Dysfunctional gaze processing in bipolar disorder

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ABSTRACT

Gaze conveys emotional information, and humans present sensitivity to its direction from the earliest days of life. Bipolar disorder is a disease characterized by fluctuating states of emotional and cognitive dysregulation. To explore the role of attentional control on face processing in bipolar patients (BP) we used gaze direction as an emotion modulation parameter in a two-back Working Memory (WM) task while high-density EEG data were acquired. Since gaze direction influences emotional attributions to faces with neutral expressions as well, we presented neutral faces with direct and averted gaze. Nineteen euthymic BP and a sample of age- and gender-matched controls were examined.

In BP we observed diminished P200 and augmented P300 evoked responses, differentially modulated by non-repeated or repeated faces, as well as by gaze direction. BP showed a reduced P200 amplitude, significantly stronger for faces with direct gaze than averted gaze. Source localization of P200 indicated decreased activity in sensory-motor regions and frontal areas suggestive of abnormal affective processing of neutral faces.

The present study provides neurophysiological evidence for abnormal gaze processing in BP and suggests dysfunctional processing of direct eye contact as a prominent characteristic of bipolar disorder.

1. Introduction

Early life experiences affect the way we learn to express and think about emotions (Frick and Morris, 2004; Graziano et al., 2010; Morris et al., 2007). Bipolar disorder is a disease typically appearing early in life, during late adolescence or young adulthood (A.P.A., DSM I-V TR, 1994), with genetic and environmental factors contributing to its development and outcome (Barnett and Smoller, 2009; Etain et al., 2008).

Emotion regulation may involve attentional and cognitive strategies (Gross and Thompson, 2007). Bipolar disorder is associated with dysfunctional attentional and cognitive regulatory processes, such as, suppression, and avoidance of thoughts/feelings and rumination (Aldao et al., 2010). It has been proposed that emotion dysregulation in bipolar patients (BP) could be explained by specific impairments of ventral and dorsal prefrontal regions involved in regulating subcortical regions (Phillips et al., 2008).

Working memory (WM) paradigms are voluntary attention control paradigms that have been used to investigate emotion regulation in BP

(Bertocci et al., 2012; Frangou et al., 2008; and see Phillips et al., 2008). Functional neuroimaging studies have demonstrated that WM processing of faces induces reduced prefrontal activity (Passarotti et al., 2012; Pavuluri et al., 2010; Vizueta et al., 2012).

When viewing emotional faces, BP perform worse in emotional face labeling (Favre et al., 2015; Kohler et al., 2011), and show hyperactivity in limbic regions (Surguladze et al., 2010). Even with neutral faces, BP show increased amygdala activation (Kim et al., 2012; Rich et al., 2006) and tend to perceive these faces as more hostile than healthy controls (Rich et al., 2006).

The eye region conveys emotional information (Itier and Batty, 2009): direct gaze augments the perception of approach-related affective states (i.e. anger, joy) while averted gaze increases the perception of avoidance-related affective states (i.e. fear, sadness) (Adams et al., 2003; Adams and Kleck, 2005). Additionally, gaze direction activates brain regions associated with emotional face processing, such as the amygdala and the fusiform gyrus (Adams et al., 2003; George et al., 2001; and see Itier and Batty, 2009). Humans present a sensitivity to

gaze direction from the earliest days of life (Farroni et al., 2002), and eye gaze interaction offers cognitive and affective learning opportunities (Lotzin et al., 2016, 2015; Stern, 1974; Tronick and Reck, 2009), and influences the development of emotion-regulation strategies (Aktar et al., 2016; Luoma et al., 2013; Möller et al., 2014). To the best of our knowledge, no previous work has investigated the neural correlates of gaze perception in BP.

Event-related Potential (ERP) studies mainly focused on differences in BP and controls in the processing of emotional face expression. An ERP component that is sensitive to face perception is the N170 (Bentin et al., 1996). Degabriele et al. (2011) reported significantly lower N170 amplitudes in patients with bipolar disorder compared to controls, but this reduction was independent of the emotional facial expression. On the other hand, a work by Sokhadze (Sokhadze et al., 2011) demonstrated that BP have decreased N170 amplitudes to emotional positive faces. Controversially, Wynn et al. (2013) found intact N170 responses to emotional faces. Ibanez et al. (2012) found that while in healthy controls happy faces elicited larger N170 amplitudes than angry faces, BD patients did not show valence differences in the N170, and suggested that BP might have a reduced affective detection threshold. Taken together, these data suggest that, while face encoding is overall preserved in BP, task instructions and affective requests may affect the N170 evoked responses in BP. Importantly, the N170 component is also sensitive to the encoding of gaze direction (Berchio et al., 2016; Conty et al., 2007; and for a review see Itier and Batty, 2009), that, as explained above, conveys emotional information. The question we thus asked in this study is whether gaze might influence the N170 component differently in BP than healthy controls due to altered emotional judgement of gaze.

A later ERP component, the P200 is related to attentional control and emotional processing in general, and is not specific to faces (Carretié et al., 2001; Correll et al., 2006). It has been shown that negative stimuli, such as threatening images, enhance its amplitude (Carretié et al., 2001; Correll et al., 2006; Schutter et al., 2004). Furthermore, the P200 amplitude is correlated with reduced WM performance (Judah et al., 2016). Therefore, the P200 appears to be another relevant component to explore attentional deployment and emotion processing in BP.

Anxiety and stress responses are potential confounding variables that must be taken into account when investigating gaze evoked responses and WM processing. Anxious individuals have an attentional bias for gaze direction (Schulze et al., 2013), and anxiety influences P200 evoked responses (Judah et al., 2016; Schmitz et al., 2012). Previous data have documented that stress responses affect behavior (for an exhaustive review on this topic, see Sandi and Haller, 2015), prefrontal attentional control (Liston et al., 2009), and the interpretation of another person's gaze (Rimmele and Lobmaier, 2012).

In the present study, we aimed to use gaze direction as an emotion modulation parameter in a WM task in order to explore the role of attentional control on face processing in BP. To this aim, we used a two-back WM paradigm in which we presented neutral faces with direct and averted gaze without explicit instruction about gaze direction. High-density EEG, a powerful neuro-imaging tool for describing brain network dynamics with high temporal resolution (Michel and Murray, 2012), was recorded while subjects performed the task.

Because we assumed that patients with bipolar disorder could be more susceptible to external stressor (Cohen et al., 2004; Dienes et al., 2006; Monroe and Harkness, 2005) compared to control subjects, we monitored stress differences between patients and controls by measuring heart rate variability, and self-perception of stress.

We hypothesized that BP would display increased activities in face-responsive brain regions, and decreased activation in dorsolateral prefrontal regions associated with WM for faces. Since the N170 is a face-sensitive component, and the P200 is modulated by attentional control and emotional processing, we expected augmented N170 and reduced P200 responses. We expected that altered neural responses would be

Table 1
Demographic and clinical features of the two study groups.

Characteristics	Control participants ($n = 19$)	Bipolar patients ($n = 19$)	t value	p value
Age: mean, SD	34.11 (10.69)	34.95 (10.49)	0.22	0.841
Gender: male, n	11	11		
Handedness: right, n	16	16		
Education[a]: mean, SD	2.27 (0.81)	2.28 (0.89)	0.052	0.749
IQ: mean, SD				
WM	11.44 (2.55)	10.41 (2.93)	− 1.376	0.595
Arithmetic	12.53 (2.29)	12.33 (2.35)	0.942	0.352
YMRS: mean, SD	0.72 (1.24)	0.69 (1.53)	− 0.084	0.379
MADRS: mean, SD	1.41 (1.53)	3.12 (3.39)	2.082	0.001
STAI-state: mean, SD	25.97 (3.49)	37.87 (12.27)	4.661	0
STAI-trait: mean, SD	30.39 (5.85)	42.53 (9.72)	4.053	0.037

[a] Education levels were classified into three groups: 3 = university studies; 2 = high school; 1 = no high school.

also reflected in lower accuracy and increased reaction times. Finally, since BP tend to identify stimuli with neutral value as emotionally negative, we hypothesized that direct gaze would reinforce these effects compared to indirect gaze.

2. Material and methods

2.1. Participants

Euthymic BP type I and II were recruited from the Mood Disorders Unit at the University Hospital of Geneva. Control subjects were recruited by advertisement. A snowball convenience sampling was used for the selection of the BD group. Control participants were matched by gender, age (± 3 years), educational level, handedness (Edinburgh inventory, Oldfield, 1971) (see Table 1). Exclusion criteria included a history of head injury, current alcohol or drug abuse, and a history of psychiatric illness. Informed written consent was obtained from all subjects and this study was approved by the Ethical Committee for Human Research of the Geneva University Hospital, Switzerland.

Three BP and one control subject were excluded from ERP analysis because of an excessive number of EEG artifacts, which resulted in 19 patients and 19 controls finally included in this study (see Table 1). All the patients were medicated, receiving pharmacological therapy including antipsychotics, antidepressants and mood stabilizers.

2.2. Clinical assessment

In order to confirm bipolar disorder diagnosis and check for co-morbidities in BP patients, and to exclude psychiatric diagnosis in the controls, all participants underwent a clinical structured interview (DIGS: Diagnostic for Genetic Studies, (Nurnberger et al., 1994) by a trained collaborator [P.C.] Consensus diagnoses were determined in consultation with psychiatrists [J-M.A.; C.P.] and psychologists [P.C.; Anne-Lise Kung]).

Euthymia was defined as the absence of major depression, hypomania, or mania. Symptoms of mania and depression were evaluated using the Young Mania Rating Scale (YMRS, Young et al., 1978), and the Hamilton Depression Rating Scale (HDRS, Hamilton, 1960), respectively. Participants were considered euthymic if they scored < 6 on YMRS and < 12 on HDRS. Both BP type I ($n = 9$), and type II ($n = 10$) were recruited. Moreover, to compare WM capacity between groups, two subtests of the WAIS-R (Wechsler, 1981) were evaluated: arithmetic, as well as forward and backward digit span.

All subjects were also assessed prior to electrophysiological recordings with the State-Trait Anxiety Inventory (STAI; state and trait; Spielberger et al., 1970).