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Original article

# Fronto-limbic disconnection in bipolar disorder

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ABSTRACT

*Background:* Bipolar disorder (BD) is a severe, disabling and life-threatening illness. Disturbances in emotion and affective processing are core features of the disorder with affective instability being paralleled by mood-congruent biases in information processing that influence evaluative processes and social judgment. Several lines of evidence, coming from neuropsychological and imaging studies, suggest that disrupted neural connectivity could play a role in the mechanistic explanation of these cognitive and emotional symptoms. The aim of the present study is to investigate the effective connectivity in a sample of bipolar patients.
*Methods:* Dynamic causal modeling (DCM) technique was used to study 52 inpatients affected by bipolar disorders consecutively admitted to San Raffaele hospital in Milano and forty healthy subjects. A face-matching task was used as activation paradigm.
*Results:* Patients with BD showed a significantly reduced endogenous connectivity in the DLPFC to Amy connection. There was no significant group effect upon the endogenous connection from Amy to ACC, from ACC to Amy and from DLPFC to ACC.
*Conclusions:* Both DLPFC and ACC are part of a network implicated in emotion regulation and share strong reciprocal connections with the amygdale. The pattern of abnormal or reduced connectivity between DLPFC and amygdala may reflect abnormal modulation of mood and emotion typical of bipolar patients.


## 1. Introduction

Bipolar disorder (BD) is a severe, disabling and life-threatening illness that affects approximately 1–2% of the general population [16]. Disturbances in emotion and affective processing are core features of the disorder with affective instability being paralleled by mood-congruent biases in information processing that influence evaluative processes, social judgment, decision making, attention, and memory [31,32]. Several lines of evidence, coming from neuropsychological studies and from functional and structural brain imaging reports, suggest that disrupted neural connectivity could play a role in the mechanistic explanation of these cognitive and emotional symptoms [1], due to brain network dysfunctions in corticolimbic circuitries connecting prefrontal regions, cingulate cortex and the amygdala (Amy) [17,43,39] and contributing to emotion generation and modulation [20,15,6].

Previous reports in the literature have shown alterations in this network connectivity in psychiatric populations. Resting state studies found reduced functional connectivity between the prefrontal cortex and the amygdale in both BD and schizophrenic patients [29] and a reduced global brain connectivity between amygdala and dorsolateral prefrontal cortex (PFC) in BD with a positive history of psychosis compared to non-psychotic patients and healthy control (HC) subjects, which did not differ among themselves [5]. The global brain connectivity method estimates the connectivity between each individual voxel and every other voxel in the brain.

Patients with bipolar disorder type II showed a significantly reduced activity and negative functional connectivity between the amygdala and the orbitofrontal cortex as well as the dorsolateral prefrontal cortex relative to HC in an emotional face-matching task [55]. Moreover in a psychophysiological interaction (PPI) study, bipolar euthimic patients showed lower activations in frontal lobe, insula, bilateral middle frontal gyrus (BA 46/9) and bilateral cingulated cortex (BA 24 and BA 23), and a significantly less negative functional connectivity between left amygdala and bilateral PFC, during a task that required viewing neutral or

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negative images and either reacting normally or reducing emotional responses through cognitive reappraisal [52]. Similar findings have been described in young patients with BD soon at the beginning of the illness. Compared with healthy controls, BD subjects had significantly reduced connectivity between the left amygdala and two regions: right posterior cingulate and right fusiform gyrus/parahippocampal gyrus [41]. Dickstein et al. reported that pediatric BD is characterized by altered functional connectivity in a fronto-temporal circuit that is also implicated in working memory and learning [13]. Recent findings also suggest that alterations in the functioning of fronto-limbic systems implicated in voluntary emotion regulation are present also in unaffected bipolar offspring [24,4]. Finally, Almeida et al. found a reduced left-sided top-down medial PFC–amygdale effective connectivity in patients with both major depressive disorder (MDD) and bipolar disorder (BD) respect to HC in an emotional labeling task. Left-sided differences involved top-down connections and discriminated between depressed and control subjects. Conversely, on the right side the abnormality was in bottom-up that was specific to bipolar disorder [3]. These pivotal data support the hypothesis of network dysfunctions in corticolimbic circuitries connecting prefrontal regions and basal ganglia, which can then be proposed as biomarkers of the disturbances in emotion and affective processing which characterize BD patients. Nevertheless, some methodological limitations could hamper the interpretations of the results. To be defined, these network dysfunctions need to be investigated in larger samples, thus allowing to study the connectivity between the multiple structures involved. Furthermore, connectivity studies in BD have been performed mainly with functional connectivity techniques, which explore correlations among activations of different areas but did not allow any inferences about the causality and directionality of the connections. Effective connectivity studies could go beyond this limitation by modeling causal effects and the possible interactions among inputs or regions. Indeed when the inputs are known, dynamic causal modeling (DCM) can be used to analyze the blood oxygen level dependent (BOLD) responses in order to measure effective connectivity by describing how the present state of one neuronal population causes dynamics (i.e., rate of change) in another, and how these interactions change under the influence of external perturbations (i.e., experimental manipulations) [14,48]. DCM can then estimate the significance of the differences between groups in responses at the network level to known stimuli. In literature, only few studies evaluated functional connectivity with DCM in bipolar patients [2,3]. The aim of the present study is to investigating the effective connectivity, with DCM methods, in a specific corticolimbic network including prefrontal areas, cingulate cortex and amygdala in a sample of bipolar depressed patients.

## 2. Materials and methods

### 2.1. Participants

The sample included 92 participants. We studied 52 inpatients affected by bipolar disorders consecutively admitted to San Raffaele hospital psychiatric ward in Milano. Inclusion criteria were to be affected by a major depressive episode, without psychotic features, with a diagnosis of bipolar disorder type I (structured clinical interview for DSM disorders). Patients underwent a one-week pharmacological washout and were drug free except for lithium (lithium = 24) at the moment of magnetic resonance acquisition. Exclusion criteria were additional diagnoses on axis I, mental retardation on axis II, pregnancy, major medical and neurological disorders, or history of drug or alcohol abuse or dependency. No patient had received electroconvulsive therapy within 6 months before study enrollment. Physical examination, laboratory tests, and electrocardiograms were performed at admission. Severity of depression was rated on the 21-item Hamilton Depression Rating Scale (HDRS) [18]. Forty healthy subjects with no previous history of psychiatric, neurological, and systemic disorders served as control subjects. Clinical and demographic characteristic of the sample are resumed in Table 1.

**Table 1**
Data are means ± standard deviations.

| | Controls ($n = 40$) | BD patients ($n = 52$) | $t$, $F$, $\chi^2$ | $P$ |
|---|---|---|---|---|
| Age | 41.85 ± 14.51 | 47.59 ± 10.85 | 2.17 | 0.032 |
| Gender | 20 M, 20 F | 16 M, 36 F | 3.51 | 0.06 |
| Familiarity | – | 39 F+, 13 F– | – | – |
| Hamilton score | – | 22.68 ± 4.7 | – | – |
| Beck Depression Inventory | – | 15.06 ± 6.47 | – | – |
| Age at onset | – | 30.76 ± 8.99 | – | – |
| Duration of illness | – | 16.90 ± 10.61 | – | – |
| Number of depressive episodes | – | 4.13 ± 4.27 | – | – |
| Number of manic episodes | – | 3.07 ± 4.14 | – | – |

M: male; F: female; F+: positive familiarity for BD.

After complete description of the study to the participants, written informed consent was obtained. The study was approved by the local ethical committee.

### 2.2. Image acquisition

Gradient echo and echo-planar images (EPIs) were acquired on a 3.0 T scanner (Gyroscan Intera; Philips, The Netherlands) using a six-channel sensitivity encoding (SENSE) head coil. For each functional run, 124 T2*-weighted volumes were acquired using an EPI pulse sequence [repetition time (TR) = 3000 ms, echo time (TE) = 35 ms, flip angle = 90°, field of view = 230 mm, number of axial slices = 25, slice thickness = 5 mm, matrix size = 80 × 80 reconstructed up to 128 × 128 pixels]. Two dummies scans before fMRI acquisition allowed us to obtain longitudinal magnetization equilibrium. Total acquisition time was 6 min and 11 s. On the same occasion and using the same magnet 22 Turbo Spin Echo (Philips), T2 axial slices [repetition time (TR) = 3000 ms; echo time (TE) = 85 ms; flip angle = 90°; turbo factor 15; 5-mm-thick, axial slices with a 512 × 512 matrix and a 230 × 230 mm field of view] were acquired to rule out brain lesions.

### 2.3. Cognitive activation paradigm

We studied neural correlates of implicit emotional processing of facial affect expressions with a face-matching paradigm [21]. This paradigm has allowed researchers to define the effective connectivity of the amygdala with an extended regulatory network encompassing the cingulate, orbitofrontal, insular and dorsolateral PFC [37,47]. Four blocks of six pictures each representing human faces with fearful or angry expressions, interspersed with five blocks of six pictures of geometric shapes, were shown to the participants. Each picture is made up of two faces/shapes in the lower side and one in the upper part. Participants had to push a button on a response box to indicate which of the two images displayed in the lower side of the picture matched the one in the upper part. Images were displayed for 4 s interleaved by a black screen.