Progress in Neuro-Psychopharmacology & Biological Psychiatry 60 (2015) 1–10

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Neural correlates of negative emotion processing in bipolar disorder

Gianna Sepede [a,b,*], Domenico De Berardis [c], Daniela Campanella [c], Mauro Gianni Perrucci [a,d], Antonio Ferretti [a,d,e], Rosa Maria Salerno [a], Massimo Di Giannantonio [a,f], Gian Luca Romani [a,d], Francesco Gambi [a]

[a] Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University Chieti-Pescara, Italy
[b] Department of Basic Medical Sciences, Neurosciences and Sense Organs, University "A. Moro", Bari, Italy
[c] National Health Trust, Department of Mental Health, Teramo, Italy
[d] ITAB — Institute for Advanced Biomedical Technologies, "G. D'Annunzio" University Chieti-Pescara, Italy
[e] Bioengineering Unit, IRCCS NEUROMED, Pozzilli, Isernia, Italy
[f] National Health Trust, Department of Mental Health, Chieti, Italy

ARTICLE INFO

Article history:
Received 14 November 2014
Received in revised form 23 January 2015
Accepted 31 January 2015
Available online 7 February 2015

Keywords:
Bipolar disorder
Euthymia
First-degree relatives
fMRI
Negative emotion processing
Trait marker

ABSTRACT

Introduction: Bipolar disorder type I (BD-I) is characterized by a severe impairment in emotional processing during both acute and euthymic phases of the illness.
The aim of the present study was to investigate negative emotion processing in both euthymic patients and non-affected first-degree relatives, looking for state and trait markers of BD-I.
Methods: 22 healthy relatives of BD-I patients (mean age 31.5 ± 7.3 years; 15 females), 23 euthymic BD-I patients (mean age 35.2 ± 7.9 years; 14 females), and 24 matched controls (mean age 32.5 ± 6.2 years; 16 females) performed an IAPS-based emotional task during 1.5 T fMRI. They were required to identify vegetable items (targets) inside neutral or negative pictures.
Results: Euthymic BD-I patients showed a significant reduced accuracy in target detection during both neutral and negative images presentation, whereas first-degree relatives performed similarly to normal comparisons. We found a reduced activation of Left precuneus during negative images condition in the patients only. By contrast, both patients and relatives hyperactivated the Left insula and hypoactivated the Right supramarginal gyrus with respect to controls. Moreover, relatives showed an increased activation of Right lingual gyrus and lower activation of pre-supplementary motor area and Right superior frontal gyrus.
Conclusions: During a negative emotion task, euthymic BD-I patients and non-affected first-degree relatives shared an abnormal activation of a limbic area (Left insula) coupled with a reduced activation of a parietal region (Right supramarginal gyrus), thus suggesting a trait-like anomalous processing of affective contents. On the other hand, functional abnormalities found only in unaffected relatives and not in patients and controls may correspond to resilience factors.

1. Introduction

Bipolar disorder type I (BD-I) is characterized by recurrent manic/mixed and depressive episodes, separated by periods of clinical remission.

During depressive episodes, the major risk for the patients' safety is related to suicide ideations and attempts (Clements et al, 2013), whereas manic/hypomanic patients are usually unable to correctly judge the negative consequences of excessive involvement in potential harmful activities on their lives (Fletcher et al, 2013). A correct processing of negative stimuli is therefore crucial to avoid dangerous situations and to protect the subject's psychophysical integrity, choosing between approach or withdrawal (Alexandrov and Sams, 2005). The cyclic mood changes observed in BD-I have been associated to altered processing and regulation of emotion (Phillips et al, 2008a). To respond appropriately to emotionally salient information, the following steps are required: 1) attention to the stimuli and identification of their emotional significance, 2) generation of an affective state congruent with the stimuli, and 3) modulation of the affective state in order to produce a contextually appropriate behavioral response.

Functional Magnetic Resonance Imaging (fMRI) data suggest that these processes may depend upon a ventral and a dorsal neural system (Phillips et al, 2003). The ventral system, including insula, amygdala, ventral anterior cingulate cortex (ACC), ventral prefrontal cortex (PFC) and basal ganglia, has an important role in the first two steps (appraisal

Abbreviations: fMRI, Functional Magnetic Resonance Imaging; ACC, anterior cingulate cortex; PFC, prefrontal cortex; IFC, Inferior frontal cortex; YMRS, Young Mania Rating Scale; HAM-D, Hamilton Rating Scale for Depression; MOG, middle occipital gyrus

* Corresponding author at: Department of Neuroscience, Imaging and Clinical Sciences, Chair of Psychiatry, ITAB — Institute for Advanced Biomedical Technologies, University "G. D'Annunzio" of Chieti, Via dei Vestini 33, 66013 Chieti Scalo, CH, Italy. Tel.: +39 0871 3556901; fax: +39 0871 3556930.
E-mail address: g.sepede@unich.it (G. Sepede).

http://dx.doi.org/10.1016/j.pnpbp.2015.01.016
0278-5846/

of emotional stimuli and production of a congruent affective state) and in the autonomic response regulation. Conversely, the dorsal system, including the dorsal ACC, dorsal PFC and hippocampus, is involved in the cognitive modulation of the affective state.

It is not fully clarified whether a deficit in negative emotion processing is or not a potential endophenotype for BD-I. Candidate endophenotypes have to be heritable, associated with illness, state independent and found in the unaffected relatives of probands at a higher rate than the general population (Gottesman and Gould, 2003), but literature findings on this topic are still controversial. Pan et al (2013) found that only manic patients, but not remitted subjects, were significantly impaired in recognition of negative emotions. On the other hand, Sagar et al (2013) reported that euthymic BD-I patient were less accurate than normal comparisons in identifying fearful faces. Moreover, a response bias toward negative information was observed in both stable BD-I patients (Gopin et al, 2011) and unaffected first-degree relatives (Brand et al, 2012). Functional neuroimaging can powerfully complement behavioral data, allowing us to identify subtle between-group differences despite comparable behavioral performances.

Several studies reported that euthymic bipolar patients performed as well as normal comparisons during negative emotion tasks, but they significantly differed in the activation of dorsolateral prefrontal cortex (DLPFC) (Hassel et al, 2008), ventrolateral prefrontal cortex (vlPFC), insula (Foland-Ross et al, 2012) and inferior prefrontal regions (Robinson et al, 2008). On the contrary, other studies found that euthymic BD-I patients did not differ from normal controls while processing negative faces or passively viewing negative images, whereas differences were observed while processing happy/neutral faces (Liu et al, 2012) or during a down-regulation task (Townsend et al, 2013).

There are only a few studies exploring the fMRI correlates of negative emotion processing in first-degree unaffected relatives of BD patients. Surguladze et al. (2010) found that patients and relatives performed similarly to controls but showed an augmented activation of Medial Prefrontal Cortex (MPFC, BA9/32) during both negative and positive emotion recognition. Roberts et al. (2013) reported a selective reduced activation of Left Inferior frontal cortex (IFC) and Left insula when inhibiting responses to fearful face stimuli in young first-degree relatives of BD patients, even though they performed better than controls. Despite BD-I being a high heritability disorder, not all first-degree relatives manifest with the illness. Resilience, the process of adapting well to adversity, traumatic events or negative starting conditions (Lutha and Cicchetti, 2000), may also be defined as the set of adaptive brain features associated with the absence of psychiatric symptoms in predisposed individuals (Frangou, 2012). Brain functional alterations that are common in BD-I patients and unaffected relatives may be therefore interpreted as a consequence of shared genetic predisposition, whereas functional abnormalities found only in unaffected relatives and not in patients and controls may correspond to resilience.

The aim of the present study was to investigate negative emotion processing in a group of euthymic patients, looking for state and trait markers of BD-I. Including a group of unrelated healthy relatives we also expected to identify the neural correlates of risk and resilience factors for BD-I.

Our hypothesis was that significant differences in the functional activation of brain regions playing a key role in negative emotion processing could be commonly observed in patients and unaffected relatives, with respect to normal subjects. We also hypothesized that relatives would show a unique pattern of activation when compared to both patients and controls in important brain areas, as expression of compensatory mechanisms.

2. Methods

2.1. Subjects

Euthymic BD-I outpatients and unrelated healthy first-degree relatives of BD-I subjects were recruited from the Department of Mental Health of Teramo, Italy. Normal comparisons were recruited through public announcements. Euthymia was defined by a score ≤ 7 on the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and ≤ 5 on the Young Mania Rating Scale (YMRS) (Young et al, 1978), for at least 3 months.

Relatives had one or more first-degree family members affected by BD-I, no current DSM-IV Axis-I or -II diagnoses, and no lifetime diagnoses of mood disorders. Normal comparisons were free of any past or present psychiatric disorders and declared no familiarity for mood disorders.

Inclusion criteria were Right-handedness, assessed using the Edinburgh Inventory (Oldfield, 1971); age 18–55 years; and Intelligence Quotient (IQ) >70, assessed using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1997).

Exclusion criteria were chronic medical disorders, neurological abnormalities, implanted metals, and pregnancy. Subjects with other current DSM-IV Axis-I psychiatric disorders or any drug or alcohol abuse within the previous six months were also excluded (cigarette smoking was allowed and equally represented among groups).

All participants were assessed with the Structural Clinical Interview (SCID) for DSM-IV Axis-I and -II disorders (First et al., 2000, 2003), received a detailed explanation of the study design, and gave their written informed consent according to the World Medical Association Declaration of Helsinki (WMADH, 1997). The general procedures were approved by the local Institutional Ethics Committee. All subjects participated without receiving any form of payment. To motivate the potential participants, they were asked by the treating clinicians to have a talk with the research staff. During the talk, the researchers explained the negative consequence of the illness on patients, their families and friends, and the crucial importance of new studies to improve the knowledge of the neurobiological basis of BD-I. Twenty-four patients, 24 unrelated relatives and 24 controls were enrolled. Data of two relatives and one patient were incomplete, so the final sample consisted of 23 patients (mean age 35.2 $\pm$ 7.9 years; 14 females), 22 relatives (mean age 31.5 $\pm$ 7.3 years; 15 females; 12 offspring and ten siblings), and 24 controls (mean age 32.5 $\pm$ 6.2 years; 16 females). Mean age of onset in the patients group was 30.1 $\pm$ 6.1 years and the mean duration of illness was 4.8 $\pm$ 4.5 years. Nineteen patients (82.6%) were under psychopharmacologic treatments at the moment of the scanning and 22 patients (95.7%) reported psychotic features during the previous acute phases of the illness. Demographic and clinical characteristics of the participants are depicted in details in Table 1.

2.2. Task procedure

One hundred twenty colored pictures were chosen from the International Affective Picture System (IAPS) on the basis of their normative ratings (Lang et al, 1999): 60 (50%) pictures depicted unpleasant scenes (IAPS valence rating: <3) and 60 (50%) pictures depicted neutral contents (IAPS valence rating: 4.5–5.5). Vegetable items, such as plants and flowers ("targets"), were clearly visible into 25% of both neutral and unpleasant pictures. Targets were always neutral in valence (for example, there were no bloody grass, burning trees, etc.) irrespective of picture main emotional contain. Stimuli were generated by a control computer located outside the scanner room, running in-house software, implemented in MATLAB (Galati et al, 2008). They were projected over a screen inside the scanner tunnel and viewed through a mirror fixed above the head coil. Each stimulus was presented for 3000 ms. Twenty-four stimulation blocks, each containing 5 pictures, all unpleasant or all neutral, in a random order, were alternated with 24 control blocks of cross fixation (Fig. 1). The total duration of the task was 12 min. Participants were instructed to respond with their Right thumb during the stimulation blocks: they had to press a "yes" or a "no" button when a vegetable target was visible or not in the picture. During the control blocks participants were only required to fixate on the cross, without giving a motor response. Percentage of correct responses and reaction times were recorded.