts due to eye blinks were corrected via a regression algorithm (Gratton et al., 1983). EEG data were divided into segments of 150 ms pre-stimulus onset and 1000 ms post-stimulus onset. The data were then baseline corrected

Table 1
Demographic characteristics of Study 1 and Study 2.

Study 1	SZ (n = 14)	SA (n = 11)	CT (n = 15)	Test	*p*-value
Age (years)	41.4 (10.1)	44.5 (8.6)	38.1 (15.8)	$F(2, 37) = .85$	.43
Education (years)	11.6 (3.2)	13.1 (1.6)	13.6 (1.6)	$F(2, 37) = .85$	.07
Gender (male/female)	10/4	3/8	4/11	$\chi^2(2) = 7.19$	.03
SANS	7.7 (3.4)	6.2 (2.9)	0.9 (1.3)	$F(1, 20) = .99$	.33
SAPS	6.1 (3.4)	4.6 (3.2)	0.3 (.5)	$F(1, 20) = .20$	.66
Age of onset	22.1 (3.7)	23.6 (9.0)	N/A	$F(1, 23) = .35$	.56
Duration of illness	31.4 (31.2)	20.8 (9.0)	N/A	$F(1, 23) = 1.19$	.29
Antipsychotics	14	9	0		
Study 2	**BD (n = 34)**	**SZ (n = 17)**	**CT (n = 26)**	**Test**	***p*-value**
Age	45.28 (10.58)	43.75 (12.87)	37.2 (13.7)	$F(2, 69) = .26$	.77
Education (years)	15.52 (2.92)	14.85 (3.57)	15.37 (3.13)	$F(2, 69) = 1.84$	.16
Gender (male/female)	16/18	16/2	15/11	$\chi^2(2) = 7.50$	.02
BDI	9.87 (7.42)	8.50 (7.33)	.78 (2.15)	$F(2, 69) = 15.14$	<.001
Altman mania scale	3.79 (3.67)	N/A	1.43 (2.21)	$F(1, 40) = 4.84$	.03
Age of onset	17.38 (8.88)	21.3 (7.10)	N/A	$F(1, 44) = 2.62$	.12
Number of psychiatric hospitalization	2.84 (4.87)	6.0 (5.86)	N/A	$F(1, 44) = 2.49$	.21
Antipsychotics	11	15	0	$\chi^2(4) = 65.9$	<.001

Note. For Study 1, means and standard deviation (SD) are given for age, and number of years of education. BDI and Altman mania scale were measured only for Study 2. The statistical testing for SANS and SAPS was only between SZ and SA for Study 1.

Table 2
Mixed factorial ANOVA for Study 1 and Study 2.

Variables	*F* (*df*1, *df*2)	Greenhouse–Geisser epsilon	*p*-value
Study 1			
Group × Task × Stimulus × Caudality × Laterality	*F* (8, 148) = 2.24	1.00	=.05
NoGo:	*F* (8, 148) = 2.36	.75	<.05
Group × Stimulus × Laterality × Caudality			
NoGo, Frontal: Group × Stimulus × Laterality	*F* (4, 74) = 2.63	.71	<.05
Central: Group × Stimulus × Laterality			NS
Parietal: Group × Stimulus × Laterality			NS
NoGo, Frontal, Left (F3): Group × Stimulus	*F* (2, 37) = 3.47	.92	<.05
NoGo, F3, RVF (Group)	*F* (2, 37) = 2.87		<.10
SZ: 3.53 ± 5.69 μV			
SA: 6.01 ± 5.09 μV			
CT: 8.14 ± 4.71 μV			
NoGo, F3, LVF (Group)	*F* (2, 37) = .17		NS
NoGo, F3, SZ (Stimulus)	*F* (1, 13) = 10.75		
RVF: 3.53 ± 5.69 μV			
LVF: 7.75 ± 4.97 μV			
SA (Stimulus)			NS
CT (Stimulus)			NS
NoGo, Frontal, Right (F4): Group × Stimulus			NS
NoGo, Frontal, Midline (Fz):			NS
Group × Stimulus			
Go: Group × Stimulus × Laterality × Caudality			NS
Study 2			
Group × Task × Stimulus × Caudality × Laterality	*F* (8, 288) = 2.77	.82	=.01
NoGo:	*F* (8, 288) = 3.43	.71	<.01
Group × Stimulus × Laterality × Caudality			
NoGo, Frontal: Group × Stimulus × Laterality	*F* (4, 144) = 2.35	1.00	=.05
NoGo, Frontal, RVF: Group × Laterality	*F* (4, 146) = 2.74	.90	<.05
NoGo, F3, RVF (Group)			NS
F4, RVF (Group)			NS
Fz, RVF (Group)	*F* (2, 74) = 3.38		<.05
SZ: 3.27 ± 2.39 μV			
BD: 5.66 ± 3.53 μV			
CT: 5.23 ± 3.29 μV			
NoGo, Frontal, LVF: Group × Stimulus			NS
NoGo, Central: Group × Stimulus × Laterality	*F* (4, 146) = 2.46	.65	<.10
NoGo, Central, RVF: Group × Laterality	*F* (4, 148) = 3.10	.63	<.05
NoGo, C3, RVF (Group)	*F* (2, 74) = 6.37		<.01
SZ: 5.46 ± 3.41 μV			
BD: 9.00 ± 5.21 μV			
CT: 11.04 ± 5.80 μV			
NoGo, C4, RVF (Group)	*F* (2, 74) = 4.86		=.01
SZ: 4.26 ± 3.10 μV			
BD: 7.53 ± 4.26 μV			
CT: 8.20 ± 5.04 μV			
NoGo, Cz, RVF (Group)	*F* (2, 74) = 5.11		<.01
SZ: 5.36 ± 3.38 μV			
BD: 8.81 ± 3.38 μV			
CT: 10.28 ± 5.61 μV			
NoGo, Central, LVF: Group × Laterality			NS
NoGo, Parietal: Group × Stimulus × Laterality			NS
Go: Group × Stimulus × Laterality × Caudality			NS

Note. NS: not significant. RVF: right visual field stimulus presentation, LVF: left visual field stimulus presentation.

before averaging. All trials with remaining artifacts were removed from further analyses. The mean amplitudes of P300 were defined by the average amplitude during the 300–450 ms time window after stimulus onset, while P300 peak latency was defined by the most positive peak during the time window.

2.1.5. Statistical analysis

Mixed factorial ANOVA: The three groups were compared for rates of accuracy for Go and NoGo trials, commission errors (i.e., failures to withhold response for NoGo trials), and omission errors (i.e., failures to press a button for Go trials). A mixed factorial ANOVA was performed separately for P300 amplitudes and latencies with Trial Type (Go, NoGo), Stimulus Location (left vs. right visual field), Laterality (left hemisphere, midline, right hemisphere), and Caudality (frontal, central, parietal) as within-subjects factors and Group as the between-subjects factor. We used Student Newman–Keuls (SNK) method for post-hoc analysis. Greenhouse–Geisser correction was applied when the sphericity assumption was violated.

Sparse Logistic Regression (*SLR*): The nature of the collected data, specifically small number of cases coupled with a relatively large number of variables, makes it vulnerable to overfitting. In order to prevent a falsely optimistic representation of the data for separation, SLR was used to identify a set of reduced number of P300 variables that best separate the diagnostic groups. We chose SLR because it trains a model in a manner that forces the weight applied to each variable to be either zero or larger, a process through which would select variables with the strongest explanatory power and disregard less informative variables (Krishnapuram et al., 2005). The learned classifier using SLR, as a result, is more generalizable to new data. We performed SLR based on NoGo P300 variables in order to select classifiers that are directly related to response inhibition.

In Study 1, we performed a 3-way SLR to separate SZ, SA, and CT. In addition, in order to find the shared NoGo P300 variables among Study 1

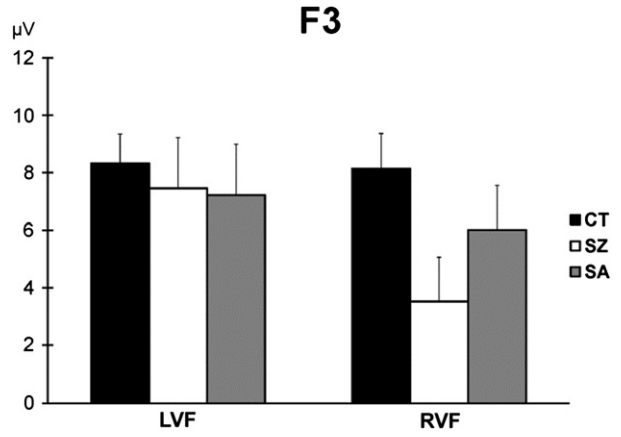

Fig. 1. Study 1 mean amplitudes of NoGo P300 over the left frontal (F3) for healthy controls, schizoaffective disorder and schizophrenic patients for left visual field stimuli (LVF) and right visual field stimuli (RVF).

and Study 2 that best differentiated SZ from CT, we performed group-binary SLR using the L1 General software (Schmidt, 2010). This jointly trains two separate binary logistic regression models, one for each study, in a manner that ensures the same subset of NoGo P300 variables are used. For both the three-way and group-binary SLR, the number of variables to include in the model was chosen using leave-one-out cross validation to maximize generalization (Bishop and Nasrabadi, 2006).

2.2. Results

2.2.1. Behavioral data analysis

The three groups showed high accuracy rate for both Go trials (SZ = 93.4 ± 9.8%, SA = 96.3 ± 7.9%, CT = 99.0 ± 1.7%) and NoGo trials (SZ = 90.9 ± 10.3%, SA = 95.3 ± 4.6%, CT = 95.6 ± 4.4%). The three groups differed in overall accuracy, $F(1, 37) = 3.82$, $p < .05$ (SZ = 92.1 ± 7.3%, SA = 95.8 ± 4.4, CT = 97.3 ± 2.5%). SNK Post-hoc testing revealed that SZ participants were less accurate than CT ($p < .05$) but not different from SA. The three groups did not differ in omission errors ($p > .10$) or commission errors ($p > .10$). No group differences were observed for reaction time (RT).

2.2.2. P300 amplitude

P300 analysis only included correct trials that were used for averaging (Go: 150–168 trials, NoGo: 59–72 trials). NoGo-P300 amplitude was larger than Go-P300 amplitude, $F(1, 37) = 10.97$, $p < .01$. Group difference in P300 amplitude was modulated by scalp sites, trial type, and stimulus location, $F(8, 148) = 2.24$, $p < .05$. Dissecting this 3-way interaction (see Table 2) revealed that the NoGo-P300 at left frontal site (F3) was reduced in SZ compared to CT ($p < .05$) but not to SA ($p > .26$), when the stimulus was presented to the right visual field (Fig. 1a, b).

2.2.3. P300 latency

P300 latency in response to NoGo trials (447 ± 21 ms) was longer than to Go trials (407 ± 19 ms), $F(1, 37) = 22.59$, $p < .001$. P300 latency at the frontal sites (F3, Fz, and F4) was shorter than that at the central (C3, Cz, and C4) and parietal sites (P3, Pz, and P4), $F(2, 76) = 10.97$, $p < .001$, $\varepsilon = .74$. No group main effect or group-related interactions were observed.

2.2.4. SLR

A three-way SLR was performed with diagnostic group (SZ, SA, and CT) as the predicted variable. Six NoGo P300 ERP variables (three amplitudes, three latencies) were selected through the SLR algorithm (Table 3a). The six variables classified participants with 75% overall accuracy and 50% leave-one-out accuracy (LOA) with highest classification accuracy for CT (80%), followed by SZ (79%) and SA (64%; Tables 3a, 3b). A group-binary SLR with seven P300 variables

Table 3a
Three-way SPMLR for Study 1 and Study 2 with NoGo features.

Study 1		95% CI for odds ratio			Study 2		95% CI for odds ratio		
	B (SE)	Lower	Odds ratio	Upper		B (SE)	Lower	Odds ratio	Upper
SA vs. SZ					BD vs. SZ				
Intercept	6.66 (5.62)				Intercept	−13.81 (5.09)			
F3 NoGo RVF Amp	.36 (.17)*	1.03	1.44	2.00	P3 NoGo RVF Amp	−.18 (.26)	.50	.84	1.40
C3 NoGo RVF Amp	.34 (.18)†	.98	1.40	2.01	P4 NoGo LVF Amp	−.15 (.24)	.54	.86	1.38
P4 NoGo LVF Amp	−.55 (.23)*	.36	.57	.91	P4 NoGo RVF Amp	.48 (.35)	.81	1.62	3.23
F3 NoGo LVF Lat	−.09 (.03)**	.87	.92	.97	Fz NoGo RVF Amp	.28 (.14)*	1.00	1.32	1.73
P4 NoGo LVF Lat	.08 (.03)**	1.03	1.09	1.15	F3 NoGo RVF Lat	.03 (.02)	.99	1.03	1.06
Cz NoGo RVF Lat	−.02 (.01)	.96	.98	1.01	C4 NoGo LVF Lat	.02 (.01)†	.99	1.02	1.05
					P4 NoGo RVF Lat	−.02 (.01)	.96	.98	1.01
CT vs. SZ					CT vs. SZ				
Intercept	−5.51 (5.48)				Intercept	−4.51 (5.34)			
F3 NoGo RVF Amp	.33 (.16)*	1.02	1.39	1.91	P3 NoGo RVF Amp	.01 (.27)	.59	1.01	1.72
C3 NoGo RVF Amp	.19 (.13)	.94	1.21	1.55	P4 NoGo LVF Amp	.10 (.24)	.69	1.11	1.78
P4 NoGo LVF Amp	−.15 (.14)	.65	.86	1.13	P4 NoGo RVF Amp	.34 (.36)	.70	1.40	2.82
F3 NoGo LVF Lat	−.04 (.02)*	.92	.96	.99	Fz NoGo RVF Amp	.15 (.15)	.87	1.16	1.55
P4 NoGo LVF Lat	.04 (.02)*	1.00	1.04	1.07	F3 NoGo RVF Lat	.03 (.02)†	.99	1.03	1.07
Cz NoGo RVF Lat	.02 (.01)	.99	1.02	1.04	C4 NoGo LVF Lat	.01 (.01)	.98	1.01	1.04
					P4 NoGo RVF Lat	−.03 (.02)†	.94	.97	1.00

	Predicted			% correct		Predicted			% correct
Observed	SZ	SA	CT	(75.0)	Observed	SZ	BD	CT	(65.8)
SZ	11	2	1	78.6	SZ	11	5	2	61.1
SA	3	7	1	63.6	BD	3	22	8	66.7
CT	1	2	12	80.0	CT	2	6	17	68.0

Note. Study 1 $R^2 = .60$ (Cox and Snell), .67 (Nagelkerke). Model $\chi^2(12) = 36.12$, $p < .001$. Study 2 $R^2 = .43$ (Cox and Snell), .49 (Nagelkerke). Model $\chi^2(14) = 42.80$, $p < .001$.
† $p < .10$.
* $p < .05$.
** $p < .01$.

Table 3b
Binary SPMLR for SZ and CT classification for Study 1 and Study 2.

Study 1		95% CI for odds ratio			Study 2		95% CI for odds ratio		
	B (SE)	Lower	Odds ratio	Upper		B (SE)	Lower	Odds ratio	Upper
CT vs. SZ					CT vs. SZ				
Constant	−13.31 (7.14)				Constant	−1.77 (5.63)			
F3 NoGo RVF Amp	.16 (.13)	.91	1.18	1.51	F3 NoGo RVF Amp	.01 (.17)	.73	1.01	1.40
C3 NoGo LVF Amp	.24 (.35)	.64	1.27	2.53	C3 NoGo LVF Amp	−.45 (.25)†	.39	.64	1.05
C3 NoGo RVF Amp	.14 (.13)	.88	1.15	1.49	C3 NoGo RVF Amp	.37 (.17)*	1.03	1.44	2.02
P3 NoGo LVF Amp	−.18 (.38)	.40	.84	1.74	P3 NoGo LVF Amp	.44 (.25)†	.94	1.54	2.54
P3 NoGo LVF Lat	.01 (.01)	.99	1.01	1.03	P3 NoGo LVF Lat	.01 (.01)	.98	1.01	1.04
P3 NoGo RVF Lat	−.05 (.03)†	.91	.96	1.01	P3 NoGo RVF Lat	−.01 (.01)	.96	.99	1.02
Cz NoGo RVF Lat	.06 (1.01)†	1.00	1.06	1.13	Cz NoGo RVF Lat	.01 (.01)	.99	1.00	1.02
Observed	SZ	CT	% correct		Observed	SZ	CT	% correct	
SZ	11	3	78.6		SZ	13	5	72.2	
CT	2	13	86.7		CT	5	20	80.0	

Note. Study 1 $R^2 = .38$ (Cox and Snell), .51 (Nagelkerke). Model χ^2 (7) = 13.59, $p = .05$. Study 2 $R^2 = .34$ (Cox and Snell), .45 (Nagelkerke). Model χ^2 (7) = 17.63, $p = .01$.
† $p < .10$.
* $p < .05$.

(four amplitudes, three latencies) identified SZ and CT with 83% overall accuracy with 64% LOA (SZ: 79%, CT: 87%; Table 3b).

2.3. Discussion

Findings on SZ from mixed factorial ANOVA was in line with the SLR result, in which F3 NoGo P300 amplitude with RVF stimulus presentation distinguished SZ from both SA and CT. Such consistent results in both analyses highlight that a left frontal P300 deficit associated with response inhibition can be a unique electrophysiological characteristic among SZ, which may be used as a biomarker for schizophrenia. The findings on SA in mixed factorial ANOVA was partially consistent with a previous ERP study (Mathalon et al., 2009) in that SA was not distinguishable from CT in P300 amplitude. However, SA in the present study was also indistinguishable from SZ in both behavioral and P300 measures. Given that the SLR classification accuracy for SA was much lower than that for SZ, our findings indicate that the diagnostic boundaries of SA are less clear.

3. Study 2

3.1. Method

3.1.1. Participants

Eighteen patients (2 women) diagnosed with SZ, thirty four patients (18 women) diagnosed with BD, and twenty five individuals (10 women) with no DSM-IV axis I diagnosis participated in this study. SCID-I/P was administered for the diagnosis of SZ. The diagnosis of BD was made with the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) and a best estimate process using two doctorate level reviewers. All interviews were conducted by medically trained interviewers. All participants' primary language was English and their vision was normal or corrected-to-normal. All participants in this study were right-handed. The three groups were demographically matched on age and education. The SZ group was more male dominant than the other two groups ($p < .05$). SZ and BD did not differ in age of onset, number of psychiatric hospitalizations, or gender (Table 1).

3.1.2. Materials and procedure

The materials and procedures were identical to Study 1.

3.1.3. Physiological recording

The physiological recording in Studies 1 and 2 were identical except Brain Vision system (Brain Products GmbH, Germany) was used.

3.1.4. Data analysis

The data analysis approach in Study 1 and Study 2 was the same.

3.2. Results

3.2.1. Behavioral data analysis

All three groups demonstrated high accuracy rates for Go (BD: 99.1 ± 8.4%, SZ: 98.4 ± 9.1%, CT: 99.1 ± 8.4%) and NoGo (BD: 97 ± 9.2%, SZ: 97 ± 8.7%, CT: 97.5 ± 8.0%) trials. No main effect of trial type, stimulus location, and group on accuracy rate was found. SZ showed the longest RT, F (2, 74) = 18.45, $p < .001$, SZ = 440 ± 132 ms, BD = 352 ± 80 ms, CT = 270 ± 69 ms. Post-hoc testing revealed that SZ showed longer RT than BD ($p < .05$) and CT ($p < .01$).

3.2.2. P300 amplitude

P300 amplitude for correct trials (Go: 155–168 trials, NoGo: 60–72 trials) was included for statistical analysis (Fig. 3a–d). P300 amplitude was larger for the NoGo trial than for Go trial, F (1, 72) = 75.58, $p < .001$ (Go = 4.27 ± 2.35 μV, NoGo = 6.42 ± 3.47 μV). A group effect was observed, F (2, 72) = 3.98, $p < .05$, with SZ showing smaller amplitude than CT ($p < .05$) but no difference was found between SZ and BD and between BD and CT. Group differences varied by trial type, F (2, 72) = 4.22, $p < .05$, such that for NoGo trials, SZ showed smaller P300 amplitude than CT ($p < .01$) and marginally smaller than BD ($p < .10$), while for Go trials no group effect was observed. Further, group differences depended on scalp site, trial type, and stimulus presentation location, F (8, 288) = 2.77, $p = .01$, $\varepsilon = .82$ (Table 2). SNK post-hoc test further revealed that SZ showed reduced NoGo P300 amplitude at midline frontal site (Fz) when the stimulus was presented to the RVF compared with BD ($p < .05$) but the difference was marginally significant when compared with CT ($p_{Fz} = .10$). Attenuated NoGo P300 amplitude among SZ was also observed over the three central sites (C3, Cz, and C4) when the stimulus was presented to the RVF compared to both CT ($p_{C3} < .01$, $p_{Cz} < .01$, $p_{C4} = .01$) and BD ($p_{C3} < .05$, $p_{Cz} = .05$, $p_{C4} < .05$) (Fig. 2a, b). Such group-related interactions were not observed for NoGo trials when the stimulus was presented to the LVF.

3.2.3. P300 latency

P300 latency was longer for NoGo trials than that for Go trials F (1, 72) = 53.01, $p < .001$ (Go: 372 ± 25 ms, NoGo: 398 ± 28 ms). Group difference in P300 latency was observed only for NoGo trials, F (2, 73) = 10.05, $p < .001$, such that BD (407 ± 27 ms) showed the longest P300 latency followed by SZ (394 ± 33 ms) and CT (389 ± 22 ms) in order. SNK post-hoc test further revealed that NoGo P300 latency

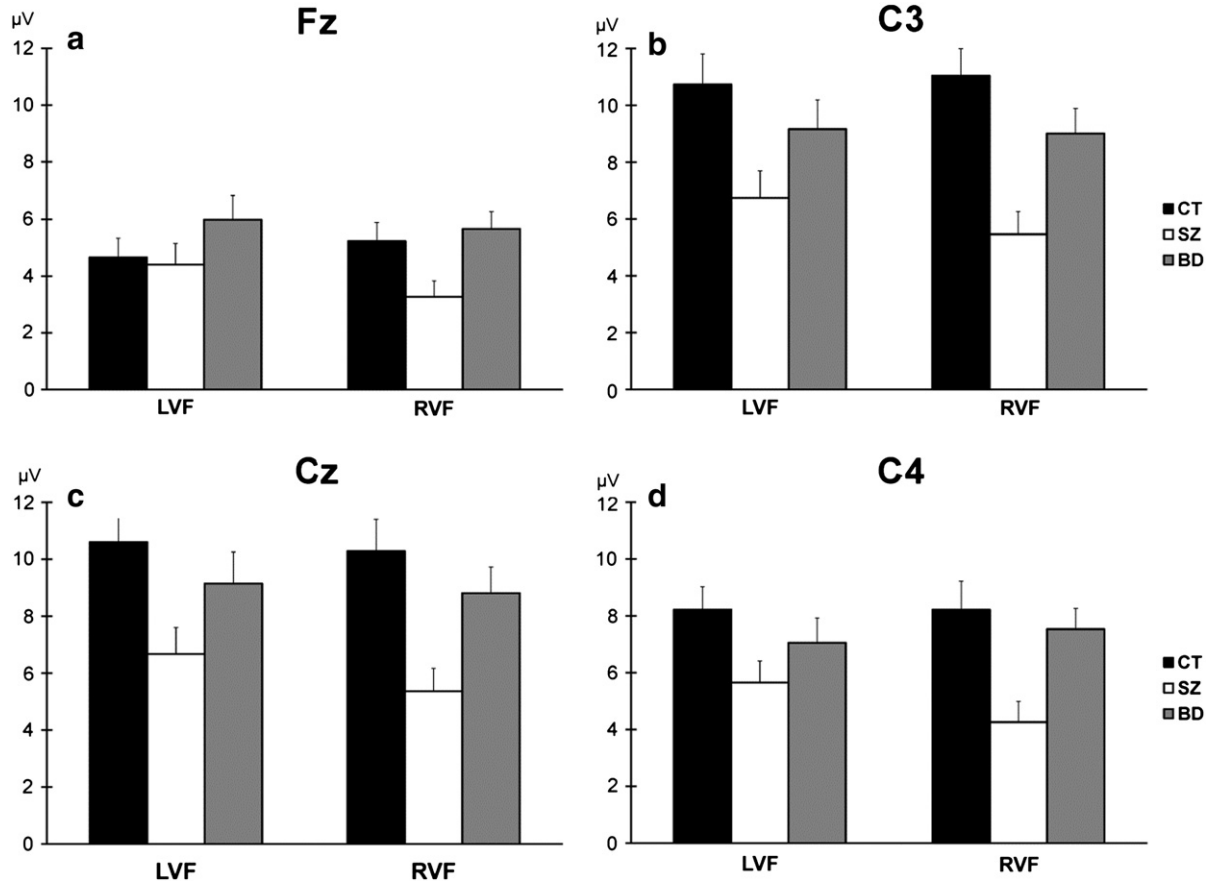

Fig. 2. Study 2 mean amplitudes of NoGo P300 for healthy controls, bipolar disorder and schizophrenic patients for left visual field stimuli (LVF) and right visual field stimuli (RVF) over the a) frontal midline (Fz), b) central left (C3), c) central midline (Cz), and d) central right (C4).

among BD was more delayed than CT ($p = .05$), while there was no difference between BD–SZ and CT–SZ.

3.2.4. SLR

A three-way SLR was performed with diagnostic group (SZ, BD, and CT) as the predicted variable (Table 2). Seven NoGo P300 ERP variables (four amplitudes, three latencies) were selected. The seven variables classified participants with 66% overall accuracy (57% LOA) with highest classification accuracy for CT (68%), followed by BD (67%) and SZ (61%; Table 3a). A group-binary SLR with the same six NoGo P300 variables as in Study 1 identified SZ and CT with 77% overall accuracy with 68% LOA (SZ: 72%, CT: 80%; Table 3b).

3.3. Discussion

Study 2 replicated the main findings of Study 1 in that SZ's reduced NoGo P300 amplitude highlighted their neural deficit in response inhibition, which separated them from BD (Fz) and from CT (C3, C4, and Cz). Further, replication of successful discrimination of SZ from other diagnostic groups based on NoGo P300 amplitude further supports that P300 differences in response inhibition may become a candidate biomarker for SZ (Ford, 1999; Hall et al., 2007b; Bestelmeyer et al., 2009; Luck et al., 2010). The relatively intact NoGo P300 amplitude in BD as compared with CT indicated preserved cognitive capacity for motor response inhibition. However, delayed P300 latency specific to NoGo trials in BD, which was not lateralized to either hemisphere, may indicate a compensatory mechanism that trades cognitive speed for accuracy during response inhibition regardless of which side of hemispheric cognitive resources they recruit.

4. General discussion

In two separate studies each utilizing samples from three populations, P300 was able to index distinct neural deficits in response inhibition in SZ (reduced amplitude) and BD (delayed latency), although SA was not clearly distinguishable from SZ and CT. Findings of SLR based on selected features of P300 were consistent with group mean comparisons demonstrating that SZ, BD, and CT may be physiologically distinguishable from each other, although SA remains a group with less clear-cut boundaries. The validity of the SLR result was supported by the similar classification accuracy for SZ and CT in Study 1 (83%) and Study 2 (77%) with the same selected P300 variables.

Our two studies demonstrated that SZ showed reduced P300 amplitude for response inhibition over the left hemisphere in frontal (Study 1) and fronto-central (Study 2) regions when asked to use left hemispheric resources. These findings strongly suggest that deficits in recruiting cognitive resources to inhibit dominant-but-context-inappropriate responses in SZ lie in the left hemisphere, consistent with the notion of left hemisphere dysfunction in SZ (Kiehl et al., 2000; Bramon et al., 2004). Findings in Study 1 that SA was not different from SZ and CT in both behavioral and P300 measures and also that only 64% of SA were correctly classified (27% as SZ, 10% as CT) compared to a much higher classification accuracy for SZ and CT did not support the distinctiveness of the SA boundaries. BD showed normal P300 enhancement but delayed P300 latency for NoGo trials, suggesting that BD is not associated with reduced cognitive resources but with a different speed/accuracy tradeoff when evaluating and withholding a response to a NoGo stimulus. Different from previous ERP studies in which BD and SZ were indistinguishable (O'Donnell et al., 2004; Bestelmeyer et al., 2009; Bestelmeyer, 2012),

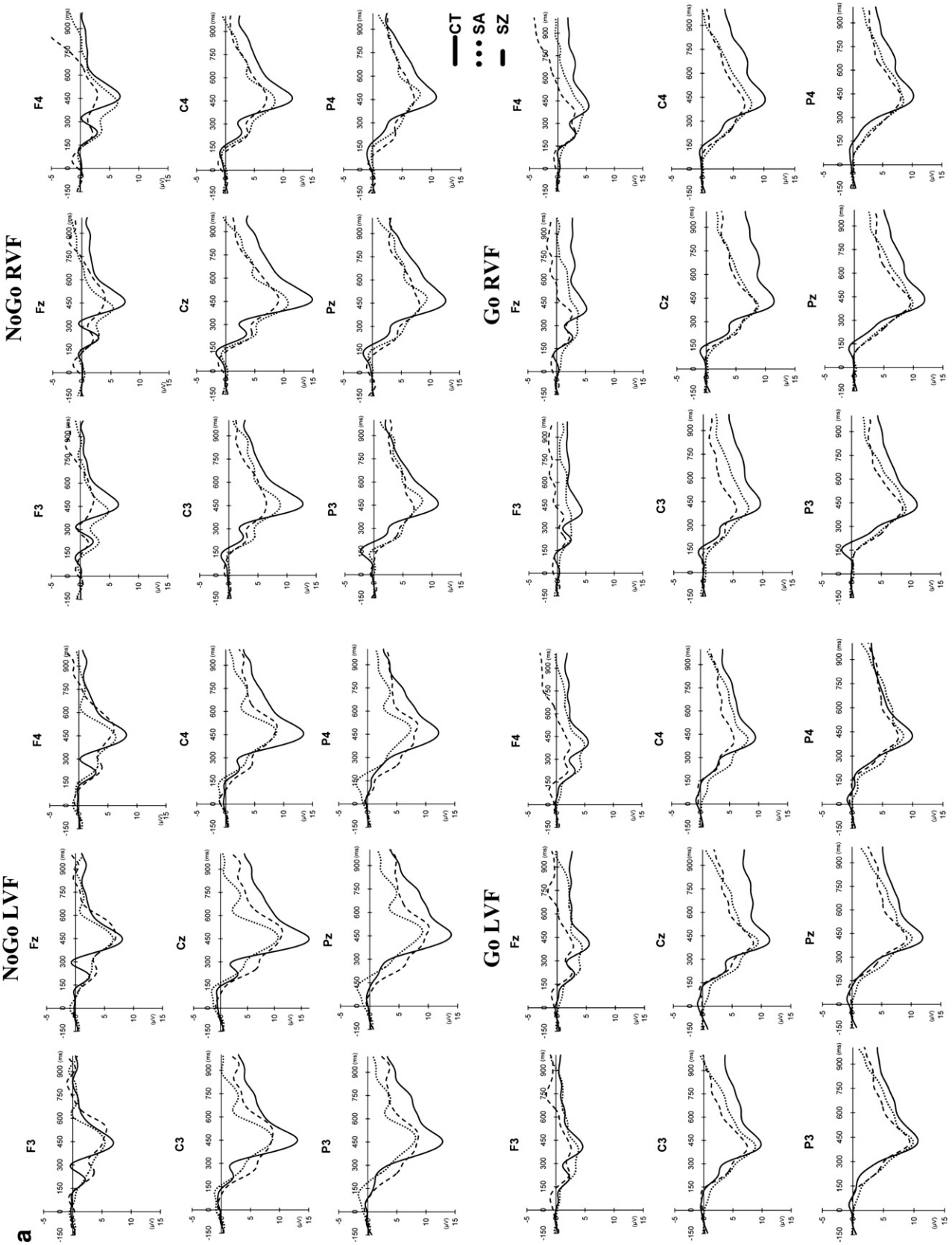

Fig. 3. a. Study 1 ERP waveforms. b. Study 2 ERP waveforms.

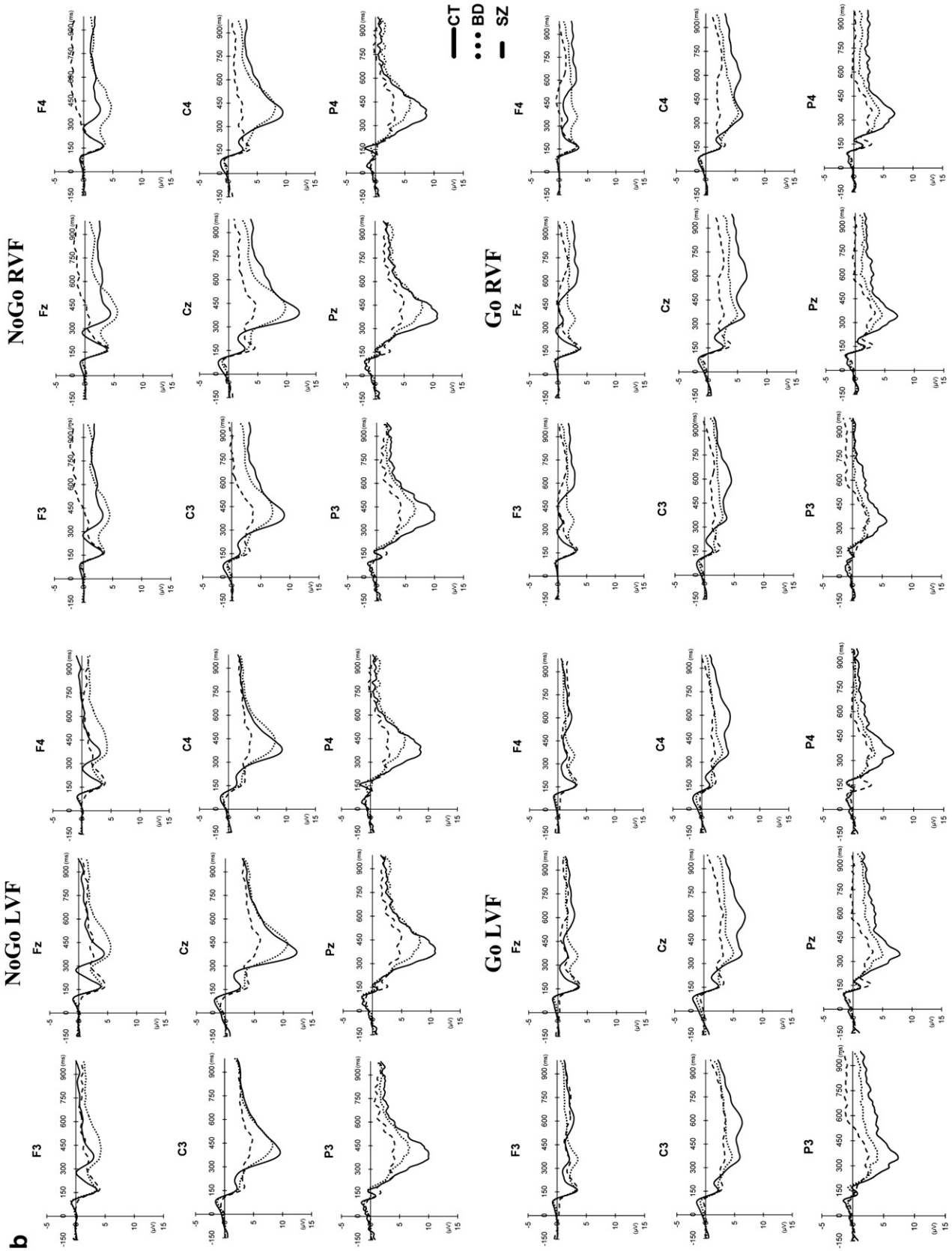

Fig. 3 (*continued*).

our findings demonstrated that fronto-central response inhibition-related P300 amplitude distinguished BD from SZ and latency differentiated BD from CT.

Due to the small number of SA in Study 1 and the fact that SA and BD were not directly compared, the findings cannot be considered definitive as to whether SA and SZ are indistinguishable, and whether SA and BD are physiologically distinct. Possible gender effects on NoGo P300 also need to be considered given that the SZ group in both studies was male dominant. Larger sample size would allow more thorough confirmatory validation for the group classification with separate model and training data subsets, compared to the leave-one-out cross-validation approach in our study. Further, diagnostic information of each participant was not blind to the experimenters conducting data collection, pre-processing, and analysis in our study, calling for replication studies better controlling for experimenter bias.

In conclusion, our studies supported a left-lateralized fronto-central deficit in SZ to inhibit dominant but context-inappropriate motor responses. Our findings that SZ, BD, and CT could be classified with high accuracy using response inhibition-related P300 measures provides further evidence that these disorders may be differentiated based on neurophysiological features.

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Contributors

JC designed the study and wrote the first draft of the manuscript. ZK completed the SPMLR analysis. LAO, FM, and IFT collected data for the study and reviewed the manuscript. PJD oversaw the study as a senior author. All authors approved the final draft of the manuscript.

Disclosure of conflicts of interest

All authors in this manuscript do not have any interests that might be interpreted as influencing the research, and ethical standards in line with the Declaration of Helsinki were followed in the conduct of the study.

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