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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, χ^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.

3. Data analysis

3.1. fMRI analysis

All images were computed, overlaid on anatomic images, and analyzed using Statistical Parametric Mapping software (SPM8, Welcome Department of Imaging Neuroscience, Institute of Neurology and the National Hospital for Neurology and Neurosurgery; London, England). Scans were corrected for slice timing and realigned for head movements. Images were then normalized to a standard EPI template volume based on the Montreal Neurological Institute (MNI) reference brain, and smoothed using a 10-mm full-width at half-maximum isotropic Gaussian kernel. The evoked hemodynamic responses were modeled as a delta function convolved with a hemodynamic response and its temporal derivative within the context of the general linear model (GLM). At the individual level, we first compared (t-test, threshold $P < 0.001$) the face-matching condition with the shape-matching condition, thereby isolating regions that were engaged in the emotional processing of faces. Contrasted images for each subject were then entered into second-level two sample t-test (patients, controls), as implemented in SPM8, to identify the peaks of maximum activation in the amygdala, anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (left hemisphere). To identify the a priori regions of interest (ROIs) a mask including amy, ACC (BA 24,32), DLPFC (BA 9, 46) was created using PickAtlas software (Wake Forest University, USA; www.fmri.wfubmc.edu).

3.2. Dynamic causal modeling (DCM) analysis

DCMs are generative models of brain responses, which provide posterior estimates of neurobiologically interpretable quantities such as the effective strength of synaptic connections among neuronal populations and their context-dependent modulation. Dynamic causal modeling aims to explain, quantitatively and mechanistically, how observed fMRI responses are generated. BOLD responses are modeled by a differential state equation, which describe:

- how the present state of one neuronal population causes dynamics (i.e., rate of change) in another via synaptic connections;
- how these interactions change under the influence of external perturbations (i.e., experimental manipulations) or endogenous brain activity.

These factors are modeled into the equation as matrices (A, B, C). The interactions between the neural states are termed as endogenous connections and quantified by A matrix parameters. The contextual experimental conditions can bilinearly modulate the connections as quantified by B matrix parameters, or affect the nodes of DCM as driving inputs, quantified by C matrix parameters [14,48]. DCM analysis include a two-step procedure that involved:

- selection of the best model from a series of candidate ones using Bayesian model selection;
- testing the hypothesis that the effective connectivity within the best model differed significantly between BD patients and HC.

Effective connectivity was estimated with dynamic causal modeling in a trinodal neural model including two anatomically defined prefrontal cortical regions, anterior cingulate cortex and the amygdala.

3.2.1. Regions of interest

The differential state equation are modeled on different nodes, seeds regions are identified a priori. We chose left amygdala, DLPFC and ACC as regions of interest for DCM analyses on the basis of their known importance in emotion processing and emotion regulation [47]. To account for individual differences, we extracted principal eigenvariates in 6 mm spheres centered in the regions above. The exact location of the 6 mm sphere was based upon the local maxima of the subject-specific statistical maps within 8 mm of the group-maxima comparison for ACC and DLPFC, amygdala was considered as a whole. The largest clusters in neural regions of interest were data driven and chosen from our standard SPM8 analyses. These included three main regions of interest: anterior cingulate cortex (BA 32, peak coordinates -18, 46, 10), dorsolateral prefrontal cortex (BA 46, peak coordinates -44, 46, 13) and the amygdala.

Left-sided regions were chosen to allow a construction of a simple, three-node unilateral model and because the left hemisphere was the location of the majority of observed clusters of activation (see Fig. 1 for a typical VOI extraction in a single subject).

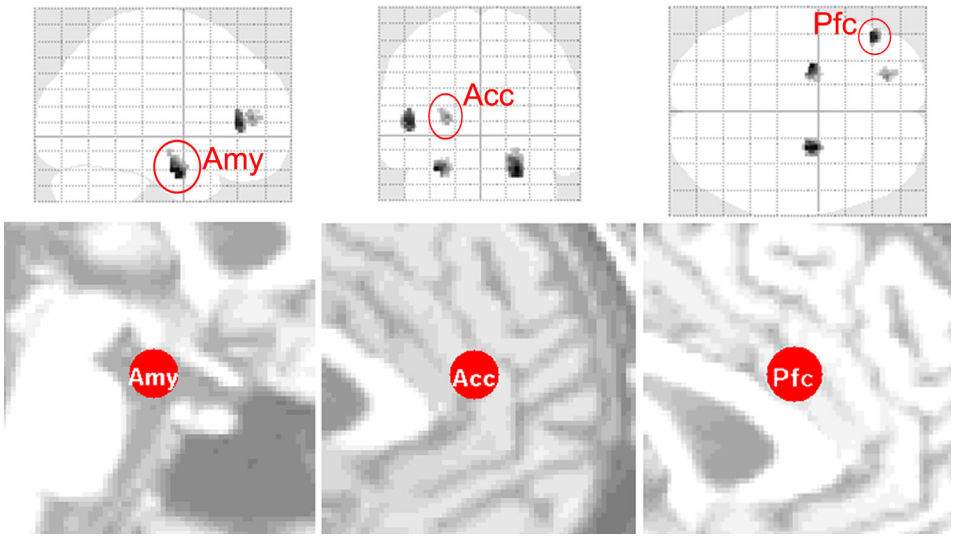

Fig. 1. Anatomical localization of the seeds for dynamic causal modeling (DCM). Abbreviations: Amy: amygdala; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex.

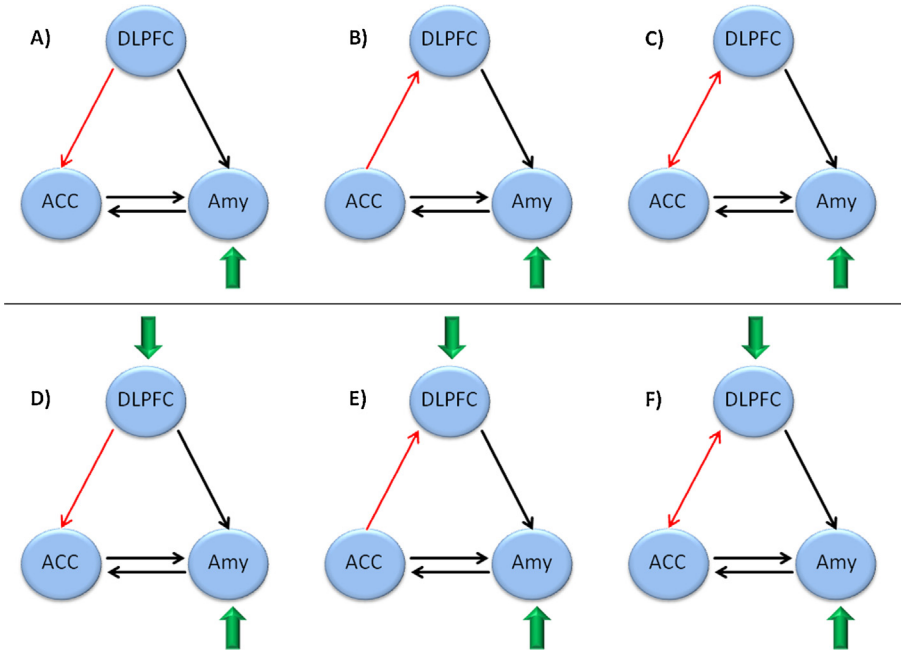

Fig. 2. The trinodal models including dorsolateral prefrontal cortex (DLPFC), anterior cingulated cortex (ACC), and amygdale (Amy) and connections among regions. Green arrows represent facial stimuli entered the model.

Previous DCM studies have similarly employed a unilateral model for analyses [2,46].

3.2.2. Models specification

Six alternative models with different endogenous connections and task inputs were constructed (models A, B, C, D, E and F on Fig. 2). All the models were defined as bilinear and stochastic. Stochastic DCM is an extension of deterministic DCM, which seeks to improve model estimation by modeling random fluctuations (or noise variance) and hidden neuronal causes. Stochastic DCMs allow for fluctuations in the hidden states, such as neuronal activity or hemodynamic states like local perfusion and deoxyhemoglobin content. These fluctuations can be regarded as a result of (endogenous) autonomous dynamics that are not explained by (exogenous) experimental inputs. This state-noise can propagate around the system and, potentially, can have a profound effect on the correlations among observed fMRI signals from different parts of the brain [27]. Daunizeau et al. have validated stochastic DCM and shown that stochastic DCM is superior over deterministic DCM in both model structure inference and model parameter inference [12]. In the first three models (A, B, C), driving inputs enter via the amygdala, while in the last three (D, E, F) via both amygala and DLPFC. We modeled the networks following LeDoux two roads theory. The low road is a direct pathway to the amygdala, which then activates a body response, it is the fast way to a bodily response. The high road is activated simultaneously and includes the cortical parts of the brain, thus creating a conscious impression of what the stimulus is [25].

For all the proposed models, we fixed a forward and backward connection between ACC and AMY, and a unidirectional connection from DLPFC to AMY. These connections were anatomically determined in macaque monkeys and validated in functional studies [47,23]. We indeed test the ACC/DLPFC connectivity for all the possible combinations. All the six alternative models are described on Fig. 2.

3.2.3. Structural and parametric analysis

Bayesian model selection (BMS) is a powerful method for determining the most likely from a set of plausible models. In the context of DCM, BMS is used to distinguish between different system architectures. If group differences were not present in DCM structure (BMS), these should be inferred at the DCM parameter level (Bayesian model averaging [BMA]).

BMA is a Bayesian approach that averages each parameter across subjects and across models such that the contribution of each model (of each subject) for that parameter is weighted by each model's posterior probability for that subject [35,49].

Seghier et al. suggested that Bayesian model comparison and averaging should be conducted separately on patients and controls [44]. For multi-subject analyses, two options exist depending on whether one assumes that the parameters of interest are fixed effects in the population (fixed effects [FFX]) or are themselves probabilistically distributed in the population (random effects [RFX]). We use in the present analysis the random effects (RFX) [49].

To investigate their clinical relevance, measures of the effective connectivity between brain regions were correlated with ratings of the core depressive symptoms (item 1-2-3-8 of the Hamilton Depression Rating Scale) [19]. Threshold for significance was set at $P < 0.05$ with Bonferroni correction for multiple comparisons.

4. Results

4.1. Bayesian model selection (BMS) and Bayesian model averaging (BMA)

Six different endogenous connection models were compared using the Bayesian selection approach (Fig. 2). To find the group-level optimal DCMs, we first used random effects Bayesian family level inference [35] in BMS to compare two families of models:

- models with task's input only in amygdala (DCMs A, B, C);
- inputs also in DLPFC (DCMs D, E, F).

After this first step, we then compared the three models belonging to the winning family.

Table 2
Strength of connectivity; data are means ± standard deviations.

	Controls ($n=40$)	BD patients ($n=52$)	F	P
Amy to ACC	0.032 ± 0.044	0.023 ± 0.039	0.20	0.65
ACC to Amy	0.032 ± 0.070	0.007 ± 0.069	2.54	0.11
DLPFC to Amy	0.047 ± 0.067	0.012 ± 0.048	5.41	0.02
DLPFC to ACC	0.048 ± 0.058	0.026 ± 0.057	1.56	0.21

BD: bipolar disorder; Amy: amygdala; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex.

The winning family was the two inputs family (DCMs D, E, F) in both groups (patients and controls). Our best model across all subjects was a forward model from the DLPFC to amygdala and from DLPFC to ACC and a bidirectional connection between ACC and amygdala (Fig. 2, model D).

To infer subjects DCM parameters BMA analysis were performed. As in BMS analysis, we accounts for heterogeneity of model structure across subjects (RFX).

4.2. Effects of diagnosis and depression severity

After extracting the values of endogenous connections between areas, we performed a one-way ANCOVA analysis for independent samples with no correction for multiple comparisons, with age as nuisance covariate, to compare parameters between BD and HC (Table 2). 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.

Strength of effective connectivity between ACC-Amy inversely correlated with HAM-D item 3 ($r=-0.45$; $P=0.002$) (suicide) (Table 3). No other correlation was significant.

5. Discussion

We observed a reduced effective connectivity between DLPFC and the Amy in BD patients during an emotional processing task (Fig. 3).

These regions are fundamental in voluntary emotion regulation strategies, including reappraisal and redirection [39], and previous findings based on a variety of functional neuroimaging techniques (functional MRI, positron emission tomography, single photon emission computerized tomography) showed that an abnormal functioning of these brain structures might be involved in the cognitive and emotional deficits typical of bipolar disorder [1,17,39,9,30].

Table 3
Correlation analysis, significances are corrected for multiple comparison.

	HAM. Item 1 (depressive mood)	HAM. Item 2 (feelings of guilt)	HAM. Item 3 (suicide)	HAM. Item 8 (retardation: psychomotor)
Amy to ACC	$r=-0.0237$ $P=0.875$	$r=-0.1952$ $P=0.189$	$r=0.1217$ $P=0.415$	$r=0.2310$ $F=0.118$
ACC to Amy	$r=0.0185$ $P=0.902$	$r=-0.1227$ $P=0.411$	$r=-0.4495$ $P=0.002$	$r=-0.0605$ $P=0.686$
DLPFC to ACC	$r=0.0651$ $P=0.664$	$r=-0.0789$ $P=0.598$	$r=-0.1575$ $P=0.290$	$r=-0.1034$ $P=0.489$
DLPFC to Amy	$r=-0.1374$ $P=0.357$	$r=-0.1929$ $P=0.194$	$r=-0.1499$ $P=0.314$	$r=-0.1098$ $P=0.462$

BD: bipolar disorder; HAM: Hamilton Psychiatric Rating Scale for Depression; Amy: amygdala, ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex.

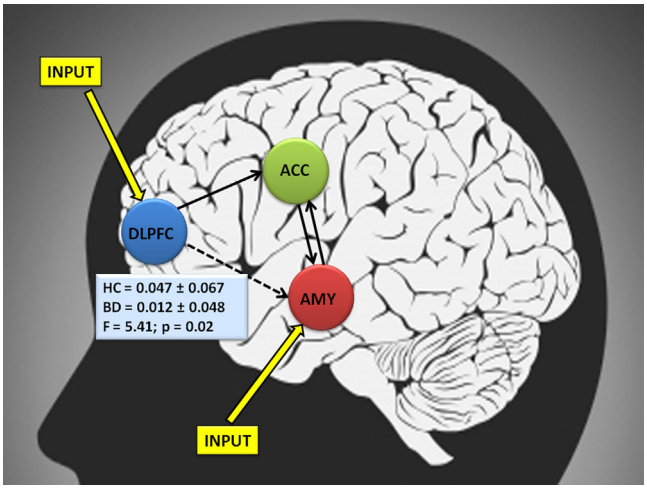

Fig. 3. Decreased effective connectivity between dorsolateral prefrontal cortex and amygdala during emotion labeling in bipolar disorder. Abbreviations: BD: bipolar disorder; HC: healthy controls; Amy: amygdala; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex. Black arrows: no significant effective connectivity differences between BD and HC. Dotted arrow: significant lower effective connectivity in BD patients versus HC between DLPFC and Amy. Yellow arrows: driving inputs.

Both DLPFC and ACC are part of a network implicated in emotion and visceromotor regulation and share strong reciprocal connections with the amygdala [33,40]. These regions are mutually connected in negative feedback loops crucial for emotion and cognitive functions known to be impaired in bipolar patients [45,42]: amygdala project in excitatory manner on prefrontal areas and on ACC, which with a negative loop on the amygdala regulate their activity [47,38]. The pattern of reduced top-down connectivity (DLPFC to Amy) may therefore reflect abnormal inhibition or reduced functional integration that may lead to altered modulation of mood and emotion [26].

The observed significant negative relationship between strength of the ACC to Amy connectivity and suicide supports a role of these abnormalities as biomarkers of core psychopathological symptoms. This finding is in agreement with previous reports in suicide attempters of a reduced functional connectivity from ACC to bilateral posterior insula [34], which are input regions for subcortical loci such as the amygdala and striatum [11].

Moreover, using an automated surface based approach (FreeSurfer) Wagner et al. found that patients with high risk for suicide showed significantly thinner cortex in the left dorsolateral, ventrolateral prefrontal cortex and the anterior cingulate then non-high risk patients [56]. Again, neurocognitive dysfunctions may lead to the development of suicidal behaviours via an inadequate regulation of emotional and cognitive responses, which in turn could facilitate self-harming acts in an emotional context [22].

A reduced functional connectivity in the prefrontal corticolimbic networks could be paralleled by a decreased integrity of white matter (WM) structures ensuring the structural connectivity among these regions. In patients with BD a loss of white matter integrity in fronto-limbic circuits has been consistently observed, and proposed to represent a major biological factor associated with the illness [7]. In particular, a reduced integrity of WM in the uncinate fasciculus, which connects the amygdala with the frontal cortex and anterior cingulate [36], has been consistently reported [57,28,50,51,54,53,8,10]. To clarify this point, further studies are needed to correlate measures of reduced functional connectivity with measures of reduced WM integrity.

Limitations of the present study, which is correlational in nature, also include issues such as generalizability, possible population stratification, concomitant lithium medication and its effects on the observed differences, nondrug naïve, no placebo control, no evaluation for compliance, varying treatment periods and no evaluation of premorbid IQ. Another possible limitation of the present study is that paradigm used cannot be considered a purely emotional, and differences between groups may potentially be due to problems in processing faces per se.

Despite these limitations, the present findings support the utility of effective connectivity studies in identifying biological markers of BD that may help identify potential biological targets for novel, personalized treatments for patients [58].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2014.04.001.

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