Psychiatry Research 220 (2014) 315–321

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Atypical right hemispheric functioning in the euthymic state of bipolar affective disorder

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A R T I C L E I N F O

Article history:
Received 27 September 2013
Received in revised form
5 August 2014
Accepted 10 August 2014
Available online 15 August 2014

Keywords:
Dichotic listening
Functional hemispheric asymmetries
Emotional prosody
Emotion regulation
Euthymia

A B S T R A C T

Bipolar disorder (BD) has been associated with right hemisphere dysfunction. These findings usually come from studies that have not distinguished between symptomatic and euthymic states of BD. The present study aims to investigate atypical right (and left) hemispheric functioning in euthymic BD patients. We evaluated 40 participants (18 healthy controls and 22 euthymic BD patients) using an emotional prosody dichotic listening task and a linguistic dichotic listening task which have been shown to produce a strong left ear advantage (LEA) and right ear advantage (REA), indicating a right and left hemisphere superiority, respectively. The results replicate the well-known LEA in emotional prosody for healthy controls. In contrast, no ear advantage was found for emotional prosody in euthymic BD patients. Both groups revealed the well-established REA in the linguistic dichotic listening task. The patient group was heterogeneous with regard to medication, as it consisted of patients with a variety of pharmacological treatments. The results are in line with previous studies in symptomatic BD patients, and suggest that atypical LEA in emotional prosody can be interpreted as a neurobehavioral vulnerability marker of emotional dysregulation and dysfunction in the right hemispheric fronto-temporal network in both symptomatic and euthymic BD patients.

1. Introduction

Bipolar disorder (BD) is a highly dynamic disorder with a cyclic pattern of mood states ranging from hypomania and moderate depression to severe mania or depression with psychotic features, as well as mixed states (Muller-Oerlinghausen et al., 2002). BD is associated with dysfunction of emotion regulation (Phillips et al., 2008), which involves the initial steps of perception of information eliciting emotional arousal.

Emotional dysregulation in BD has also been linked to atypical functional hemispheric asymmetries as shown by neuroimaging studies (Yurgelun-Todd et al., 2000; Foland et al., 2008; Killgore et al., 2008; Strakowski et al., 2011; Liu et al., 2012) suggesting a deviation from the typical right hemisphere advantage in emotion perception. For example, Killgore et al. (2008) found a decrease in right inferior orbitofrontal activation in BD patients with manic symptoms during passive viewing of a series of black and white fearful facial expressions. A similar pattern has been reported by Jogia et al. (2008), who found a reduced right ventrolateral PFC activation in BD patients with manic symptoms compared to healthy controls during recognition of sad facial expressions. Further evidence for right frontal dysfunction in mania has been suggested by an fMRI study revealing decreased right-sided activation in the dorsolateral region of the PFC in BD patients with manic symptoms while identifying fearful expressions in a facial emotion task (Killgore et al., 2008). These findings suggest that orbitofrontal and prefrontal areas in the right hemisphere are associated with a failure to inhibit emotional salience in BD patients during manic episodes.

Atypical functional hemispheric asymmetries in emotion perception have also been found in depressive BD patients. However, evidence here indicates left rather than right orbitofrontal and prefrontal areas (e.g., Lawrence et al., 2004; Altshuler et al., 2008). Specifically, Altshuler et al. (2008) found reduced left orbitofrontal activation in depressive BD patients compared to healthy controls in a match facial emotion task using neutral and negative expressions. Decreased activation in left dorsolateral prefrontal cortex has also been found in depressive BD patients for the perception of sad facial expressions (Lawrence et al., 2004). In line with these findings an electrophysiological study by Allen et al. (1993), found higher right than left frontal activation in depressive BD patients compared to healthy controls. Overall these studies suggest that

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http://dx.doi.org/10.1016/j.psychres.2014.08.015
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the degree (and sometimes even the direction) of functional hemispheric asymmetries in BD patients change according to their manic and depressive episodes. These findings can be interpreted with respect to the Valence-Specific Hypothesis of emotion perception, which proposes left hemisphere specialization for processing positive emotions and right hemisphere bias for processing negative emotions (Ahern and Schwartz, 1979; Wedding and Stalans, 1985; Adolphs et al., 2001). According to this model, atypical functioning of the left hemisphere is related to an increase in negative emotional states whereas atypical functioning in the right hemisphere is related to increases in positive emotional states. Although mania can occur as a consequence of more positive and/or less negative emotions (Gruber et al., 2008, 2011), studies of symptomatic BD suggest a state-dependent imbalance in positive and negative emotions, which probably relates to atypical functional hemispheric asymmetries. Based on these studies one could assume that manic and depressive mood changes lead to atypical functional hemispheric asymmetries in fontal areas. The latter has been shown by several mood induction studies in healthy subjects (e.g., Altenmuller et al., 2002; Flores-Gutierrez et al., 2007). If atypical functional hemispheric asymmetries were also identified during euthymic states (the absence of depressed or elevated mood outside the normal range), this would challenge the idea that atypical functional hemispheric asymmetries in BD patients occur as a consequence of pathological mood states. Rather, this would imply that atypical functional hemispheric asymmetries constitute a vulnerability marker of BD.

Although only a few previous studies differentiated between symptomatic and euthymic BD patients (e.g., Wessa et al., 2007; Robinson et al., 2008; Chen et al., 2010; Keener et al., 2012), the majority of these studies also found atypical functional hemispheric asymmetries in emotion perception involving the right fronto-amygdala network in symptom free BD patients. For example, Chen et al. (2010) reported increased activation in the right amygdala and right orbitofrontal cortex in euthymic BD patients relative to healthy controls during a facial emotion task in which participants were explicitly asked to rate the affective intensity of faces depicting one of six emotion types (happiness, sadness, disgust, fear, surprise, and anger). Atypical increase in right prefrontal activation in euthymic BD patients was also found with an emotional face matching task (Robinson et al., 2008), and an emotional go/no-go paradigm where subjects responded to a target emotional face (Wessa et al., 2007). Moreover, a recent fMRI study (Keener et al., 2012) in euthymic BD patients found an increase in activation of the right amygdala, especially in response to happy faces. The study's task required participants to label color flashes that were superimposed on dynamically changing background faces comprising morphs from neutral to angry, sad, fearful, or happy expressions. Emotional expressions were task irrelevant and therefore were only implicitly processed by participants. In line with the proposed predominant role of the right hemisphere in emotional processing (Borod et al., 1998) the findings from the above neuroimaging studies suggest that BD patients perceived emotional faces as more emotional than healthy controls. This might also explain the increased right hemisphere involvement in BD euthymia in this study. Also resting encephalogram in children with both parents and grandparents diagnozed with major depressive disorder showed greater alpha asymmetry, with relatively less right than left hemisphere activity, compared with children at lower risk for depression (Bruder et al., 2007). Although atypical right hemisphere functioning seems to be a trait characteristic associated with BD and major depression disorder, it is unclear whether this atypical functional hemispheric asymmetry reflects dysfunction, or a compensatory/adaptive mechanism of these disorders.

A simple and reliable technique to study functional hemispheric asymmetries in emotional and non-emotional processing is the dichotic listening paradigm (Hugdahl, 2000; Voyer and Flight, 2001). In dichotic listening, a participant is simultaneously presented with two different auditory stimuli (usually speech) separately to each ear via headphones. After each trial, participants are asked to repeat the stimulus (usually one) they have identified. The dichotic listening paradigm typically shows a better reproduction of speech stimuli presented to the right ear (right ear advantage, REA; Hugdahl et al., 1999). Due to the predominantly contralateral projection in the auditory system (Kimura, 1967), the REA has been interpreted as indicating a left hemisphere advantage in language processing. Following the same logic, a left ear advantage (LEA) generally found for non-verbal stimuli, such as complex tones (e.g., Sidtis, 1981) and emotional prosody (e.g., Bryden and MacRae, 1989; Grimshaw et al., 2003), indicates right hemisphere specialization. A right hemisphere asymmetry in emotional prosody is also supported by CT and MRI studies, showing impaired emotional prosody comprehension in patients with right temporal posterior lesions (Gorelick and Ross, 1987; Ross, 1981; Ross and Monnot, 2008). In contrast, patients with left hemisphere lesions showed preserved emotional prosody comprehension (e.g. Blonder et al., 1991).

In line with atypical right hemisphere functioning in BD, two dichotic listening studies in symptomatic BD patients found a reduced LEA for processing complex tones (Bruder et al., 1989, 1994). Bruder et al. (1994) tested BD patients during manic and again during euthymic states using the complex tone dichotic listening task, in which participants were asked to discriminate pitch in a dichotic pair of complex tones. Here, BD patients revealed a reduced LEA during mania compared to healthy controls. During euthymia, however, the LEA was preserved, suggesting that a reduced right hemisphere advantage for the processing of complex tones is specific to symptomatic BD patients. Similarly, Bruder et al. (1989) found a reduced LEA in melancholic depressive BD patients in the complex tone dichotic listening task. Overall, these findings suggest that symptomatic BD patients show atypical functional hemispheric asymmetries due to right hemisphere dysfunction. However, none of these dichotic listening studies assessed emotional prosody in BD. For example, Bruder et al. (1994) used pitch of complex tones rather than emotional prosody as stimuli.

Another study assessed functional hemispheric asymmetries of speech processing in BD patients during manic episodes with psychotic symptoms, and euthymic episodes (Kaprinis et al., 1995). The study used a free-recall paradigm in which the listener was asked to repeat two different spoken digits, simultaneously presented to the right and left ear. The authors found that, similar to healthy controls, manic BD patients after recovery (i.e. euthymia) showed the expected REA. However, during manic states, the same BD patients showed an LEA, indicating an atypical right hemisphere advantage in speech processing. The authors hypothesized that this result may be explained by hyperactivation of the right hemisphere in symptomatic BD patients. Contrary to Kaprinis et al.'s findings, Bruder et al. (1994) found the expected REA in manic BD patients using a dichotic listening consonant vowel task involving verbal processing. Also, in contrast to Bruder et al., Kaprinis et al.'s study included BD patients with psychotic symptoms. Thus, a reduced left hemisphere advantage for verbal processing might be related to psychosis rather than BD. In other words, similar to the fMRI studies reported above, dichotic listening findings also suggest that symptomatic BD patients show atypical functional hemispheric asymmetries. However, in order to investigate the idea that right hemisphere dysfunction is a correlate of BD, the present study aims to investigate functional hemispheric asymmetries in euthymic BD patients with an emotional/prosodic dichotic listening and a non-emotional/linguistic dichotic listening task. Both tasks have previously been shown to