Response Inhibition and Emotion modulation effect on response inhibition in Bipolar I disorder and Schizophrenia

By

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To my family, mentors and friends,

who's trust inspires me to reach beyond my limits...

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Chapter I.

Overview

Schizophrenia (SZ) and Bipolar disorder (BD) are chronic, severe forms of mental illness that are accompanied by detrimental outcomes (e.g. suicidal attempts, substance abuse; Baldessarini, 2006; Simon et al., 2007). SZ is characterized by positive symptoms (e.g. hallucination and delusions), and negative symptoms (e.g. blunted affect and social withdrawal) and affects about 1.1 percent of the population. BD is characterized by recurrent episodes of mania and depression and affect approximately 5.7 million (2.6%) adult Americans (American Psychiatric Association [*DSM-IV-TR*], 2000; Kessler et al., 2005; U.S. Census Bureau Population Estimates by Demographic Characteristics, 2005). Even though the historically Kraepelinian classification of mental disorders, and current nomenclatures make an explicit, fundamental distinction between dementia praecox (schizophrenia) and manic-depressive psychosis (bipolar disorder), clinically, BD with psychotic features often appears phenomenologically similar to SZ, which can lead to misdiagnosis (Goodwin and Jamison, 2007; Weiser et al., 2001). This nosological distinction between the disorders has been widely accepted in the diagnosis and treatment of SZ and BD (Goodwin and Jamison, 2007), and has been supported by empirical research (Kendler et al., 1998; Dikeos et al., 2006).

However, the delineation of a group showing the mixture of psychotic and affective symptoms (e.g. schizoaffective disorder, SAD) has led an alternative perspective that BD and SZ disorders may actually be on the same psychosis-affective continuum (Crow, 1998). Although the schizoaffective disorder continuum hypothesis has not been fully supported (Cheniaux et al., 2008; Goldstein, Shemansky, and Allen, 2005; Szoke et al., 2008; Vieta et al., 2001), recent genetic linkage studies have found an overlapping candidate region for susceptibility genes in BD and SZ, although specific candidate genes are not yet available (Maier et al., 1999). Epidemiological similarity has also been found in the two disorders including lifetime risk, stress vulnerability, and risk for suicide (Berretini, 2000). Furthermore, the literature suggests that both SZ and BD have similarly impaired cognition such as attentional and executive control (Burdick, Goldberg, and Harrow, 2006; Tabares-Seisdedos et al., 2003). In turn, executive control has been closely associated with impulsive behaviors which likely increase the risk of substance abuse and repetitive suicidal attempts in these populations (Christodoulou et al., 2006).

Neurocognitive studies have suggested that an array of frontal/executive function deficits in SZ and BD (Burdick et al., 2006; Hill et al., 2004; Shad et al., 2006; Szoke et al., 2008) may have a stronger genetic basis than the full clinical syndromes themselves (Bramon et al., 2005). Among the deficient components of executive functioning, response inhibition (withholding inappropriate behavioral responses) plays a very crucial role in organizing human behaviors (Bellgrove et al., 2005; Fassbender et al., 2006; Folstein & Van Patten, 2008; Kiefer et al., 1998; Kaladjian et al., 2007; Weisbrod et al., 2000) and emotions (Goldstein et al., 2007; Hare et al., 2008; Schulz et al., 2009). Thus,

deficits in response inhibition may result in disorganized speech (e.g. derailment, tangentiality), difficulty with goal-directed behaviors, or impulsivity and related risk behaviors (e.g. suicidal attempts, substance abuse) that are commonly found in SZ and BD (Christodoulou et al., 2006; Enticott, Ogloff, & Bradshaw, 2008).

One measure of response inhibition is the ability to withhold prepared responses in a specific context (Weisbrod et al., 2000). A task that is frequently used to investigate response inhibition is the Go/NoGo task, in which participants are asked to respond to the frequent target (Go trials), but to with hold a respond to the less frequent distracter stimuli (NoGo trials). A standard model of the Go/NoGo task suggests that prefrontal regions of the brain are responsible for inhibiting NoGo responses by signaling the motor system to override an automatic tendency to respond (Swick, Ashley, & Turken, 2008).

Event-related brain potentials (ERPs) studies have identified two robust components that index the cognitive processes associated with the visual Go/NoGo: an early negative component with a fronto-central distribution between 250-400 millisecond (ms) post-stimulus (N200 component) and a late positive component with centro-parietal distribution between 300-600 ms after stimulus onset (P300 component). Both N200 and P300 are larger for NoGo trials than for Go trials, which suggested that withholding responses to less frequent NoGo trials requires more attentional resources than executing responses for Go stimuli (for review see Folstein and Van Petten, 2008; Polich, 2009). Enhanced P300 for NoGo trials has been considered a prominent index of inhibition (Eimer, 1993; Bruin, Wijers, and Van Staveren, 2001; Folstein and Van Petten, 2008; Polich, 2009), while the nature of enhanced NoGo N200 amplitude is less clear (Donkers and Van Boxtel, 2004; Eimer, 1993; Nieuwenhuis and Yeung, 2003). Studies that support

that NoGo N200 is associated with inhibition have noted that it is enhanced with equiprobable Go/NoGo paradigm (Eimer, 1993; Van Boxtel, 2001), while proponents of conflict monitoring hypothesis have argued that NoGo N200 was enhanced for low-frequency stimuli irrespective of whether these stimuli were associated with response execution (Go) or response inhibition (NoGo) (Donkers and Van Boxtel, 2004; Folstein and Van Petten, 2008; Niuewenhuis and Yeung, 2003). Therefore, both interpretations of N200 need to be considered.

Though a general reduction of P300 amplitude is arguably the most reliable biological findings among SZ (Pitchard, 1986; Regan, 1989; Keifer et al., 1998; Weisbrod et al., 2000, Wood et al., 2006), there has been little literature on whether such attenuated NoGo P300 is specific to SZ compared to SAD and BD. The specificity of SZ abnormal P300 is important because it provides key information whether such deficit is unique to schizophrenia (Chapman & Chapman, 1973; Garber & Hollon, 1991) and therefore whether it can become a physiological endophenotype of SZ. Supporting evidence of P300 as a promising endophenotype of schizophrenia, P300 amplitude reduction and P300 latency delay were found in patients with schizophrenia and their first-degree relatives (see Bramon et al., 2005 for review; Turetsky et al., 2007). Furthermore, given that the robust findings of NoGo P300 among SZ were obtained from simple non-affective stimulus (e.g. letters, shapes, symbols), studies on whether Go/NoGo responses in ERPs can be preserved with more complicated stimuli (e.g. emotional faces) are seemingly nonexistent. Because there are fewer studies of emotion in SZ than cognition (Kring & Moran, 2008), assessing the impact of emotion on cognitive response inhibition can fill a gap between research of cognition and emotion

among SZ. This eventually can contribute to developing more effective assessments and treatments for social cognition in schizophrenia, which requires higher cognitive functioning and emotional information processing (Barch, 2008; Green et al., 2005).

In summary, for theoretical (e.g. diagnostic delineation between individuals with psychotic and affective symptoms) and clinical reasons (misdiagnosis), it is important to directly compare SZ, SAD, and BD (Daban et al., 2006; Szoke et al., 2008) in a single paradigm. Thus, this dissertation aims to investigate disorder-specific patterns of response inhibition among SZ, SAD, and BD by varying stimulus type utilizing the Go/NoGo paradigm in the following three studies:

(1) An archival study examining left-lateralized response inhibition deficit in SCZ compared to SAD and controls,

(2) A original study examining response inhibition deficit in SZ compared to BD and controls,

(3) The second original study will further extend the first two studies by replacing letter stimuli of Go/NoGo paradigm into facial stimuli with four categories of emotions (e.g. happy, sad, angry, and neutral) comparing SZ, BD and controls.

Chapter II.

Inhibition dysfunction and event-related potentials in schizophrenia and schizoaffective disorder

Introduction

Response inhibition, the ability to inhibit inappropriate responses in order to prevent detrimental social outcome, is a core mechanism of the frontal executive control system (Norman & Shallice,1986) and may be dysfunctional in schizophrenia (Henik et al., 2002; Thoma et al., 2007b; Wang et al., 2005). In fact, the inhibition deficits in schizophrenic patients (SZ) noted in Kraepelin (1913) and Bleuler (1911) were described as similar to those shown by patients with frontal lobe damage (Berman et al., 1986; Bushcbaum et al., 1992). The purpose of this study is to investigate deficits in neural response inhibition that may support the notion of frontal lobe dysfunction of SZ.

The neural mechanisms of response inhibition likely encompass structures of the prefrontal cortex (PFC) including inferior prefrontal cortex, anterior cingulate cortex (ACC), and/or supplementary motor area (SMA) (Aron et al., 2003; Chevrier, Noseworthy, & Schachar, 2007; Fassbender et al., 2006; Ford, 2004; Garavan et al.,1999; Kelly et al., 2004;Knight et al., 1999; Konishi et al., 1998). A response inhibition deficit

in SZ has been reported as reduced activation over left anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC) (Rubia et al., 2001a), and right frontal and parietal regions (Fort et al., 2004).

Two components of the event-related brain potential (ERP) are widely utilized in investigating response inhibition. First, an enhanced P300 amplitude and delayed P300 latency to the infrequent distractor (NoGo trials) compared to the frequent target (Go trials) has been regarded as an index of response inhibition because it requires more attentional resources to suppress an infrequent stimulus than to respond to more frequent stimulus , (Eimer, 1993; Polich, 2009). In this paradigm, the P300 component is defined as a positive wave with centro-parietal scalp distribution at approximately 300 and 600 ms post-stimulus (Hillyard et al., 1976; Johson & Donchin, 1980; see Polich, 2009 for review). N200 is a negative potential with a fronto-central peak that occurs around 200 ms post-stimulus indexing an early process of response inhibition. There have been disputes as to the exact nature of the N200 component in the Go/NoGo task (Donkers and Van Boxtel, 2004; Folstein & van Petten, 2008 ;Nieuwenhuis and Yeung, 2003). Enhanced or delayed frontocentral N200 for NoGo stimulus (NoGo-N200) has be interpreted as either an index of cognitive effort in stimulus classification prior to motor response inhibition (Boruka et al., 2001; Donchin & Coles, 1988; Eimer, 1993) or as difficulty in conflict monitoring between a target and a distractor (Donkers and Van Boxtel, 2004; Nieuwenhuis and Yeung, 2003).

Further, the neural indices of response inhibition may be lateralized. Specifically, recent fMRI studies with healthy controls or patients with frontal lobe damage have suggested that the right inferior PFC is the most strongly associated with response

inhibition (Garavan et al., 1999; de Zubicaray et al., 2000; Zheng, Oka, Boruka, and Yamaguchi, 2008) while others studies have shown the strongest activation over left inferior frontal gyrus (IFG) (Picton et al., 2007; Swick, Ashley, and Turken, 2008), and yet other studies have suggested the process is bilateral (Kawashima et al., 1996; Konishi et al., 1998, 1999). Perhaps these studies have artifactually found different regions of interest because of the temporal limitations associated with fMRI. Evidence for this conjecture comes from a recent source localization ERP study using LORETA which located the neural generator of NoGo N200 in the right orbito-frontal cortex (OFC), and the generator of the NoGo P300 in the left lateral OFC (Boruka et al., 2001). This suggests that response inhibition may require attentional resources from both hemispheres, but at different time points and for different sub-processes that fMRI might not be temporally sensitive enough to differentiate.

SZ have consistently shown reduced P300 amplitude relative to controls (Ford et al., 2004; Kiefer et al., 1998; Kiehl et al., 2000; Weisbrod et al., 1999, 2000). However, only a couple studies have investigated N200 deficits among SZ using response inhibition tasks. Kiehl et al. (2000) found reduced visual N200 amplitude for NoGo trials in SZ . However, NoGo N200 amplitude deficits were not found in a second study that utilized a binaural Go/NoGo task (Weisbrod et al, 2000) perhaps because the pitch of rare tone (NoGo) was individually adjusted beforehand and therefore SZ were able to discriminate the rare tones as well as CT.

Given that response inhibition is probably lateralized it is not surprising that there is evidence that SZ deficits may also be lateralized. Specifically, some studies have shown left hemisphere ERP deficits (N200, Kiehl et al., 2000 and P300 Hill and

Weisbrod, 1999; Weisbrod et al., 1997, 2000) while other studies have shown right hemisphere deficits (Bellgrove et al., 2005) and blunted activation over right ventrolateral prefrontal cortex (vlPFC; Kaladjian et al., 2007). Lateralization differences are theoretically important because Crow and his colleagues have suggested that SZ have a developmental failure in establishing left hemisphere dominance for language. This developmental failure would most likely be associated with the symptoms thought disorder. Thought disorder, in turn, may be caused by dysfunctional inhibition in maintaining a stream of thought and not being distracted by inappropriate or unrelated thoughts (Crow, 1990, 1995; Crow et al., 1996; review by Mahrer & Deldin, 2001, *p*351-352).

To this end, this study tested whether SZ have deficits in response inhibition and whether this deficit is lateralized over the left frontal region. In order to test this hypothesis, the current study used a modified Go/NoGo paradigm (Eimer, 1993) with lateralized stimulus presentation (Eimer, 1993; Clarke, Halgren, and Chauvel, 1999). It was hypothesized that if SZ is more affected by left hemisphere dysfunction, reduced ERPs over the left-side electrodes would be observed only when the stimulus is presented to the right visual field. If SZ is more affected by a right hemisphere dysfunction, then reduced ERPs over the right-side electrodes would be observed only when the stimulus is presented to the left visual field.

Finally, this study explored whether response inhibition deficit is specific to SZ or if it is also present in schizoaffective disorder (SAD), a disorder intermediately positioned between schizophrenia and affective disorders. In many studies, patients with SAD are combined with schizophrenics on the assumption that the two disorders are not

discrete disorders. However, an extensive meta-analysis, examining the validity of SAD as a distinct nosologic category found that SAD could not simply be interpreted as atypical forms of SZ or mood disorders (Cheniaux et al., 2008; Szoke et al., 2008). Furthermore, a recent ERP study with auditory oddball paradigm reported that patients with schizoaffective disorder demonstrated significantly delayed P300 latency, while schizophrenic patients showed both attenuated and delayed P300 (Mahaler et al., 2008). Thus, in this study, it was hypothesized that all three groups, SZ, SAD and CT will have differential abilities to inhibit responses.

In summary, this study investigated response inhibition deficit in patients with schizophrenia (SZ) and schizoaffective disorder (SAD) with a lateralized visual Go/NoGo paradigm. The hypotheses are as follows:

(1) SZ will show a left-lateralized inhibition deficit manifested as reduced N200 and P300 amplitude over the frontal region.

(2) ERP indices of response inhibition (e.g. reduced P300 amplitude, prolonged N200 latency) will differentiate SZ from SAD.

SZ will make more commission errors when the stimulus is presented to the right visual field (Left hemisphere projection) than to the left visual field. SZ will show the lowest overall accuracy rate, the controls the highest, with SAD falling in the middle.

Method

Participants

Fourteen SCZ (4 women), eleven SAD (8 women), and fifteen healthy controls (11 women) with age range of 19 – 62 years old participated in this study. All research

participants diagnosed with SZ and SAD were outpatients at the Dr. John C. Corrigan Mental Health Center, Fall River, MA, USA. Staff and chart diagnoses were confirmed using the Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-I/P), administered by a doctoral-level clinical psychologist or graduate students trained in SCID administration (First et al., 1995). Demographic information, including age and parental years of education, were obtained from all study participants, while year of illness, types of anti-psychotic medication and its dosage were further provided by patient groups. Control participants were recruited from the Fall River, Massachusetts area through newspaper advertisements and were prescreened over the telephone. Control participants with no self-reported history of seizures or head injuries and who had no learning, neurological, or medical disorders were invited to participate in a SCID interview. Those participants who were found to have no current or past DSM-IV Axis I psychiatric diagnosis were then asked to return for the physiological data recording session. All participants' primary language was English and their vision was normal or corrected-to-normal. To ensure that all participants were right-handed, the Annett's Handedness questionnaire was administered. According to Harvard Institutional Review Board approval, the details of the study were explained to all participants and written consent obtained. Participants were compensated with $ 10 dollars for each hour of their time.

	Schizophrenia (n=14)	**Schizoaffective** (n=11)	**Control** (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)	$F(2,37) = .85,$	= .072
Gender (male/female)	10/4	3/8	4/11	$\chi^2(2) = 7.19$, p	= .027
Handedness 12 = right 36 = left	13.5 (2.1)	13.3 (1.2)	12.9 (1.3)	$\chi^2(2) = .65$	= .72
PANSS	63.4 (13.9)	61.5 (10.3)	39.1 (5.0)	$F(2,37) = 23.76$	< .001
SANS	7.7 (3.4)	6.2 (2.9)	0.9 (1.3)	$F(2,37) = 25.77$	< .001
SAPS	6.1 (3.4)	4.6 (3.2)	0.3 (.5)	$F(2,37) = 19.36$	< .001
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
Chlorpromazine Equivalents (mg)	266.4 (191.8)	227.8 (193.8)	0	$F(1,23) = .25$	= . 62

Note. Means and standard deviation (SD) are given for age, number of years of education, handedness, Scale of Assessment of Positive Symptoms (SAPS), Scale of Assessment of Negative Symptoms (SANS), Positive and Negative Syndrome Rating Scale (PANSS), length of illness and chlorpromazine equivalent of antuosychotic daily dosage.

Table 1. Demographic characteristics and medical status of participants

Materials and Procedure

Participants' electroencephalograms (EEGs) were recorded while they completed a modified version[1] of a visual Go/NoGo task (Eimer, 1993).Visual stimuli were created using the Corel Photopaint 6.0 graphics program. The central plus sign or central arrow, subtending 1 degree of visual angle (deg), was flanked by two squares that each subtended 2 deg of visual angles. Each square was 6 deg to the left and right on the horizontal meridian. Two letters (M and W), subtending 1 deg each, were presented at the center of either the right or left square. All stimuli were presented in white on a blue

[1] In Eimer et al's original paradigm (1993), 25% of the pre-cues were mismatched and 75% were matched with the stimulus presentation. However, only valid pre-cues generated larger NoGo amplitudes for N200 and P300. Therefore, this study only included valid pre-cues.

background displayed from the screen located 120 cm in front of the subject. Participants were seated in a darkened room and were instructed to focus on a centrally located cross before the onset of the first trial. Subjects were presented with the arrow, followed by a fixation period. The pre-cue indicated which side the target stimulus would appear. Two letters, M and W, were designated as the Go/NoGo cues respectively. Each trial included a pre-cue (200 ms), followed by an inter-stimulus interval, (700 ms) and the onset of the cue (150 ms). The interval between letter offset and the onset of the next arrow was 1750 ms. Participants had a maximum of 1900 ms from the onset of the cue to make a response (Appendix I). The subjects were told that the letter cues would appear at the center of either the right or left positioned squares. 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 were instructed to withhold response when the NoGo-stimulus was presented on either side. Overall, for each subject, there were 60 trials (42 Go (70 %) and 18 NoGo (30 %)) in each of the four separate blocks of the experiment, with a total of 240 trials.

Physiological Recording

EEG was recorded from ten sites (F3, Fz, F3, C3, Cz, C4, P3, Pz, P4, Oz) on the scalp during the task, using a conductive gel and tin electrodes located on the electrode cap (Electro Cap International, Inc., Eaton OH) arranged according to the International 10-20 System. Electrooculograms (EOG) were recorded using tin electrodes placed on the outer canthus (horizontal) and supraorbital/infraorbital (vertical) positions of the left eye. EEG was referenced to the left mastoid (A1) and algebraically re-referenced to both

ears off-line. Impedance for all electrodes was checked prior to the presentation of stimuli and kept below 10 kΩ. During acquisition, a high-pass filter was set for 0.01 Hz, while a low-pass filter was fixed at 30 Hz. Signals were digitally sampled at 512 Hz for the duration of the experiment.

Data Analysis

Analysis of the physiological data was completed using software designed by the James Long Company. Of the original 10 sites, 9 were further analyzed (F3, Fz, F3, C3, Cz, C4, P3, Pz, P4)[2] in order to ascertain effects of Caudality (frontal, central and parietal) and Laterality (left, center, right). As N200 amplitude is maximal at the fronto-central regions of the scalp (Donkers & van Boxtel, 2004; Eimer, 1993; Jodo & Kayama, 1992), only these regions (F3, Fz, F4, C3, Cz, and C4) are included in the N200 analyses.

EEG data was resampled to 225 Hz and digitally filtered using an 8 Hz low-pass filter. All trials with remaining artifacts (e.g. large muscle movement, eye movement, skin conductance, slow voltage shift) were removed from later analyses. Artifact due to eye blinks was corrected via a regression algorithm in the time domain to derive parameters characterizing the appearance and spread of EOG artifact in the EEG channel. The EEG data were baseline corrected at 150 ms before averaging. Individual ERPs were obtained separately for each group: Stimulus type (Go-left/Go-right/NoGo-left/No-Go-right) and Laterality. The P300 latency window was defined as 300-450ms after stimulus presentation, while N200 latency window was defined as 250-300 ms after stimulus presentation (Folstein & van Petten, 2008). The mean amplitudes of P300 and N200 were centered on their peak latency in grand-average waveforms.

[2] EEG was also collected at the Oz site but was not included in the analysis because of technical problems with the electrode.

Task performance in target detection was assessed by calculating the accuracy score as a percentage of correct responses (button push for 'M' or no button press for 'W'). Commission error, an index of failure in response inhibition, was also calculated by counting the number of NoGo items to which participants responded. A three-way ANOVA was performed with Task (Go/NoGo) and Stimulus (left/right) as within-subject factors and with Group (controls/ SCZ/ SAD) as a between-subject factor. For the Go task, differences in the reaction times of each group were analyzed in a Group x Stimulus ANOVA. A four way ANOVA was performed for ERP amplitudes and latencies for Group, Stimulus, Laterality, and Caudality. Simple effect ANOVAs and Newman-Keuls tests were performed as post hoc tests. An interaction effect among variables was reported only when its preceding higher-order interactions were also significant. For example, a 2-way interaction was only reported if the preceding 3-way interaction was also significant. Greenhouse- Geisser correction was applied to the variables that violated sphericity assumption. Discriminant function analyses (DA) were performed to determine whether the three groups could be distinguished from one another based on the linear combination of ERP amplitudes or latencies, and also to determine which variables contribute to the separation (Norusis, 2008). Wilk's lambda was used to test the significance of the discriminant function as a whole.

Results

Behavioral data analysis

The three groups differed in overall accuracy F (1,37) = 3.82, $p < .032$. Consistent with our expectation, Newman-Keuls analysis revealed that the SZ group performed

worse than controls ($p < .037$). SZ were also marginally less accurate than SAD, ($p = .075$). No difference in overall accuracy was found between the control and SAD. Contrary to our hypothesis, differences between groups were not modified by task or stimulus presentation. Analyses of the error responses revealed that the three groups differed in neither omission errors (not pressing the button for the Go stimulus) ($p > .10$) nor commission errors (inappropriately pressing the button for the NoGo stimulus) ($p > .10$) despite the overall group difference in error rate, $F(2,37)= 4.02$, $p < .05$. However, post hoc analysis demonstrated that SZ made more errors in both omission and commission errors than controls ($p < .05$), but there was no difference between SZ and SAD ($p > .30$), nor controls and SAD ($p > .19$) (Table 2).

For reaction time (RT), no group difference was observed. However, participants responded more quickly to stimuli presented to the right visual field (right button press, 531 ms) than to the left visual field (left button press, 561 ms), Stimulus, $F(1,37) = 8.13$, $p < .01$.

	Go-Left Hit (SD)	Go-Left Omission (SD)	Go-Right Hit (SD)	Go-Right Omission (SD)	NoGo-Left Hit (SD %)	NoGo-Left Commission (SD)	NoGo-Right Hit Rate (SD)	NoGo-Right Commission (SD)
Controls	98.9 (1.9)	0.9 (1.9)	99.1 (1.7)	0.9 (1.6)	96.1 (5.53)	3.9 (5.5)	95.2 (5.7)	4.8 (5.7)
SZ	93.2 [a] (8.6)	6.2 [a] (7.8)	93.5 [a] (11.2)	5.9 (10.4)	90.7 [a, b] (12.7)	8.5 [a] (12.6)	91.1 [a, b] (8.5)	8.3 [a] (.5)
SAD	95.9 (8.7)	3.7 (8.4)	96.7 (7.16)	2.9 (6.9)	95.2 (5.4)	4.5 (5.6)	95.4 (5.3)	4.5 (5.3)

Table 2. Mean accuracy rate, Omission error rate, and Commission error rate with standard deviation for controls, SCZ, and SAD for the Go and NoGo task with left (LVF) and right visual field (RVF) stimuli. [a]. difference between SZ and CT ($p < .05$), [b.] difference between SZ and SAD ($p < .05$)

P300

P300 latency in response to NoGo stimuli (447 ms) was longer than in response to Go stimuli (407 ms), Task, F (1,37) = 22.59, $p < .001$. P300 latency was the shortest at the frontal leads (F3, Fz, and F4) followed by central leads and parietal leads, Caudality, F (2,76)= 10.97, $p < .001$. No difference in P300 latency was found between central and parietal regions, and no latency group effects or interactions with group were observed.

NoGo-P300 amplitude was larger than Go-P300 amplitude, Task, F (1,37) = 10.97, $p < .01$. P300 amplitude was larger along the midline than left ($p < .05$) or right leads ($p < .05$), Laterality, F(2,74)=20.90, $p < .001$. Frontal-P300s were the smallest ($p < .01$) and there was no difference between central and parietal P300s, Caudality, F(2,74) = 54.82, $p < .001$. When the stimulus was presented to the left visual field, NoGo-P300 was consistently larger than Go-P300 on the three lateral positions of electrodes. However, when the stimulus was presented to the right visual field of a subject, larger NoGo-P300 than Go-P300 was observed only over the midline electrodes (Fz, Cz, Pz), Stimulus × Task × Laterality, F(1.49, 55.02) = 3.78, $p < .05$. Furthermore, NoGo-P300 was larger than Go-P300 at C4 (right-central) only when the stimulus was presented to the left visual field, Task × Stimulus × Caudality × Laterality, F(4,148) = 5.81, $p < .0001$.

As predicted, P300 amplitude varied by group, Group × Task × Stimulus × Caudality × Laterality, F (8,148)=2.23, $p< .05$. Specifically, simple effects ANOVAs dissecting the 5-way-interaction produced a series of significant effects including Group × Stimulus × Laterality × Caudality interaction only for NoGo task, F (5.27, 97.59) = 2.36, $p < .05$. Over the frontal region, NoGo P300 amplitude was smaller over the left

side electrodes compared to right and midline electrodes Group × Stimulus × Laterality, $F(2.31, 42.79) = 2.63$, $p < .05$. Specifically over the frontal left electrode (F3), NoGo P300 amplitude was more reduced when the stimulus was presented to the right visual field (RVF) than to the left visual field (LVF), Group × Stimulus, $F(2,37) = 3.47$, $p < .05$ (Figure 1a.,1b). Post-hoc tests indicated that the NoGo-P300 at F3, especially when the stimulus was presented to RVF, was reduced in SZ compared to CT ($p < .05$) but not to SAD ($p > .26$), while none of group-wise comparisons were significant for LVF stimulus presentation ($p_{SZ\text{-}SAD} > .72$, $p_{SZ\text{-}CT} > .80$, $p_{CT\text{-}SAD} > .56$). Furthermore, within each group when the stimulus was presented to the right visual field, P300 amplitude at left frontal (F3) was smaller than at left midline (Fz), whereas no such difference was observed for the left visual field stimulus presentation, Stimulus, $F(1,13) = 6.17$, $p < .05$. No difference in NoGo P300 was found when frontal left (F3) was compared with frontal right (F4) ($p = .62$). SAD and controls NoGo-P300 at F3 were not different ($p = .283$).

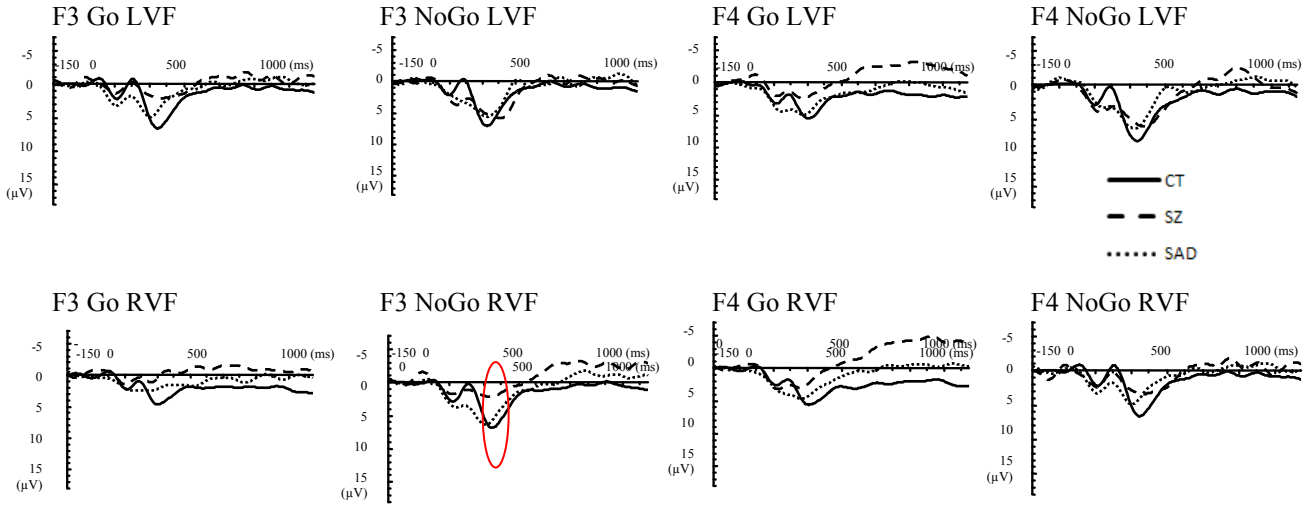


Figure 1-a. Grand Average ERP waveforms over frontal left and frontal right with left visual field (LVF) and right visual field (RVF) presentation

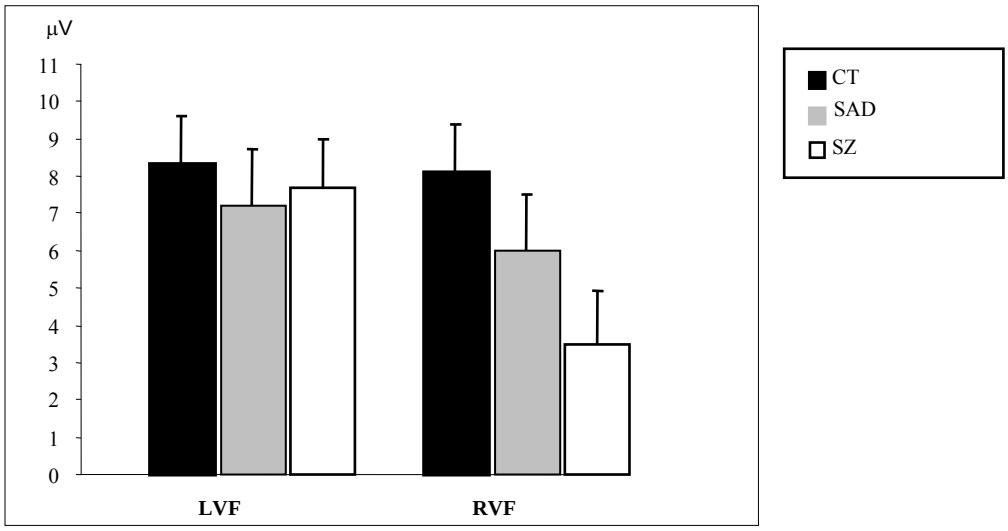


Figure 1-b. Mean amplitudes of NoGo P300 over the left frontal (F3) for healthy controls, schizoaffective disorder and schizophrenic patients for left visual field stimuli (LVF) and right visual field stimuli (RVF)

N200

The N200 latency for the NoGo task (302 ms) was longer than that of Go task (289ms), Task ($F(1,37) = 8.89$, $p = .005$). The latency differed by groups, Group, $F(2,37) = 3.62$, $p < .05$. The SAD group showed longer latency (309 ms) than the SZ (291 ms) ($p = .05$) and controls (287 ms) ($p < .01$). This effect varied by stimulus type, Group × Stimulus, $F(2,37) = 3.62$, $p < .05$, indicating that such group difference in N200 latency was observed only when the stimulus was presented to the left visual field, Group, $F(2,37) = 5.73$, $p = .01$, SZ = 291.93 ± 27.47 ms, SAD = 313.88 ± 28.85 ms, CT = 278.96 ± 15.76 ms. Post-hoc tests revealed that N200 latency differed between CT and SAD ($p < .01$), while the difference was marginal between SZ and SAD ($p < .10$). No significant correlation was found among N200 latency for the Go task and reaction time.

Consistent with previous studies, N200 amplitudes showed regional variation for the NoGo task (Donkers & van Boxtel, 2004; Eimer, 1993; Jodo & Kayama, 1992; Kok, 1986; Pfefferbaum, Ford, Weller, & Kopell, 1985). Specifically, N200 amplitude was enhanced for NoGo task in comparison to the Go task, Task, $F(1,37) = 6.35$, $p < .05$. Compared to the central electrodes, frontal N200 showed greater negativity, Caudality, $F(1,37) = 49.31$, $p < .0001$ (Appendix 2). N200 amplitude was greater over the left side of the electrodes than those on the right side, Laterality, $F(2,74) = 5.12$, $p < .01$. Specifically, over the left side electrodes (F3, C3), N200 amplitude was greater when the stimulus was presented on the left visual field than to the right visual field, Laterality × Stimulus, $F(2,74)=4.07$, $p < .05$. Over the frontal electrodes (F3, Fz, and F4), N200 amplitude was larger when the stimulus was presented to the right than to the left visual field, Caudality × Stimulus, $F(1,37) = 4.15$, $p < .05$. No difference between N200 in response to stimulus presentation was found over the central leads.

As predicted, N200 amplitude differed by groups, Group × Task × Stimulus, $F(2,37) = 4.57$, $p < .05$. Dissecting this three-way interaction demonstrated that controls showed greater fronto-central N200 negativity for NoGo task than SZ and SAD, Group × Stimulus, $F(2,37) = 4.18$, $p < .05$. Post-hoc test further revealed that in SZ, N200 for NoGo task was smaller for left visual field stimulus presentation than right, Stimulus, $F(1,13) = 12.01$, $p = .004$ (Figure 1-a, 2). Such stimulus presentation effect in NoGo N200 amplitude was not observed in control and SAD.

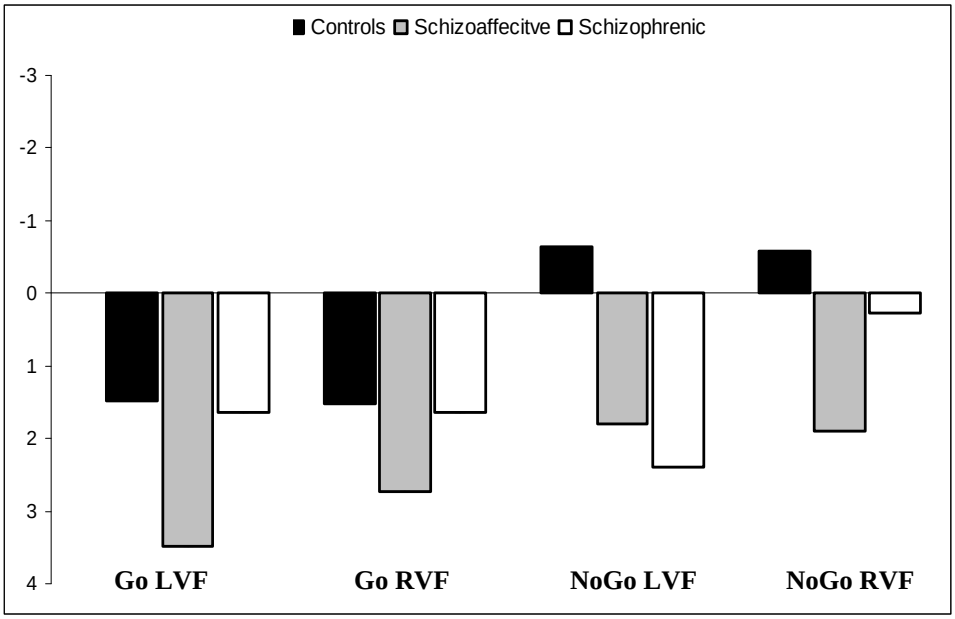


Figure 2. N200 amplitude for Group × Task × Stimulus at fronto-central region

Discriminant Function Analysis[3]

Discriminant Function analysis (DA) was performed in order to test whether the P300 amplitude could discriminate the three groups. Among the thirty six independent variables (laterality × caudality × stimulus × task; 3 × 3 × 2 × 2), four variables under NoGo right visual stimulus presentation failed to pass the tolerance test, and therefore were excluded from the discriminant function analysis. The two functions, specifically P300 amplitude classified the three groups with 100% accuracy (Wilk's Lamda =.008, p = .001). Even with only six variables representing Frontal-right visual field, DA classified 67.5% of the group (Wilk's Lamda = .58, p = .09). High canonical correlation coefficients for Function 1 (r = .96) and Function 2 (r = .95) indicated that discriminant

[3] DA resulted in 95% classification (Wilk's Lambda= .08, p=.07) with all frontal and central leads (F3, F4, Fz, C3, C4, Cz), and 77.5% classification (Wilk's Lambda=.22, p=.003) with variables representing only frontal leads.
DA for P300 amplitude difference between left electrodes (F3, C3, P3) and midline electrodes (Fz, Cz, Pz) was not significant enough to discriminate three groups (Wilk's Lambda= .41, p = .25). DA with all variables for P300 latency was not significant to discriminate the group membership (Wilk's Lambda= .26, p = .39).

scores based on P300 amplitudes were well explained by differences between the three groups. As shown in Table 3, Function I consisted of many variables related to NoGo task, while Function II consisted of variables related to the Go task. Function I discriminates the control group from the patient groups ($M_{Control}$ = 4.14, M_{SZ} = -1.75, M_{SAD} = -3.42), while Function II discriminate schizophrenic group ($M_{control}$ = .76, M_{SZ} = -3.69, M_{SAD} = 3.66) from the other groups (Figure 3).

The discriminant function analyses of N200 latency revealed that it classified the three groups with 91% accuracy (Wilk's Lambda = .07, $p < .05$), while N200 amplitude failed to discriminate the three groups (Wilk's Lambda = .14, p= .38). Canonical correlation coefficients ($r_{\text{Function 1}}$ = .91, $r_{\text{Function 2}}$ = .77) were high enough to indicate that N200 latency discriminant scores predicted group membership well. Among the sixteen variables (Laterality × Caudality × Stimulus × Task; 2 × 2 × 2 × 2), seven variables comprised Function I mainly consisted of N200 for Go LVF and NoGo RVF presentation , while Function II was a combination of Go RVF and NoGo LVF presentation (see Table 4). As shown in Figure 4, Function I clearly discriminated controls from SAD, while Function II separates SZ from the other two groups. Function I discriminates SAD from the other two groups ($M_{Control}$ = - .66, M_{SZ} = -1.85, M_{SAD} = 3.26), while Function II separated control group from the patient groups ($M_{Control}$ = 1.46, M_{SZ} = -1.20, M_{SAD} = - .46). Specifically, the fact that Function I mainly consisted of NoGo-right variables indicated that response inhibition among SAD was distinctively different from SZ and even from controls when they were asked to withhold response with their dominant (right) hands.

Function I				Function II			
Variable	coefficient	Variable	coefficient	Variable	coefficient	Variable	Coefficient
P3 NoGo Left	.11	P4 NoGo Right	.08	F4 Go Left	.14	F3 Go Right	.08
P4 NoGo Left	.11	Cz Go Left	.08	C3 Go Right	.12	C4 Go Right	.08
C3 NoGo Right	.10	Fz NoGo Right	.08	F4 Go Right	.10	P3 Go Right	.07
Pz NoGo Left	.10	Pz Go Left	.07	C4 Go Left	.10	F4 NoGo Right	.07
C4 NoGo Left	.10	Cz Go Right	.06	Fz Go Left	.10	P4 Go Left	.06
C3 NoGo Left	.10	F4 NoGo Left	.05	F3 Go Left	.09	P4 Go Right	.06
Cz NoGo Left	.09	Fz NoGo Left	.04	C3 Go Left	.08	Pz Go right	.05
F3 NoGo Right	.09	F3 NoGo Left	.03	Fz Go Right	.08	P3 Go Left	.05

Table 3. Structural matrix of P300 amplitude Discriminant Functional Analysis.

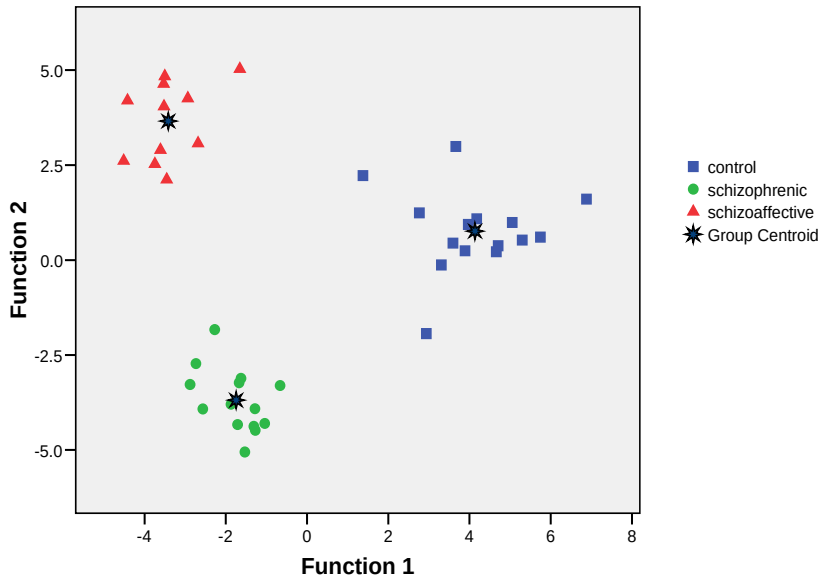


Figure 3. Discriminant analysis group classification based on P300 amplitude. Function I consisted of NoGo P300 amplitude, which separated control group from patients group, while Function II consisted of Go P300 amplitude which separated schizophrenic group from the other two. Overall, P300 amplitude classified the three different groups with 100% accuracy.

Function I				Function II			
variable	coefficient	variable	coefficient	variable	coefficient	variable	coefficient
C4 Go Left	.24	C4 NoGo Right	.12	F3 Go Right	-.34	C4 NoGo Left	- .21
Cz Go Left	.23	C3 NoGo Right	.10	F4 Go Right	-.27	F4 NoGo Right	.21
F3 NoGo Right	.23	F3 Go Left	.10	C3 Go Right	- .27	Fz NoGo Left	- .21
Cz NoGo Right	.13			C3 Go Right	- .24	F3 NoGo Left	- .20
				Cz NoGo Left	-.24	C4 Go Right	- .17
				Cz Go Right	.16	Fz NoGo Right	-. 21
				F4 NoGo Left	-.16	C3 Go Left	- .10
				Fz Go Right	- .06	F4 Go Left	- .04

Table 4. Structural matrix of N200 latency in discriminant functional analysis

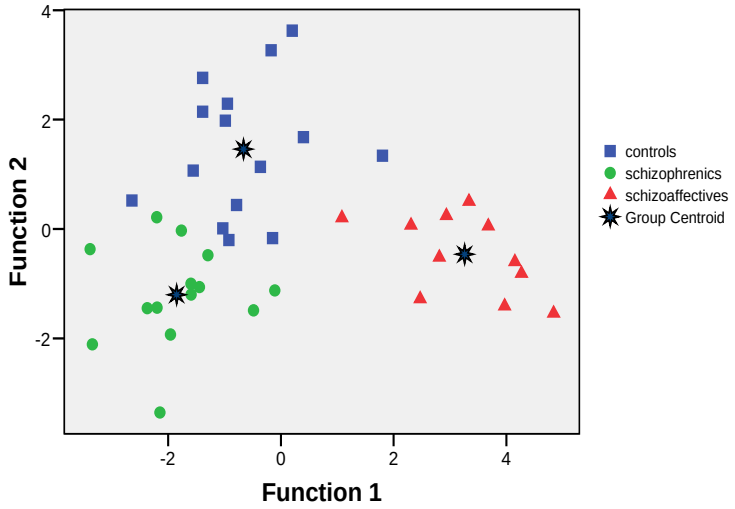


Figure 4. Canonical Discriminant Functions for N200 latencies. Function I consisted of N200 latency for NoGo – RVF and Go-LVF, which separated SCZ from the other two groups, while Function II consisted of N200 latency for Go-RVF and NoGo-LVF , which separated controls from the patients group. Overall, N200 latency classified the three different groups with 91% accuracy.

Discussion

This study investigated response inhibition deficits in schizophrenia (SZ) and schizoaffective disorder (SAD) using a lateralized Go/NoGo paradigm. Discriminant function analysis (DA) demonstrated that the three groups could be perfectly distinguished based on P300 amplitude and N200 latency, which strongly supports the notion that both P300 amplitude (Bramon et al., 2005; Turetsky, 2007) and N200 latency may be physiological endophenotypes of SZ and SAD. Given that executing responses with non-dominant (left) hand and inhibiting the prepotent responses with dominant (right) hand was harder for right-handed participants, Go-left and NoGo-right conditions could be cognitively more challenging than Go-right and NoGo-left conditions. This suggests that early stage response inhibition deficit in SAD may manifest when they perform cognitively demanding tasks. To this end, the findings of N200 latency delay in SAD provides physiological evidence demonstrating that SAD are distinguishable from both SZ and CT in the speed of stimulus evaluation and provide further support that SAD is a nosologically independent diagnostic category (Cheniaux et al., 2008).

The findings also indicated that neural response inhibition deficits in SZ were left-lateralized over the frontal region. Further, different hemispheres were involved in different stages of SZ deficient response inhibition Specifically, the P300 deficit reflected SZ's difficulty in allocating attentional resources to inhibit motor responses during right visual field (the left-frontal hemisphere activity), while reduced N200 reflecting the earlier stage of response inhibition may reflect earlier right hemisphere dysfunction. The deficits are specific to the regions found in a previous study which demonstrated that

N200 is mediated by the right orbito-frontal cortex (OFC), while P300 is mediated by the left OFC (Boruka et al., 2001).

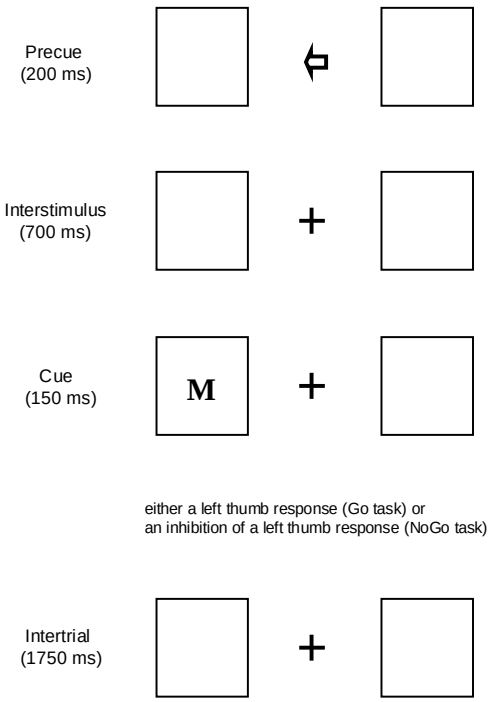
The specificity of response inhibition deficit in SZ was supported by their intact neural responses to Go trials. In addition to the lateralized P300 deficit for NoGo trials, SZ showed fronto-central N200 amplitude deficits for NoGo trials when the stimulus was presented to left visual field (LVF) but not to the RVF. Based on sensory information processing in a lateralized stimulus presentation, the findings reflect the involvement of right hemisphere dysfunction in stimulus classification during the early stage of response inhibition (Clarke, Halgren, and Chauvel, 1999). In lateralized stimulus presentation, a stimulus presented to LVF would be projected to right hemisphere contralaterally and to left hemisphere ipsilaterally. Difficulty in allocating attentional resources from the right hemisphere for early NoGo stimulus processing may negatively affect contralateral processing of stimuli presented stimulus to the right hemisphere. In SAD, N200 amplitude did not differ from that in SZ and from CT, but they showed delayed N200 latency when the stimulus was presented to the LVF. This finding indicates that SAD can recruit attentional resources for inhibiting response though they needed a longer time to do so.

In conclusion, the present study highlighted specific deficits of response inhibition in schizophrenia and schizoaffective disorder and further suggests the possibility of utilizing neural responses in lateralized Go/NoGo task as biological marker of the two disorders. In patients with schizophrenia, response inhibition deficit in early stage of response inhibition reflected right hemispheric dysfunction, while the deficit was specifically observed over the left frontal region during the later stage of response

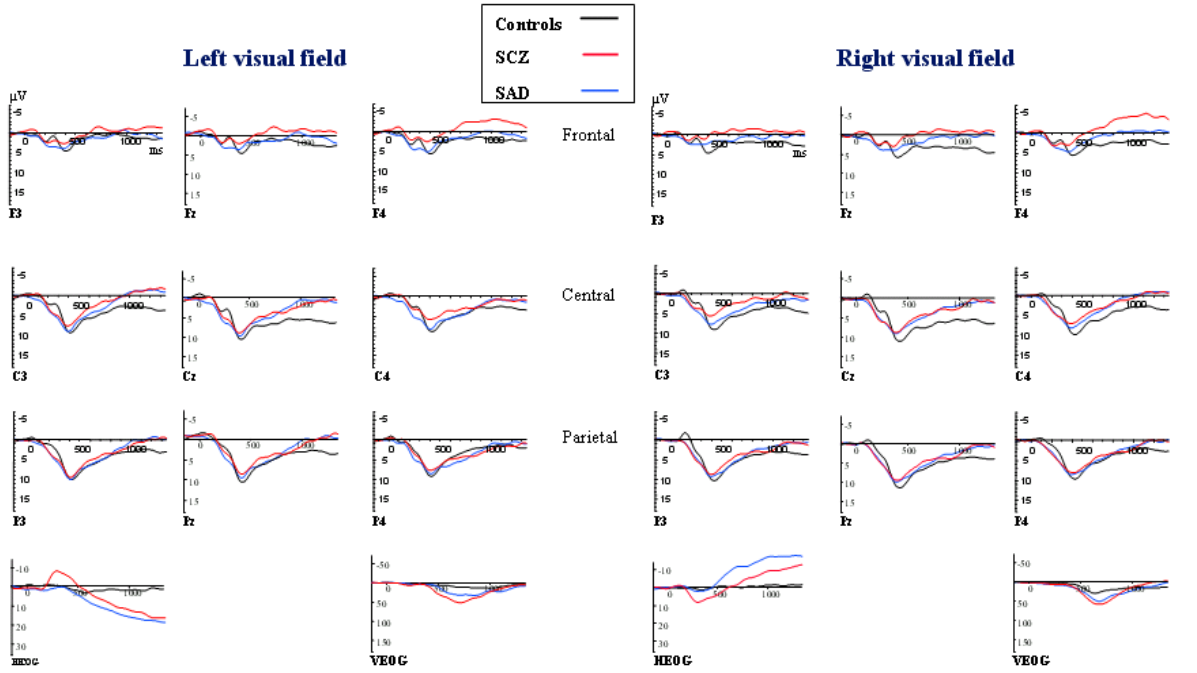
inhibition. However, it should be noted that discriminant function analysis in this study was used for the limited purpose of identifying ERP variables (e.g. P300 amplitude, N200 latency) that separated the three groups. Thus, in order to test whether the same discriminant functions as in this study can classify different psychiatric groups including SZ and SAD, cross-validation method such as leave-one-out measure needs to be considered in the future studies. Further, more ERP source localization studies with larger sample sizes should be utilized to replicate the findings of current study and to provide more spatial information about the role of the two hemispheres in different stages of response inhibition in SZ and SAD. Due to the poor time resolution, neuroimaging studies may have difficulty in separating the lateralized cognitive processing deficits in SAD and SZ.

Chapter II. APPENDICES

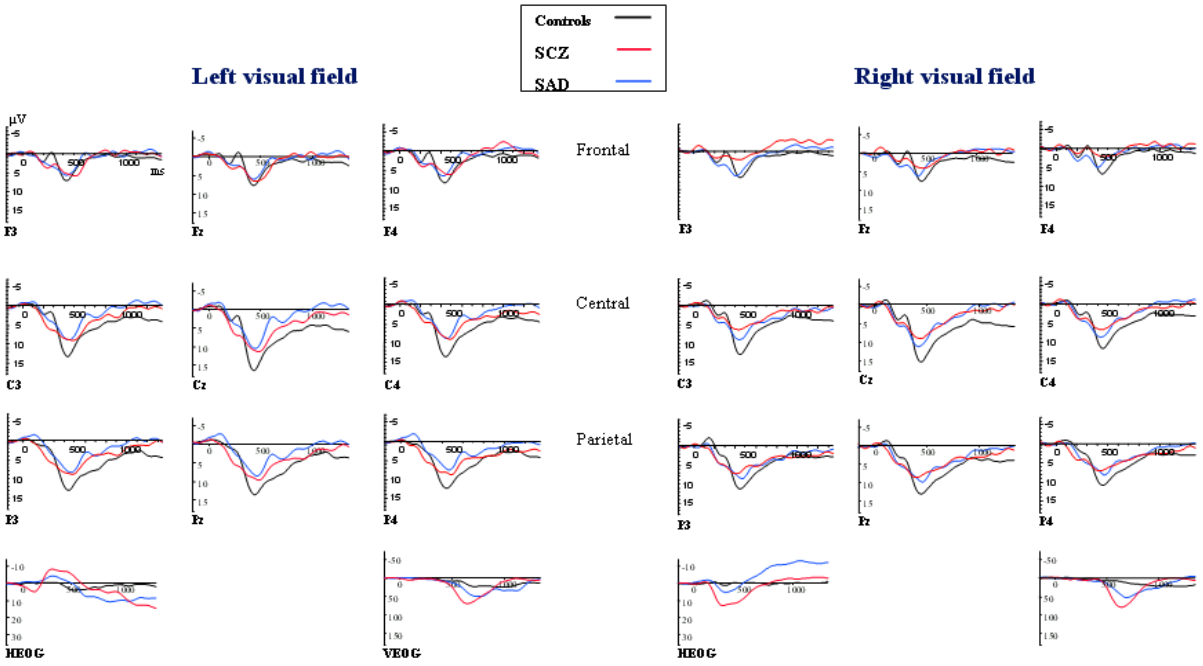
Appendix 1. Visual Go/NoGo paradigm



Appendix 2-a. Grand Average ERP waveforms for Go task



Appendix 2-b. Grand Average ERP waveforms for NoGo task



Appendix 3. Repeated-measure ANOVA for P300 amplitude

	F-value	*p*-value
Group	*F* (2,37) = 2.40	= .104)
Stim	*F* (1,37) = 3.09	= .087)
	F (1,37) = 10.97	= .0021
Task		
Lat	*F* (2,36) = 16.88	< .001
Cau	*F* (2,36) = 30.55	< .001
Task x Stim	*F* (1,37) = 4.25	= .046
Stim(Go)	*F* (1,37) = 0.21	= .65
Stim(NoGo)	*F* (1,37) = 4.8	= .035
Task x Lat	*F* (2,36) = 7.05	= .003
Task x Cau	*F* (2,36) = 27.99	< .001
Cau (Go)	*F* (2,36) = 42.24	< .001
Cau (NoGo)	*F* (2,36) = 23.57	< .001
Task (frontal)	*F* (1,37) = 26.08	< .001
Task (central)	*F* (1,37) = 13.33	< .001
Task (parietal)	*F* (1,37) = .34	= .57
Lat x Cau	*F* (4,34) = 9.39	< .001
Task x Cau x Lat	*F* (4,34) = 7.31	< .001
Cau x Lat (Go)	*F* (4,34) = 12.14	< .001
Cau x Lat (NoGo)	*F* (4,34) = 9.4	< .001
Cau (Go, left)	*F* (2,36) = 51.97	< .001
Cau (Go, right)	*F* (2,36) = 29.08	< .001
Cau (Go, central)	*F* (2,36) = 42.39	< .001
Cau (NoGo, left)	*F* (2,36) = 20.03	< .001
Cau (NoGo, right)	*F* (2,36) = 21.29	< .001
Cau (NoGo, central)	*F* (2,36) = 24.18	< .001
Task x Stim x Cau x Lat	*F* (4,34) = 4.97	= .003
Task x Cau x Lat (left)	*F* (4,34) = 8.28	< .001
Task x Cau x Lat (right)	*F* (4,34) = 5.09	= .003
Task x Cau (left, left)	*F* (2,36) = 17.26	< .001
Task (left, left, frontal)	*F* (1,37) = 36.35	< .001
Task (left, left, central)	*F* (1,37) = 10.55	= .002
Task (left, left, parietal)	*F* (1,37) = .82	= .37
Task x Cau (left, right)	*F* (2,36) = 12.42	< .001
Task (left, right, frontal)	*F* (1,37) = 28.02	< .001
Task (left, right, central)	*F* (1,37) = 17.99	< .001
Task (left, right, parietal)	*F* (1,37) = 3.12	= .081
Task x Cau (left, middle)	*F* (2,36) = 15.2	< .001
Task (left, middle, frontal)	*F* (1,37) = 26.33	< .001
Task (left, middle, central)	*F* (1,37) = 19.62	< .001
Task (left, middle, parietal)	*F* (1,37) = 2.3	= .081
Task x Cau (right, left)	*F* (2,36) = 34.07	= .014
Task (right, left, frontal)	*F* (1,37) = 11.83	< .001

Task (right, left, central)	F (1,37) = 6.44	= .015
Task (right, left, parietal)	F (1,37) = 1.38	= .25
Task x Cau (right, right)	F (2,36) = 5.36	= .009
Task (right, right, frontal)	F (1,37) = 4.39	= .043
Task (right, right, central)	F (1,37) = 2.71	= .11
Task (right, right, parietal)	F (1,37) = 0.003	= .96
Task x Cau (right, middle)	F (2,36) = 21.25	< .001
Task (right, middle, frontal)	F (1,37) = 12.08	< .001
Task (right, middle, central)	F (1,37) = 7.37	= .01
Task (right, middle, parietal)	F (1,37) = 0.74	= .79
Lat x Cau (Go, left)	F (4,34) = 7.98	< .001
Lat (Go, left, frontal)	F (2,36) = 4.07	= .025
Lat (Go, left, central)	F (2,36) = 21.23	< .001
Lat (Go, left, parietal)	F (2,36) = 11.77	< .001
Lat x Cau (Go, right)	F (4,34) = 16.55	< .001
Lat (Go, right, frontal)	F (2,36) = 8.89	< .001
Lat (Go, right, central)	F (2,36) = 16.73	< .001
Lat (Go, right, parietal)	F (2,36) = 14.92	< .001
Lat x Cau (NoGo, left)	F (4,34) = 11.73	< .001
Lat (NoGo, left, frontal)	F (2,36) = 1.63	= .21
Lat (NoGo, left, central)	F (2,36) = 23.12	< .001
Lat (NoGo, left, parietal)	F (2,36) = 16.92	< .001
Lat x Cau (NoGo, right)	F (4,34) = 5.92	< .001
Lat (NoGo, right, frontal)	F (2,36) = 5.07	= .011
Lat (NoGo, right, central)	F (2,36) = 20.84	< .001
Lat (NoGo, right, parietal)	F (2,36) = 16.87	< .001
Cau (Go, left, left)	F (2, 36) = 38.06	< .001
Cau (Go, left, right)	F (2, 36) = 21.78	< .001
Cau (Go, left, midle)	F (2, 36) = 36.87	< .001
Cau (Go, right, left)	F (2, 36) = 48.50	< .001
Cau (Go, right, right)	F (2, 36) = 32.90	< .001
Cau (Go, right, middle)	F (2, 36) = 42.98	< .001
Cau (NoGo, left, left)	F (2, 36) = 14.68	< .001
Cau (NoGo, left, right)	F (2, 36) = 15.87	< .001
Cau (NoGo, left, midle)	F (2, 36) = 23.53	< .001
Cau (NoGo, right, left)	F (2, 36) = 22.26	< .001
Cau (NoGo, right, right)	F (2, 36) = 24.29	< .001
Cau (NoGo, right, middle)	F (2, 36) = 23.69	< .001
Group x Task x Stim x Cau x Lat	F (4,70) = 2.22	= .036
Group x Stim x Lat x Cau (Go)	F (8,70) = 7.66	= .63
Group x Stim x Lat x Cau (NoGo)	F (8,70) = 2.36	= .026
Group x Stim x Lat (NoGo, frontal)	F (4,74) = 3.53	= .011
Group x Stim (NoGo, frontal, left)	F (2,37) = 3.47	= .042
Group x Stim (NoGo, frontal, right)	F (2,37) = 0.74	= .48
Group x Stim (NoGo, frontal, middle)	F (2,37) = 1.18	= .32
Task x Stim x Lat x Cau (controls)	F (4,11) = 8.86	= .002

Task x Lat x Cau (controls, left)	F (4,11) = 11.28	= .001
Task x Lat x Cau (controls, right)	F (4,11) = 3.26	= .051
Lat x Cau (controls, left, Go)	F (4,11) = 6.32	= .007
Lat (controls, left, Go, central)	F (4,13) = 19.78	< .001
Lat (controls, left, Go, parietal)	F (4,13) = 4.8	= .028

Chapter III.

Response inhibition deficits among Bipolar I disorder and Schizophrenia: an ERP study

Introduction

Impulse control is a prominent characteristic of Bipolar disorder (BD) and may lead to problematic coping behaviors such as substance abuse or repetitive suicidal attempts (Chirstodoulou et al., 2006). Impulsivity has been conceptualized as being related to dysfunctional response inhibition by definition, impulsivity means having difficulties withholding inappropriate responses or making poor decision regardless of the outcome (Quraishi & Frangou, 2002; Strakowski et al., 2005; Roth et al., 2006). Neuropsychological studies suggest that, although response inhibition deficit is worse during the active affective state of illness in BD (Dixon et al., 2004; Murphy et al., 1999), such deficit persists across different phases of illness, including during the absence of mood symptoms (Bearden et al., 2001; Martinez-Arran et al., 2004; McClure et al., 2005; Olley et al., 2005; Roth et al., 2006; Strakowski et al., 2005). This suggests that BD's dysfunctional response inhibition is a trait rather than a state deficit (Bearden et al., 2001; Daban et al., 2006; Dixon et al., 2004) and therefore, may serve as an endophenotype of BD.

Behavioral data during Go/NoGo tasks, which assesses response inhibition, often shows normal accuracy, perceptual sensitivity, and reaction time in euthymic BD

compared to healthy controls (Altshuler et al., 2005; Kaladjian et al., 2009;; Roth et al., 2006), although other studies found lower accuracy in BD during reponse inhibition tasks including counting Stroop task (Langenecker et al., 2010; Strakowski et al., 2005). However, a number of neuroimaging studies using a variety of inhibition tasks (e.g., counting Stroop interference task, stop-signal task) have shown reduced brain activation in the following areas that have been associated with response inhibition in euthymic BD patients: left frontopolar cortex and bilateral dorsal amygdala (Kaladjian et al., 2009), right inferior and medial frontal gyri (Roth et al., 2006; Strakowski et al., 2005), orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Altshuler et al., 2005; Elliott et al., 2004). These findings provide evidence of reduced resources allocated toward the suppression context-inappropriate dominant responses in BD.

Response inhibition is a complex psychological construct, involving at least two distinct cognitive processes: response execution (Go trials) and response inhibition (NoGo trials). It is likely that these two processes may occur in serial within a very brief period of time or in parallel. For example, a number of authors suggest that response inhibition occurs within 600 ms after the onset of the stimulus (Kaladjian et al., 2009; Roth et al., 2006; Strakowski et al., 2005). Therefore, stages of cognitive processing involved in response inhibition may not be revealed by commonly used neuroimaging techniques such as fMRI because of its low temporal resolution. Therefore, ERPs may have an advantage over other neuroimaging studies to investigate the different cognitive stages in response inhibition because of its excellent temporal resolution. Specifically, in Go/NoGo paradigms, two ERP components, N200 (200-300 ms post-stimulus) and P300 (300–500 ms post-stimulus) have been consistently reported to be enhanced when

suppressing (NoGo task) than executing (Go task) a prepared response responses (Boruka et al., 2001; Kiefer et al., 1998; Nieuwenhuis et al., 2003; Lavric et al., 2004). Larger P300 amplitude for NoGo than Go suggests that more attentional resources are require for withholding than executing prepared responses.

Reduced P300 and prolonged P300 latency BD have been noted in a few ERP studies using simple auditory paradigms (i.e. oddball task; Hall et al., 2007; Degabriele and Lagopoulous, 2009), while intact P300 amplitude was reported in one study (Lahera et al., 2009). In addition to the inconsistent P300 findings in novelty detection in BD, ERP studies specific to response inhibition in BD are, to our knowledge non-existent, leaving it a question as to whether response inhibition deficits in BD are attributable to resource allocation deficits indexed by P300.

Another question is whether the neural mechanisms associated with the observed response inhibition deficits are similar in BD and SZ. As discussed in previous chapters, there is compelling neural evidence for response inhibition deficits in schizophrenia from previous studies (Hill and Weisbrod, 1999; Kiehl et al., 2002; Weisbrod et al., 1997, 2000). The results of Study 1 of this dissertation suggest that response inhibition deficits among schizophrenia patients lie in a failure to recruit attentional resources to inhibit inappropriate response.

This study explores the neural abnormalities that are associated with response deficits in BD and compare them with those found in SZ. Specifically, if neural responses in this Go/Nogo paradigm separate the three groups without overlap, it would support a nosological dichotomy (Bleuler, 1911; see Goodwin and Jamison, 2007 for review) rather than a spectrum (Benabarre et al., 2001; Berrettini, 2000; Crow et al., 1998; Cheniaux et

al., 2008; Szoke et al., 2008), thereby addressing the controversy over where to appropriopriately split the affective/psychotic disorders.

In summary, this study aims to explore the psychophysiological differences in response inhibition between SZ and BD. Behavioral (accuracy, reaction time) and psychophysiological responses (amplitudes and latencies of N200 and P300) during a Go/NoGo task with lateralized stimulus presentation (Eimer, 1993) were examined among three groups of participants: SZ, BD, and healthy controls (CT). Unlike traditional centralized stimulus presentation, lateralized presentation allows projection of stimuli to one hemisphere at a time, thus enabling the test of any lateralized ERP abnormalities in response inhibition. While a left response inhibition deficit has been reported in some schizophrenia studies (e.g., Hill & Weisbrod, 1999; Weisbrod et al., 2000 reported), data regarding lateralized deficits in response inhibition in BD, to our knowledge, is non-existent.

The hypotheses of this study are as follows:

(1) Response inhibition deficits, as indexed by reduced P300 and/or N200 amplitudes and delayed latencies, will be observed for NoGo trials in euthymic BD compared to CT. This would support the notion of previous studies that suggest response inhibition deficits are a stable and state-independent endophenotype of BD (Burdick et al., 2006; Dixon et al., 2004; Strakowski et al., 2005).

(2) SZ are expected to show reduced P300 amplitudes over frontal regions for NoGo trials relative to CT, replicating the finding of Study 1 and other previous studies (Kiehl et al., 2002 ; Rubia et al., 2001a ;Weisbrod et al., 1999, 2000).

(3) BD, SZ, and healthy controls (CT) would demonstrate different ERP patterns in this lateralized Go/NoGo task. In particular, ERP variables are expected to discriminate these three groups from one another, thus supporting the notion that BD and SZ are two distinct illness entities with differential neural mechanisms underlying their response inhibition deficits.

Method

Participants

Twenty individuals (women = 4) diagnosed with schizophrenia, twenty-five individuals (women = 14) diagnosed with bipolar I disorder, and twenty-seven individuals (women = 11) with no DSM-IV axis I diagnosis participated in this study. There were no group differences in age and parental education between the three groups. SZ and BD did not differ in the age of onset or in the number of hospitalization, and sex (Table 5). Individuals diagnosed with schizophrenia and bipolar I were recruited (1) among the outpatients treated in the Washtenaw County Community Support and Treatment Services clinics (WCCSTS, Ellsworth and Towner sites); (2) From the Adult Ambulatory Psychiatric clinics at Pretcher Bipolar Research Lab in the University of Michigan and (3) Community advertisements placed in the hospital, on campus, local newspapers, the Engage website of the UM, and the Internet (e.g., Google text ads, Facebook, Craigslist). The Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-I/P) was administered by a doctoral-level clinical psychologist or two graduate students trained in SCID administration (First et al., 1995) to assure schizophrenia diagnoses in the SZ group and no Axis I diagnosis in the CT group. Participants were

only included when both interviewers came to consensus on the diagnosis of all participants. All controls were phone screened before participation and only those who do not have history of mental disorders, seizures, head injuries, or learning, neurological, or medical disorders were invited for a SCID interview. After the SCID interview, those who were found to have no current or past DSM-IV Axis I psychiatric diagnosis proceeded to the physiological data recording session. Since the BD patients who participated in this study were also part of the genetic studies of UM Longitudinal Study of Bipolar disorder, the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) was administered, which is the standard in genetic research with compatibility to DSM-III-R. All DIGS interviews were completed by a medically trained interviewer who was either a junior psychiatrist or a research nurse trained extensively in psychiatric interviewing. All participants' primary language was English and their vision was normal or corrected-to-normal. To ensure that all participants were right-handed, the Edinburgh Handedness Inventory was administered. Consistent with University of Michigan Institutional Review Board approval, the details of the study was explained to all participants and written consent was obtained. Participants were compensated with $15 for each hour of participation.

	Bipolar I	Schizophrenia	Control	Group difference	*p*-value
Sex (M/F)	11/14	16/4	16/11	χ_2 =1.21 (BD - CT)	.27
				χ_2 = 2.27(SZ - CT)	.13
Age	45.28 (10.58)	43.75 (12.87)	37.22 (13.74)	$F_{(2,69)}$ = .26	.77
Parental Education	15.52 (2.92)	14.85 (3.57)	15.37 (3.13)	$F_{(2,69)}$ = 1.84	.16
Age of Onset	17.38 (8.88)	21.3 (7.10)	N/A	$F_{(1,44)}$ = 2.62	.12
Number of Hospitalization	2.84 (4.87)	6.0 (5.86)	N/A	$F_{(1,44)}$ = 2.49	.21

Table 5. Demographic data of bipolar I patients, schizophrenic patients and healthy controls

Procedure

Task: Lateralized Go/NoGo task

All participants completed four blocks of standard Go/NoGo task during the physiological recording. They were seated in a darkened room with 120 cm distance from the LCD monitor (60 Hz refresh rate). Participants performed four blocks of Go/NoGo task using computer keyboard. Two alphabet letters (M and W) served as Go and NoGo stimulus. Half of the participants were shown M as Go stimulus, while the other half of them were presented W as Go stimulus. The stimulus was presented for 150 ms either on the left or right side of the screen after 200 ms of pre-cue was presented. Between the actual stimulus and the pre cue, there was 700 ms interval. The maximum response time was 1750 ms. The pre-cue indicated to which side the letter would be presented. They were specifically asked to press the right/left shift keys for Go stimulus according to where the stimulus was presented and not to press any buttons when the NoGo stimulus was presented. All visual stimuli were created and presented via E-Prime software (Psychology Software Tools, Pittsburgh).

Physiological Recording and EEG data preprocessing

The electroencephalogram (EEG) was recorded from 32 electrodes using BrainCap MR-32 (Brain Products GmbH, Germany) designed for EEG data acquisition. The electrode positions included all standard positions of the International 10/20 system. Data from nine electrodes were further analyzed (F3, Fz, F3, C3, Cz, C4, P3, Pz, P4) in order to ascertain effects of Caudality (frontal, central and parietal) and Laterality (left, center, right). As N200 amplitude is maximal at the fronto-central regions of the scalp (Donkers & van Boxtel, 2004; Eimer, 1993; Jodo & Kayama, 1992), only these regions

(F3, Fz, F4, C3, Cz, and C4) are included in the N2 analyses. An electro-oculogram (EOG) electrode was placed beneath the left eye and at FP1 to monitor eye blinks. Common recording reference was FCz. Impedance for all electrodes was kept below 5 kΩ during the course of the study. During data acquisition, a high-pass filter was set for 0.01 Hz, while a low-pass filter was fixed at 30 Hz. Signals were digitally sampled at 512 Hz.

Vision Analyzer 1.05 (Brain Products GmbH, Germany) was used to analyze the EEG data. The EEG data were re-referenced to right mastoid (TP10) and left mastoid (TP9), re-sampled to 256 Hz. The continuous recording was divided into 1000ms segment for each trial, beginning 150ms before stimulus onset. Trials in which participants responded erroneously or over the inter-trial-interval (1000ms) were discarded. The EOG artifact was corrected via a regression-based algorithm described by Gratton et al. (1983) with EOG channel referenced to Fp1 lead. After baseline was corrected, any trials in which subjects responded outside the inter-trial-interval (1000ms) or containing over 80μV in amplitude were eliminated before averaging. Individual ERPs were obtained separately for each group: Stimulus type (Go-left, Go-right, NoGo-left, NoGo-right), Laterality (left, middle, right), Caudality (frontal, central, and parietal).

Data Analysis

All statistical analyses described below were performed using the SPSS software package (Version 17.0; SPSS Inc, Chicago, USA). Outliers were defined as data points that fell beyond two standard deviations and were eliminated before statistical analysis. Data from two participants (1 BD, 1 CT) was eliminated due to substantial, uncorrectable eye

movement artifact. In all statistical contrasts, including repeated-measure analysis of variance (ANOVAs), the Greenhouse - Geisser (CG) epsilon correction was applied to adjust the degree of freedom of the F-ratios. For the significant *F*- tests, Student-Newman Keuls post-hoc comparisons were applied in order to determine where the effect emerged ($\alpha < .05$).

Behavioral Analysis

Omission (OE) and commission error (CE) rates (i.e. no responses in Go trials and button presses in NoGo trials, respectively, divided by the number of trials) and reaction time (RT) for correct Go responses were analyzed. For RT, outliers (defined as responses that went beyond two standard deviations (SD)) were eliminated. Three-way repeated-measure ANOVAs were performed for accuracy rate, OE, and CE and varied with the types of task (Go/NoGo), stimulus presentation (left visual field presentation/right visual field presentation) as within-subject factors and group (BD/SZ/CT) as the between-subject factor. For the Go task, differences in RT in the three groups were analyzed in a Group × Stimulus ANOVA.

ERP analysis

In order to test whether P300 and N200 components were present in ERP data, components explaining most of the ERP variance in temporal domains were detected and quantified through temporal principal component analysis (tPCA). The main advantage of tPCA over visual inspection of ERPs based on temporal windows of interest is that it presents each ERP component separately with clean shape, extracting and quantifying it without being influenced by adjacent components (Chapman and McCrary, 1995; Coles

et al., 1986; Donchin and Heffley, 1978). In this study, tPCA was performed by computing the covariance between all ERP time points (-150ms – 1000ms), which resulted in a set of independent factors consisting highly covarying time points corresponding to ERP components. Temporal factor scores, the tPCA derived parameter where extracted temporal factors were quantified. Extracted components were submitted to Varimax rotation, which confirmed the presence of P300 and N200. The time window of P300 in the present dataset was identified between 300-500ms, while N200 time window was set between180 -280ms (Appendix I).

Consistent with previous studies (Boruka et al., 2003; Donkers & Van Boxtel, 2004; Kiehl et al., 2002; Weisbrod et al., 2000), the ERP data from nine electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4) were included in data analysis to investigate laterality (left, middle, and right) and caudality (frontal, central, and parietal) effects. Based on the temporal window identified by tPCA, mean amplitudes of P300 and N200 were obtained by averaging amplitudes within the temporal window of each ERP component. P300 and N200 latency data were obtained by 50 percent area latency measure, which was calculated but computing the area under each ERP waveform over a given temporal window identified by tPCA and then searching the time point (ms) which divides that area into 50 percent. This technique has been recently recommended (Luck, 2005) because of the following advantages over the simple peak latency measure: 50 percent area latency measure 1) is less sensitive to noise than is peak latency measure, 2) can detect timing of a component without any distinct peak or with multiple peaks, 3) it corresponds to grand average waveforms better than does simple peak latency measure.

In this present study, 50 percent latency was carried out using the MATLAB software (version 7.7; MathWorks Inc, Natick, USA) (Appendix 5).

For ERP data, a five-way ANOVA was performed for ERP amplitudes and latencies: Group × Laterality × Caudality × Task × Stimulus. Main effect simple effect ANOVAs and Newman-Keuls tests were performed as post hoc tests. In performing planned post-hoc contrasts using ANOVA was applied to break down the omnibus effect, interaction effect among variables was reported when its preceding higher-order interactions were also significant. For example, a 2-way interaction was only reported if the preceding 3-way interaction was also significant. Any interaction effect among variables was reported only when its preceding higher-order interactions were also significant. In terms of statistical power, high statistical power of 0.91 was expected for five-way interaction, Caudality (frontal, central, parietal) × Laterality (left, middle, right) × Task (go, NoGo) × Stimulus (LVF, RVF) × Group (bipolar I, schizophrenia, controls) with medium ANOVA effect size (f = .30 or η^2 = .08) under α = .05(Cohen, 1988).

Discriminant functional analysis (DA)

Discriminant functional analyses (DA) was performed to test whether the three groups could be discriminated based on the linear combination of ERP amplitudes or latencies, and also to determine which variables contribute to the separation. In order to achieve this aim, Wilk's Lambda smaller than .20 , Chi-square *p*-value less than .05, Eigen values larger or close to 1.0 were used as testing parameters (Norusis, 2008). In brief, Wilk's Lambda, which is the proportion of the total variance in the discriminant scores not explained by group difference was used to test the significance of the

discriminant function as a whole, becomes smaller for a function that is more important than the other. Chi-square and its *p*-value test the null hypothesis that there is no mean group difference in population for any discriminant functions (Huberty, 1984).

Descriptive and predictive functions were considered in interpreting the results of the DA. The focus of descriptive discriminant analysis (DDA) was to interpret the linear combination of the variables associated with group difference (Thompson, 1998), while predictive discriminant analysis (PDA) focuses more on allocating new cases to previously defined groups (Huberty & Lowman, 2000). Since the specific aim of DA for the present study was to find variables (behavioral and/or ERPs) that separates the three groups, DDA was considered to be more useful than PDA. Although predicting the diagnostic groups (bipolar I, schizophrenia, and healthy controls) based on each participant's task performance and/or physiological responses was not the main focus of the present DA, classification accuracy (CA) was also reported to estimate how well the three groups were separated. Leave-one-out classification method (LOOC), where the classification rule is determined from one set of samples and then used to classify another set of sample was not applied because of the relatively small sample size (< 30) in each group (Hwang, 2001; Norusis, 2008). Thus, structure matrices presenting the weights of each variable on each discriminant function and classification accuracy rate were reported in result section.

Result

1. Behavioral Data

1-1. Accuracy

All three groups demonstrated high accuracy rate for both Go (BD: 99.15%, SZ: 98.4%, Control: 99.1%) and NoGo (BD: 97%, SZ: 97%, CT: 97.54%) trials. The effect of stimulus presentation differed in number of omission error (OE) and commission error (CE), Task × Stimulus, $F(1,67) = 22.11$, $p < .001$. For Go stimulus, participants made more OE when the stimulus was presented to RVF than to LVF, Stimulus, $F(1,67) = 7.52$, $p = .008$, while they made more CE for the NoGo stimulus presented to LVF than to RVF, $F(1,67) = 12.17$, $p = .001$. Among the three groups, it was only BD that was less accurate when the stimulus was presented to the left visual field (LVF) than to the right visual field (RVF), Stimulus × Group, $F(2,67 = 3.84$, $p < .05$, LVF = 3.04 ± 3.87, RVF = 2.20 ± 3.12. No main effect of task, stimulus presentation, and group was found.

1-2. Reaction Time (RT)

Reaction time was obtained from correct Go trials. As expected, SZ showed the longest RT with BD in the middle and CT in order, Group, $F(2,67) = 18.45$, $p < .001$, SZ = 439.77 ± 132.31 ms, BD = 352.16 ± 79.83 ms, CT = 270.16 ± 68.87 ms. Post-hoc test revealed that SZ showed longer latency than BD ($p < .05$) and CT ($p < .01$). Longer RT was observed when the stimulus was presented to LVF than to RVF, Stimulus, $F(1,63) = 22.72$, $p < .001$, LVF = 353.65 ± 114.37 ms, RVF = 337.31 ± 112.95 ms. There was no interaction effect between Stimulus and Group.

2. ERP Data

2-1. P300 Amplitude

As predicted, P300 amplitude was larger for NoGo task than for Go task, Task, F (1,66) = 45.04, p <.001, NoGo = 2.83 ± 2.66 μV, Go = 4.81 ± 3.71 μV. Consistent with the hypothesis, SZ demonstrated the smallest P300 amplitude for NoGo task over the frontal region when the stimulus was presented to RVF, Caudality × Stimulus × Task × Group, F (2,66) = 2.31, p = .056, SZ = .67 ± 3.02 μV, CT = 2.49 ± 4.77 μV, BD = 3.76 ± 3.61 μV. Dissecting this four-way interaction resulted in a series of significant interactions including Stimulus × Task × Group only over the frontal region, F (2,66) = 2.79, p = .056. Over the frontal region, Stimulus × Group was significant only for NoGo task, F (2,66) = 6.05, p < .01. The three groups differed specifically in NoGo task that was presented to RVF, Group, F (2,66) = 2.89, p = .05. Post-hoc test revealed that the interaction effect emerged from the amplitude difference between SZ and of BD (p <.05), while marginally significant with that in CT (p < .10).

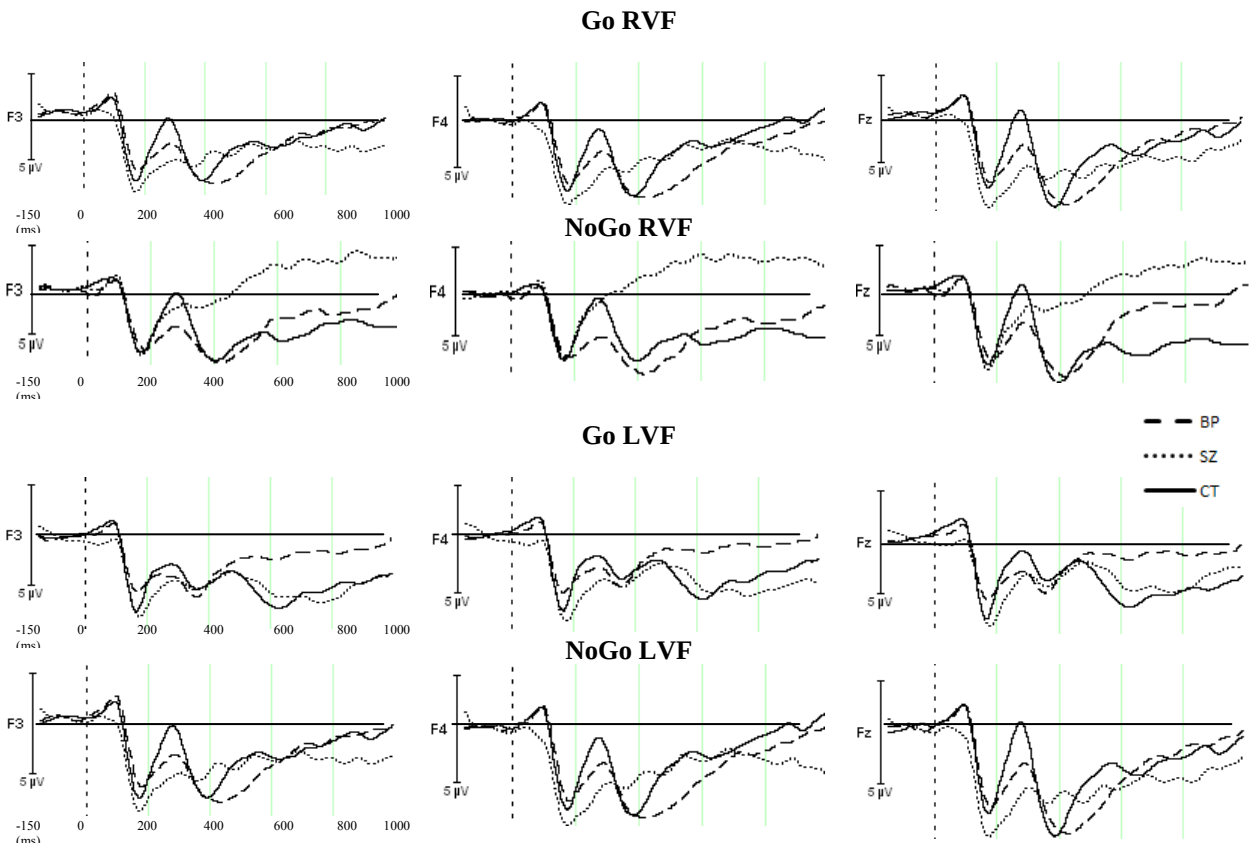


Figure 5-a. Grand average waveforms over frontal region with right visual field (RVF) and left visual field (RVF) presentation. In each waveform, positive polarity (0 – 2.5 µV) was down and negative polarity was up (-2.5 – 0 µV).

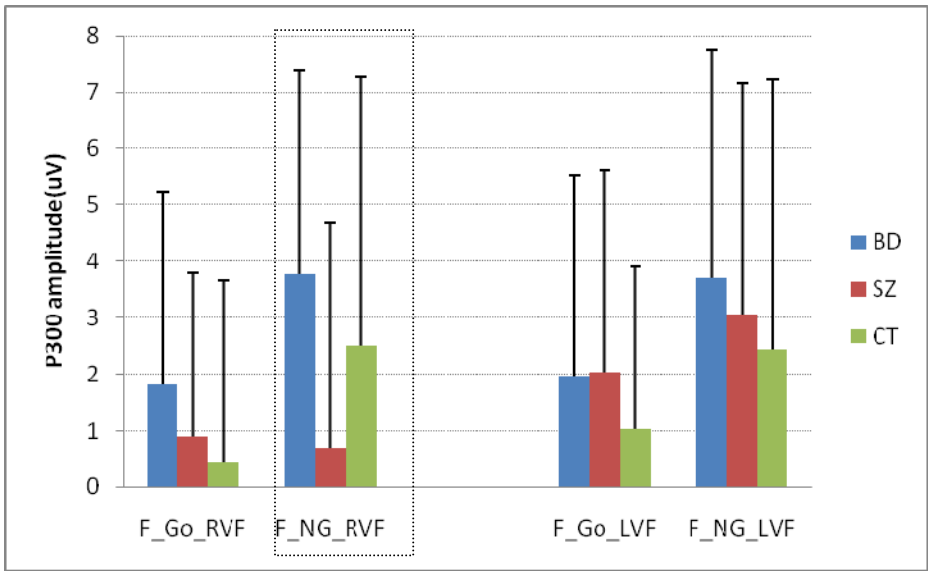


Figure 5-b. P300 mean amplitude over frontal region among bipolar group (BD), schizophrenic group (SZ), and control (CT) (F: frontal, G: Go, NG: NoGo, RVF: Right visual field stimulus presentation, LVF: left visual field presentation) Error bars are presented.

2-2. P300 Latency

As predicted, longer P300 latency for NoGo task than for Go task was observed (F (1,65) = 42.89, $p < .001$). Bipolar showed the longest P300 latency for NoGo task among the three groups, Task × Group (F (2,65) = 3.82, $p < .03$, BD = 426.76 ± 30.03 ms, SZ = 410.0 ± 35.29 ms, CT = 399.55 ± 33.65 ms). Post-hoc tests suggested that the interaction effect was due to the difference between BD and CT ($p < .05$). BD was delayed P300 latency for NoGo stimulus compared to the other two groups only at the parietal sites, Group × Task × Caudality (F(2.78, 9.04) = 3.46, $p < .02$, BD = 431.24 ± 21.40 ms, SZ = 413.26 ± 41.39 ms, CT = 397.08 ± 33.46 ms). Post-hoc test revealed there were differences between BD and CT ($p < .05$) (Figure 6-a, b). Different from expectation, there was no stimulus presentation main effect or its related interaction effect.

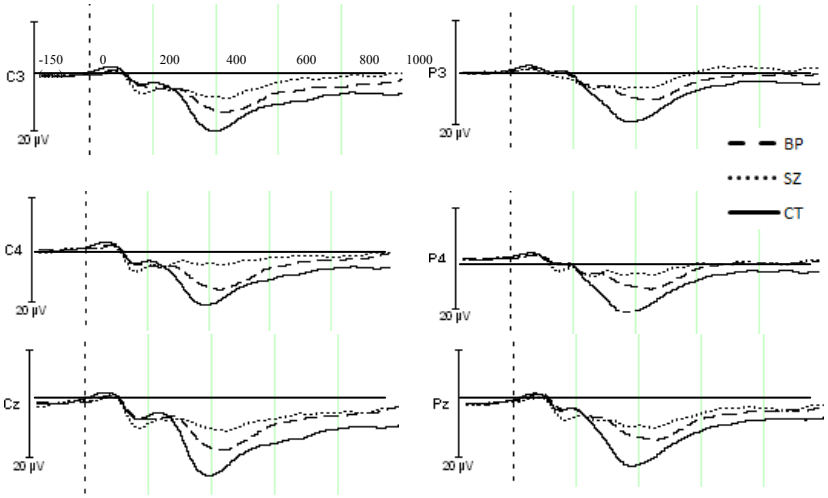


Figure 6-a. ERP grand average waveforms for NoGo Right visual field (RVF) stimulus presentation. In each waveform, positive polarity (0 - 10 μV) was down and negative polarity was up (-10 – 0 μV).

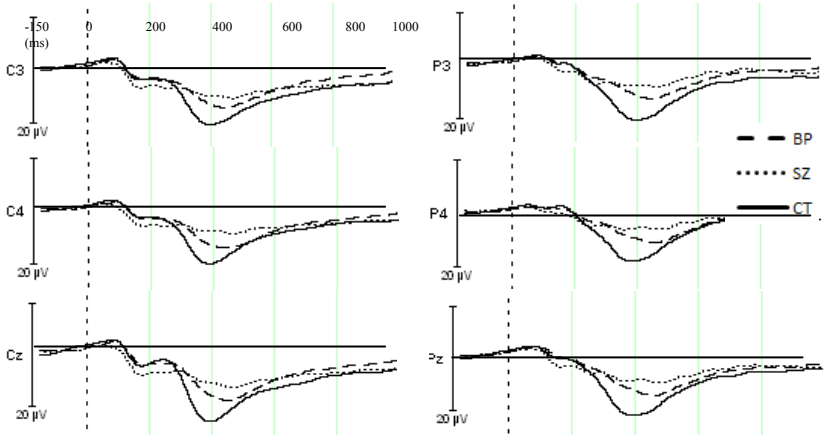


Figure 6-b. ERP waveforms for NoGo Right visual field (LVF) stimulus presentation. In each waveform, positive polarity (0 - 10 μV) was down and negative polarity was up (-10 – 0 μV). Each waveform was presented with -200 – 1000(ms) based on the onset of stimulus.

2-3. N200 Amplitude

The mean amplitude of N200 amplitude (180-280 ms) obtained from six fronto-central electrodes (F3, F4, Fz, C3, C4, Cz) were included for data analysis. N200 amplitude negativity was larger over the frontal region compared to central region, Caudality, F (1,66) = 7.54, $p < .01$, Frontal = .66 ± 3.07 μV , Central = 1.29 ± 2.74 μV.

N200 amplitude for NoGo was the larger in CT over the frontal region compared to the patient groups, Group × Caudality × Task, F (2,66) = 2.54, p = .05, CT = -.74 ± 1.27 μV, SZ = 1.45 ± 1.87 μV, BD = 1.57 ± 1.41 μV (Figure 2-b). Post-hoc test further revealed that the effect emerged from CT's large N200 amplitude compared to SZ (p < .05) and BD (p < .05). BD and SZ did not show N200 amplitude differences. Contrary to our expectation, no task main effect was observed.

2-4. N200 Latency

The three groups differed in N200 latency over the right-central site (C4), specifically when the stimulus was presented to RVF, Laterality × Caudality × Stimulus × Group (F (3.66, 120.78) = 2.56, p < .05). As expected, SZ showed longer N200 latency for RVF stimulus presentation over the right central site (C4) than CT, but did not differ from BD, Group, F (2,67) = 3.57, p < .05, SZ = 257.68 ± 24.59 ms, BD = 249.44 ± 29.50 ms, CT = 237.08 ± 23.67 ms. Post-hoc test further revealed that the interaction effect emerged from the difference between SZ and CT (p <.05), indicating that SZ was slower than control by approximately 20 ms in evaluating NoGo stimuli when the stimulus was presented to RVF.

3. Discriminant Functional Analysis (DA)

3-1. P300

Discriminant Function analysis (DA) was performed in order to test whether the P300 amplitude could separate SZ, BD, and CT. With thirty six variables (Laterality × Caudality × Stimulus × Task; 3 × 3 × 2 × 2), P300 amplitude identified the group membership with 94.2% accuracy (Wilk's Lambda = .106, p = .003). Two BD patients

were grouped incorrectly, one as a schizophrenic and the other as a control. One schizophrenic patient was placed in control group, while another patient was grouped as bipolar. There were two control cases that were not classified in any groups. Function I mainly consisted of Go P300 amplitudes, while Function II consisted of NoGo P300 amplitudes (Table 2). Frontal P300 amplitudes showed different signs in correlation coefficient with Function I, which indicated that large amplitudes in centro-parietal region and small amplitudes over frontal region separated control group from the two patient groups while Function II discriminated schizophrenic group from bipolar group (Figure 7). DA based on P300 latency failed to provide a model to classify the three groups (Wilk's Lambda = .17, p = .14) . DA for P300 latency was not valid to discriminate the group membership (Wilk's Lambda = .31 , p = .18).

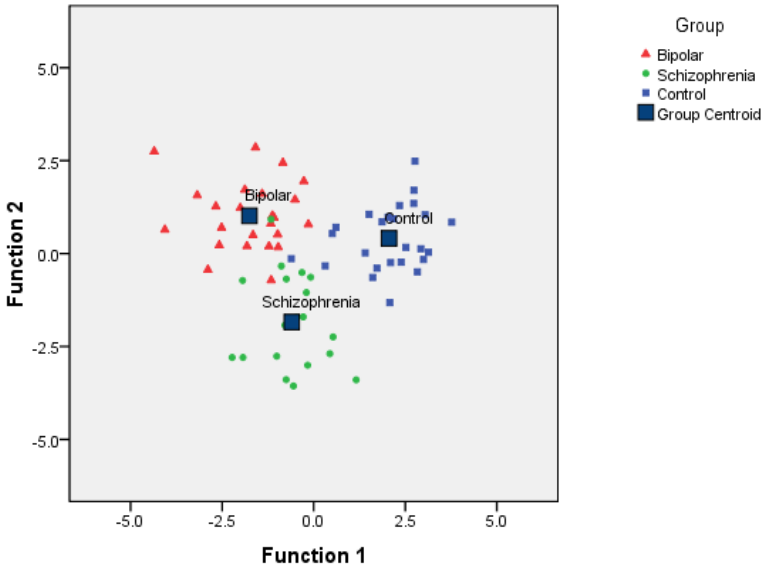


Figure 7. Discriminant Analysis for P300 amplitude. Function I group centroid score: SZ (-.59), BD (-1.75), CR (2.06). Function II group centroid score: SZ (-1.84), BD (1.02), CT (.41).

3-2. N200

Discriminant Function analysis (DA) was applied to test whether the N200 latency classified SZ, BD, and CT. With twenty four variables (laterality × caudality × stimulus× task; 3 × 2 × 2 × 2), N200 latency classified the group membership with 77% accuracy (Wilk's Lambda = .29, p = .03). Based on N200 latency, two bipolar patients were placed in schizophrenic group, one as CT, while one schizophrenic patient was placed in BD, while four of them grouped as CT. Two controls were not classified in any groups. Function I consisted of Go RVF N200 latency, while Function II consisted of NoGo N200 latency. Function I discriminated SZ from CT and BD, while Function II separated BD from CT (Table 3, Figure 8). DA for N200 amplitude was not valid (Wilk's Lambda= .42, p = .66).

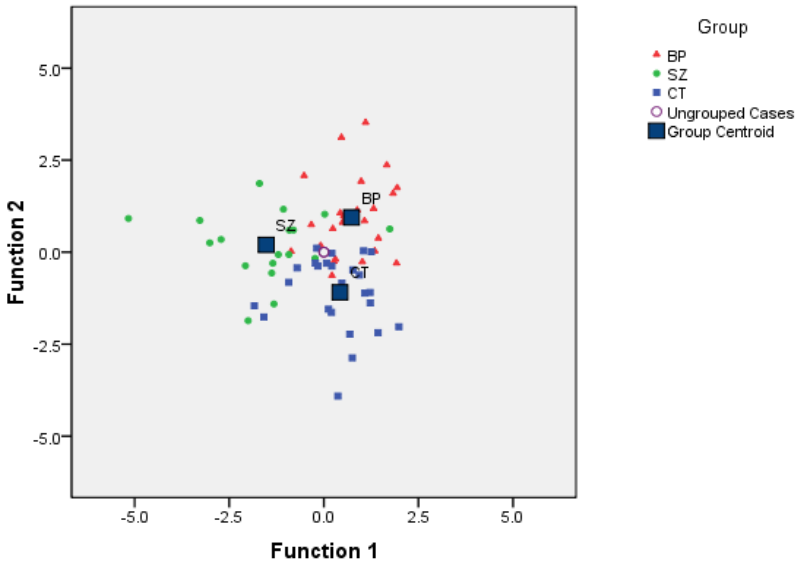


Figure 8. Discriminant Analysis for N200 latency. Function I group centroid score: SZ (-1.52), BD (.73), CR (.42). Function II group centroid score: SZ (.196), BD (.94), CT (-1.09).

Discussion

This study investigated response inhibition deficit in SZ and BD with lateralized Go/NoGo paradigm. It is the first ERP study to directly compare response inhibition of BD with that in SZ. As predicted, SZ showed reduced P300 amplitude for NoGo task over the frontal region specifically when the stimulus was presented to the right visual field. Furthermore, reduced NoGo P300 amplitude was found only when the stimulus was presented to the right visual field (RVF) and projected to the left hemisphere suggesting that SZ had difficulty in recruiting attentional resources from the left hemisphere needed to suppress prepotent responses. Findings from discriminant functional analysis further supported that NoGo P300 amplitude with RVF stimulus presentation successfully discriminated SZ from the other two groups (Table 2).

Intriguingly, BD showed larger frontal NoGo P300 amplitude compared to that of SZ and even that of CT when the stimulus was presented to RVF, which indicated that BD did not have difficulty in this task recruiting resources from left hemisphere. The findings are inconsistent with the previous neuroimaging studies, where reduced activation over the frontal region was found. However, counting Stroop tasks (Roth et al., 2006 ; Strakowski et al., 2005) measured cognitive resistance to interference along with motor response inhibition by adding the 'ignore' piece to inhibition process, which may increase cognitive burden for BD. NoGo P300 amplitude highlighted SZ's neural deficit in response inhibition is differentiated from BD, combined with the findings that the three groups did not differ in overall accuracy. Further, replicated findings in successful discrimination of SZ based on P300 for NoGo trials added to the literature that neural

deficits in response inhibition may become a candidate of endophenotype for schizophrenia.

Although NoGo P300 amplitude showed that BD have the cognitive resources available for inhibiting motor responses, their longer overall P300 latency than CT and SZ, indicated deficits in cognitive speed in stimulus evaluation among BD. In addition, our findings that BD's prolonged latency was not modulated by task suggested that delay cognitive evaluation in BD may be more general deficits in classifying stimuli rather than specific to response inhibition. This view can be supported by the consistent findings from the previous studies that reported BD's prolonged P300 latency for oddball stimuli that do not require cognitive inhibition. These findings suggest that P300 latency may become a candidate for BD's endophenotype if the findings can be further replicated.

Further, concerns often arise in psychophysiological research regarding medication effects on ERPs. Even though medication was not experimentally controlled, it is noteworthy that the largest P300 NoGo amplitude was in BD even though all BD patients were taking psychotropic medication (46.1 % on antidepressants, 57.7% on mood stabilizers and 19.2% on antipsychotics, 38.5% were on multiple medications). Therefore, the typically found reduced P300 amongst psychiatric patients is unlikely due to simple medication effects.

In contrast to the results of previous chapter that reported lateralized inhibition deficit in SZ (Bellgrove et al., 2005; Kaladjian et al., 2007; Rubia et al., 2001a; Weisbrod et al., 1997, 2000), the findings were not replicated here. This failure to replicate may be due to the horizontal eye movement between the pre-cue stimulus and the letter stimulus in this lateralized Go/NoGo paradigm. As seen in Figure 5 (solid lines), horizontal eye

movement occurred before the off set of pre-cue stimulus (-900 – -700 ms) and continued until the onset of the actual stimulus, which propagated on frontal left (F3) and frontal right (F4). Such lateral eye movement between the pre-cue and actual stimulus can be problematic in two ways. First, the stimulus would be presented directly to the central foveal region instead of lateral visual field. This could weaken the association between left hemispheric dysfunction in SZ and response inhibition deficits such that NoGo stimulus presented to the right-side of the screen may not have correctly projected to left hemisphere through right visual field. Further, failure in presenting the stimuli on the lateral visual field in this study may have caused lateralized EEG activity in this study. Although regression-based ocular correction was applied (dashed lines in Figure 9-a) with F7 as HEOG channel and F8 as its reference channel, those two channels were also sensitive to the brain activity. Furthermore, it was not clearly monitored whether participants moved their eyes back to the central fixation point after stimulus onset. If there was a significant group difference in post-stimulus eye movement, then there could be differences in post-stimulus ERP activities related to the eye movement, which may have been subtracted or added to during the horizontal eye movement correction (Figure 9-b). Thus, in the future studies, more attention needs to be paid to control horizontal eye movement in order to obtain clear laterality effect. As Eimer (1993) suggested, having a practice block to train participants to keep their eyes in the middle of the screen during the task would improve the quality of lateralized ERPs.

As expected, frontal N200 amplitude for NoGo was attenuated in both SZ and BD compared to CT, indicating an early deficit in the inhibition process among patients . Given the controversy in the nature of NoGo N200 (see Folstein & van Patten, 2008 for

review), patients' attenuated NoGo N200 amplitude may also reflect their deficit in conflict monitoring between the execution and the inhibition processes (Donkers & van Boxtel., 2004; Nieuwenhuis & Yeung, 2003) not just inhibition process itself. In this study, N200 amplitude for Go task did not differ for the three groups which supported the view that patients groups can recruit cognitive resources to execute responses and therefore they had deficits specific to response inhibition. However, according to the proponents of conflict monitoring, it could be due to the low-frequency of NoGo stimulus (30%) not because of the nature of NoGo stimulus (generating inhibition). Therefore, obtaining N200 amplitudes from equiprobable Go/NoGo task would be beneficial to clarify patients' early deficit in NoGo N200, since NoGo N200 amplitude would be enhanced than Go amplitude if NoGo N200 specifically reflects inhibition process.

In conclusion, this study suggests that neural response inhibition deficits in SZ are associated with processing stimulus projected to the frontal left hemisphere. This was not found in BD. Current findings of delayed P300 latency in BD supported the previous findings that P300 latency could become a biological marker of bipolar disorder. Further, as indicated by a 98% overall accuracy rate, it was speculated that the Go/NoGo task in this study may not have been challenging enough to capture response inhibition deficits in BD that have previously been noted in neuropsychological studies (Burdick et al., 2006; Daban et al., 2006). Given the prolonged latency in BD, tasks with greater time pressure may reveal BD's dysfunctional neural responses associated with response inhibition.

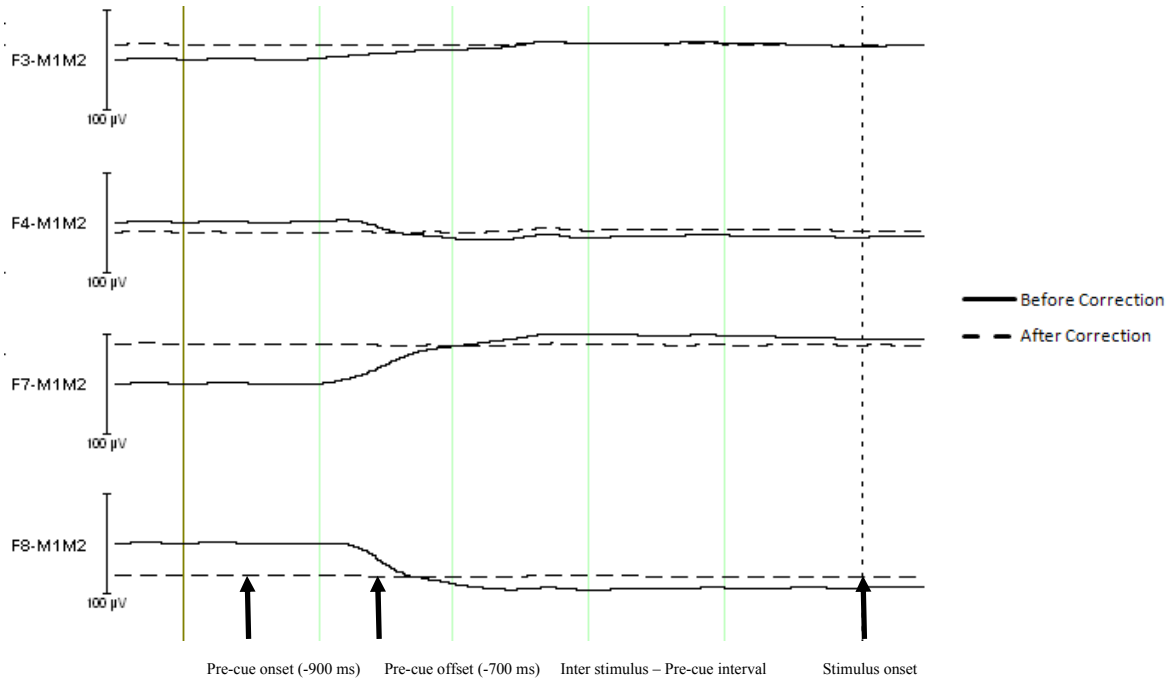


Figure 9-a. Grand average of horizontal eye movements between the onset of the precue and the onset of the stimulus. Gratton & Coles ocular correction algorithm was applied with F7 as HEOG channel and F8 was its reference channel.

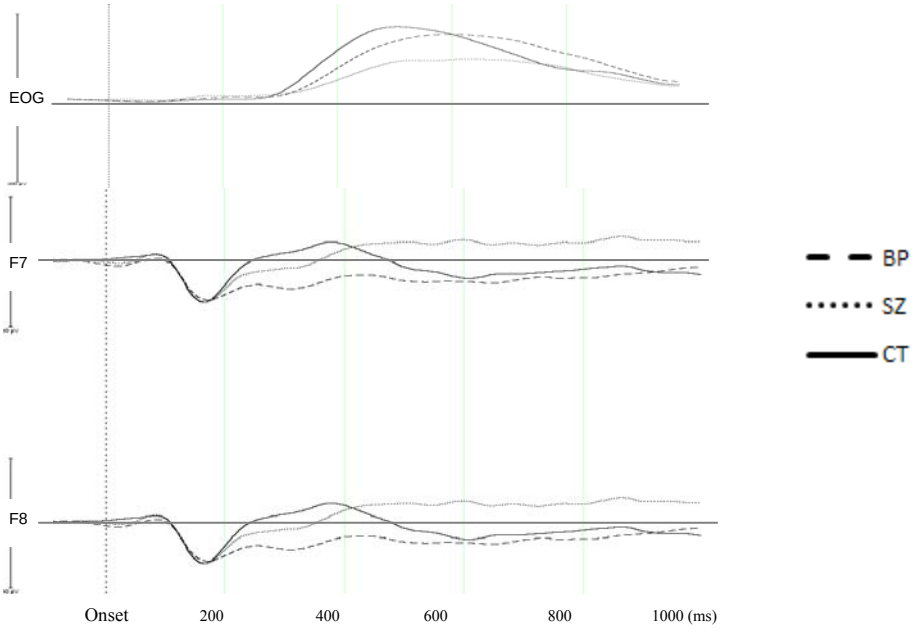
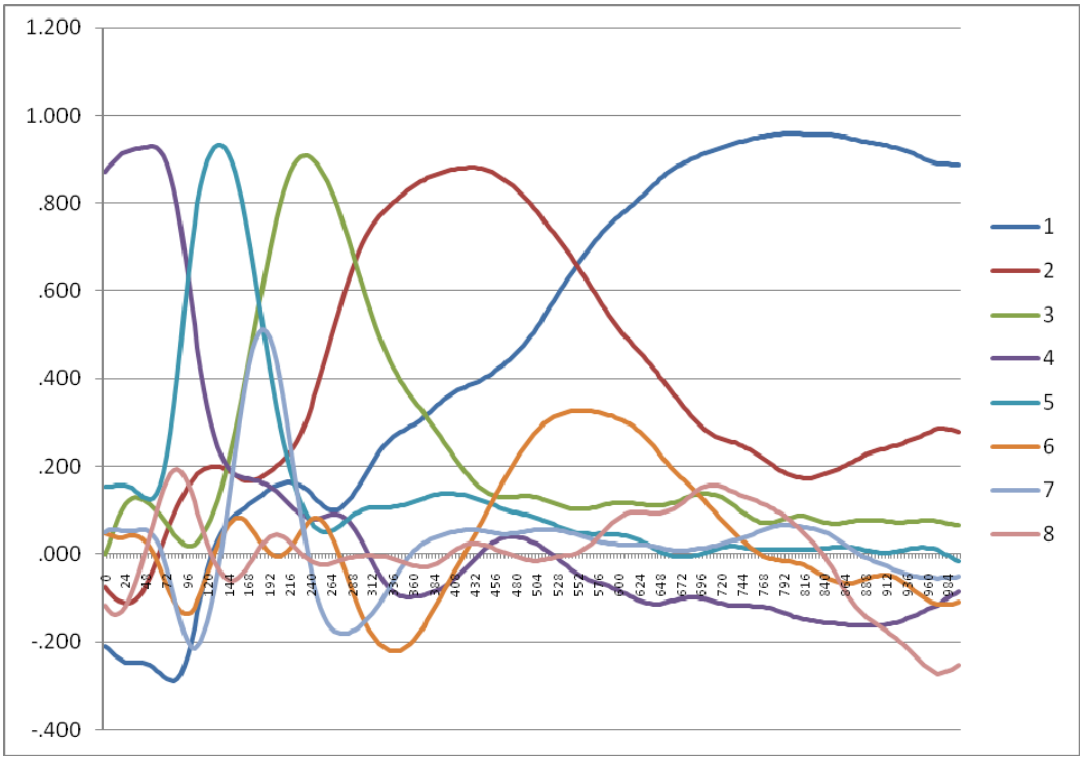


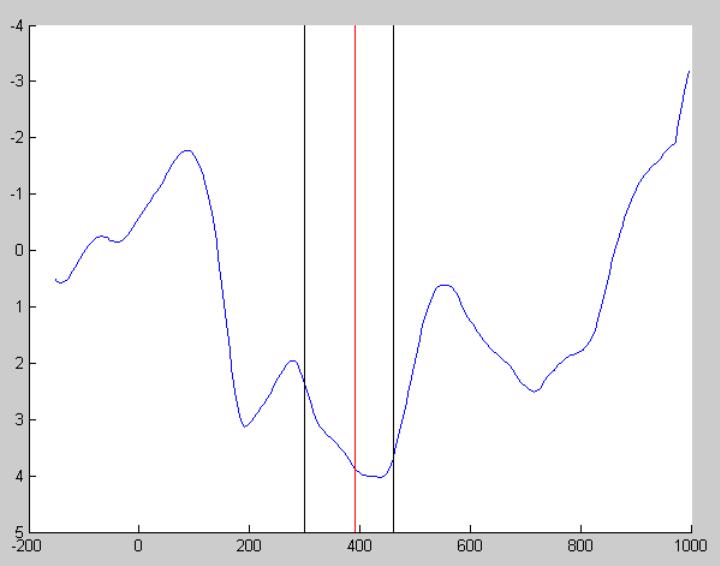
Figure 9-b. Grand average of eye movements after the onset of the stimulus (-150ms – 1000ms) on VEOG and HEOG (F7, F8) channels. Gratton & Coles ocular correction algorithm was applied with F7 as HEOG channel and F8 was its reference channel, while EOG was used as VEOG channel and Fp1 was its reference.

Chapter III. APPENDICES

Appendix 4. Temporal principal component analysis (tPCA) with eight temporal factors. P300 time window was identified between 300 – 500ms and 180 – 280ms for N200 component



Appendix 5. An example of 50 percent latency measure in MATLAB. In this example, 396 ms was identified as 50 percent latency of P300 amplitude on F3.



Appendix 6. Main effects and interaction effects for repeated measure ANOVA for P300 amplitude (NS: *p*-value > .10)

Main effect and interaction effect	F (df1, df2)	*p*-value
Caudality	$F_{(1.49,98.22)} = 42.67$	$p < .001$
Central (mean = 4.77 μV, SD = 3.71 μV)		
Parietal (mean = 4.65 μV, SD = 3.06 μV)		
Frontal (mean = 2.04 μV, SD = 3.44 μV)		
Stimulus	$F_{(1,66)} = 8.29$	$p < .01$
Right visual field (RVF) (mean = 3.60 μV, SD = 2.99 μV)		
Left visual field (LVF) (mean = 4.04 μV, SD = 3.17 μV).		
Task × Group	$F_{(2,66)} = 2.60$	$p < .10$
Go (Group)	NS	NS
NoGo (Group)	$F_{(2.84,93.6)} = 4.39$	$p < .01$
SZ (mean = 3.29 μV, SD = 3.46 μV)		
BD (mean= 5.10 μV, SD = 3.03 μV)		
CT (mean = 5.66 μV, SD = 4.22 μV)		
Laterality × Stimulus × Group	$F_{(2.88,95.11)} = 2.38$	$p < .10$
Left-sites (Stimulus × Group)	NS	NS
Right-sites (Stimulus × Group)	$F_{(2,66)} = 6.12$	$p < .01$
Right-sites RVF (Group)	$F_{(2,66)} = 4.29$	$p < .05$
SZ (mean = 4.20 μV, SD = 2.72 μV)		
BD (mean= 1.86 μV, SD = 3.15 μV)		
CT (mean = 4.39μV, SD = 3.39 μV)		
Right-sites LVF (Group)	NS	NS
Midline (Stimulus × Group)	NS	NS
Caudality × Laterality × Stimulus × Task	$F_{(2,66)} = 2.31$	$p = .056$
Frontal (Laterality × Stimulus× Task)	$F_{(1.70,112.24)} = 15.25$	$p < .001$
Frontal, Go task (Laterality × Stimulus)	$F_{(1.77,118.8)} = 13.11$	$p < .001$
Frontal-left (F3) Go (Stimulus)	$F_{(1.77,118.80)} = 13.11$	$p < .001$
RVF (mean = .92 μV, SD = 2.93 μV)		
LVF (mean = 1.93 μV, SD = 3.28 μV)		
Frontal-right (F4) (Stimulus)	NS	NS
Frontal-midline (Fz) (Stimulus)	$F_{(1,67)} = 4.82$,	$p < .05$
RVF (mean = .93 μV, SD = 3.50 μV)		
LVF (mean = 1.51 μV, SD = 3.49 μV)		
Frontal, NoGo task (Laterality × Stimulus)	$F_{(1.77,117.29)} = 2.90$	$p = .065$
Frontal-left (F3) (Stimulus)	NS	NS
Frontal-right (F4) (Stimulus)	$F_{(1,66)} = 7.14$	$p < .01$
Frontal-midline (Fz) (Stimulus)	$F_{(1,67)} = 7.10$,	$p = .01$
Central (Laterality × Stimulus× Task)	$F_{(1.45,97.19)} = 42.13$	$p < .001$
Central, Go task (Laterality × Stimulus)	$F_{(1.30,87.34)} = 48.48$	$p < .001$
Central-left (C3) Go (Stimulus)	$F_{(1,67)} = 41.49$	$p < .001$
RVF (mean = 2.14 μV, SD = 3.10 μV)		
LVF (mean = 3.89 μV, SD = 3.45 μV)		
Central-right (C4) Go (Stimulus)	$F_{(1,67)} = 12.24$	$p = .001$
RVF (mean = 3.88 μV, SD = 3.60 μV)		
LVF (mean = 2.73 μV, SD = 3.28 μV)		
Central-midline (Cz) Go (Stimulus)	NS	NS

Appendix 7. Main effects and interaction effects for repeated measure ANOVA for N200 latency (NS: *p*-value > .10)

Main effect and interaction effect	$F_{(df1, df2)}$	*p*-value
Caudality	$F_{(1,66)} = 37.15$	$p < .001$
Frontal (mean=261.36 ms, SD = 20.66 ms)		
Central (mean=249.54 ms, SD = 24.64 ms)		
Laterality × Stimulus	$F_{(1.98,130.87)} = 2.68$	$p = .069$
Right visual field (RVF) (Laterality)	$F_{(1.89,124.73)} = 4.66$	$p < .05$
Right-site (mean=253.07 ms, SD=23.93 ms)		
Left-site (mean= 254.87 ms, SD = 22.36 ms)		
Midline (mean = 257.72ms, SD = 23.37ms)		
Left visual field (LVF) (Laterality)	NS	NS
Laterality ×Caudality × Task × Stimulus	$F_{(1.58,104.38)} = 2.8$	$p = .068$
Frontal (Laterality × Task × Stimulus)	NS	NS
Central (Laterality × Task × Stimulus)	$F_{(1.78,119.63)} = 3.26$	$p < .05$
Central Go task (Laterality × Stimulus)	$F_{(1.97,136.3)} = 5.37$	$p < .05$
RVF (Laterality)	$F_{(1.78,123.39)} = 4.04$	$p < .05$
Right-site (mean=245.71ms, SD=30.48 ms)		
Left-site (mean=251.86ms, SD=32.38ms)		
Midline (mean =252.91ms, SD=32.11ms)		
LVF (Latearlity)	NS	NS
Central NoGo task (Laterality × Stimulus)	NS	NS

Appendix 8. P300 mean amplitude Discriminant functional analysis Structural matrix.

Function I.		Function II.	
variable	correlation coefficient	variable	correlation coefficient
P3 Go LVF	.231	C4 NoGo RVF	.303
P4 Go LVF	.200	P4 NoGo RVF	.295
Pz Go LVF	.191	F4 NoGo RVF	.287
P3 Go RVF	.191	P3 NoGo RVF	.228
Pz Go RVF	. 168	Pz NoGo RVF	.223
F3 Go RVF	-.114	P4 NoGo LVF	.216
Fz Go RVF	-.098	Cz NoGo RVF	.214
C3 Go LVF	.094	C4 Go RVF	.208
C4 Go LVF	.091	Fz NoGo RVF	.207
Fz Go LVF	-.085	F3 NoGo RVF	.195
Cz Go LVF	.081	P4 Go RVF	.194
F3 Go LVF	-.080	Pz NoGo LVF	.182
F3 NoGo LVF	-.076	P3 NoGo LVF	.175
Fz NoGo LVF	-. 071	C3 NoGo RVF	.175
F4 Go LVF	-. 071	C4 NoGo LVF	.166
F4 NoGo LVF	- .067	Cz NoGo LVF	.126

Appendix 9. N200 latency Discriminant Functional Analysis Structural matrix

Fucntion I.		Function II.	
variable	correlation coefficient	variable	correlation coefficient
C4 Go RVF	-. 292	C4 NoGo RVF	. 305
Cz Go RVF	-. 248	C4 Go LVF	. 301
C3 Go RVF	-. 157	C4 NoGo LVF	. 273
F4 Go LVF	-. 154	C3 NoGo RVF	. 268
F4 Go RVF	-. 148	C3 NoGo LVF	. 262
F3 NoGo RVF	-. 106	Cz NoGo RVF	. 236
Fz Go RVF	-. 085	Cz NoGo LVF	. 224
F3 Go LVF	-. 082	C3 Go LVF	. 221
Fz NoGo LVF	. 061	F3 NoGo LVF	-.204
		Cz Go LVF	. 197
		F3 Go RVF	-185
		Fz Go LVF	. 106
		F4 NoGo RVf	. 091
		F4 NoGo LVF	. 063
		Fz NoGo RVF	-.018

Chapter IV.

Emotion modulation in response inhibition in schizophrenia and bipolar I disorder: an ERP study

Introduction

Selecting context-appropriate responses and, at the same time, inhibiting competing context-inappropriate responses, is critical to adaptation to the environment (Schulz et al., 2009). For humans, the demand for appropriate response selection and inhibition often occurs in the social context, particularly in social situations that involve emotions (e.g., suppressing inappropriate sexual behavior when an attractive member of the opposite sex is smiling at you). Given the close relationship between successful social adaptation and response inhibition in the face of emotional stimuli, the investigation of emotion modulation in response inhibition in SZ and BD may provide insight into the prevalent, maladaptive behaviors (e.g., substance abuse, social withdrawal, suicidality) that may stem from response inhibition deficits.

Recent studies have provided evidence that emotional cues, including emotional faces, modulate response inhibition (Hare et al., 2005; Schulz et al., 2007, 2009). For example, compared to neutral stimuli, exposure to positive stimuli (e.g. happy faces, positive words) facilitates 'approach' behaviors in research participants, making it more difficult for them to inhibit task-inappropriate behavior (Albert et al., 2010; Johansson &

Ronnberg, 1996; Schulz et al., 2009). This positive bias illustrates how emotion may interrupt ongoing cognitive process by competing for attentional resources with the ongoing task demands (Pessoa, 2009; Verbruggen & De Houwer, 2007). Researchers have also used affective versions of the Go/NoGo task to assess how emotion influences response inhibition in healthy individuals, such as those with affective words (Chiu et al., 2008), facial emotions (Luo et al, 2010; Wessa et al., 2007; Schulz et al., 2009), or emotion-provoking images (e.g., car accident; Albert et al., 2010). However, findings have been inconsistent. In some studies, emotional stimuli generated larger NoGo P300 amplitudes relative to the neutral faces (Albert et al., 2010), greater activation over the frontal cortical regions including dorso-lateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and inferior frontal gyrus (IFG) (Elliot et al., 2000; Hare et al., 2008; Schulz et al., 2009), indicating that inhibiting affective stimulus requires larger amount of attentional resources than inhibiting non-affective stimulus. In other studies, however, affective stimuli elicited larger N200 and P300 amplitudes only for Go trials (response execution) but not for NoGo trials (response inhibition) (Chiu et al., 2008). These findings, taken together, suggest that emotion modulates response inhibition in healthy control and that it may affect not only the inhibition process but also the response execution process, though the presence of the effect on Go trials could involve some process other than response execution.

There is compelling evidence that both SZ and BD have deficits in response inhibition and social cognition (see Pinkham, Penn, Perkins, & Lieberman, 2003 for review). Specifically, SZ have lower accuracy (Seok et al., 2005; Suslow et al., 2003) and reduced ERP amplitudes for facial affect recognition (Streit et al.,2001; Turetsky et al.,

2007), and blunted activation in the limbic network for discriminating emotion tasks (Gur et al., 2002; see Kring & Moran, 2008 and Pinkham et al., 2003 for review). It was noted that this impairment was more profound when processing negatively valenced than positively valenced stimulus (Dougherty et al., 1974; Bell et al., 1997; An et al., 2003). This was further supported by the increase in neural activation over the right amygdala for the fearful faces (Holt et al., 2006; Silver et al., 2002).

Since facial expression processing is a complex, multifaceted task (Bentin et al., 1996; Carretié et al., 2001; Eimer and McCarthy, 1999; Kiefer et al., 1998; Lew et al., 2005; Luo et al., 2010), it likely involves multiple cognitive processes. Indeed, there are at least two face-specific cognitive processes that have been frequently reported in ERP studies using face stimuli. First, N170, a negative-going ERP component detected at the lateral occipito-temporal electrodes that peaks around 170ms post-stimulus, is thought to be an index of structural encoding of the face (Bentin et al., 1996; Bentin & Deouell, 2000; Rossion et al., 2003). Second, N250, which peaks at approximately 250ms post-stimulus, is thought to be an index of decoding of the emotional content of the face (Streit et al., 1999, 2001a; Tanaka et al., 2006). In addition, in some cases, the P300 component is thought to reflect further affect decoding in the processing of facial emotions (Johnston et al., 1986; Oliver-Rodriguez et al., 1999).

The exact nature of the facial processing deficit in SZ is unclear. Some studies have found normal N170 but reduced N250 amplitudes (Streit et al., 2001b; Wynn et al., 2008) suggesting normal structural encoding but impaired facial affect decoding, while others found reduced N170 but normal N250 amplitudes (Johnston et al., 2005; Turetsky

et al., 2007) suggesting deficits in early facial structure encoding but relatively intact facial affect decoding

In contrast, a reduced asymmetry in N170 amplitude has often been reported in SZ (Hermann et al., 2004; Johnston et al., 2005; Streit et al., 2001b; Turetsky et al., 2007), suggesting that the impairment in early facial structure encoding in SZ may be due to a lateralization abnormality. Additionally, P300 reduction, regardless of valence is typically observed in patients with schizophrenia (Turetsky et al., 2007). Further, there appears to be further P300 reduction in response to negative faces than to positive faces (An et al., 2003). These findings suggest that deficits in early facial expression may make it more difficult for SZ patients to allocate attentional resources for response inhibition, and result in a reduced P300 for inhibition task. Taken together, these findings suggest that it is possible that deficits in early facial emotion processing in SZ interfere with later attentional resources allocation. If applied to the context of a response inhibition task, such early facial emotion processing deficits may interfere with response inhibition performance through reducing attentional resources allocation.

It is unclear whether BD is also associated with deficits in facial emotion recognition (Gets et al., 2003). Euthymic BD showed blunted activation in the anterior limbic structures compared to healthy controls (CT) in one study (Strakowski et al., 2000), while relatively intact behavioral performance was reported in other studies (Addinton and Addington, 1998).

Given the deficits in emotion processing in SZ and BD, it is likely that emotion affects response inhibition in these two populations. However, no data exist as to if and how emotion modulates response inhibition in SZ. However, a recent fMRI study using

an emotional Go/NoGo task reported that increased neural activity over the fronto-striatal region for emotional NoGo faces than neutral NoGo faces for euthymic BD when compared to healthy controls (Wessa et al., 2007), suggesting that individuals diagnosed with BD require excessive attentional resources to inhibit inappropriate response to emotional faces. However, it was not clear from their findings whether the overactivation for emotional faces was only observed for NoGo trials because they did not include the contrast between emotional Go versus neutral Go. Further, the absence of emotion modulation effect in CT, which is inconsistent with other studies where CT showed greater activation for emotional NoGo stimuli (Elliot et al., 2000; Hare et al., 2008; Schulz et al., 2009), makes it difficult to interpret the significant group difference resulting from the double contrast (BD(NoGo-Go)>CT(NoGo-Go)).

The main focus of the current study is to investigate how affective information influences response inhibition in SZ, BD and HC. Further, as shown in the previous two dissertation studies, neural responses to emotional Go/NoGo task will be used to attempt to discriminate the three groups. To this end, an affective version of Go/NoGo task with four different types of facial stimuli (neutral, happy, angry, and sad) was developed. Emotion modulation effect will be measure by amplitudes and latencies from three ERP components: N170, N250, and P300. The hypotheses are as follows:

(1) Emotion will modulate both response inhibition (NoGo trials) and response execution (Go trials) since processing facial emotions should occur prior to both Go and NoGo trials. Both N250 and P300 would be larger for faces with emotions than those for neutral faces. However, if emotion modulates only response inhibition, then larger N250 and P300 amplitude for faces with emotion would be observed only for NoGo trials. If

emotion modulates only response execution, then enhanced ERPs by faces with emotion would be only observed for Go trials.

(2) N170 amplitude will not differ in Go and NoGo tasks, while N250 and P300 will be larger for NoGo trials than for Go trials. No task effects on the N170 component will suggest that the inhibition effect in ERP amplitudes may stem from differences in early structural encoding.

(3) Emotion modulation effects of the Emotional Go/NoGo task will characterize SZ group, BD group, and CT group differentially. It particular, SZ group is expected to show the smallest NoGo ERP enhancement in response to emotional faces, followed by BD group and then the CT group. If this is found, it would reflect diminished attentional resources for response inhibition during facial recognition.

Method

Task and procedure

In this task, participants were presented with twelve active task blocks, where they had to respond as quickly as possible to a face with a target emotion (Go) and to withhold the response to a face with a distractor emotion (NoGo). In every block, one type of emotional face (happy, sad, and angry) served as target while neutral faces were distractor and vice versa. This resulted in six sets of Go-NoGo pairs including Go happy – NoGo neutral, Go angry – NoGo neutral, Go sad – NoGo neutral, Go neutral – NoGo happy, Go neutral – NoGo sad, and Go neutral – NoGo angry. All face stimuli consisted of grey-scaled faces with happy, sad, angry, and neutral expression from 32 individuals (9 female) taken from the NimStim set (Tottenham et al., *in press*; http://

www.macbrain.org.) In order to control race/ethnicity effect on amplitudes or latencies of ERP components, only Caucasian faces will be used.

In each block, 35 Go (70%) stimuli and 15 NoGo (30%) stimuli (Eimer,1993) were presented for 150 ms on the center of the screen on a black background after 500 ms of fixation cross. The order of Go/NoGo stimuli was pseudorandomized in order not to have two consecutive NoGo stimuli (Schulz, 2007). The maximum amount of response time allowed was 1500ms. In order to obtain enough number of trials for ERP analysis, each set was repeated with the reverse order of stimulus presentation. The order of presenting twelve blocks was counterbalanced across participants in each group (Appendix 10).

All participants performed the task in a darkened, electrically shielded room. Prior to each block, participants were given a written instruction on the screen indicating to which type of face they should respond. All participants were encouraged to respond as quickly as possible to establish the prepotency effect of Go stimulus. Responses and reaction times were recorded online via E-data Aid (Psychology Software Tools, Pittsburgh, USA), while EEG data were recorded via Vision Recorder (BrainProducts, GmbH, Munich, Germany) at the same time. A total of twelve blocks with 600 trials took about 20-25 minutes. After completing the computerized task, all participants were given a rating booklet in which they are going to rate the level of valence and arousal of each face.

Data Analysis

The same data pre-processing were completed as in study 2 (see Study 2 data analysis section). The temporal domain of N170, N250, and P300 were detected and

quantified through covariance matrix-based temporal principal component analysis (tPCA). (Chapman & McCray, 1995). As explained in detail later in the Appendix 11, the presence of N170, N250 and P300 were confirmed.

For behavioral data, omission and commission error rates (i.e. no responses in Go trials and button presses in NoGo trials, respectively), and reaction time (RT) for correct Go responses were analyzed. For RT, outliers defined as responses above and beyond 2 SD were eliminated. Repeated-measure ANOVAs on error rates were applied to Task (2) × Facial emotion (4). For RT, a univariate repeated-measure ANOVAs was carried out using facial emotion as a factor.

Consistent with previous studies, individual ERPs were obtained from nine electrodes (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz) separately for each variable for further analysis: Task type (Go, NoGo), Facial emotion (happy, angry, sad, and neutral), Laterality (left, middle, and right), and Caudality (frontal, central, and parietal). A five-way ANOVA was performed for ERP mean amplitudes and 50 percent area latencies for Group (BD, SZ, and CT) × Task (Go, NoGo) × Facial emotion (Happy, Sad, Angry, neutral) × Laterality (left, middle, and right) × Caudality (frontal, central, and parietal), which will result in high statistical power of .92 with medium ANOVA effect size (f = .30 or η^2= .08) under α= .05(Cohen, 1988). As Simple effect ANOVAs were performed to test main effects and interaction effects among the abovementioned variables and Newman-Keuls tests will be performed as post hoc tests for any significant effects. Any interaction effects among variables were reported only when its preceding higher-order interactions are also significant.

Discriminant function analyses (DA) were performed for N170, N250 and P300 amplitudes and latencies to determine whether the three groups could be delineated and also to describe which variables contribute to the separation (Norusis, 2008). Given the purpose of applying DA in this present study, DA structure matrices and classification accuracy rate were reported to explore how the amplitudes and latencies in each ERP component separates the three groups.

Result

1. Behavioral Data

Accuracy Rate, omission and commission error: within-subject effects

Among the four categories of emotion, accuracy rate was the lowest for sad faces when compared to other types of emotions, Emotion, F (1.84, 128.87) = 95.13, $p < .0001$, Happy = 96.0 ± 3.7 %, Angry = 95.5 ± 3.5 %, Neutral = 90.3 ± 7.4 %, Sad = 82.1 ± 8.3. For neutral faces, NoGo was more accurate than the Go task, Emotion × Task, F (1, 70) =43.84, $p < .0001$, Go = 84.7 ± 14.8 %, NoGo = 95.9 ± 1.2 %, while Go responses were more accurate than the NoGo responses for happy , Emotion × Task , F(1,70) =17.67, $p < .0001$, Go = 97.9 ± 2.83 %, NoGo = 94.2 ± 6.92% and sad faces Emotion × Task , F(1, 70)=11.35, p= .001, Go = 86.1 ± 12.2 %, NoGo = 78.1 ± 12.2%. For angry faces, no task effect was observed. Dissecting the Emotion × Task based on task type, an emotion effect was found for both the Go, Emotion, F (2.01.141.27) = 51.10, $p < .001$ and the NoGo task, Emotion, F (1.71, 119.93) = 120.99, $p < .001$. Post-hoc tests further revealed that for Go task, neutral faces showed lower accuracy rate than that for angry faces ($p < .001$) and happy faces ($p < .001$) but not to sad faces ($p > .58$). For the NoGo task, the post-hoc

tests showed that NoGo responses were significantly more accurate for neutral faces than for sad faces ($p < .001$) and happy faces ($p < .05$), while there was no difference was found between neutral and sad ($p > .38$; Figure 1).

Accuracy Rate, omission and commission error: between-subject(Group) effects

Twenty six BD (women = 14), twenty SZ (women = 4), and twenty seven CT (women = 11) performed an Emotional Go/NoGo task. The three groups were marginally different in overall accuracy rate, F (2,70) = 2.75, p = .07 (SZ = 85.2 ± 10.8 %, BD = 89.5 ± 8.13 %, CT = 91.4 ± 8.1 %). Post-hoc tests revealed that the SZ group was less accurate than the CT group (p = .05), while BD was not different from the other two groups. Accuracy rate difference for emotion and task marginally differed by diagnosis, Emotion × Task × Group, F (2.31, 161.41) = 2.11, p= .07[4]. Within BD, Go was more accurate than NoGo for happy and sad faces, while NoGo was more accurate for neutral faces, Emotion × Task , F(1.89, 47.48) = 28.64, p< .0001. CT also showed higher Go accuracy rates for happy, angry, and sad faces than for NoGo, while their neutral NoGo was more accurate than neutral Go, Emotion × Task, F(2.19, 57.57) = 19.99, p< .0001. SZ were more accurate for neutral NoGo than neutral Go but happy Go was more accurate than happy NoGo, Emotion × Task F(2.38, 48.25) = 12.20, p< .001 (Figure 1).

Relatively higher numbers of OE was observed in neutral faces and in sad faces compared to happy and angry faces, Emotion, F (2.02, 141.2) = 51.07, p< .0001. As predicted, SZ made the most OE with BD in the middle and CT the least, Group, F (2,70) = 4.51, $p < .05$. Post-hoc tests revealed that SZ made more OE than CT ($p < .05$) but did not differ from BD (Table 1). Participants also made more commission errors (CE) for

[4] Emotion × Task × Group violated sphericity assumption ($p < .000$). Without Greenhouse-Geisser adjustment, this three-way interaction was significant (p =.05)

sad faces followed by neutral faces, happy faces, and angry faces, respectively , Emotion, F (2.35, 164.61) = 78.83, p < .0001, Sad = 7.01 ± 4.12, Neutral = 4.42 ± 3.79, Happy = 1.86 ± 2.21, Angry = 1.67 ± 1.85. No group main effect and related interaction effects were found in CE (Table 6).

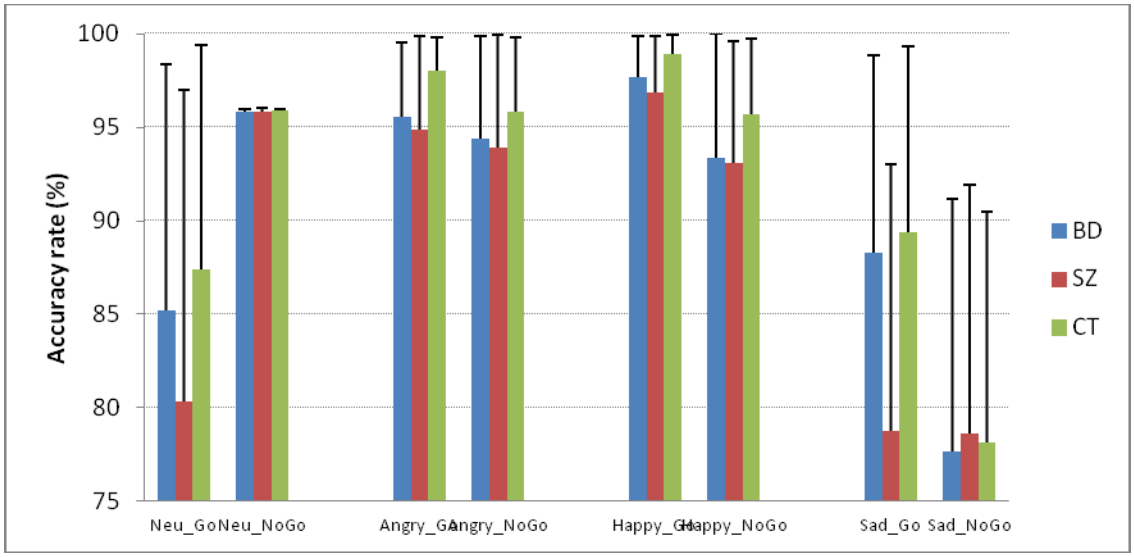


Figure 10. *Emotion* × *Task* × *Group* Accuracy rate. BD=bipolar group, SZ= Schizophrenia group, CT= healthy controls.

Omission Error	Group	Mean	Post-hoc *p*-value	Standard Deviation	Commission Error	Mean	Standard Deviation
Neutral Go	BD (N=26)	10.05	SZ – CT ($p < .05$)	8.92	Neutral NoGo	1.81	1.77
	SZ (N=20)	13.37		11.33		1.95	2.33
	CT (N=27)	8.62		10.11		1.33	1.54
Angry Go	BD	3.04	SZ – CT ($p < .05$)	3.16	Angry NoGo	7.15	4.33
	SZ	3.50		4.22		6.85	4.28
	CT	1.37		1.24		7.00	3.95
Sad Go	BD	7.96	SZ – BD ($p < .05$)	7.16	Sad NoGo	2.12	2.12
	SZ	14.45		9.70		2.20	2.69
	CT	7.22	SZ – CT ($p < .05$)	6.77		1.37	1.88
Happy Go	BD	1.58	SZ – CT ($p < .05$)	1.45	Happy NoGo	4.85	4.16
	SZ	2.15		2.94		4.69	4.58
	CT	.74		.98		3.96	2.72

Table 6. Number of omission errors and commission errors for neutral, angry, sad, and happy faces. BD=bipolar group, SZ= Schizophrenia group, CT= healthy controls.

Reaction Time (RT) for Go stimulus

The speed of response differed by facial emotion, Emotion, F (2.29, 158.50) = 133.63, $p < .0001$. As predicted, RT for neutral faces was the longer than all emotional faces (Neutral – Angry = 96.43 ± 50.04 ms, Neutral – Happy = 110.92 ± 66.41 ms, Neutral – Sad =38.57 ± 50.32 ms, $p < .01$ for all). RT differed for the three groups, Group, F (2,69)= 11.13, $p < .001$. Post-hoc tests revealed that RT among SZ was significantly delayed (61.60 ± 22.28 ms; $p < .05$) compared to BD ($p < .05$) and controls (103.35 ± 21.91 ms; $p < .001$), (Table 7). No interaction effect between emotion and group was found.

Go Stimulus	Group	RT Mean (ms)	Standard deviation (ms)
Neutral Go	BD SZ CT	428.97 495.26 388.55	93.46 86.67 77.29
Angry Go	BD SZ CT	343.17 383.20 288.83	87.11 78.78 62.77
Sad Go	BD SZ CT	383.75 457.65 350.59	102.02 86.47 73.81
Happy Go	BD SZ CT	315.59 381.78 276.50	71.38 87.37 58.63

Table7. Reaction Time (RT) for correct Go response in three groups (BD= bipolar group, SZ= schizophrenia group, CT= healthy controls). Neutral Go RT was obtained by averaging the three RTs where neutral faces were paired with angry, sad, and happy faces.

2. ERP data

Among the seventy two subjects that participated in this study, one data set from BD was excluded from ERP data analysis because ocular artifact was not successfully corrected due to the numerous consecutive blinking within a trial.

2-1. N170

N170 Amplitude

As hypothesized, emotion did not modulate N170 amplitude, Emotion, F (2.83, 192.21) = 2.09, p = .19. However, consistent with expectation, N170 amplitude over the right site (P8) was larger than over the left site (P7), Laterality, F (1,68) = 7.76, $p < .01$

(Figure 3-a). Specifically, N170 for Go task was larger in CT than the patient groups for sad, Task × Group, F (2, 69) = 3.34, $p < .05$ and angry faces, Task × Group, F (2,69) = 4.28, $p < .05$ at P8. Post-hoc comparison revealed that compared to CT, SZ showed smaller Go N170 for angry faces ($p < .05$), while BD showed reduced Go N170 for sad faces ($p < .05$). There was no main effect of emotion for NoGo N170 over P8 (Figure 11, 12-a, b). There was no five-way interaction of Group × Task × Emotion × Caudality × Laterality for N170 amplitude.

N170 Latency

As predicted, at P8, BD showed a marginally delayed latency compared to that of CT ($p < .05$), Group, F(1.31, 49.27) = 2.99, $p = .06$, BD = 171.43 ±12.76 ms, CT = 163.23 ±12.32 ms). N170 latency in BD was not different from that in SZ ($p > .21$) This effect depended marginally on task , Group × Task , F (2,68) = 2.45, $p = .07$. For the NoGo task, N170 latency in BD was delayed compared to CT, Group × Task, F (2,68) = 4.67, $p < .05$, BD = 171.26 ±10.74 ms, CT = 162.49 ±10.06 ms. There were no further main effects or interactions of emotion, laterality, task, and group.

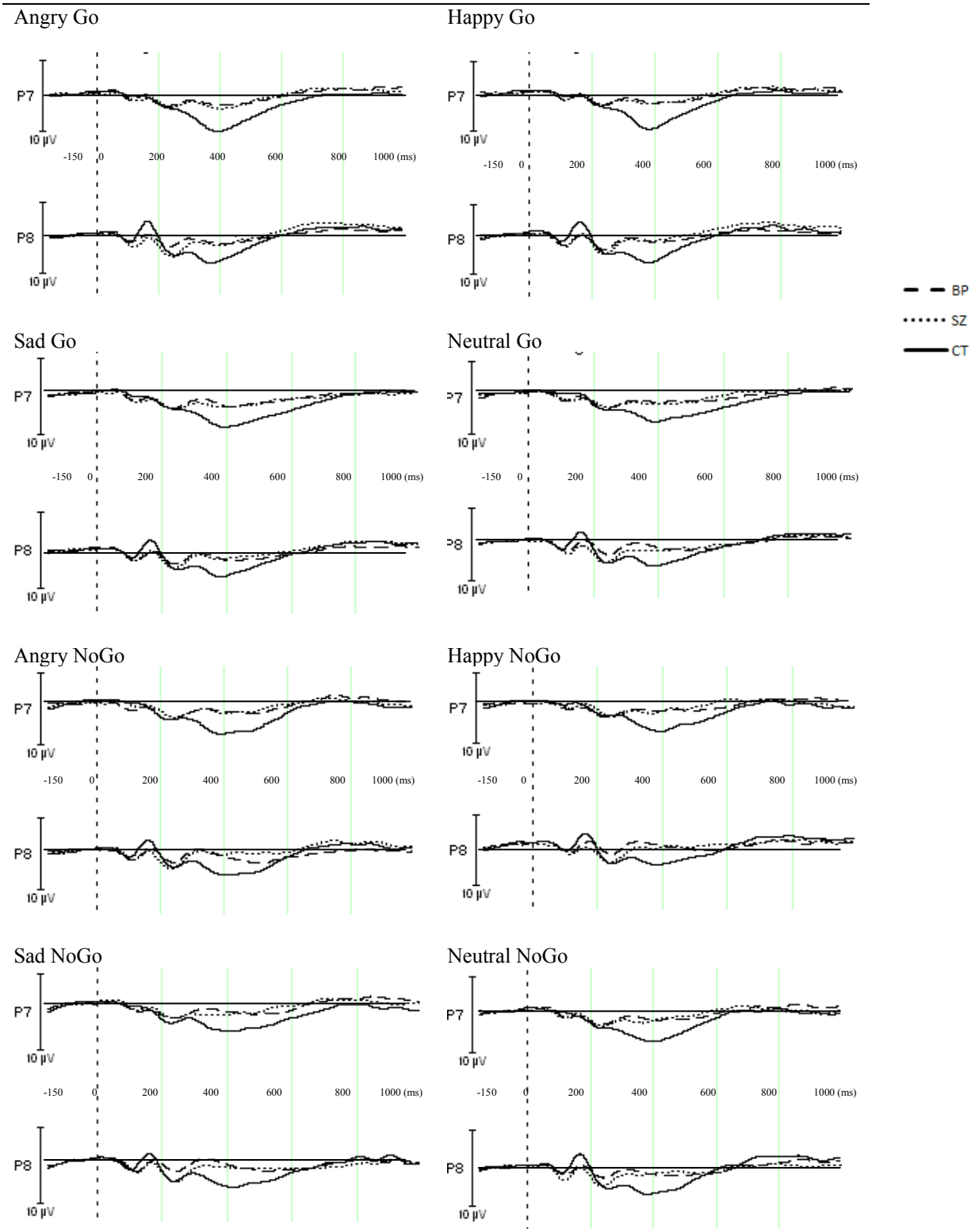


Figure 11. waveforms over occipito-temporal (P7 and P8) sites. (± 5µV for both positive and negative polarity)

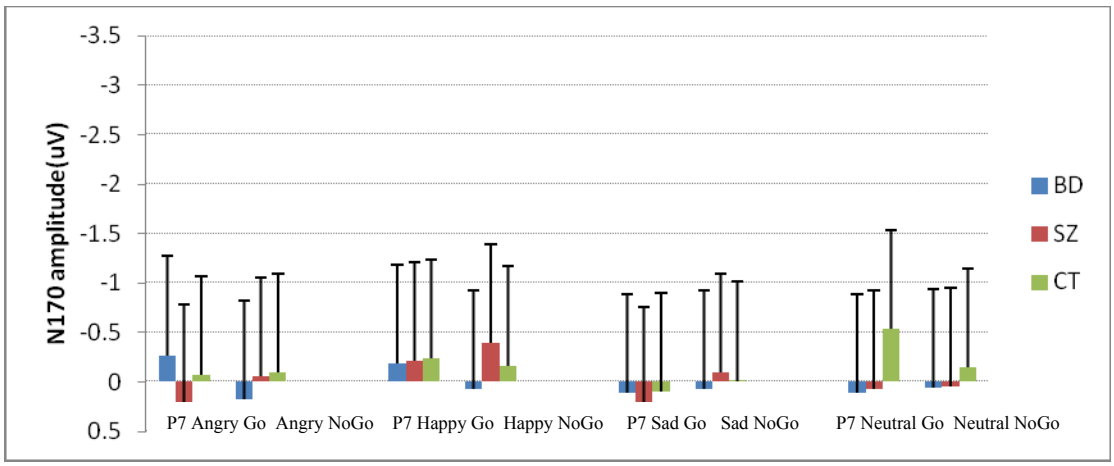


Figure 12-a. N170 mean amplitude over P7 for angry, happy and neutral faces. (Standard error bars are presented.)

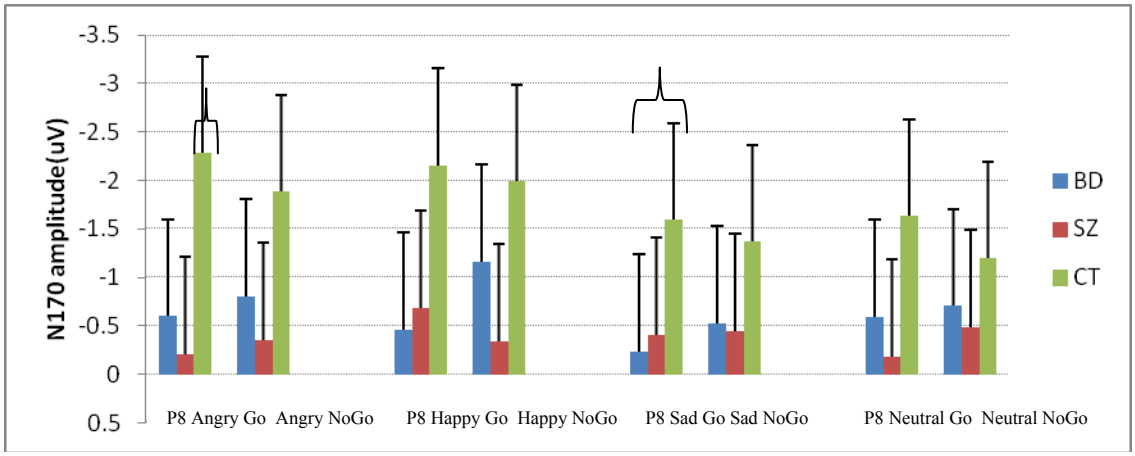


Figure 12-b. N170 mean amplitude over P8 (right temporal-occipital) for angry, happy and neutral faces. (Standard error bars are presented.)

2-2. N250

N250 Amplitude

Six fronto-central leads (F3, F4, Fz, C3, C4, and Cz) were included in data analysis (Appendix 12). As predicted, N250 amplitude was modulated by emotion, F (2.76, 191.02) = 22.19, p < .000, Neutral = -2.51 ± 2.59 μV, Happy = -1.88 ± 2.77 μV, Angry = -1.48 ± 2.95 μV, Sad = -1.39 ± 2.63 μV. Post-hoc tests revealed that N250 amplitude was larger for neutral faces than for sad faces (p <.05). NoGo N250 amplitude

was marginally larger for Go task, Task, F (1, 69) = 2.88, p = .075, NoGo = -1.91± 2.67μV, Go = -1.70 ± 2.71 μV. There was no group main effect and group-related interactions.

N250 latency

As expected, longer N250 latency for NoGo than for Go task was found, Task, F (1, 66) = 38.97, p< .0001, NoGo = 265.17 ± 14.48 ms, Go = 251.94 ± 15.50 ms. However, no emotion modulation effect was found in N250 latency. Among the three groups, SZ showed the longest N250 latency, Group, F (2,66) = 3.12, p= .05, SZ = 259.45 ±14.95ms, BD = 254.98 ±16.63ms, CT = 248.86 ±10.99ms. Post-hoc tests revealed that N250 was significantly delayed in SZ compared to CT (p < .05), while there was no difference between BD and CT, and BD and SZ. There were no group-related interactions.

2-3. P300

P300 Amplitude: within-subject effects

P300 mean amplitudes (350 – 550ms) from all nine electrodes were included (Appendix 14). P300 amplitude was the largest over the parietal, followed by central, and frontal, respectively, Caudality, F (2,134) = 51.39, p < .001. As predicted, P300 amplitude was modulated by emotion, Emotion, F (3,201) = 4.60, p= .004, Neutral = 5.20 ± 3.29 μV, Angry = 5.86 ± 3.47 μV, Happy = 5.63 ± 3.30 μV, Sad = 5.75 ± 3.21μV. Post-hoc test showed that P300 amplitude for neutral faces was smaller than that for angry faces (p = .004), happy faces (p = .003), and sad faces (p = .005). Unexpectedly, however, emotion modulation was differentially manifested in the Go and NoGo task,

where enhanced P300 amplitude was observed for emotional Go faces, while attenuated P300 amplitude was shown for NoGo task, Emotion × Task, F (3,201) = 4.52, p< .01. Specifically, NoGo task P300 amplitude for neutral faces was larger than Go P300 amplitude, Task, F (1,68) = 5.04, p< .05, while Go P300 amplitude was larger than that for NoGo P300 amplitude for sad faces, Task, F(1,67) = 4.27, p< .05, and happy faces, Task, F(1,67) = 2.78, p = .05 (Figure 13).

P300 Amplitude: between-subject (Group) effects

Over the parietal region, all three groups showed *larger* Go P300 amplitude for faces with emotions than for neutral faces, while only CT showed *smaller* NoGo P300 amplitude for faces with emotions compared to that for neutral faces, *Group* × *Emotion* × *Task* × *Caudality, F*(8.04, 269.35) = 2.98, p < .01. In BD, parietal Go P300 amplitude was larger for angry faces (p < .05) and sad faces (p < .01) compared to that for neutral faces, while the difference was marginal for happy (p = .059). Parietal Go P300 amplitude in SZ was larger for angry faces (p <. 05) compared to neutral P300 amplitude, while marginal enhancement was found for happy (p = .06) and sad (p = .057) faces. In CT, all three categories of emotions enhanced parietal Go P300 compared to neutral faces (Happy-neutral: p <.001, Angry-neutral: p < .001, Sad-neutral: p = .001) (Figure 14, 15).

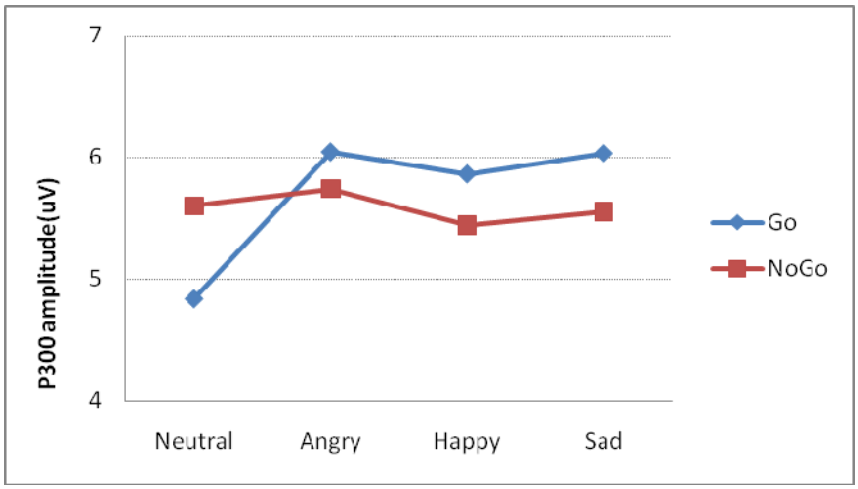


Figure 13. Emotion modulation effect on Go and NoGo task P300 mean amplitudes. All nine electrodes were included.

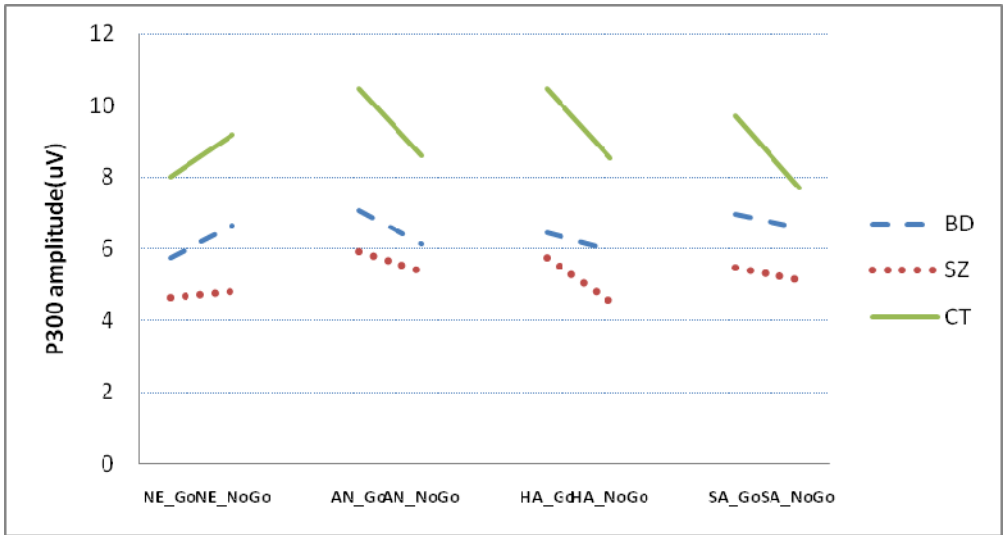


Figure 14. Group difference in emotion modulation effect over the parietal Go and NoGo P300 mean amplitudes

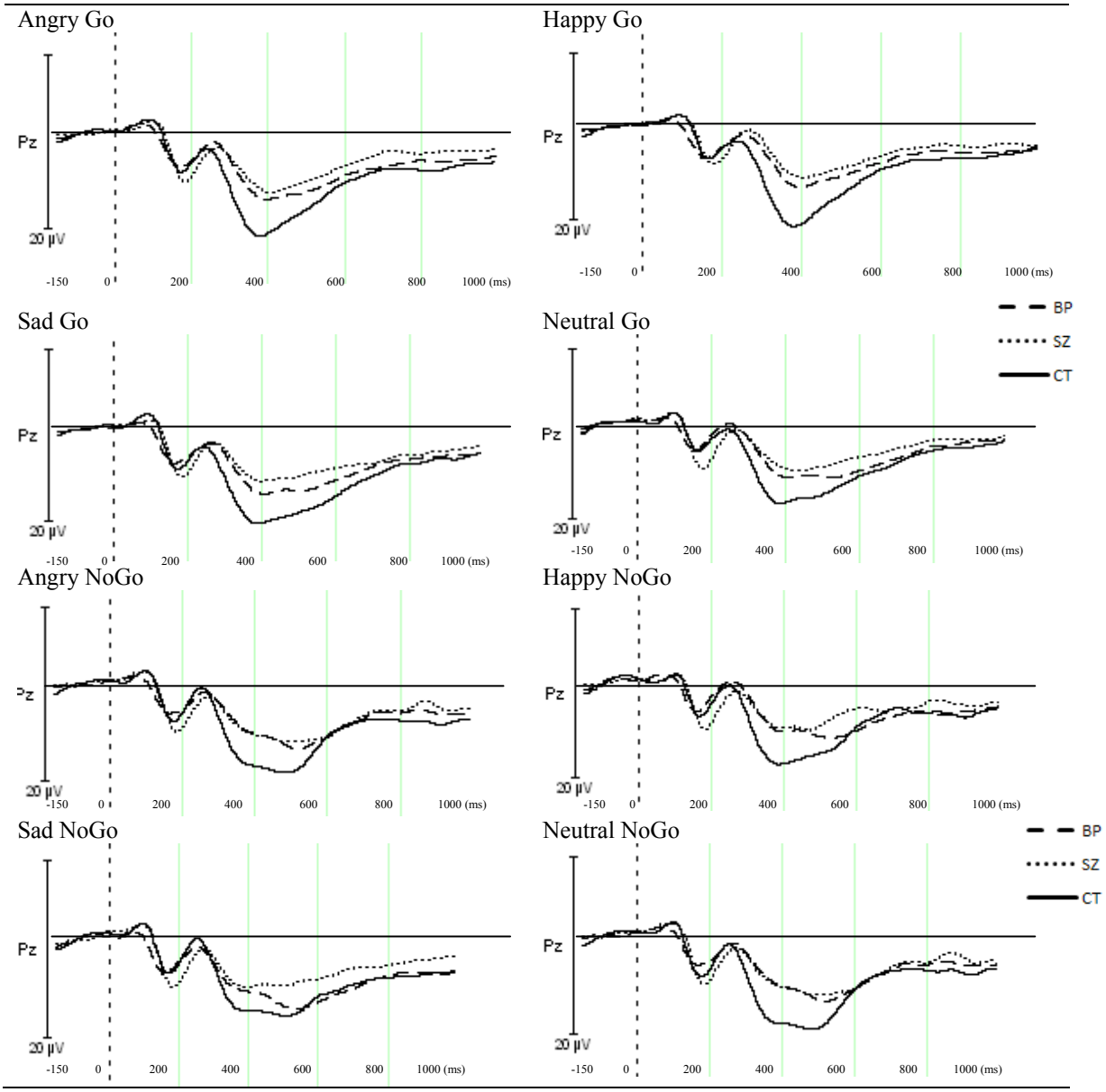


Figure 15. ERP waveform over Pz for BD, SZ, and CT (± 10µV for both positive and negative polarity)

P300 latency: within-subject effect

P300 latency was longer for NoGo than Go, Task, $F(1,67) = 23.31$, $p < .001$, NoGo = 392.29 ± 27.34 ms, Go = 383.70 ± 21.38 ms. Compared to neutral, emotional faces elicited shorter Go P300 latency, Emotion, $F(3, 204) = 3.58$, $p < .05$, Happy – neutral: $p < .05$, Angry - neutral: $p < .05$, Sad – neutral: $p > .63$. NoGo P300 latency difference in emotion was marginally significant, Emotion, $F(2.47,165.71) = 2.47$, $p = .076$. Compared to neutral faces longer NoGo P300 latency was observed only for angry faces ($p < .05$).

P300 latency: between-subject (Group) effect

Among the three groups, BD showed the longest overall latency, Group, $F(2,67) = 15.10$, $p < .001$, BD = 404.17 ± 22.87 ms, SZ = 388.06 ± 18.53 ms, CT = 374.52 ± 15.70 ms. Post-hoc revealed that BD showed longer overall P300 latency than both SZ ($p < .05$) and CT ($p < .001$). BD was the only group that showed longer NoGo P300 latency than that for Go task, Task × Group, $F(2,67) = 12.96$, $p < .001$, BD = 415.29 ± 29.45 ms, SZ = 385.66 ± 14.86 ms, CT = 376.18 ± 16.88 ms. Emotion modulation effect in P300 latency was marginal only in BD for Go task, Task × Emotion × Group, $F(5.37, 179.99) = 1.96$, $p = .069$. Only in BD was observed faster Go P300 latency for faces with emotions compared to neutral faces, Emotion, $F(3,72) = 3.29$, $p < .05$. Post-hoc test further revealed that Go P300 latency was significantly faster for happy faces than for neutral faces in BD ($p < .007$).

3. Discriminant functional Analysis (DA)

DA for behavioral data

A series of DA was performed including accuracy rate, RT for Go task, and number of omission and commission error. Based on Wilk's Lambda and Chi-square p-values, DA was not valid to classify the three groups based on both accuracy rates (Wilk's Lambda = .71, p >.48) and number of OE and CE (Wilk's Lambda = .60, p >.10).

Go RTs for neutral, sad, happy, and angry faces classified the three groups with 63.9% accuracy (Wilk's Lambda = .62, p < .001). All four variables were strongly correlated with Function I, which discriminated SZ from the other groups (Appendix 18, Figure 16).

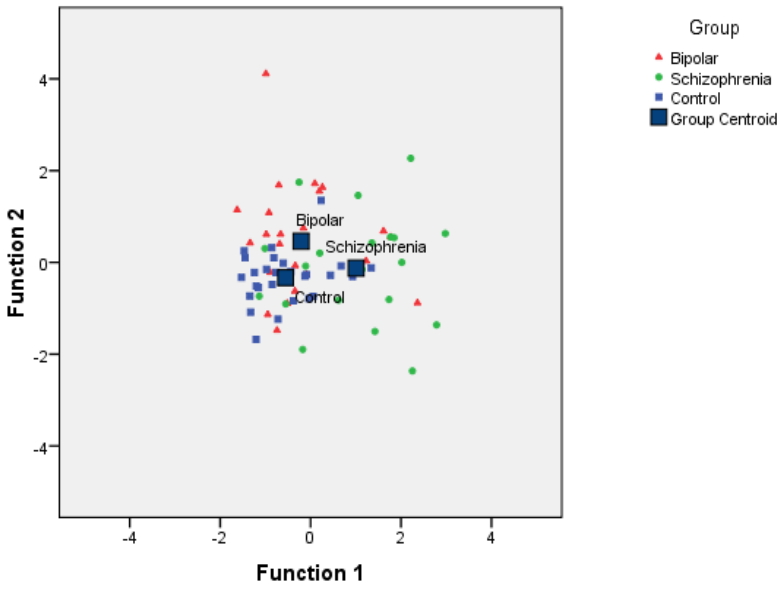


Figure 16. Canonical Discriminant Functions for Go reaction time (RT). Group centroid scores for Function I: BD (-.21), SZ (1.0), CT (-.55).

DA for N170

Discriminant functional analysis was not valid to classify the three groups based on both N170 mean amplitude (Eigen value < 1.0, Wilk's Lambda = .372, p >.20), N170 latency (Eigen value <.10, Wilk's Lambda = .53, p >.22).

DA for N250

Discriminant function analysis (DA) was significant for N250 latency (Wilk's Lambda = .06, p =.05), but not N250 amplitude. Function I and II separated the three groups with 92.8% accuracy based on fronto-central N250 latency. Function I discriminated SZ from CT, which mainly consisted of neutral Go, neutral NoGo, and angry NoGo over central region (Appendix 15). Function II mostly included sad Go and NoGo, which separated BD from CT (Figure 17). Discriminant functional analysis was not valid to classify the three groups based on both N170 mean amplitude (Eigen value < 1.0, Wilk's Lambda = .372, p >.20), N170 latency (Eigen value <.10, Wilk's Lambda = .53, p >.22), and N250 amplitude (Eigen value < 1.0, Wilk's Lambda = .477, p >.64)

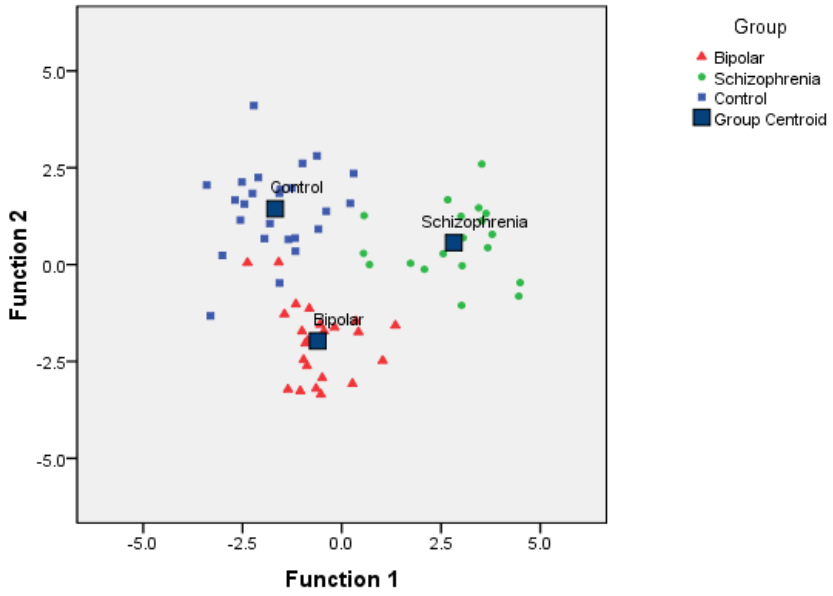


Figure 17. Discriminant function analysis for N250 latency. Function I group centroid score: SZ (2.82), BD (-.60), CR (-1.68). Function II group centroid score: SZ (.56), BD (-1.97), CT (1.44).

DA for P300

When P300 amplitudes from all nine electrodes were included, Function I and II in this model classified group membership with 98.6% accuracy (Wilk's Lambda= .002, $p < .001$). Function I discriminated SZ from the other two groups, which consisted of P300 amplitudes for happy NoGo, angry NoGo, neutral Go and NoGo over fronto-central region. Function II mostly included parietal P300 amplitudes, which separated BD from CT (Figure 18, Appendix 17).

With P300 latency from all nine electrodes, DA identified the three groups with 100% accuracy (Wilk's Lambda= 0.001, $p <.0001$). Function I discriminated BD from the other two groups, which mainly consisted of emotional NoGo latencies from central and parietal region, while Function II included neutral Go and happy Go which separated SZ from CT (Figure 19, Appendix 16).

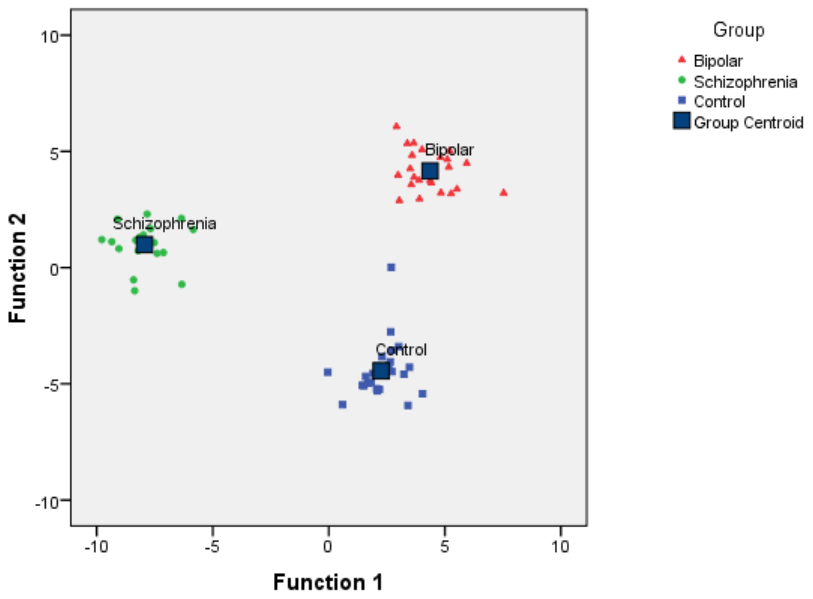


Figure 18. Discriminant functional analysis for P300 amplitude with all nine electrodes: Function I group centroid score: SZ (-7.94), BD (4.36), CT (2.25). Function II group centroid score: SZ (.99), BD (4.16), CT (-4.44)

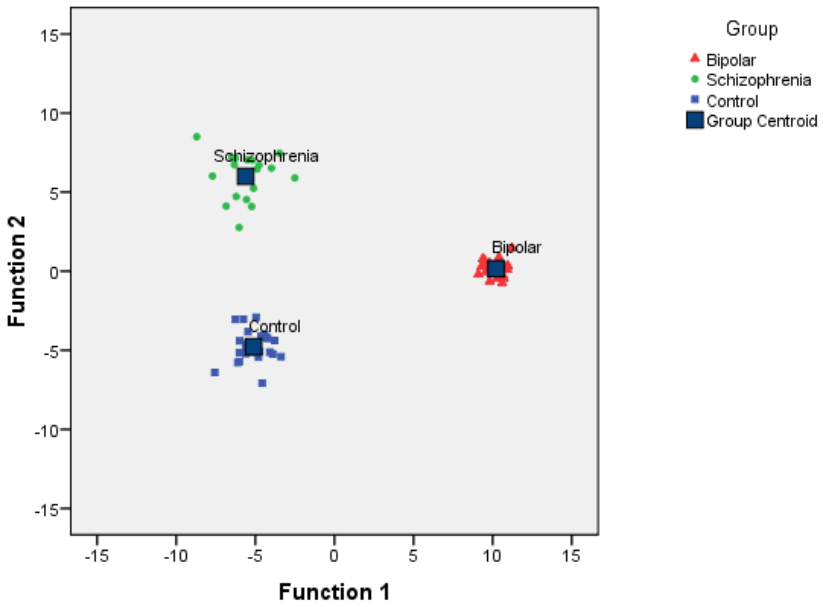


Figure 19. Discriminant functional analysis for P300 latency. Function I group centroid score: SZ (-5.61), BD (10.22), CT (-5.11). Function II group centroid score: SZ (6.03), BD (.16), CT (-4.77).

Discussion

In this study, the neural responses to emotion-modulated response inhibition separated bipolar disorder and schizophrenia in comparison with healthy controls using emotional Go/NoGo paradigm. These findings supported the view that ERPs (N250 latency, P300 amplitude, P300 latency) could become an endophenotype of schizophrenia (Bramon et al., 2005;Turetsky et al., 2007) and bipolar disorder (O'Donnell et al., 2004; Souza et al., 1995). Further, findings from N250 and P300 latency indicated that groups were separated by neural responses to emotion rather than by task types (Go/NoGo), while scalp region (e.g. fronto-central vs. parietal) separated the groups in P300 amplitude. Both SZ and BD patients demonstrated deficient initial structural encoding of faces as indicated by reduced N170 amplitudes over right occipito-temporal region. However, affect decoding was relatively intact in the early visual components, as indicated by normal N250 amplitude and latency. Between the two cognitive processes involved in Go/NoGo paradigm, emotion modulated response execution process, but not the inhibition process.

N170: Structural encoding and response inhibition

As predicted, no emotion modulation effect was found (no difference between neutral vs. affective faces or any differences between affective faces) in early visual component (N170), which supported the previous studies that there is no difference in encoding facial structure of faces with and without emotions (Eimer & Holmes, 2002; Holmes et al., 2003; Luo et al., 2009). When the three groups were compared, patients' N170 amplitude was less lateralized to the right occipito-temporal region than controls.

Given that right hemisphere dominance in N170 component has been replicated in previous studies with controls (Bentin et al., 1996; Luo et al., 2009; Lynn et al., 2008 Sagiv and Bentin, 2001), the findings in this study reflect the deficit in the initial encoding of facial structures over the right side of the brain in both BD and SZ. Specifically, N170 amplitude was more reduced in BD with negative stimuli (sad faces), while such reduction in amplitude was more prominent in schizophrenic patients with threat-provoking stimuli (angry faces). This indicates that SZ showed deficits in processing faces with negative high-arousal, while euthymic BD showed impaired early face processing for the faces with negative low-arousal. These results are consistent with the previous studies which showed profound deficit in schizophrenics' ability to accurately recognizing negative emotions (Dougherty et al., 1974; Bell et al., 1997; An et al., 2003). Specifically, schizophrenic patients demonstrate less activation in left-amygdala and bilateral hippocampus when processing threat-related stimuli (i.e. fearful faces, threat-words ; Gur et al., 2002; Kosaka et al., 2002), fusiform, cingulate areas (Russell et al., 2007; Streit et al., 2001a; Williams et al., 2007) and attenuated N170 amplitude for fearful faces in recent studies of emotion recognition task (Lee et al., 2010; Turetsky et al., 2007). Lower accuracy rate and longer reaction time in BD has been reported for faces expressing fear and sadness (for review, see Rocca et al.,2009; Derntl et al., 2009). Thus, findings from this study suggest that schizophrenic patients have prominent deficit in encoding threat-provoking faces, while euthymic bipolar patients may have difficulty in encoding negative affect such as sad faces.

N250: Structural decoding and response inhibition

In line with Chiu et al. (2008), N250 amplitude for Go task was more enhanced for neutral faces than for emotional faces. Given that N250 amplitude has been associated with affect decoding (Streit et al., 2001; Wynn et al., 2008), the findings from this study may reflect that detecting neutral targets (Go) among affective distractors (NoGo) was more cognitively demanding than detecting emotional targets among neutral distractors. In support of this idea, accuracy rate for Go neutral faces was less accurate and RT was longer than those for Go faces with emotions, suggesting that executing responses to neutral faces was more difficult than faces with emotions. In contrast to the N170 component, N250 amplitude in patient groups was not modulated by task type, emotion, or hemispheric location. This indicated that both SZ and BD can discriminate neutral faces from emotionally salient faces in order to generate correct responses. Further, patients' normal N250 for facial affect decoding may reflect that patients could utilize cognitive resources to identify neutral versus faces with emotions despite their restricted amount of structural information of a face. The findings supported previous studies (Lee et al., 2010; Johnston et al., 2005; Turetsky et al., 2007) that also reported reduced N170 and intact N250 in SZ.

P300: Emotion processing and response inhibition

Emotion affected P300 and N200 go responses differently. Larger Go P300 amplitude for faces with emotion was found than for neutral faces, indicating that emotion facilitated detecting targets among the neutral distractors. However, N250 amplitude was larger for neutral than all emotional Go faces, supporting the notion that

ERPs to response execution (Go task) did not vary by affective valence but by affective intensity (arousal) (Chiu et al., 2008; Bradley and Lang, 2007). However, in other studies with emotional Go/NoGo paradigm, emotion modulation effect was exclusive to NoGo task (Wessa et al., 2007; Luo et al., 2010), where larger NoGo N200 or P300 amplitudes were reported for emotional stimuli than for neutral stimuli. Such discordance in findings may be attributed to the difference in the duration of stimulus presentation across the studies. Both studies that showed NoGo emotion modulation effect used much longer stimulus presentation (> 500ms) than in Chiu et al. (2008; 280 ms) and in this study (150 ms). Presenting stimuli for longer period of time may help establishing the prepotency effect of neutral Go stimulus by lowering the task demand of discriminating neutral target from emotional distractors . Similar behavioral accuracy between neutral and affective stimuli (Schulz, 2007) provides converging evidence.

Emotion modulation effect on NoGo ERP components was not clearly observed. NoGo P300 amplitudes for emotional were not enhanced compared to neutral faces. Substantial evidence has accumulated that emotional stimuli interfere with ongoing cognitive activities by capturing attention automatically (Pessoa, 2009; see Verbruggen and De Houwer, 2007 for review). When applied to the findings in this study, affective information in NoGo stimulus may have restricted the availability of cognitive resources for suppressing motor response, as instantiated by reduced P300 amplitudes for emotional faces compared to the neutral faces. Limited attentional resources for inhibition may also weaken the prepotency effect combined with short stimulus presentation, which was further supported by larger Go P300 amplitude than that for NoGo with emotional faces in this study.

Different from a priori hypothesis, all three groups showed enhanced Go P300 amplitude for faces with emotions compared to neutral faces over the parietal region, although Go P300 amplitudes of patients were smaller than those for controls across all types of emotions. Emotion facilitation effect in Go task was consistent with accuracy rate which was higher for angry and happy faces compared to neutral faces in all three groups. In P300 latency, however, it was observed that bipolar patients showed delayed overall P300 latency, reflecting that it took more time for bipolar patients to evaluate stimuli to execute correct responses than other groups. Specifically, only happy faces generated shorter Go P300 latency compared to neutral faces in bipolar patients, indicating that positive emotion facilitated bipolar patient's ability to evaluate the stimulus for executing responses. This was further supported by reaction time, where bipolar patients showed much shorter RT for happy faces compared to neutral faces.

In sum, this study showed that emotion facilitated executing responses in all three groups, while emotion may have interrupted suppressing motor responses by restricting attentional resources for inhibition processing. Although emotion modulation effect on both response execution and response inhibition did not differ between the three groups, discriminant functional analysis further demonstrated how these groups could be separated based on linear decomposition of the original ERP scores.

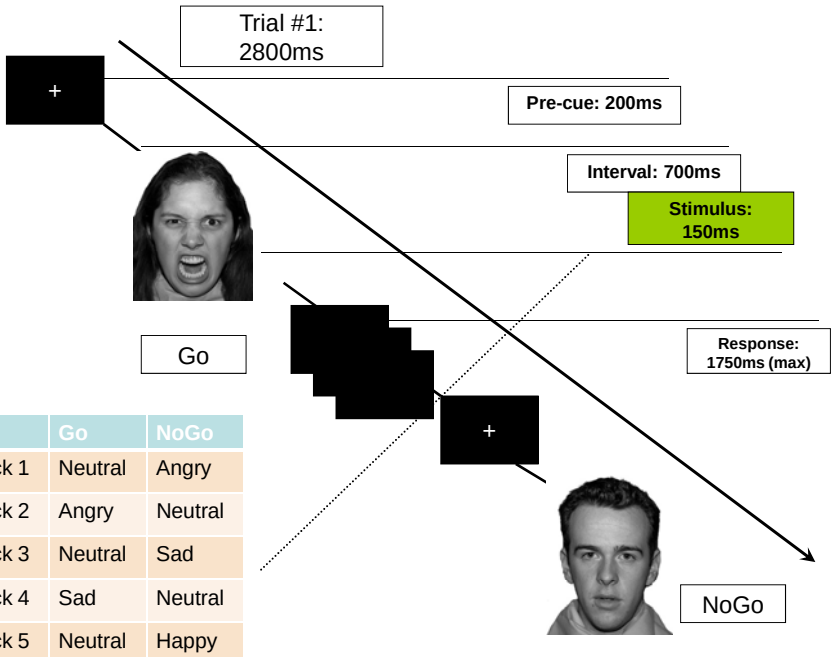
This is important because reduced N170 in both schizophrenic patients and euthymic bipolar patients might lead them to misinterpret initial structural information. However, as indicated by their relatively intact N250 amplitude, patients were able to compensate for the deficit in the early stage of face processing by generating correct responses for this task. Such findings can be applied to the rehabilitation of social

cognition deficit: focusing the patient's attention on correctly decoding affective information to strengthen their compensatory mechanism should benefit both groups of patients.

In comparison with previous studies with longer stimulus presentation, this study showed that the duration of stimulus presentation may have compromised establishing prepotency effect in response inhibition specifically with affective facial stimuli. Thus, in the future studies with emotional Go/NoGo paradigm need to pay more attention to secure prepotency effect by having longer stimulus presentation than 150 ms in all types of emotion in order to better understand the time course of the neural inhibition processing modulated by emotion in order to establish prepotency effect between Go and NoGo trials. Further, the present study only included correct responses which may have narrowed the variability in the perception of neutral faces in patient groups. Thus, further research that reflects subjective feelings (e.g. like vs. dislike) in response inhibition may benefit the field to search for the emotion processing deficits associated with response inhibition in patient groups.

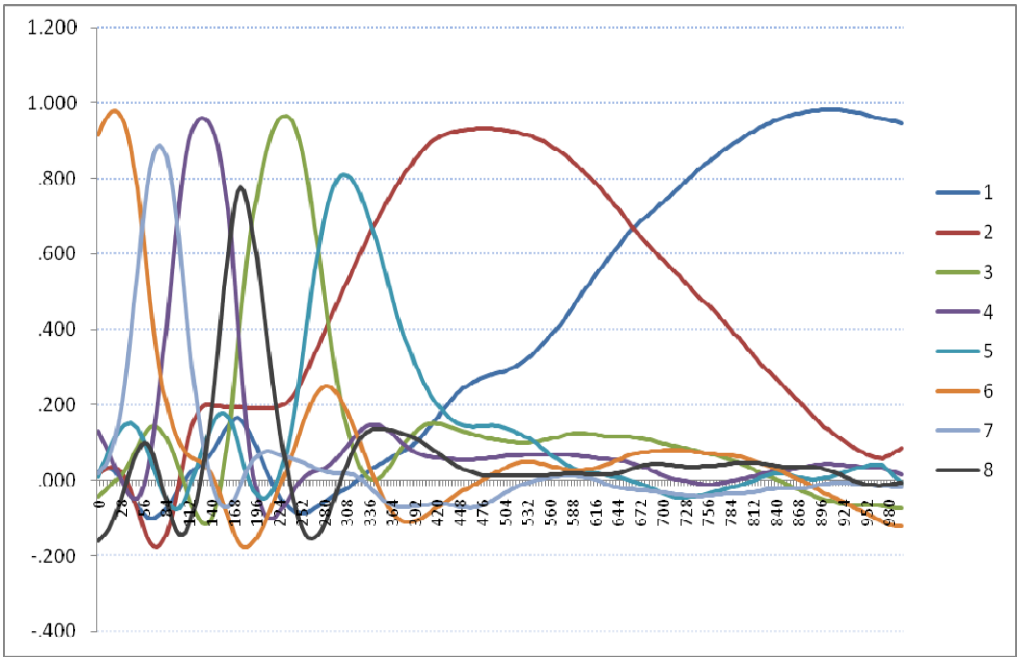
Chapter IV. APPENDICES

Appendix 10. Structure of emotional Go/NoGo Task (Block 2 example)



	Go	NoGo
Block 1	Neutral	Angry
Block 2	Angry	Neutral
Block 3	Neutral	Sad
Block 4	Sad	Neutral
Block 5	Neutral	Happy
Block 6	Happy	Neutral

Appendix 11. Temporal principal component analysis (tPCA) with eight factors. Temporal factor 8 corresponded to N170 component (160 – 190 ms), factor 3 for N250 (200 – 280 ms), and factor 2 for P300 (330 – 580 ms)



Appendix 12. N250 amplitude repeated-measure ANOVA

variable	*F* (*df*1, *df*2)	*p*-value
Laterality	*F* (1.96, 135.12) = 22.02	*p* < .001
Left: -1.60 ± 2.38 μV		
Right: -1.57 ± 2.67 μV		
Midline: -2.25 ± 3.02 μV		
Laterality × Task	*F* (1.94, 134.04) = 7.91	*p* = .001
Left-side (Task)	NS	
Right-side (Task)	*F*(1,69) = 4.20	*p* < .05
Right-side Go: -1.45 ± 2.74 μV		
Right-side NoGo: -1.69 ± 2.69 μV		
Midline (Task)	*F*(1,70) = 4.56	*p* < .05
Midline Go: -2.09 ± 3.09 μV		
Midline NoGo : -2.39 ± 3.03 μV		
Caudality × Laterality × Task	*F*(1.99, 137.64) = 2.87	*p* = .054
Frontal (Laterality× Task)	*F*(2,138) = 2.98	*p* = .05
Frontal Go (Laterality)	*F*(1.59, 110.14) = 12.10	*p* < .001
Left-side: -1.45 ± 2.39 μV		
Right-side: -1.57 ± 2.66 μV		
Midline: -2.07 ± 2.75 μV		
Frontal NoGo (Laterality)	*F*(1.52, 104.64) = 13.67	*p* < .001
Left-side: -1.53 ± 2.40 μV		
Right-side: -1.74 ±2.74 μV		
Midline: -2.27 ± 2.79 μV		
Central (Laterality× Task)	*F*(2,140) = 7.51	*p* = .001
Central Go (Laterality)	*F*(1.77,123.72) = 9.71	*p* < .001
Left-side: -1.68 ± 2.75 μV		
Right-side: -1.32 ± 3.10 μV		
Midline: -2.13 ± 3.85 μV		
Central NoGo (Laterality)	*F*(1.84,128.87) = 19.48	*p* < .001
Left-side: -1.72 ± 2.75 μV		
Right-side: -1.64 ± 3.06 μV		
Midline: -2.53 ± 3.70 μV		
Central Left-side (Task)	NS	
Central Right-side (Task)	*F*(1,70) = 4.84	*p* < .05
Go: -1.32 ± 3.10 μV		
NoGo: -1.64 ± 2.50 μV		
Central Midline (Task)	*F*(1,70) = 4.72	*p* < .05
Go: -2.13 ± 3.85 μV		
NoGo: -2.53 ± 3.70 μV		
Caudality × Task × Emotion	F(3, 207) = 2.64	*p* = .05
Frontal (Task × Emotion)	NS	NS
Central (Task × Emotion)	*F*(2.3, 160.81) = 3.21	*p* < .05
Neutral (Task)	*F*(1, 70) = 4.82	*p* < .05
Go: -2.78 ± 3.13 μV		
NoGo: -2.26 ± 3.24 μV		
Angry (Task)	NS	
Happy (Task)	NS	
Sad (Task)	*F*(1, 70) = 5.94	*p* < .05
Go: -1.14 ± 3.10 μV		
NoGo: -1.77 ± 3.33 μV		

Appendix 13. N250 latency repeated measure ANOVA

variable	*F* (*df1, df2*)	*p*-value
Caudality × Task	$F(1,66) = 3.18$	$p = .079$
Frontal (Task)	$F(1,69) = 23.64$	$p < .001$
Go: 252.25 ± 15.62 ms		
NoGo: 255.62 ± 14.56 ms		
Central (Task)	$F(1,69) = 30.21$	$p < .001$
Go: 251.60 ± 16.79 ms		
NoGo: 256.44 ± 15.92 ms		
Caudality × Task × Laterality	$F(1.67,110.52) = 5.61$	$p < .01$
Frontal (Task × Laterality)	NS	NS
Central (Task × Laterality)	$F(1.70,117.6) = 7.17$	$p < .01$
Left-side (Task)	$F(1,70) = 15.19$	$p < .001$
Go: 251.83 ± 16.08 ms		
NoGo: 255.13 ± 15.59 ms		
Right-side (Task)	$F(1,70) = 27.42$	$p < .001$
Go: 251.05 ± 18.18 ms		
NoGo: 256.85 ± 17.14 ms		
Midline (Task)	$F(1,69) = 34.28$	$p < .001$
Go: 251.59 ± 16.88 ms		
NoGo: 256.95 ± 16.21 ms		

Appendix 14. P300 amplitude repeated measure ANOVA

variable	*F* (*df1, df2*)	*p*-value
Caudality × Laterality × Task	$F(3.10, 208) = 3.02$	$p < .05$
Frontal (Laterality × Task)	$F(2,136) = 6.24$	$p < .01$
Left (Task)	$F(1,68) = 3.85$	$p = .054$
Go: 3.68 ± 3.17 μV		
NoGo: 4.06 ± 3.51 μV		
Right (Task)	NS	NS
Midline (Task)	NS	NS
Central (Laterality × Task)	$F(2,136) = 9.59$	$p < .001$
Left (Task)	$F(1,68) = 6.16$	$p < .05$
Go: 4.87 ± 3.02 μV		
NoGo: 5.44 ± 3.71 μV		
Right (Task)	NS	NS
Midline (Task)	NS	NS
Parietal (Laterality × Task)	$F(2,138) = 2.75$	$p = .067$
Left (Task)	$F(1,69) = 6.04$	$p < .05$
Go: 6.79 ± 3.36 μV		
NoGo: 6.30 ± 3.45 μV	$F(1,69) = 18.83$	$p < .001$
Right (Task)		
Go: 6.98 ± 3.47 μV		
NoGo: 6.21 ± 3.51 μV		
Right (Task)	$F(1,69) = 12.26$	$p = .001$
Go: 8.43 ± 3.93 μV		
NoGo: 7.74 ± 4.02 μV		

Appendix 15. Discriminant functional analysis Structural matrix for N250 latency

Function I. variable	correlation coefficient	Function II. variable	correlation coefficient
Cz neutral Go	.224	Cz angry Go	-.133
F4 angry NoGo	.223	C4 sad Go	-.133
C3 neutral Go	.205	Cz sad Go	-.128
Cz neutral NoGo	.200	F4 sad NoGo	-.109
Fz angry NoGo	.199	Cz sad NoGo	-.104
C4 neutral NoGo	.195	Cz happy NoGo	-.079
Cz happy Go	.192	F3 happy Go	-.071
C4 angry NoGo	.190	Fz happy NoGo	-.070
C4 neutral Go	.184	C4 sad NoGo	-.057
C3 neutral NoGo	.182	F4 sad go	-.057
F3 angry NoGo	.182		
Cz angry NoGo	.161		
C3 angry NoGo	.161		
C4 happy Go	.157		
C3 happy Go	.143		
C3 sad NoGo	.136		
Fz sad NoGo	.130		
Fz neutral Go	.128		
C4 happy Nogo	.127		
F4 neutral NoGo	.124		
Fz happy Go	.124		
C4 angry Go	.117		
F3 neutral Go	.109		
C3 sad Go	.106		
F4 happy Go	.105		
F3 sad NoGo	.103		
F3 neutral NoGo	.102		
C3 angry Go	.096		
Fz neutral NoGo	.092		
F3 angry Go	.088		
F3 neutral NoGo	.087		
F4 angry Go	.077		

Appendix 16. Discriminant functional analysis Structural matrix for P300 latency.

Function I. variable	correlation coefficient	Function II. variable	correlation coefficient
C3 angry NoGo	.112	F3 neutral Go	.087
C4 sad NoGo	.097	F4 neutral Go	.081
P4 sad NogO	.095	Fz neutral Go	.076
F3 angry NoGo	.095	C3 neutral Go	.074
Pz sad NoGo	.088	Fz happy Go	.071
C4 angry NoGo	.087	P4 happy Go	.066
F4 angry NoGo	.083	F4 happy Go	.066
P3 sad NoGo	.082	F3 happy Go	.064
C4 sad NoGo	.082	C4 neutral Go	.060
P3 happy NoGo	.080	Cz happy Go	.058
Fz happy NoGo	.080	Pz sad Go	.054
P3 angry NoGo	.079	Pz happy Go	.052
Cz happy NoGo	.078	F3 sad Go	.049
Cz angry NoGo	.076	P4 sad Go	.048
C4 happy NoGo	.075	P3 happy Go	.048
F3 happy NoGo	.075	C4 happy Go	.041
Fz sad NoGo	.074	C3 happy Go	.041
P4 happy NoGo	.071	Fz angry Go	.039
Fz angry NoGo	.070	F4 angry Go	.038
C3 happy NoGo	.069	F3 angry Go	.036
P4 neutral Go	.068	F4 sad Go	.033
F4 neutral NoGo	.066		
F3 neutral NoGo	.066		
P3 neutral Go	.065		
P4 angry NoGo	.064		
F3 sad NoGo	.062		
F4 sad NoGo	.061		
Pz angry NoGo	.059		
Fz neutral NoGo	.059		
C3 sad NoGo	.058		
C3 sad Go	.058		
Pz happy NoGo	.056		
P3 sad Go	.054		
Cz sad Go	.054		
F4 happy NoGo	.051		
P3 angry Go	.051		
Pz neutral Go	.051		
Cz angry Go	.049		
C4 sad Go	.044		

Fz sad Go	.043
C4 angry Go	.042
C3 angry Go	.042
Pz angry Go	.038
P4 angry Go	.034

Appendix 17. Discriminant functional analysis Structural matrix for P300 amplitude

Function I. variable	correlation coefficient	Function II. variable	correlation coefficient
F4 angry NoGo	.062	P3 happy Go	-.161
C4 sad Go	.059	P4 happy Go	-.152
C4 happy NoGo	.057	P3 angry Go	-.133
F3 neutral Go	.057	P4 angry Go	-.128
C3 neutral NoGo	.055	P4 sad Go	-.128
F4 neutral Go	.054	P3 sad Go	-.127
C3 happy NoGo	.053	P4 neutral NoGo	.-101
F4 happy NoGo	.051	P4 neutral Go	-.097
C4 neutral NoGo	.051	P3 neutral NoGo	-.096
Fz happy NoGo	.051	P4 happy NoGo	-.094
C4 angry Go	.050	P4 angry NoGo	-.091
C4 angry NoGo	.050	Pz angry NoGo	-.088
C3 sad Go	.049	P3 happy NoGo	-.087
F3 happy NoGo	.047	P3 angry NoGo	-.083
F3 angry NoGo	.047	P3 neutral Go	-.082
Cz happy NoGo	.047	C4 happy Go	-.079
C4 neutral Go	.047	C3 happy Go	-.076
Cz neutral NoGo	.046	Fz sad Go	.071
Fz neutral Go	.046	F3 sad Go	.061
C3 sad NoGo	.045	Cz happy Go	-.060
P3 sad NoGo	.045	P4 sad NoGo	-.060
C3 angry NoGo	.043	F4 sad Go	.058
C3 neutral Go	.043	F4 sad NoGo	.056
F4 happy Go	.043	F3 sad NoGo	.053
C4 sad NoGo	.042	Fz angry Go	.050
C3 angry Go	.039	F3 angry Go	.049
Cz sad NoGo	.039		
F3 neutral NoGo	.039		
F4 neutral NoGo	.038		
Fz angry NoGo	.036		
Cz neutral Go	.034		
Cz angry Go	.025		

Appendix 18. Discriminant functional analysis Structural matrix for reaction time for emotional Go/NoGo

variable	Function I. correlation coefficient	Function II. correlation coefficient
Happy Go	.90*	.29
Neutral Go	.76*	.27
Sad Go	.74*	.14
Angry Go	.71*	.59

Chapter V.

General discussion

The three studies investigated response inhibition deficits and emotion modulation of response inhibition utilizing event-related brain potentials (ERPs) in schizophrenia, schizoaffective disorder, bipolar I disorder, and healthy controls. The findings were consistent: all psychiatric groups had response inhibition deficits. Specifically, in all three studies, N200 latency (N250 for face stimuli) and P300 amplitude discriminated psychiatric groups with high accuracy which strongly suggest the possibility that these components are potential biological markers of these psychiatric illnesses. Treatment implication and future direction are discussed below.

Response inhibition deficit in schizophrenia

Individuals diagnosed with schizophrenia (SZ) showed reduced frontal P300 amplitude for response inhibition when the stimulus was presented to their left hemisphere (Study 1 & Study 2). These findings strongly suggest that SZ have deficits in recruiting attentional resources to inhibit on-going responses when utilizing left hemisphere. In line with previous studies (Hill and Weisbrod et al., 1999; Weisbrod et al., 2000), the first two studies further support the notion of left hemisphere dysfunction in

schizophrenia (Crow et al., 1995). However, NoGo P300 reduction over the frontal region was more left-lateralized in Study 1 than in Study 2 with contralateral stimulus presentation (electrode located on the left side while the stimulus was presented to the right visual field). Such differences in laterality effect, however, might be due to the fact that there was much eye movements toward the stimuli which means the stimuli were presented to both hemispheres of the brain, thus eliminating the possibility of finding lateralized deficit in SZ in Study 2.

Findings were also discordant in N200 response inhibition deficits. In Study 1, the NoGo deficits in N200 amplitude in SZ was affected by stimulus presentation location not electrode location, demonstrating SZ's deficits in allocating resources from right hemisphere in the early stage of response inhibition (N200 left visual field < N200 right visual field) and not electrode location (e.g. frontal) as in study 2. Therefore, the association between right hemisphere dysfunction and SZ's deficits in response inhibition seen in study 1 was not replicated.

In study 3, SZ when compared to controls demonstrated an overall P300 reduction regardless of stimulus type. This is consistent with the previous literature which consistently suggests that SZ have overall difficulty in allocating attention for cognitive tasks (see Maher and Deldin, 2001 for review).

Perhaps deficits in initial visual processing as indexed by the N170, limited the available resources required for a later stage of response execution and response inhibition. This interpretation was supported by recent studies that investigated three stages model of facial information processing where SZ's reduced N170 was positively correlated with attenuation in the later ERP components (Lee et al., 2010; Turetsky et al.,

2007). Consistent findings from discriminant function analysis (DA) of the three studies highlighted SZ's distinct neural deficits in response inhibition. In all studies, P300 amplitude and N200 latency discriminated SZ group from other groups (Table 8). With facial stimuli, face-specific N250 amplitudes for neutral faces and angry NoGo faces also separated SZ from CT and also from BD (Study 3 function I). In sum, findings from DA in three studies strongly supports the view that deficits manifested in P300 amplitude (and perhaps in N200 latency) in Go/NoGo paradigms can become biological markers for schizophrenia (see Bramon et al., 2005 for review).

ERP component	Groups discriminated	Study	Discrimination Accuracy	Supporting evidence
NoGo P300 amplitude	SZ / CT	Study 1 (Function I)	100%	Frontal NoGo P300 amplitudes with right visual field stimulus presentation (RVF) were highly correlated with the functions that that separated SZ from SAD (Study 1) and from BD and CT (Study 2 & Study 3)
	SZ / BD	Study 2 (Function II)	94.2%	
		Study 3 (Function I)	98.6%	
Go N200 latency	SZ/ CT, SZ/ SAD	Study 1 (Function II)	91%	SAD showed prolonged overall N200 latency with left visual stimulus presentation (LVF)
	SZ/ BD, CT	Study 2 (Function I)	77%	SZ showed delayed N200 latency over central right site (C4) with RVF, which is included in discriminant function I
P300 latency	BD/SZ, BD/CT	Study 3 (Function I)	100%	In Study 3, BD showed longer Go P300 latency than that in CT and that in SZ.

Table 8. Discriminant analyses in three studies

Schizoaffective disorder and response inhibition

Patients with schizoaffective disorder (SAD) were only included in Study 1 and were run in the non-affective Go/NoGo paradigm. Relatively intact P300 and N200 amplitudes for NoGo trials suggest that individuals diagnosed with SAD do not have difficulty in recruiting attentional resources during response inhibition. However,

prolonged N200 latency with left visual field presentation (LVF) raised the question whether the delayed latency reflected SAD's deficits in cognitive stimulus evaluation time associated with right hemisphere because such delay was not observed for stimulus presented to RVF. However, to date, no data have been existent in SAD's hemispheric deficits in response inhibition. Further, due to the small number of SAD the results and suggestion of N200 latency as a biological marker in this group must be considered with caution. Future studies with larger sample sizes of SAD will help to clarify whether N200 latency in Go/NoGo task is an endophenotype of SAD.

Bipolar disorder and response inhibition

BD showed normal P300 enhancement for NoGo trials for non-affective (Study 2) and affective (Study 3) stimuli, suggesting that BD did not show reduced attentional resources for response inhibition. However, in the non-affective Go/NoGo task, patients with Bipolar I disorder (BD) showed the largest frontal NoGo P300 amplitude compared to both SZ and CT when the stimulus was presented to RVF (Study 2). These are quite striking findings because few, if any, previous studies have found larger P300s in a psychiatric group when compared with a normal population. The BD, however, demonstrated longer P300 latency for NoGo task (Study 2 & Study 3) and even compared to SZ (Study 3). The results suggests that BD may use a different speed/accuracy tradeoff when evaluating NoGo regardless of stimulus types (affective vs. non-affective).

In both Study 2 and Study 3 P300 responses to Go/NoGo P300 latency discriminated BD from SZ (Study 2- Function II, Study 3- Function I) and CT (Study 3,

Function I), while parietal P300 amplitudes separated BD from CT (Study 3, Function II), again highlighting the potential endophenic nature of ERPs.

Treatment implication

Deficits in response inhibition may to detrimental behavioral and psychological problems such as addiction to drugs or alcohol (Christodoulou et al., 2006; Kiehl et al., 2000; Thoma, Wiebel, and Daum, 2007). About 50% of individuals diagnosed with SZ and between 14% and 60% of individuals diagnosed with BD also develop substance abuse or dependence at some point in their life (Buckly, 2006; Cassidy et al., 2001). In a previous study, individuals with better performance during a Go/NoGo task was better able to abstain from alcohol (Thoma, Wiebel, and Daum, 2007). This suggests that remediation of response inhibition deficits could improve deleterious impulse related problems in these populations. As indicated by P300 amplitudes in this study, treatment focused on response inhibition may help SZ who show generalized lack of attentional resources, and SAD that showed delayed stimulus evaluation time in this study. Given their deficit in early visual ERPs, it will further benefit both BD and SZ to strengthen their initial structural encoding of faces or other complex affective stimuli. Furthermore, reduced P300 amplitudes with facial stimuli in SZ suggest that they might benefit from affective response inhibition training that focuses on increasing cognitive availability when processing affective information.

Limitations and Future directions

Considering the controversy as to whether BD and SZ are on a continuum (Crow et al., 1998) or are nosologically distinct (Bleuler, 1911), one of the major focus of these three studies was set to investigate whether the ERP components could delineate the three psychiatric groups – schizophrenia, schizoaffective disorder, and bipolar disorder from each other and from controls. The findings from this study suggest that a deficit in early neural response to inhibition among SAD group was unique to that group. However, due to the small number of SAD patients in study 1 and also to the fact that SAD and BD were not directly compared in the same study, the findings cannot address whether SAD and BD are nosologically distinct. Thus, larger sample size than in studies that include SZ, SAD, and BD has the potential to provide answers to this controversy.

In this series of studies, P300 amplitude and N200 latency consistently discriminated the groups. This supports the robust literature that suggest P300 amplitude reduction and/or delay as a stable endophenotype for schizophrenia (Bramon et al., 2005; O'Donnell et al., 2004; Souza et al., 1995; Turetsky et al., 2007)However, little has been previously reported as to whether N200 component is also a strong candidate endophenotype. More N200 studies including psychiatric patients will facilitate the understanding of early neural processing of response inhibition.

Finally, due to the different stimulus presentations (Study 1 & 2: lateralized presentation, Study 3: central presentation), it was not possible to test the impact of face on the task performance by direct comparison across the studies. Thus, in the future testing two Go/NoGo paradigms with faces, one with facial emotion as Go/NoGo cues

and the other one with non-emotional features (e.g. gender) will be helpful to elucidate the effect of emotion information on response inhibition.

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