Title: Emotional Processing, P50 Sensory Gating and Social Functioning in Bipolar Disorder

Abstract

Emotional processing has been reported to affect sensory gating as measured by the event-related potential known as P50. As both P50 and emotional processing are dysfunctional in bipolar disorder, we sought to investigate the impact that concurrent emotion processing has on sensory gating in this psychiatric population. P50 was recorded using a paired click paradigm. Peak-to-peak amplitudes for stimulus 1 (S1) and stimulus 2 (S2) were acquired during the presentation of disgust and neutral faces to young adults with bipolar disorder (N=19) and controls (N=20). Social functioning and quality of life self-reported measures were also obtained. The bipolar disorder group had significantly larger P50 amplitudes elicited by the S2-disgust response compared to controls, however no significant difference in overall P50 sensory gating was found between the groups. There were also no differences between groups in S1-disgust, nor in either of the neutral P50 amplitudes. The bipolar disorder group showed significant associations between sensory gating to disgust and measures of social functioning. Importantly, bipolar disorder showed impaired filtering of auditory information when paired to an emotionally salient image. Thus, it appears that patients with the greatest impairment in sensory gating also have the most difficulty to engage in social situations.

Keywords

Auditory sensory gating; bipolar disorder; emotion; P50; social functioning

Introduction

Bipolar disorder (BD) is an affective disorder characterised by mood fluctuation and is associated with social, emotional and cognitive impairment[1, 2, 3]. Fundamentally, BD has also been associated with impaired filtering of early sensory information[4, 5]. In humans, the brain's ability to filter repetitive, redundant information is crucial to prevent a flooding of irrelevant information to the cortex[4, 6, 7]. This process known as 'sensory gating' allows higher-order cognitive functions to proceed efficiently. Sensory gating is typically assessed via an auditory paired-click paradigm[4, 8, 9] using electrophysiological techniques to quantify the magnitude of each response. Normal sensory gating corresponds to a reduction in the amplitude of the P50 event-related potential elicited from the first (S1) to the second stimulus (S2) of two identical auditory stimuli usually presented at 500ms interval; it is expressed as a difference score ($S1_{amplitude} - S2_{amplitude}$), whereby a smaller value reflects poorer sensory gating.

While it has been suggested that P50 sensory gating deficits may be associated with impaired cognitive functioning in BD[4, 6], the impact that concurrent emotion processing has on sensory gating has not been examined in this patient group. In healthy controls, negatively valenced images have been found to disrupt the normal suppression of the magnetoencephalographic equivalent of P50, while positively valenced stimuli show no effect; these finding suggest that negative emotions may have a unique role in the modulation of sensory gating[10]. To our knowledge only one study has examined the relationship between P50 sensory gating and measures of social function. Marshall et al.[11] investigated this in healthy children (aged seven to 13 years) and while the majority of the sample showed P50 suppression, there were no significant correlations between sensory gating and social withdrawal.

While fronto-limbic emotional dysregulation has been implicated in the neurobiology of BD[12, 13] no studies have examined whether individuals with BD show any fundamental, pre-attentive disturbances (i.e. sensory gating) in the context of emotion processing and whether this is associated with higher-order measures of psychosocial functioning.

Aims of the study

As both P50 and emotional processing are dysfunctional in BD, we sought to investigate the impact that concurrent emotion processing has on sensory gating in this psychiatric population. In line with previous studies, it was hypothesised that BD patients would demonstrate less sensory gating in the context of processing a negative emotion compared to a healthy control group. Furthermore, it was hypothesised that the degree of sensory gating would be associated with indices of social functioning.

Methods

Participants

Nineteen patients with BD (14 females; mean age 25 years, SD = 5.9) and 20 matched healthy controls (9 females; mean age: 25.3 years, SD = 4.3) were recruited for this study. Patients were recruited from a specialized youth mental health service[12, 13] after being diagnosed by a psychiatrist using DSM-IV criteria. Twenty-six percent (N=5) met criteria for bipolar I disorder, 32% (N=6) bipolar II disorder, and 37% (N=7) for bipolar disorder not otherwise specified. Patients were tested under their normal medication: two were medication free, three were using one medicine, nine were using two medicines and three were using three medicines. The medications taken by the sample included mood stabilizers, anticonvulsants, atypical antipsychotics

and/or antidepressants. One patient provided no information about his treatment. Twelve subjects also presented a comorbid disorder including personality disorder (N= 3), social anxiety (N=2), eating disorder (N=1), attention-deficit hyperactivity disorder (N=1), substance and/or alcohol abuse (N=3) or presented with psychotic features (N= 2). Healthy controls (N=20) were recruited through advertisement in the local media.

Participants completed a self-report questionnaire that included two scales to quantify an array of psychosocial functioning factors: (i) the social functioning scale (SFS)[14] which has seven subscales (withdrawal/social engagement; interpersonal communication; independence-performance; independence-competence; recreation; prosocial; and employment) and (ii) the World Health Organization Quality of Life (WHO-QoL BREF)[15] which has four subscales (physical; psychological; social; and environment). For both patients and controls, exclusion criteria were medical instability, history of neurological disorder, history of head injury, medical illness known to impact cognitive and brain function, intellectual and/or developmental disability and insufficient English for assessment. All participants were asked to abstain from illicit drug or alcohol use for 48 hours prior to testing. The University of Sydney Human Research Ethics Committee approved the study. Written informed consent was obtained from the subjects.

Paired-Click Design

Participants were presented, via headphone, with 28 pairs of binaural pure tones (‘clicks’; square waves, intensity = 70dB, frequency = 1000Hz, duration = 1ms including 10% rise/fall envelope) with an inter-stimulus interval of 500ms between S1 (the first click) and S2 (the second click). Subjects were instructed to attend the clicks whilst viewing randomly presented pictures of disgust (n=42) or neutral (n=42) faces

from the Ekman Pictures of Facial Affect Series[16]. The 'disgust' emotion was specifically chosen because patients with BD, even when in an euthymic stage, show a particularly robust recognition of this emotion[1]. Face stimuli were presented on a monitor (placed 1.5m from the subject) 1000-1500ms (pseudo-randomised, mean = 1250ms) before the presentation of the click pairs and remained on the screen for 1500ms, thus completely overlapping the auditory click pair stimuli. Visual and auditory stimuli were presented using E-prime software (Psychology Software Tools, Inc.).

EEG Data Collection

EEG data were recorded continuously using a 64-channel Quick-cap (Neuroscan) with electrodes placed according to the standard 10-20 International System. EEG data were grounded midway between Fz and Fpz and referenced to the nose electrode. Horizontal and vertical electro-oculograms (EOG) were recorded for eye-blink artifacts. The EEG/EOG data were amplified and digitized continuously at 500 Hz (SyncAmp2, Scan 4.3.1 software) and were stored for subsequent off-line analysis.

EEG Data Analysis

Data were offline analysed using BrainVision Analyzer Software (Brain Products, version 2.0). The data were re-referenced to the Mastoids electrodes and EOG corrected[17]. This was followed by segmentation of the data between disgust and neutral face stimuli and subsequent segmentation between S1 and S2 stimuli, therefore creating four types of segments for each participant (Disgust S1, Disgust S2, Neutral S1 and Neutral S2). Each segment was epoched from 200ms pre- to 500ms post-

auditory stimulus (S1 or S2) and baseline corrected using the 200ms pre stimulus interval. Before averaging, data were bandpass filtered between 10 and 50 Hz [18] and an automatic artefact rejection procedure excluded trials in which the activity was exceeding +/- 75 μV in any EEG channel[19].

P50 peaks were detected using a semi-automatic detection procedure (Brain Vision Analyser, Brain Product) and the computer marked points were then verified and/or adjusted (by LV) according to the criteria set by Boutros et al.[9]. On a separate occasion, peaks were further verified and/or adjusted independently by two researchers (DH and JL) who were blinded to the diagnosis of each subject. According to Boutros et al.[9], the P50 was scored as the second major positive component after the Pa (or P30) in the 30-80ms interval or as the largest positive deflection in the 40-80ms interval if no Pa could be identified. For the S2 peak analysis, if there was no peak in the previously mentioned range, the amplitude was scored as 0.01μV. P50 peaks were scored from peak to preceding peak at Cz only; however, for inclusion in the final analysis a P50 component needed to be present in at least one additional neighbouring channel.

Peak to peak amplitudes for each of the four conditions were exported for statistical analysis using the Statistical Package for the Social Sciences (SPSS), version 20, software. Sensory gating was measured as the difference between S1 and S2 amplitudes (in each condition; neutral vs. disgust) as it has been proved to be more reliable than the S1/S2 ratio, [20]. Smaller differences reflect less attenuation of the S2 component and correspond to ‘weaker sensory gating’.

Statistical analyses

Two-tailed independent t-tests were used to assess group differences for demographic, social functioning and neurophysiological variables ($p < .05$ was considered significant). If equality of variance was compromised (according to Levene's test) the corrected degrees of freedom and p-values were reported. Pearson's correlations were conducted between the sensory gating and social functioning variables for each group.

Results

Demographics

As shown in Table 1, the groups were matched in terms of gender, mean age and years of education. Patients with bipolar disorder showed significantly worse ratings for most of the SFS subscales and in all four domains of the WHO-QoL (Table 1).

Neurophysiological findings

The BD group showed less sensory gating, in both disgust and neutral conditions, compared with controls; however, these differences did not reach statistical significance (Table 2). Further inspection of each stimulus, for each condition, revealed a significant between-group effect with the BD group showing significantly ($p<.05$) larger P50 amplitude for S2 in the disgust condition compared to controls. There were no significant between-group differences in the remaining three variables (i.e. S1 to disgust; S1 and S2 to neutral).

Correlational analyses

Separate Pearson's correlations were then undertaken for BD and controls. Controls showed no significant correlations, therefore only the correlations in the BD group are presented (Table 3). In total, there were five significant, positive associations between sensory gating scores and social measures in the disgust condition only. Essentially, for each association, a lower sensory gating difference score (weaker gating ability) was associated with a poorer score in each of the social functioning measures. Figure 1 shows scatter plots representing two of these significant correlations, where individuals with BD tended to cluster at the worse end of each spectrum, that is, those with less sensory gating under the disgust condition had the worst scores in SFS total and WHO-QoL (physical).

Discussion

For the first time, this study investigated the impact of emotion, as determined by processing of emotional visual stimuli, on P50 sensory gating in young patients with BD. The P50 amplitude elicited by S2 during the disgust condition was significantly larger in the BD group compared to controls. Additionally, within the BD group, the amplitude at S2 was significantly larger during processing of the disgust emotion compared to neutral processing. While we found no overall significant difference between patients and controls in P50 sensory gating, the significant difference at S2 suggests that processing of the disgust emotion is associated with disinhibition following a repetitive stimulus in bipolar disorder.

Impairment at S2 has been suggested to be reflective of a deficit in filtering of redundant information, whereas increased amplitude at S1 is thought to be a deficit in information encoding[21]. Given the lack of inhibition noted at S2 in the present study, it appears that processing of the disgust emotion decreased the capacity of the P50

system to filter out irrelevant information. This result is in agreement with a recent study[21] that identified the sensory gating deficit observed in bipolar disorder as being driven by a deficit in the S2 amplitude. Conversely, Lijffijt et al.[4] reported that the overall sensory gating impairment in their BD cohort was mediated by a difference in the S1 component. The authors suggested this might reflect less activity at S1 rather than disinhibition. It must be noted that this sample was made purely of bipolar I patients and were significantly older than our youth sample of mixed bipolar diagnoses.

The specificity of our finding to the disgust condition is interesting. It has been hypothesised that differential processing of affective signals, such as recognising facial expressions, could be indicative of abnormalities of neural networks mediating mood[1]. Specifically, disgust is processed by the anterior insula and caudate which both have connections with the frontal and subcortical structures that regulate mood[1, 22]. Accordingly evidence suggests that people with BD display both state and trait abnormalities in facial recognition of this emotion[1, 23, 24], and therefore investigation in this area has been considered a useful tool to explore emotional processing[23]. A recent study has identified that, compared to controls, patients with BD were unable to engage key prefrontal cortical structures whilst processing the disgust emotion, and instead they activated the hippocampus and caudate[23]. This evidence suggests that patients have greater engagement in bottom-up processes during disgust processing when controls activate top-down processes[23]. Top-down processes also mediate P50 and hence our finding corroborates the theory that top down processes are dysfunctional in BD and this may be more evident when concurrently processing the disgust emotion.

The finding that the S2 response for the disgust condition was correlated with indices of social functioning in BD patients is interesting, especially given that worse sensory gating was associated with lower scores in social functioning. Damage to the prefrontal cortex has been associated with impaired social and emotional functioning[25], providing further support for a dysfunctional frontal neural network in BD. Ultimately the mechanisms that underpin the observed changes in P50 elicited by the S2 stimuli in our study may be mediated via the prefrontal cortex.

There are several limitations to the current study. Firstly, the sample size is relatively small, which might explain the lack of significant group differences in P50 sensory gating. Furthermore, due to a small sample size, we could not determine whether there were any differences among the three bipolar subtypes, which may have contributed the larger variability observed within the BD group. A previous study[21] investigating N=126 BD patients noted a significant difference in P50 (elicited by a paired auditory stimulus paradigm; in the absence of emotionally salient stimuli) in bipolar I but only a trend in bipolar II, which may explain why the significant difference seen in S2 in our BD patients was not large enough to elicit an overall difference in P50 as our sample was much smaller and highly heterogeneous. In terms of psychosocial functioning and psychological distress however we have found in previous studies[26] that in this age group the bipolar subtypes have the same levels. Additionally, it has been demonstrated that BD patients show an impaired capacity to recognise disgust[24] as well as an impaired gating[27] during manic episodes compared to euthymic state. In the present study, mood state at time of testing was not formally recorded, however no patients were acutely manic. Moreover, two of our patients had a history of psychosis, which has been proved to worsen the sensory gating

impairment[5] and may further explain the variability in the results. Finally, the BD patients were taking a range of different psychotropic medications at time of testing and we cannot entirely discount any effect this may have had on the final results. However in this regard, previous studies have reported P50 gating changes in BD regardless of treatment with mood stabilizers or antidepressant[4, 5].

In conclusion, our results revealed that young adult BD patients are less able to attenuate the neurophysiological response to redundant information when concurrently processing the disgust emotion. Our results suggest that impairments seen in P50 in BD are most likely due to impairments in frontal driven; top down processes and this is prominent during facial recognition of disgust.

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Figures and Tables

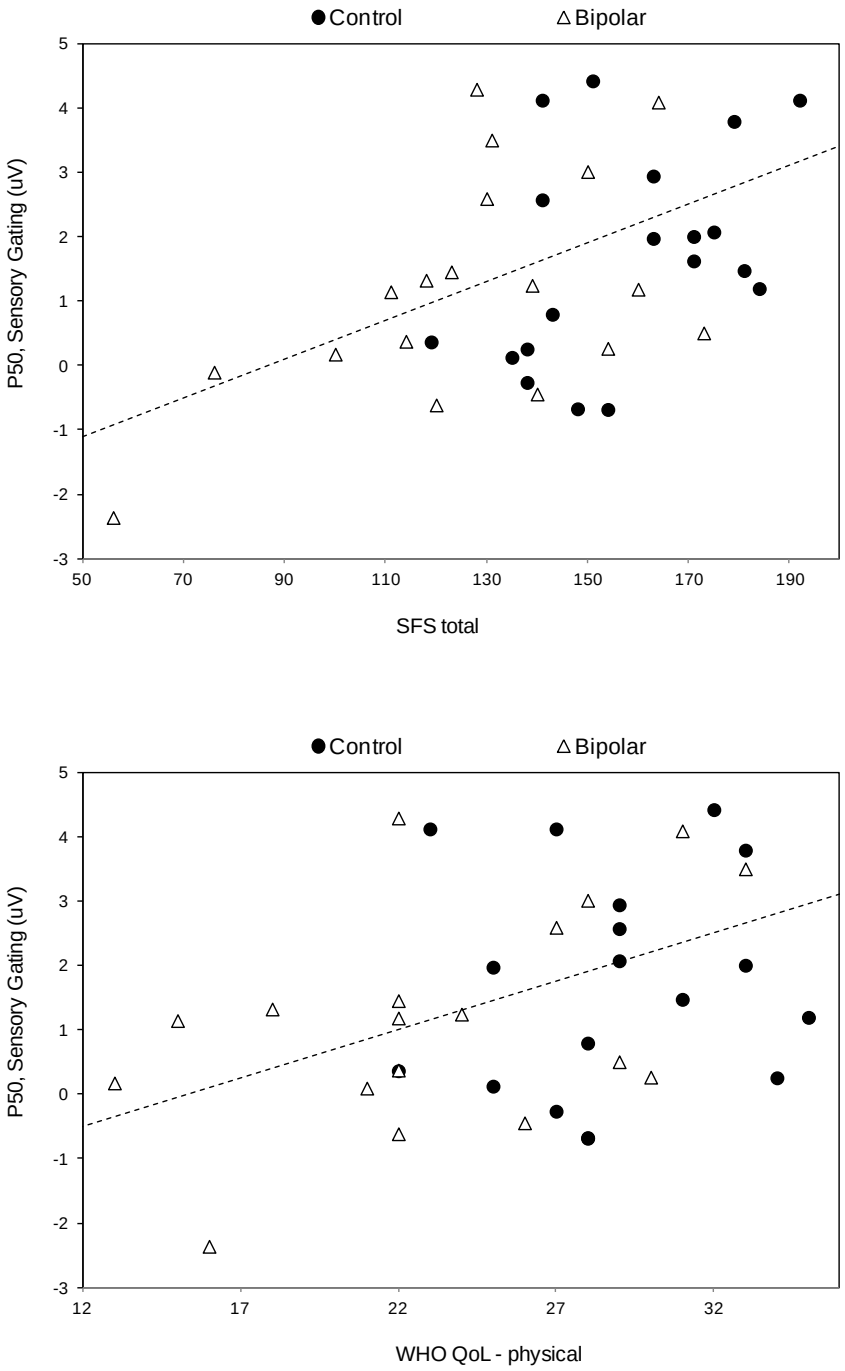

Figure 1: Scatter plot of P50 sensory gating (amplitudes; uV) during the Disgust condition versus (above) SFS total score and (below) WHO-QoL: physical scores. Bipolar disorder individuals are denoted by a clear triangle and control individuals are denoted by a black circle; a regression line (dotted) is shown for the bipolar disorder group, only, given the significant positive correlations between SG amplitudes and the

corresponding social functioning score. In both associations, bipolar cases tended to cluster in the worse end of each spectrum.

Table 1: Mean scores (± standard deviation) for demographic and social variables for bipolar disorder and normal controls; between group differences were tested by chi-square or independent samples t-tests (in bold for p<.05). Note: SFS: social functioning scale; QoL= quality of life.

	Bipolar	*Controls*	*Between-group differences*
Sex (f/m)	14/5	9/11	$\chi 2 = 3.31$, df = 1, p=.069
Age, years	25.0±5.9	25.3 ± 4.3	t = 0.18, df = 37, p = .856
Education, years	13.4±2.2	14.5±1.8	t = 1.79, df = 37, p = .081
SFS engagement	10.2 ± 3.1	11.74 ± 2.4	t = 1.78, df = 36, p=.083
SFS communication	7.6 ± 1.3	8.6 ± 0.7	**t = 2.80, df = 27.45, p=.009**
SFS performance	27.2 ± 7.5	22.6 ± 6.3	**t = 4.32, df = 31.71, p<.001**
SFS recreation	19.8 ± 10.2	22.6 ± 6.3	t = 1.01, df = 36, p=.319
SFS prosocial	18.5 ± 8.2	30.4 ± 9.9	**t = 4.02 df = 36, p<.001**
SFS competence	35.4 ± 3.5	38.5 ± 1.2	**t = 3.63, df = 22.4, p=.001**
SFS employment	7.6 ± 3.5	9.2 ± 1.6	t = 1.83, df = 23.4, p=.08
SFS total	127.1 ± 29.8	157.2 ± 20.1	**t = 3.62, df = 35, p=.001**
QoL: Physical	23.4 ± 5.7	28.8 ± 3.7	**t = 3.38, df = 34, p=.002**
QoL: Psychological	15.9 ± 4.5	22.4 ± 3.0	**t = 5.07, df = 33, p<.001**
QoL: Social	8.6 ± 3.3	11.7 ± 2.5	**t = 3.24, df = 36, p=.003**
QoL: Environment	25.6 ± 6.2	30.4 ± 4.7	**t = 2.6, df = 35, p=.014**

Table 2: Mean (± standard deviation) P50 peak-to-peak amplitudes (μV) for stimulus 1 (S1), stimulus 2 (S2) and the mean P50 sensory gating (SG) during disgust (D) and neutral (N) emotional conditions for the bipolar (N=19) and control (N=20) groups. Note: Significant ($p<.05$) independent samples t-tests are denoted in bold font.

		Bipolar	*Controls*	*Between-group t-test*
Disgust	P50, S1	3.44 ± 1.9	2.93 ± 1.6	t = -0.94, df = 37, p = .354
	P50, S2	2.30 ± 1.3	1.26 ± 1.3	**t = -2.49, df = 37, p = .017**
	P50, SG	1.15 ± 1.7	1.67 ± 1.6	t = 0.98, df = 37, p = .332
Neutral	P50, S1	3.92 ± 2.2	3.44 ± 1.8	t = -0.75, df = 37, p =.457
	P50, S2	2.24 ± 2.0	1.46 ± 1.3	t = -1.48, df = 37, p =.146
	P50 SG	1.68 ± 1.8	1.98 ± 1.4	t = 0.59, df = 37, p = .562

Table 3: Pearson's correlation coefficients (* denotes p<.05; ** denotes p<.01) between P50 sensory gating (difference scores) for (i) Disgust and (ii) Neutral conditions versus psychosocial measures (SFS and QoL) in patients with bipolar disorder (N=19), only. Note: SFS: social functioning scale; QoL = quality of life.

	P50, Sensory Gating	
	Disgust	Neutral
SFS engagement	.59**	-.01
SFS communication	.54*	.04
SFS performance	.38	.37
SFS recreation	.31	.32
SFS prosocial	.57*	.04
SFS competence	.20	-.06
SFS employment	.40	-.12
SFS total	.52*	.21
QoL: Physical	.49*	-.04
QoL: Psychological	.39	.06
QoL: Social	.28	.04
QoL: Environment	.36	-.01