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Neural correlates of negative emotion processing in bipolar disorder

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Highlights

- Euthymic BD-I patients performed worse than controls during a negative emotion task
- Healthy first-degree relatives of BD-I appeared behaviorally intact
- Patients and relatives shared limbic and frontoparietal functional alterations
- A disrupted processing of negative stimuli may be a trait marker of BD-I

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.

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

Keywords

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

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 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, First et al., 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 ± 7.9 years; 14 females), 22 relatives (mean age 31.5 ± 7.3 years; 15 females; 12 offspring and ten siblings), and 24 controls (mean age 32.5 ± 6.2 years; 16 females). Mean age of onset in the patients group was 30.1 ± 6.1 years and the mean duration of illness was 4.8 ± 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.

Table 1. Demographic and clinical variables.

Subject details	**Controls**		**Patients**		**Relatives**		**ANOVA**	
	(n = 24)		**(n = 23)**		**(n = 22)**		**F**	***p***
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age (years)	32.5	6.2	35.2	7.9	31.5	7.3	1.55	0.22
Education (years)	15.1	2.4	13.7	2.9	14.5	2.3	1.79	0.17
Parental education (years)	12.0	4.2	10.6	3.4	10.6	3.2	0.97	0.39
IQ	99.1	4.3	96.7	5.4	97.0	5.4	1.61	0.21
Age of onset (years)			30.1	6.1				

Subject details	Controls		Patients		Relatives		ANOVA	
	(n = 24)		(n = 23)		(n = 22)		F	*p*
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Duration of illness (years)			4.8	4.5				
Acute episodes of illness			3.3	1.6				
Depressive episodes			1.9	0.9				
Manic/hypomanic/mixed episodes			1.5	0.9				
HAMD scores	1.4	1.9	2.4	2.6	1.7	2.3	1.33	0.27
YMRS scores	0.2	0.5	0.6	0.8	0.4	0.7	2.54	0.09
							Chi square	
	n	%	n	%	n	%	χ^2	*p*
Gender							0.25	0.88
Female	16	66.7	14	60.9	15	68.2		
Male	8	33.3	9	39.1	7	31.8		
Cigarette smokers	9	37.5	10	43.5	8	36.4	0.21	0.90
Ethnicity							0.01	0.99
Caucasians	23	95.8	22	95.7	21	95.5		
Latin Americans	1	4.2	1	4.3	1	4.5		
Married	6	25.0	8	34.8	7	31.8	0.83	0.66
Employed	20	83.3	20	87.0	17	77.3	0.11	0.95
Lifetime psychiatric comorbidity	0	0.0	3	13.6	1	4.5		
Past alcohol abuse	0	0.0	1	4.3	0	0.0		
Past anxiety disorders	0	0.0	2	8.7	1	4.5		
Current treatment			19	82.6				
Lithium			3	13.0				
Mood stabilizers			10	43.5				
Typical antipsychotics			2	8.7				
Atypical antipsychotics			14	60.9				

Subject details	Controls		Patients		Relatives		ANOVA	
	(n = 24)		(n = 23)		(n = 22)		F	*p*
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Antidepressants			10	43.5				
Benzodiazepines			8	34.8				
Medication load index			2.8	1.7				
Last episode: manic/mixed			11	47.8				
Last episode: depressive			12	52.2				
Psychotic features during the acute phases of the illness			22	95.7				

SD = standard deviation; IQ = Intelligence Quotient; HAMD = Hamilton rating scale for Depression; YMRS = Young Mania Rating Scale.

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.

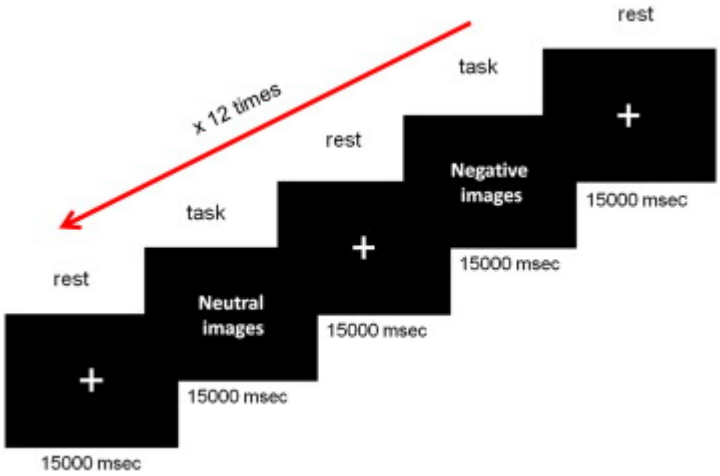

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Fig. 1. IAPS based paradigm. Twenty four blocks of images (12 neutral, 12 negative) were alternated with 24 blocks of cross fixation. There were five pictures per block.

2.3. Behavioral analysis

Statistical analyses were performed using Statistica 6.1 software [Statsoft Italia srl., Vigonza (Padova), Italy, 2003].

A *3 group* (patients, relatives, controls) × *2 valence* (neutral and negative) mixed Analysis of Variance (ANOVA) was used to analyze the percentage of correct responses (accuracy) and the mean Reaction Times (RT). The difference in accuracy between negative and neutral condition (*delta accuracy*) was also calculated and a one-way ANOVA was used to inspect for any group effect. Significant effects ($p < 0.05$) were dissected using Duncan post-hoc test. When a significant between-group effect was observed, an effect size estimate (Cohen's d) was computed for each group comparison (Cohen, 1988). To take into account the possible confounding effects of residual mood symptoms on behavioral performance, they were entered as covariates into a *3 group* × *2 valence* × *2 scale* (HAMD and YMRS) Analysis of Covariance (ANCOVA).

2.4. Post scanning questionnaire

After scanning, participants were asked to rate the unpleasantness of negative stimuli, ranging from 1 (not unpleasant al all) to 9 (extremely unpleasant) and the mean rating score was compared between-group using a one-way ANOVA. Participants were also asked how many errors they thought they had made and the number of correct answers in each group was entered into an expected versus observed frequencies chi-square (χ^2) test.

2.5. Imaging procedure

A Philips ACHIEVA 1.5 T scanner (Philips Medical Systems, Best, the Netherlands) was use to acquire functional [T2*-weighted echo-planar imaging sequence, repetition time (TR) = 3000 ms, echo time (TE) = 50 ms, matrix size = 64 × 64, voxel size = 4 × 4 mm, flip angle = 90°, slice thickness = 4 mm, no gap, 30 transaxial slices] and structural images (T1-weighted 3D-sequence, TR = 25 ms, TE = 4.7 ms, flip angle = 30°, voxel size = 1 × 1 mm).

Participants requiring eyeglasses were fit with vision-correcting lenses in all-plastic frames.

2.6. fMRI data analysis

A block design paradigm was used to acquire the fMRI data. Data were analyzed by means of BrainVoyager QX 2.2 software (Brain Innovation, Maastricht, The Netherlands).

Functional volumes of each subject were pre-processed (motion correction, linear and nonlinear detrending, slice scan-time correction), co-registered with the corresponding structural data set and transformed into the Talairach space (Talairach and Tournoux, 1988) using a piecewise affine and continuous transformation. Functional volumes were resampled at a voxel size of 3 × 3 × 3 mm and the time series from each subject was z-normalized prior to the statistical computation.

Statistical analysis was performed for individual subjects using the general linear model (GLM) (Friston et al, 1994). Two predictors of interest, "neutral" and "negative" condition were considered, whereas the cross fixation condition was used as "baseline". With this analysis, an estimate of the BOLD signal variation (normalized beta values) during the neutral or negative condition with respect to the baseline was obtained for each voxel. The normalized beta values estimated in individual subject analysis were entered in a second-level voxel-wise Random Effect (RFX) group analysis in order to search for activated areas that were consistent for the whole group of participants. Within and between group effects were evaluated by means of a *3 group* (patients, relatives, controls) × *2 valence* (negative, neutral) RFX-GLM analysis, controlling for behavioral performance and residual mood symptoms entering accuracy, mean RT, HAM-D and YMRS scores as covariates.

Statistical maps of the significant effects were thresholded at $p < 0.05$, corrected for multiple comparisons and superimposed on the Talairach-transformed structural scan of a representative subject for the visualization of activated areas. The correction for multiple comparisons was performed using a cluster-size thresholding algorithm (Cox, 1996, Forman et al., 1995) based on Monte Carlo simulations and implemented in the BrainVoyager QX software (Goebel et al, 2006). A threshold of $p < 0.001$ (uncorrected) at the voxel level and an estimate of the spatial correlation of voxels were used as input in the simulations (5000 iterations), yielding a minimum cluster-size of four voxels to obtain statistical maps thresholded at a standard alpha level: $p < 0.05$, corrected for multiple comparisons. Post-hoc comparisons on significant effects were performed using Duncan post-hoc test.

2.7. Correlation analysis

Pearson's correlation analysis was performed first in the whole sample and then in each group separately to examine the association among mood symptoms (HAM-D and YMRS scores) behavioral (task accuracy, mean RT) and functional variables (BOLD signal variation in regions showing between-group effects). In the patient group, the association among task results (behavioral and fMRI findings) and clinical/demographic variables (age of onset, years of illness, number of depressive and manic/mixed episodes, medications) was also inspected. To control for the potential confounding effects of multiple pharmacological treatments we generated a medication load index (Phillips et al, 2008b): the dose of each drug was coded as absent = 0, low/medium = 1, or high = 2, with reference to the midpoint of the recommended daily dose range for each medication (for antipsychotics, doses were first converted into chlorpromazine dose equivalents) and then summed together.

Statistical significance for correlation analysis was set at $p < 0.05$, and corrected for multiple comparisons using a Bonferroni correction (p corrected = 0.05 / number of comparisons). The Bonferroni corrected p values were therefore:

i) $p = 0.05 / 4 = 0.0125$ when HAM-D score, YMRS score, mean task accuracy and mean RT where entered in the analysis involving all participants;

ii) $p = 0.05 / 5 = 0.01$ when entering age of onset, years of illness, number of depressive episodes, number of manic/mixed episodes and medication load index in the exploratory analysis limited to the patients group.

2.8. Potential impact of different medications on fMRI findings in the patients group

To better ascertain whether there was an impact of different medication classes on the fMRI results, we divided the patients in subgroups (*on* versus *off* for each medication class) as follows:

- Any medications at the moment of the scanning (*on*/*off* = 19/4);
- Mood stabilizers and lithium (*on*/*off* = 13/10);
- Antipsychotic agents (*on*/*off* = 14/9);
- Antidepressants (*on*/*off* = 10/13);
- Benzodiazepines (*on*/*off* = 8/15).

Then, we ran an ANOVA, entering the BOLD signal variation in those regions showing significant group differences as dependent variables.

3. Results

Groups did not differ in terms of ethnicity, gender, age, IQ, education, parental education, marital and employment status, frequency of cigarette smoking, HAM-D and YMRS scores (Table 1).

3.1. Behavioral results (Table 2)

With regard to accuracy [3 *group* × 2 *valence* (neutral, negative) ANOVA] a main effect *group* was observed: patients performed worse than both relatives and controls (Fig. 2). A main effect *valence* was observed within-group: accuracy was lower for negative images, with respect to neutral ones. No significant *group* × *valence* interaction was found.

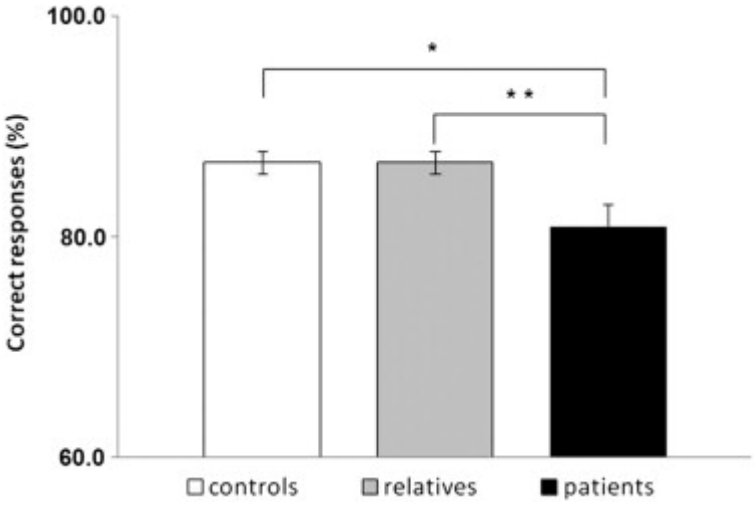

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Fig. 2. Task accuracy. Main effect group, controlled for HAM-D and YMRS scores: [F(2,64) = 3.41, p = 0.04]. Patients performed worse than both controls and relatives. Vertical bar denotes the standard errors. Duncan's post hoc test results: patients < controls (*p = 0.016); patients < relatives (**p = 0.012).

The three groups did not differ in terms of delta (*negative* – *neutral*) accuracy.

With regard to mean RT [3 *group* × 2 *valence* ANOVA] neither between-group effects nor *group* × *valence* interactions reached significance. A significant effect of *valence* was found within-group: all participants were slower on negative images, with respect to neutral ones.

The behavioral results remained significant after controlling for residual mood symptoms [3 *group* × 2 *valence* × 2 *scale* (HAMD, YMRS) ANCOVA].

3.2. Post scanning questionnaire

The groups were comparable in rating the unpleasantness of negative images [F(1,66) = 0.024, p = 0.97] and in giving the correct number of errors (χ^2 = 1.67, df = 2, p = 0.43).

3.3. fMRI results (Table 3)

A 3 *group* × 2 *valence* RFX-GLM design was used to evaluate significant within and between group effects. Significant differences were controlled for behavioral performance and residual

mood symptoms, entering accuracy, mean RT, HAMD and YMRS scores as covariates. (See Table 2.)

Table 2. Behavioral results: accuracy and mean Reaction Times.

Performance variable	**Controls**		**Patients**		**Relatives**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Percentage correct responses (accuracy)						
Negative images	76.9	10.0	71.5	11.1	77.2	6.9
Neutral images	96.6	4.9	90.2	10.6	96.3	4.5
Total	86.8	6.9	80.8	10.4	86.7	4.7
Delta (neutral – negative) accuracy	19.7	7.2	18.7	6.2	19.1	6.9
Mean Reaction Time (ms)						
Negative images	1105.2	222.2	1145.0	238.3	1170.5	160.9
Neutral images	966.0	216.1	999.9	214.3	998.3	153.2
Total	1035.6	209.8	1072.5	223.7	1084.4	143.1

***3 group* × *2 valence* ANOVA — depending variable: accuracy**					
Factor	**df effect, error**	**F**	***p***	**Duncan post-hoc test on significant effects**	**Cohen's d**
Group	2, 66	4.49	0.015*	BP < NC	0.68
				BP < REL	0.73
Valence	1, 66	553.66	< 0.001	Negative < Neutral	/
Valence × group	2, 66	0.14	0.872	/	/

3 groups × *2 valence* ANOVA — depending variable: mean Reaction Times					
Factor	df effect, error	F	*p*	Duncan post-hoc test on significant effects	Cohen's d
Group	2, 66	0.39	0.678	/	/
Valence	1, 66	125.74	< 0.001	Neutral < Negative	/
Valence × group	2, 66	0.55	0.579	/	/

3 group* × *2 valence **ANOVA — depending variable: accuracy**					
Factor	**df effect, error**	**F**	***p***	**Duncan post-hoc test on significant effects**	**Cohen's d**

3 group one-way ANOVA — depending variable: delta accuracy

Factor	df effect, error	F	*p*	Duncan post-hoc test on significant effects	Cohen's d
Group	2, 66	0.14	0.871	/	/

df = degrees of freedom; NC = normal controls; BP = bipolar patients; REL = first-degree relatives.

* Between-group differences remained significant after controlling for HAM-D and YMRS scores. [3 *group* × 2 *valence* × 2 *scales* ANCOVA: $F(2,64) = 3.41$, $p = 0.04$].

Table 3. FMRI results. 3 *group* × 2 *valence* Random effect-General Linear Model (RFX-GLM) analysis. Brain regions showing significant effects, controlled for residual mood symptoms and behavioral results (HAMD scores, YMRS scores, accuracy and mean RT were entered as covariates). The statistical threshold was set at: $p < 0.05$, corrected for multiple comparisons. The baseline was the "cross fixation" condition.

Within group effects							
ROI names	**Effect**	**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (1, 66)**
Neutral valence versus baseline-activated regions in all subjects							
Right precentral/inferior frontal gyrus	Neutral > Baseline	6/9	44	1	32	1274	7.18
Left precentral/inferior frontal gyrus	Neutral > Baseline	6/9	– 48	0	33	1178	7.24
Right middle frontal gyrus	Neutral > Baseline	46	44	17	26	376	6.84
R precentral gyrus	Neutral > Baseline	6	37	– 9	50	353	6.70
Supplementary motor area	Neutral > Baseline	6	– 1	2	48	2269	7.19
Right middle occipital gyrus	Neutral > Baseline	18/19	38	– 74	– 5	5538	9.64
L middle occipital gyrus	Neutral > Baseline	18/19	– 39	– 76	– 6	4108	9.06
Left brain stem	Neutral > Baseline		– 15	– 27	– 4	1414	7.66

Within group effects							
ROI names	**Effect**	**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (1, 66)**
Left thalamus	Neutral > Baseline		– 14	– 19	9	448	7.48
Left putamen	Neutral > Baseline		– 24	– 2	5	1203	7.35
Right cerebellum	Neutral > Baseline		16	– 50	– 19	1348	9.01
Left cerebellum	Neutral > Baseline		– 28	– 44	– 18	722	8.33
Cerebellar vermis	Neutral > Baseline		3	– 61	– 19	981	9.30
Right angular gyrus	Baseline > Neutral	39	46	– 59	24	1068	7.36
Left angular gyrus	Baseline > Neutral	39	– 46	– 63	25	1724	7.27
Anterior cingulate cortex	Baseline > Neutral	24/32	– 1	45	11	5215	7.57
Posterior cingulate cortex	Baseline > Neutral	31	– 2	– 56	26	8107	8.76
Negative valence versus baseline-activated regions in all subjects							
Right precentral/inferior frontal gyrus	Negative > Baseline	6/9	44	1	32	1252	7.34
Left precentral/inferior frontal gyrus	Negative > Baseline	6/9	– 48	0	33	1151	7.59
Left motor cortex	Negative > Baseline	4	– 42	– 22	49	3901	7.52
Supplementary motor area	Negative > Baseline	6	– 1	2	48	3159	7.50
Right middle occipital gyrus	Negative > Baseline	18/19	30	– 82	1	3523	9.80
Left middle occipital gyrus	Negative > Baseline	18/19	– 26	– 86	2	1191	9.39
Right lingual gyrus	Negative > Baseline	17	11	– 86	– 4	2436	9.87
Left lingual gyrus	Negative > Baseline	17	– 9	– 87	– 9	1421	9.49
Right superior parietal lobule	Negative > Baseline	7	25	– 69	35	1332	8.72
Left superior parietal lobule	Negative > Baseline	7	– 26	– 63	39	1475	7.81
Left brain stem	Negative > Baseline		– 15	– 27	– 4	1398	8.23
Left putamen	Negative > Baseline		– 24	– 2	5	1185	7.06
Right cerebellum	Negative > Baseline		17	– 49	– 19	1053	9.04
Cerebellar vermis	Negative > Baseline		3	– 61	– 20	435	9.37
Right angular gyrus	Baseline > Negative	39	46	– 59	24	1053	7.03

Within group effects							
ROI names	**Effect**	**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (1, 66)**
Left angular gyrus	Baseline > Negative	39	– 46	– 63	25	1294	7.22
Anterior cingulate cortex	Baseline > Negative	24/32	– 1	45	11	2250	7.29
Posterior cingulate cortex	Baseline > Negative	31	– 2	– 56	26	4889	8.16

Within condition effect: negative versus neutral valence-activated regions in all subjects

	Condition effect	Brodmann Area	Mean x	Mean y	Mean z	mm^3	F (1, 66)
Right occipitotemporal area	Negative > Neutral	37/39	41	– 66	7	4201	8.98
Left occipitotemporal area	Negative > Neutral	37/39	– 45	– 68	5	2106	9.13
Right parahippocampal cortex	Negative > Neutral	36	37	– 51	– 17	717	7.24

Between group effects								
Main effect group								
	Group effect		**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (1, 66)**
Left middle insula	BP > NC	BP > REL	13	– 33	– 1	11	239	4.02
Right hippocampus	BP < NC	BP < REL		32	– 26	– 5	462	4.36
L temporo-parietal junction	BP > NC	REL > NC	22	– 53	– 3	– 3	302	3.95
Left thalamus	BP > NC	REL > NC		– 11	– 24	1	291	4.21
Left angular gyrus[a]	BP > NC	REL > NC	39	45	– 55	20	667	3.81
Left parahippocampal cortex	BP < NC	REL < NC	36	– 29	– 46	– 11	463	3.76
Left occipitoparietal cortex	BP < NC	REL < NC	19	– 8	– 84	29	322	3.90
Left lingual gyrus	NC > REL	BP > REL	18	– 2	– 70	– 1	697	3.87
Cerebellar vermis	NC > REL	BP > REL		– 4	– 57	– 24	425	3.88
Right dorsolateral prefrontal cortex	NC > REL	BP > REL	9	38	23	38	437	3.89
Ventral anterior cingulate cortex[a]	NC > REL	BP > REL	24	0	35	6	564	4.07

Between group effects							
Main effect group							
	Group effect	**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (1, 66)**
Between group × within condition interaction							
Between group effect during neutral valence condition							
ROI names	**Group effect Duncan post-hoc test**	**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (2, 66)**
Right middle frontal/precentral gyrus	REL > NC	8/9	37	20	39	943	4.03
Right superior frontal gyrus	REL > NC	10	16	56	19	1080	3.91
Between group effect during negative valence condition							
ROI names	**Group effect Duncan post-hoc test**	**Brodmann area**	**Mean x**	**Mean y**	**Mean z**	**mm^3**	**F (2,66)**
Left precuneus	BP < NC	7	– 10	– 66	35	531	4.21
Right supramarginal gyrus	BP < NC REL < NC	40	44	– 40	28	469	5.25
Left insula	BP > NC REL > NC	13	– 46	3	– 2	400	4.00
Right superior frontal gyrus	NC > REL BP > REL	8	21	32	41	381	4.07
Pre-supplementary motor area	NC > REL BP > REL	6/8	4	22	50	482	4.75
Right lingual gyrus	NC < REL BP < REL	18	22	– 65	7	603	4.11

BP = bipolar patients; NC = normal controls; REL = first-degree relatives.

a Differences in the amount of deactivation.

3.3.1. Within-group effects: activated regions in all subjects (Fig. 3)

During the neutral valence condition, with respect to the baseline, all subjects were significantly activated: bilateral inferior frontal gyrus (IFG), Right middle frontal gyrus (MiFG), supplementary motor area (SMA), bilateral middle occipital gyrus (MOG), cerebellum, Left

putamen and Left thalamus. A significant deactivation, with respect to the baseline, was observed in: ACC, posterior cingulate cortex (PCC) and bilateral angular gyrus.

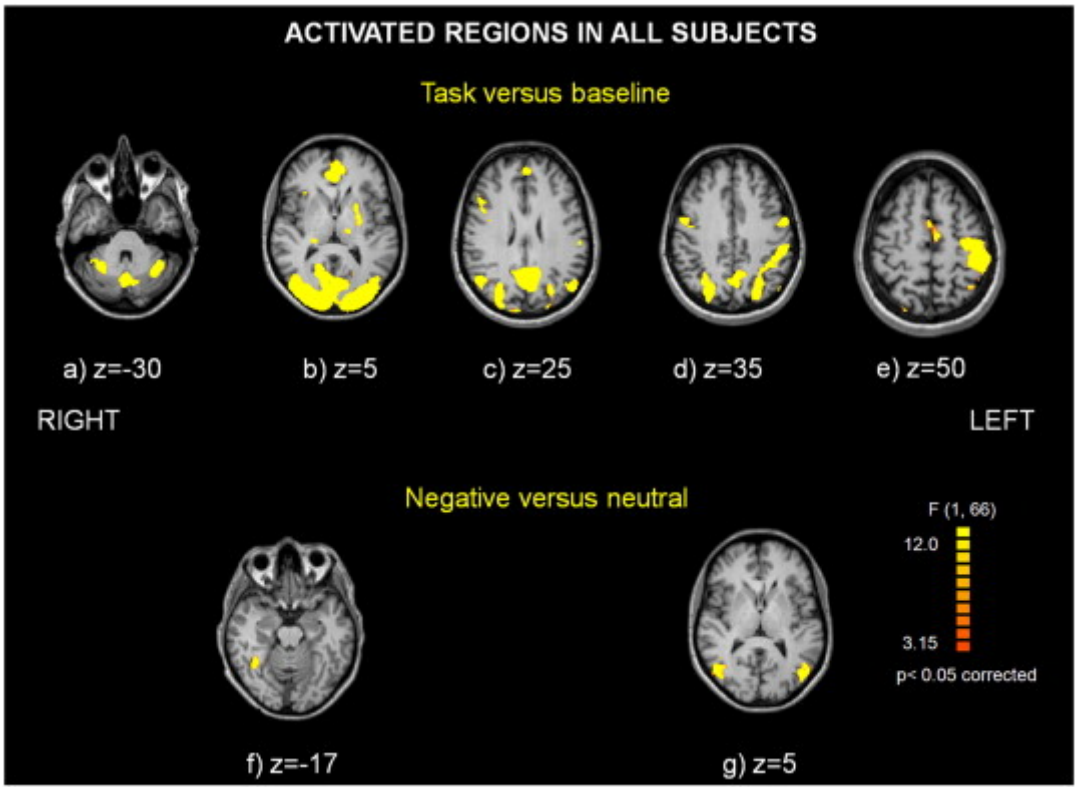

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Fig. 3. FMRI results, general linear model random effect analysis. Regions showing within group significant effects ($p < 0.05$, corrected for multiple comparisons) by radiological convention, the vertical colored bar denotes the F-value scale.

a) Bilateral cerebellum and cerebellar vermis.

b) Anterior cingulate cortex, posterior cingulate cortex, bilateral middle occipital gyrus, bilateral lingual gyrus, Left thalamus, Left putamen.

c) Anterior cingulate cortex, posterior cingulate cortex, bilateral middle occipital gyrus, bilateral angular gyrus, Right middle frontal gyrus.

d) Posterior cingulate cortex, bilateral precentral gyrus, bilateral superior parietal lobule, Left motor area.

e) Supplementary motor area, Left motor area.

f) Right parahippocampal cortex.

g) Bilateral occipitoparietal cortex.

During the negative valence condition, with respect to the baseline, significant activations were observed in: bilateral IFG, Left motor cortex, SMA, bilateral MOG, bilateral lingual gyrus, bilateral superior parietal lobule (SPL), cerebellum and Left putamen. A significant deactivation was observed in: ACC, PCC and bilateral angular gyrus.

The contrast map *negative* versus *neutral* valence showed three regions that were significantly more activated during negative with respect to neutral condition in all groups: the bilateral occipitoparietal areas and the Right parahippocampal cortex.

3.3.2. Between-group effects: regions showing a BOLD signal variation that significantly differentiated the groups (Fig. 4)

A main effect group, regardless of the stimuli valence, was observed in several brain regions. The post hoc comparisons showed the following significant results:

i) patients ≠ relatives and controls: an augmented activation of the Left middle insula, with respect to both relatives and controls, was observed in the patients only.

ii) patients and relatives ≠ controls: with respect to normal controls, both patients and relatives showed an increased activation of Left temporo-parietal junction (TPJ) and Left thalamus, a reduced activation of Left parahippocampal cortex and Left occipitoparietal cortex, and a higher deactivation of the Left angular gyrus.

iii) relatives ≠ patients and controls: relatives differed from both patients and controls because of lower activation of Right dorsolateral prefrontal cortex (DLPFC), Left lingual gyrus and cerebellar vermis, and lower deactivation of the ventral ACC.

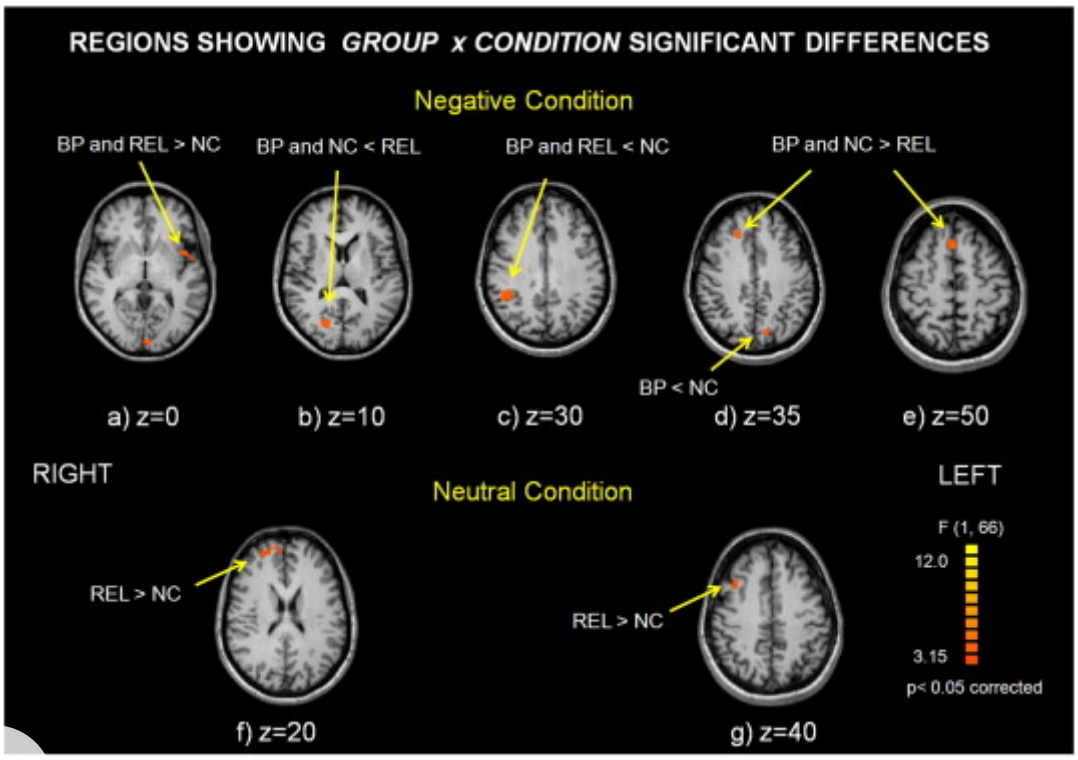

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Fig. 4. FMRI results, general linear model random effect analysis. Regions showing *group* × *condition* significant effects ($p < 0.05$, corrected for multiple comparisons) by radiological convention. The vertical colored bar denotes the F-value scale. Duncan's test was used to perform the post hoc comparisons.

NC = normal controls; BP = bipolar patients; REL = relatives.

a) Left insula

b) Right lingual gyrus

c) Right supramarginal gyrus

d) Right superior frontal gyrus and Left precuneus

e) Right pre-supplementary motor area

f) Right middle frontal/precentral gyrus

g) Right superior frontal gyrus.

3.3.3. Between-group × within-condition significant interactions

A) Regions showing a BOLD signal variation that significantly differentiated the groups during the neutral condition
   i) relatives ≠ controls: relatives showed a greater activation, with respect to controls, in two frontal regions, the Right MiFG/precentral gyrus and in the Right superior frontal gyrus (SFG)

B) Regions showing a BOLD signal variation that significantly differentiated the groups during the negative condition
   i) patients ≠ controls: during the negative condition, patients showed a reduced activation of the Left precuneus, with respect to controls.

   ii) patients and relatives ≠ controls. Patients and relatives activated the Left insula more than controls and the Right supramarginal gyrus (SMG) less than controls.

   iii) relatives ≠ patients and controls: relatives differed from both patients and controls because of higher activation of Right lingual gyrus and lower activation of pre-SMA and Right SFG.

To control for the possible confounding effect of lifetime psychiatric conditions on fMRI results, we repeated the analyses after removing four subjects with a lifetime history of other psychiatric disorders (a patient with previous alcohol abuse, two patients and a relative with past anxiety disorders) and all the above mentioned main effects and interactions remained significant.

3.4. Correlation analysis

3.4.1. In those regions showing significant group effects (Right MiFG/precentral gyrus, Right SFG, Left precuneus, Left insula, Right SMG, pre-SMA, Right SFG)

Pearson's correlation was performed first in the whole sample and then in each group separately to examine the association among mood symptoms (HAM-D and YMRS scores), behavioral variables (task accuracy, mean RT) and BOLD signal variations, but no significant result was found (Bonferroni corrected $p = 0.05 / 4 = 0.0125$).

3.4.2. Exploratory analysis conducted on the patients group

In those brain regions differentiating the patients from the other groups we correlated the BOLD signal variations to clinical and demographical variables, but we did not find any significant influence of medication load index, age of onset, years of illness and number of previous depressive or manic/hypomanic episodes on the level of functional activation (Bonferroni corrected $p = 0.05 / 5 = 0.01$).

3.5. Potential impact of different medications on fMRI findings in the patients group

Patients were divided in subgroups based on their current pharmacological treatments (any medication; mood stabilizers and lithium; antipsychotic agents; antidepressants; benzodiazepines). Then, the BOLD signal variation in the regions showing significant group effects (Right MiFG/precentral gyrus, Right SFG, Left precuneus, Left insula, Right SMG, pre-SMA, Right SFG) was entered into an ANOVA design. As a result, we did not find any significant difference between patients subgroups in all the above mentioned regions, except for the L precuneus. In the L precuneus, we observed that the level of activation was lower in the patients without any pharmacological treatment, with respect to those under current medication [$F(1,21) = 4.69$, $p = 0.041$], but the result lost its statistical significance after controlling for residual mood symptoms [HAM-D and YMRS scores were entered as covariates: ANCOVA $F(1,19) = 3.49$, $p = 0.077$].

4. Discussion

In our study we used a task based on the IAPS, a well known approach to explore the neural correlates of emotion processing (Lang et al, 2005). As expected, responding to target in a negative contest significantly affected the performance, all participants resulting slower and less accurate with respect to neutral images conditions. Unlike the relatives, who performed similarly to controls, patients showed a poorer accuracy. On the other end, the loss of accuracy during the negative condition, compared to the neutral one (*delta accuracy*) was almost 20% in all groups, suggesting that the attentional resources were basically reduced in euthymic BD-I patients, regardless of the emotional valence of the stimuli, as previously reported during sustained attention tasks (Robinson et al., 2013, Sepede et al., 2012).

In all groups, responding to negative images significantly activated bilateral IFG, bilateral parietal and occipital regions, ventromedial prefrontal cortex (VMPFG), and parahippocampal gyrus, accordingly with other emotional tasks (Aldhafeeri et al., 2012, Rubino et al., 2007, Viinikainen et al., 2010). These results confirm that a wide-spread cortical network is involved in the recognition of unpleasant emotions, with activations in frontal, parietal, occipital and limbic regions.

During negative image presentation, patients activated the Left precuneus (BA7) less than normal comparisons. In healthy subjects, the precuneus, due to its strategic location in the posterior part of the medial parietal lobe, has multiple connections with cortical and subcortical structures (Cavanna and Trimble, 2006) and it is particularly sensitive to negative images (Nielen et al., 2009, Radua et al., 2014). A Left-lateralized activation of the precuneus was found during the vision of negative pictures (Meseguer et al, 2007) and when participants were required to increase their negative emotions in response to aversive stimuli (Ochsner et al, 2004). Brooks et al (2009) found a reduced metabolism of the Left precuneus in a group of old euthymic BD patients during a PET study. A significant different activation of precuneus in euthymic BD patients, with respect to normal comparisons, has been previously reported during both emotional (Hassel et al., 2008, Sagar et al., 2013, Wessa et al., 2007) and cognitive tasks (Costafreda et al, 2011). Even though we could not find a significant correlation between the level of functional activation of precuneus and the performance during negative condition, we can argue that its hypoactivation in BD-I patients may somehow interfere with their ability to process emotional contents, also during euthymia. We found a statistical trend (after controlling for residual mood symptoms) for a lower activation of L precuneus in those without a current pharmacological treatment, with respect to medicated subjects. Our results suggest that psychotropic medications may partially normalize the functional differences between BD-I patients and normal controls, as proposed in a comprehensive review by Hafeman et al (2012).

When confronted with negative stimuli, patients and relatives similarly hyperactivated the Left insula with respect to normal comparisons. The augmented activation of the insular cortex is an interesting finding, due to its crucial role in integrating cognitive and emotional resources (Corbetta et al., 2008, Kurth et al., 2010). Using an IAPS-based task on healthy volunteers, Anders et al (2004) found that the activity of the Left anterior insula increased with reported negative valence. A meta-analysis of emotion activation studies (Phan et al, 2002) suggested a preferential involvement of the insula in those emotional tasks with adjunctive cognitive components (as required in our experimental paradigm), with respect to passive viewing tasks. Due to its involvement in homeostatic regulation and emotion evaluation, the insula is considered an alarm center for physical or psychical internal dangers (Reiman et al, 1997). An abnormal functioning of the insula during affective task has been already reported in euthymic BD-I patients (Foland-Ross et al., 2012, Krüger et al., 2003, Wessa et al., 2007) and non-affected relatives (Krüger et al., 2006, Roberts et al., 2013).

Patients and relatives also shared a reduced activation of the Right SMG (BA40) when compared to controls. SMG was bilaterally activated in healthy subjects in response to fear-

related sounds (Köchel et al, 2013). A normal functioning of the Right SMG is required to avoid emotional egocentricity bias (the tendency to misjudge other's mental state using in an inappropriate way a self-referential point of view) (Silani et al, 2013) and to successfully regulate negative emotions (Vanderhasselt et al, 2013). Using a Theory of Mind (ToM) task, Malhi et al (2008) reported a reduced activation of bilateral SMG in euthymic BD-I patients, with respect to normal comparisons.

Our findings of an increased activation of Left insula, associated to a reduced Right SMG activation in both euthymic patients and healthy relatives during negative stimuli processing, suggest a state-independent abnormal warning versus internal emotions. Hence, as proposed by Green et al (2007), a disturbed interaction between cortical and limbic regions, may represent a trait marker to BD.

On the other hand, the activation pattern of unaffected relatives was not simply an intermediate way of functioning between patients and controls, but it differed from the other two groups in several brain regions, so we can hypothesize the influence of resilience factors. In particular, relatives showed a higher activation of Right lingual gyrus and a lower activation of pre-SMA and Right SFG during negative stimuli. A greater activation of Right SFG and Right MiFG/precentral gyrus with respect to controls was also observed during neutral stimuli. The lingual gyrus has a role in the processing of emotional stimuli, such as faces (Fusar-Poli et al, 2009), unpleasant pictures (Aldhafeeri et al, 2012) and words presented in negative contexts (Maratos et al, 2001). SMA constitutes a link between emotion and motor control (Mazzola et al, 2013), whereas superior and middle frontal gyrus are involved in both cognitive and affective tasks: visuo-spatial attention (Simpson et al, 2011), orienting/executive attention (Fan et al, 2005) and emotion regulation (Blair et al, 2007). In an fMRI study conducted on young unaffected offspring of BD patients, Ladouceur et al (2013) reported alterations in the functioning of fronto-limbic systems implicated in voluntary emotion regulation, during an emotional working memory task. Moreover, a recent meta-analysis of cognitive and emotional fMRI studies on subjects at high risk for BD (Lee et al, 2014) reported an increased activity in key cognition and emotion-processing regions (i.e., insula, DLPFC, parietal cortex) in unaffected offspring of BD (but not in pediatric BD patients and normal comparisons), as presumable compensatory mechanisms.

So, a possible interpretation of our findings is that unaffected relatives of BD-I succeeded in maintaining a good “overt” behavioral performance (to correctly identify “targets”) through a high activation of prefrontal areas during neutral stimuli. As a consequence, diminished prefrontal resources were available for the “covert” processing of negative emotions, and occipital regions were hyper-activated to compensate this deficit. However, this interpretation is speculative at this stage, and a clear distinction between risk and resilience factors on unaffected relatives of BD-I will require longitudinal data.

4.1. Limits of the study

Almost all our BD-I patients reported psychotic symptoms during the acute periods of the illness, a feature found to affect negative emotion processing (Thaler et al., 2013). Further

studies comparing psychotic/non-psychotic patients are needed to better clarify this point.

Another study limitation is the large age range of our unaffected relatives (22–43 years), thus including individuals still at higher risk of future illness plus those who are at lower risk due to older age (Azorin et al., 2013, Leboyer et al., 2005).

5. Conclusions

A correct processing of negative stimuli is fundamental in everyday living. Euthymic BD-I patients performed worse than controls during a negative emotion task, whereas healthy first-degree relatives of BD-I appeared behaviorally intact. On the other hand, when analyzing the task-related neural activations, both patients and relatives showed limbic and frontoparietal functional alterations, thus suggesting a trait-like anomalous processing of affective contents.

Contributors

Dr. Sepede, Dr. Gambi, Dr. Ferretti, Dr. Perrucci, Dr. Di Giannantonio, Dr. Salerno and Dr. Romani designed the study. Dr. Sepede, Dr. Gambi, Dr. Campanella and Dr. De Berardis, enrolled and managed the participants. Dr. Sepede, Dr. Gambi, Dr. Ferretti, Dr. Perrucci and Dr. Romani acquired fMRI studies. Dr. Sepede and Dr. Gambi performed the statistical analysis. Dr. Sepede, Dr. Gambi, Dr. De Berardis, Dr. Campanella and Dr. Salerno wrote the first draft of the manuscript. Dr. Di Giannantonio and Dr. Romani reviewed the manuscript.

All authors contributed to and have approved the final manuscript.

Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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