Title: Bipolar Disorder: Functional Neuroimaging Markers in Relatives

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Abstract

Neural models of anatomical and functional alterations have been proposed for bipolar disorders (BD). However, studies in affected patients do not allow disentangling alterations linked to the liability to BD from those associated with the evolution, medication and comorbidities of BD. Explorations in high risk subjects allow the study of these risk markers. We reported and summarized all functional magnetic resonance imaging (fMRI) studies focusing on first-degree relatives of BD patients. We found 29 studies reporting neural correlates of working memory (WM), emotional processing, executive functions and resting state in relatives of BD patients, compared to healthy subjects. Overall, the same regions that have been involved in patients, such as the inferior frontal gyrus and limbic areas, seem to be functionally altered in high-risk subjects.

We conclude that the same brain regions already implicated in the pathophysiology of the disease such as the amygdala are also associated with the risk of BD. However longitudinal studies are required to understand their implication in the transition to BD.

Key words

Bipolar disorder; fMRI; vulnerability; high-risk; relatives

Introduction

Bipolar disorder (BD) affects between 1 and 3% of the population (Merikangas et al., 2007). It is part of the 10 leading causes of years lost due to disability (The Global Burden of Disease, 2004 update, WHO). Genetic factors weigh a lot more heavily than in Major Depressive disorder, heritability being between 59 and 85% (Lichtenstein et al., 2009; McGuffin et al., 2003). Familial aggregation in bipolar disorder has been known for a long time. Recently several long-running longitudinal studies have shown that the offspring of bipolar disorder patients (BDP) have an increased risk of developing psychiatric disorders, and in particular mood disorders (Birmaher et al., 2009; Mesman et al., 2013; Rasic et al., 2014; Vandeleur et al., 2012). The risk of developing bipolar disorder is tenfold higher in this population and studying the offspring and the unaffected relatives of bipolar patients could help to shed light on this vulnerability.

Studies in healthy relatives of BDP found subtle changes in various domains, such as cognitive impairments in specific executive functions or verbal memory (Balanzá-Martínez et al., 2008; Bora et al., 2009; Raust et al., 2014), immune functions (Duffy et al., 2012; Hamdani et al., 2013) or circadian rhythms (Friess et al., 2008; Milhiet et al., 2014). These findings, if replicated, might represent endophenotypes of the disease (Hasler and Wolf, 2015; Raust et al., 2014) although the heterogeneity of the findings is still important (Balanzá-Martínez et al., 2008).

Recent neural models of BD assume that this disorder affects the emotion processing/regulation pathways, as well as the reward network (Phillips and Swartz, 2014; Strakowski, 2012). Regions consistently affected by the disease are the ventrolateral prefrontal cortex (vlPFC), the limbic system, particularly the amygdala, the orbitofrontal cortex (OFC), and the medial prefrontal cortex (mPFC), showing an imbalance in the

connectivity between the cognitive control areas in the prefrontal cortex and the emotional or reward processing areas.

The actual dynamics of how the disease develops are not yet known and many questions are still open regarding the risk, trait, state or degenerative aspects of these deficits. It is therefore crucial to study populations at a higher risk of developing bipolar disorder. To our knowledge, only few review papers have been published on the subject. One is a review and meta-analysis based on 37 articles that include the healthy relatives of BDP, but only 5 articles reporting fMRI studies (Fusar-Poli et al., 2012). This review concludes that both the medial and superior frontal cortex and the insula present higher activation in UR compared to controls, in a variety of tasks. The authors link this compensatory hyperactivation to an established cognitive deficit in UR (functional inefficiency). Another review paper has been published on the topic, reviewing neuroimaging studies of patients and at-risk subjects for BD with a specific focus on neurodevelopmental and illness-related neuropathologic changes (Schneider et al., 2012). This review includes 9 studies that use fMRI on at risk-individuals, 3 of which were included in the previous meta-analysis. This broad review concludes that discrepancies found in some regions and/or modalities, such as amygdala volume for example, could be explained by a combination of developmental changes during a period of non-linear dynamic maturation and illness-related changes. Although it includes structural, diffusion tensor imaging and fMRI data, the results are not consistent enough to draw conclusions, but do suggest which parameters need to be taken into account in future studies. More recently, a meta-analysis of fMRI studies in high-risk and bipolar children and adolescents has highlighted robust differences in these two groups compared to normally developing children (Lee et al., 2014). However, this meta-analysis included again only 11 fMRI studies using whole-brain approaches and thus excludes most of the fMRI studies.

The purpose of this qualitative review is therefore to provide a more exhaustive landscape on the current state of knowledge of fMRI data in populations vulnerable to BD. By doing so, we can propose a broader understanding of neuroimaging circuits subtending vulnerability models of BD.

Methods

Systematic research on databases (PubMed and PsychInfo) was conducted from inception until April 30, 2015, using a combination of keywords "bipolar disorder" + "offspring" or "relatives" or "high risk" or "siblings" + "neuroimaging" or "fMRI" or "functional magnetic resonance imaging" by 2 independent researchers. Upon consensus by the authors, 29 articles were finally included. Some studies that were cited by our selected articles but that had not appeared in the search were included as relevant to our criteria. Namely, these were original English-written studies published in peer-reviewed journal that included first-degree relatives of bipolar disorder patients (offspring or siblings/parents), a matched control group, and used fMRI with groups of size 12 and more, except for dizygotic twins. Clinical diagnostic for patients had to be based on SCID (Structured Clinical Interview for DSM-IV) or K-SADS (Kiddie Schedule for Affective Disorders and Schizophrenia) or other recognized clinical diagnostic criteria (e.g. Diagnostic Interview for Genetic Studies). Table 1 reports the characteristics of the 25 selected fMRI studies that use cognitive/emotional tasks (without the 4 studies based on resting state), including populations and clinical instruments. Table 2 reports the methodology used in these studies (field strength of MRI, whole-brain versus regions of interest (ROI) analyses, type of task, other types of complementary analyses) as well as the ensuing main results, with a focus on results reported for the relatives of patients. We detail a selection of studies, including references to bipolar patients, in the body of the manuscript. We do not report correlations with dimensional trait measures for the sake of

simplicity, even though some may be of interest (for e.g. depression and cyclothymia score with Hayling Sentence completion test (Whalley et al., 2011)). We use "UR" for short for unaffected (by BD) relatives, however some studies additionally included a group of first-degree relatives suffering from Major Depressive Disorder (MDD) ((Pompei et al., 2011a, 2011b; Whalley et al., 2013), and in many studies relatives were not excluded if suffering from a psychiatric condition other than bipolar disorder (details below).

RESULTS

1. Studies included

The majority of the studies were conducted in adults, although some included children (Kim et al., 2012; Singh MK et al., 2014), adolescents (Brotman et al., 2014; Ladouceur et al., 2013; Mourão-Miranda et al., 2012; Olsavsky et al., 2012; Tseng et al., 2015) or young adults (Roberts et al., 2013; Whalley et al., 2013, 2012a, 2012b, 2011). We report studies on subjects younger than 18 years old in a separate paragraph at the end of the result section, the developmental aspect being a confounding factor.

Four studies used data from the same cohort, analyzing different aspects (Whalley et al., 2013, 2012a, 2012b, 2011). Others studies were conducted by the same group on approximately the same cohorts (Allin et al., 2010; Drapier et al., 2008; Surguladze et al., 2010);(Lelli-Chiesa et al., 2011; Pompei et al., 2011a, 2011b);(Ladouceur et al., 2013; Mourão-Miranda et al., 2012). Existence of a psychiatric diagnosis in relatives was assessed through standard semi-structured clinical interview. Relatives were sometimes included only at the condition of no axis-I disorder (Costafreda et al., 2009; Erk et al., 2013; Kanske et al., 2015, 2013; Kim et al., 2012; Ladouceur et al., 2013; Linke et al., 2012; Mourão-Miranda et al., 2012; Pompei et al., 2011a, 2011b; Sepede et al., 2012; Singh MK et al., 2014), however sometimes inclusion of relatives meeting criteria for some psychiatric disorders was allowed, such as personality disorder of psychosis spectrum (Lui et al., 2014), ADHD or anxiety

disorders (Brotman et al., 2014; Olsavsky et al., 2012; Tseng et al., 2015). Finally, sometimes the criteria for relatives were exclusion of bipolar/mood disorder plus psychotic disorder and dependence in the past 12 months or lifetime (Drapier et al., 2008; Lelli-Chiesa et al., 2011; Surguladze et al., 2010; Thermenos et al., 2010; Whalley et al., 2013, 2011), or exclusion of BD only (Roberts et al., 2013). Diagnosis of bipolar proband was also confirmed by state-of-the-art diagnostic interview. Only a few studies explicitly explained how they assessed the parents of healthy controls for psychiatric disease (Ladouceur et al., 2013; Mourão-Miranda et al., 2012; Thermenos et al., 2010), the others just reported no family history of psychiatric or neurological diseases.

Current knowledge on BD cognitive correlates implicates deregulation of the emotional, attentional, and working memory networks (Phillips and Swartz, 2014; Strakowski, 2012; Strakowski et al., 2012). Therefore, most of the functional neuroimaging literature focuses on these processes, albeit by different means, thus rendering comparisons challenging. fMRI studies were classified accordingly to the type of cognitive tasks involved: paradigms testing memory function, either using working memory tasks such as N-back (Drapier et al., 2008; Thermenos et al., 2010) or episodic memory (Erk et al., 2013), emotion processing paradigms, mainly using emotional faces (Brotman et al., 2014; Kanske et al., 2015; Lelli-Chiesa et al., 2011; Mourão-Miranda et al., 2012; Olsavsky et al., 2012; Surguladze et al., 2010), paradigms testing executive functions (Allin et al., 2010; Costafreda et al., 2009; Kim et al., 2012; Linke et al., 2012; Pompei et al., 2011b; Sepede et al., 2012; Whalley et al., 2013, 2012a, 2012b, 2011) and paradigms testing the interaction between cognitive and emotional processing (Kanske et al., 2013; Ladouceur et al., 2013; Roberts et al., 2013), including reward processing (Singh MK et al., 2014).

Resting state is an area of very recent interest; only 4 studies investigated the differences in resting state between patients and first-degree-relatives (Khadka et al., 2013; Lui et al., 2014; Meda et al., 2012; Singh et al., 2014).

Regarding the type of analyses, 12 studies used whole-brain approaches (Allin et al., 2010; Drapier et al., 2008; Erk et al., 2013; Kanske et al., 2013; Mourão-Miranda et al., 2012; Pompei et al., 2011b; Roberts et al., 2013; Tseng et al., 2015; Whalley et al., 2013, 2012a, 2012b, 2011), 5 provided both whole-brain and ROI analyses (Brotman et al., 2014; Kim et al., 2012; Olsavsky et al., 2012; Singh MK et al., 2014; Surguladze et al., 2010), and 8 computed results for ROI only (Costafreda et al., 2009; Kanske et al., 2015; Ladouceur et al., 2013; Lelli-Chiesa et al., 2011; Linke et al., 2012; Pompei et al., 2011a; Sepede et al., 2012; Thermenos et al., 2010).

2. Results

2.1 Behavioral results

Ten studies found no differences in relatives of BDP compared with HC, both for accuracy and reaction times (RT), in different domains such as executive functions (Costafreda et al., 2009; Kim et al., 2012; Pompei et al., 2011b; Whalley et al., 2011), memory with or without emotional distractors (Erk et al., 2013; Ladouceur et al., 2013), emotion processing or labeling (Mourão-Miranda et al., 2012; Olsavsky et al., 2012; Surguladze et al., 2010) and reward (Singh MK et al., 2014). Some studies identified differences between UR and HC, sometimes intermediate with deficits found in BDP (Tseng et al., 2015), or equivalent to BD (Brotman et al., 2014; Linke et al., 2012; Sepede et al., 2012; Thermenos et al., 2010). Two studies found differences in UR and not BDP: a trend toward longer RT for fearful faces (Olsavsky et al., 2012), and less down-regulation of positive emotion, with a less positive rating of faces (Kanske et al., 2015), and one study did not have the comparison with BDP but found diminished accuracy for fearful stimuli in UR (Roberts et al., 2013). Finally, four

studies found differences for BDP only and not for UR compared to HC (Allin et al., 2010; Drapier et al., 2008; Kanske et al., 2013; Lelli-Chiesa et al., 2011). Given the variability in paradigms, the lack of reproducibility, and the fact that these studies and tasks have been designed mostly for neuroimaging comparisons, it is difficult to draw firm conclusions from these data. Cognitive endophenotypes are proposed for vulnerability to BD, however they still lack consistency and specificity (Balanzá-Martínez et al., 2008; Raust et al., 2014). This might arise not only from the choice of task, but also from in the level of difficulty for example, of valence-specific deficits. Brain imaging may be a more sensitive tool to detect early alterations.

2.2 Memory tasks

The first study in the field was conducted by Drapier *et al.* using a working memory paradigm (1-back, 2-back and 3-back tasks) (Drapier et al., 2008). Patients showed significantly lower accuracy compared to HC and UR. During the 2-back task, patients showed greater activation in the bilateral precunei, and UR in the left fronto-polar cortex relative to HC, which might account for compensatory mechanisms.

A second study using a sequential letter 2-back task was performed by Thermenos *et al.* (2010). BDP also showed a significant decrease in task performance, whereas UR showed only a tendency towards decreased accuracy. At the neural level, BDP and UR showed a significantly increased activity in the left anterior insula (compared to HC) and BDP a decreased activity in the left fronto-polar cortex (compared to UR and HC). UR showed a significant increase of activity in the left OFC, at the boundary of the right superior parietal lobule and at the superior postcentral gyrus compared to HC. Again, this might account for compensatory mechanisms. Only control subjects showed a significant reduction of activity in the insula, the OFC and the parietal cortex during the WM task compared to the baseline task.

2.3 Emotion processing

Emotion processing has been investigated both implicitly and explicitly, using mainly emotional faces as stimuli. More recently, emotion regulation paradigms have been used. Originally, an extension of Drapier's study was performed by Surguladze *et al.* (2010) using an implicit emotional face recognition task. They showed that, with no differences in RT or accuracy, both BDP and their UR had a significant increase in the activation of the mPFC in response to both happy and fearful faces and in the left putamen to moderately fearful faces, compared to control. When amygdalae were analyzed by a ROI approach, both BDP and their UR showed greater activation in the left amygdala in response to intensely happy faces compared to controls.

Further than emotion processing, a paper looked at two emotion regulation strategies, reappraisal and distraction with arithmetic calculations (Kanske et al., 2015). They found the same differences for patients and UR compared to controls, i.e. difficulty in down-regulating amygdala activation in the reappraisal condition, mediated by an altered connectivity between OFC and amygdala. UR also rated faces as less positive and had more difficulties to down-regulate positive emotions.

Some studies used more complex tasks that involve executive functions interwoven with emotional stimuli to study their interaction. For example, Roberts *et al.* (2013) recruited UR of BD type I or II in a study investigating the neural correlates of an emotional Go/No-Go task. In terms of accuracy, UR performed better than HC for fearful stimuli only. At the neural level, the authors found no significant differences between UR and HC for non-emotional inhibition. However, in the case of inhibition of fearful faces only, UR showed a significant decrease in left inferior frontal gyrus activity.

In a different type of paradigm, Kanske *et al.* (2013) investigated the neural correlates of emotional distraction on mental arithmetic problems in euthymic BDP type I, UR and subjects with hypomanic personality. Although they found increased activation for all 3 samples in the dorsolateral and dorsomedial PFC and the parietal cortex, as well as in bilateral insula for UR and hypomanic samples, only BDP had a significantly increased right parietal cortex activation compared to HC. This increased activity was also positively correlated with increased RT for the emotional distraction effect, although no differences were found between groups for RT or accuracy.

Taken together, these results on emotional processing show differential modulation of amygdala and mPFC regions in BDP and relatives compared to controls, with an impairment of down-regulation of the amygdala activity, although results are still discordant and need further exploration. Interaction of cognitive and emotional processes might involve differences of activation in more attention-related regions, such as the inferior frontal gyrus and parietal cortex.

2.4 Executive functions

2.4.1 Attention, Inhibition and Cognitive Flexibility tasks

One simple way to test attention is the continuous performance test (CPT): it has been used in UR with 2 levels of difficulty (Sepede et al., 2012). In terms of behavioral results, BDP and UR had significant lower accuracy during the correct target condition relative to HC. During this condition, BDP had significantly lower right insula activation compared to HC and UR. The latest had a greater deactivation of the PCC compared to BDP and HC. During the most difficult condition, UR also showed increased activity in the bilateral inferior parietal lobule and the left insula. Finally, during the incorrect target condition, increased activity of the

posterior part of the middle cingulate cortex and of the insula bilaterally was observed in both BDP and UR compared to HC (with intermediate activation level of the left insula in UR).

Other cognitive processes that are supposedly impaired in affective disorders are cognitive flexibility and inhibition. Another task targeting inhibition processes is the Stroop Color Word Test (SCWT), used with a verbal version by Pompei *et al.* (2011b). This study showed that patients and both affected and unaffected relatives displayed significantly lower activation levels in the superior and inferior parietal lobules compared to controls. However, BDP also showed significantly less activity in the right vlPFC and in the head of the left caudate nucleus compared to both controls and their relatives (while affected relatives had no difference in this latter area compared to all groups). After applying psychophysiological interaction (PPI) analysis to examine the functional connectivity of the inferior frontal gyrus during the SCWT, BDP elicited a reduced functional connectivity of the vlPFC with both the vACC and the basal ganglia (caudate nucleus and globus pallidus) while showing a positive connectivity with the insula (Pompei et al., 2011a). Their affected relatives also showed reduced connectivity between the vlPFC and the vACC and basal ganglia, but also with the insula compared to controls. Finally, the unaffected relatives showed only reduced connectivity with the vACC and the insula, with additional positive connectivity with the dorsolateral PFC compared to healthy subjects.

2.4.2 Language functions

Language production has also been under investigation. Two studies used a verbal fluency task with 2 levels of difficulty. Allin *et al.* (2010), with almost the same population cited in Surguladze's study, found that UR had a similar behavioral pattern than HC. They showed that , in comparison to control subjects, increased retrosplenial/posterior cingulate cortex

activation was observed in both BDP and their UR during the easy and demanding conditions. However, in the easy condition, UR also showed increased precuneus activation and a decreased left fronto-temporal cortex activation, whereas BDP only showed decreased left frontal cortex activation. In the hard condition, only UR displayed decreased activation in the mPFC. Consequently, when BDP and their UR were compared to each other, UR had lower vlPFC activation (easy condition) and mPFC activation (hard condition). Costafreda et al., on the other side, included a large number of bipolar or schizophrenia patients, as well as their monozygotic twins (Costafreda et al., 2009) but chose to look only into Brodmann area (BA) 44 or 45 (inferior frontal cortex) and found that both BDP and their UR showed no significant difference compared to HC, whereas schizophrenia patients and their monozygotic twins did. Another way of studying verbal production is the Hayling sentence completion test, used by Whalley *et al.* (2011) with 4 levels of difficulty. They recruited a large number of first or second-degree relatives of BDP and found no significant difference in the performance of both groups. However, UR had higher depressive symptoms and a trend towards higher cyclothymia (measured with TEMPS-A questionnaire) and use of sedatives. They also showed that when the difficulty of the task increased, UR displayed significantly higher activation in the left amygdala compared to HC. They did not show a significant difference between groups during the task compared to baseline. The same group (Whalley et al., 2013) then performed a longitudinal study that showed that 20 previously unaffected relatives developed MDD while 1 developed BD type I and another developed BD type II, over a period of 2 years. In the control group, only 4 subjects developed MDD. They still found no significant behavioral difference across all groups during the Hayling task as opposed to baseline condition. However, when the difficulty of the task increased, relatives affected by MDD showed increased activation in the insula bilaterally and the inferior parietal cortex compared to HC and UR.

Again, tasks testing for executive functions show differences for relatives in regions already implicated in the disease, but with a focus on PCC, precuneus and ventrolateral PFC, as well as basal ganglia, as expected from the networks underlying these cognitive processes.

2.5 Reward processing

Although reward processing is probably altered in bipolar disorder (Strakowski, 2012), only two studies so far investigated this aspect in relatives, and only one in adults.

Linke *et al.* (2012) used a probabilistic reversal learning task to investigate defects in the reward system. No difference in RT was observed between all groups, however both BDP (non significantly) and UR (significantly) won less money (in terms of reward) than HC, probably because they interpreted the rewards less efficiently. At the neural level, BDP showed significantly greater activation in the medial and right lateral OFC, the right amygdala, the dorsal ACC and the putamen during rule reversal, whereas reward elicited a greater activation only in the medial OFC compared to controls. No greater activation was observed during punishment. UR also displayed higher levels of activity than controls in the medial OFC when presented with reward or rule reversal, as well as during punishment. In addition to these findings, UR had greater activation of the right amygdala during reward compared to BDP and HC. Finally, BDP showed greater activation in the right lateral OFC and the putamen during rule reversal compared to their unaffected siblings.

More studies are needed to disentangle the impact of different subprocesses of reward processing in subjects vulnerable to bipolar disorder.

2.6 Resting state studies

Meda *et al.* (2012) investigated functional network connectivity during resting states in schizophrenia and bipolar patients, and their relatives, using an across-network approach, namely functional network connectivity (FNC) analysis. BDP and their UR (along with schizophrenia patients) showed a reduced connectivity between 2 networks compared to controls, namely 1) fronto-occipital, linked to visual perception and higher-order visual processing, and 2) anterior default mode-prefrontal, linked to theory of mind and social cognition. Moreover, UR (along with schizophrenia patients and their UR to a lesser extent) showed a reduced functional connectivity between the mesolimbic-paralimbic and sensory-motor network compared to HC. Khadka *et al.* (2013) extended the above-mentioned study by performing a within-network analysis on the same dataset. UR of bipolar patients presented non-specific disturbances in the connectivity of the frontal-thalamic-basal ganglia network and sensory-motor network that were shared with the other groups.

Another study analyzed the amplitude of low-frequency fluctuations (ALFF, measuring regional brain function), and functional connectivity with a seed voxel correlation approach (Lui et al., 2014). It found that UR presented the same type of alteration than bipolar and schizophrenic patients, namely increased connectivity between precentral/postcentral gyrus and the caudate nucleus, bilaterally. Another classical analysis of resting state is through independent component analysis (ICA) and ROI-based connectivity, as in the study from Singh et al. (2014). UR presented differences only in the ROI-based connectivity analyses: greater connectivity between the left vlPFC and the left superior parietal lobule. However, they displayed decreased connectivity between the left amygdala and pregenual ACC, sgACC and supplementary motor cortex, and left vlPFC and left caudate. Some of these findings correlated with age in UR and not in HC, and increased connectivity in vlPFC region was interpreted as compensatory mechanism and a marker of resilience.

Probably due to the disparities of methods, these results were not replicated yet. Overall, the at-rest connectivity between frontal cortex and basal ganglia or limbic/paralimbic regions seems altered in a non-specific fashion in UR.

2.7 Results of adolescents and children studies

Adolescents and children offspring/siblings of patients with BD are of particular interest as they are at greater risk of developing BD than adults UR. The same types of paradigms were used in these populations, mainly using emotional faces as stimuli. We separately report here these studies since the developmental aspect of this population could constitute a confounding factor, and therefore their interpretation must be cautious. However they are also consistent with the general theoretical framework of neural changes in BD and shed a specific light on vulnerability markers. A very recent study published a face memory task in a small sample of young relatives of bipolar patients (Tseng et al., 2015). They report a trend toward intermediate accuracy in relatives of patients, who displayed hypoactivation of the middle frontal gyrus and hyperactivation of the parahippocampal gyrus for correctly identified faces compared to incorrectly identified faces. Another study used emotional faces in a N-Back task with 2 memory conditions (0-back and 2-back task) (Ladouceur et al., 2013). They targeted voluntary attentional control in the presence of emotional distractors (neutral, happy or fearful faces). During the 2-back task, UR had a significantly higher right vlPFC activity compared to HC in response to happy face distracters, which was the reverse in response to fearful faces. In addition to these findings, PPI analyses showed that UR had significantly decreased connectivity between the right vlPFC and the right amygdala during the fearful face distracter, and between the right vlPFC and both the left amygdala and the left dlPFC during the happy face distracters.

Another study, investigating this time explicit response to emotional (angry, happy or fearful) and neutral faces, was performed by Olsavsky et al. in adolescent patients and relatives (Olsavsky et al., 2012).A ROI approach showed that when fearful faces were presented for subjective rating of fear, both BDP and UR displayed more right amygdala activity than HC, whereas happy faces did not elicit group differences. This difference was greater for siblings than offspring. Whole brain analysis showed the same results in the right parahippocampal gyrus/amygdala. UR were more affected than BDP, who in turn were more affected than HC.

Mourão-Miranda *et al.* (2012) conducted a study on a small group of young patients and offspring, using an emotional face task with both implicit and explicit emotion recognition. In this study, they also combined machine learning, namely Gaussian Process Classifiers (GPC) with fMRI in order to classify each individual, based on his fMRI data, to a specific group, thereby predicting the risk the UR had of developing BD. There was no behavioral differences, but pattern classification analysis (GPC) based on whole brain activity showed that the morphed happy faces task accurately differentiated UR from HC to a significant level. The accuracy decreased from neutral (75%) to mild (68.5%) and intense (37.5%) happy faces. The task using morphed fearful faces did not discriminate. Twelve to 45 months of follow up showed that GPC predictive probabilities were significantly more accurate for relatives who developed mood or anxiety disorder compared to unaffected relatives who did not develop any disorder, thus making this technique a promising tool. It is also worth noting that the ventromedial prefrontal cortex and superior temporal sulcus activity best differentiated UR from HC during the happy face task.

A recent study by Brotman et al. (2014) used a parametric face paradigm with both explicit and implicit components. In terms of behavior, both BDP and UR rated angry, neutral and

100% happy faces as less hostile compared to HC. Amygdala ROI analysis showed that both BDP and the UR group had decreased bilateral amygdala modulation in response to angry faces but not to happy faces. Whole brain analysis for angry faces showed that BDP and UR had decreased modulation in the left inferior frontal gyrus during hostile ratings, whereas only BDP showed increased modulation in the right ACC compared to both UR and HC. Patients also showed decreased modulation of the same area during the implicit condition compared to HC. Regarding happy faces, only UR had decreased modulation for the explicit condition but increased modulation for the implicit condition in the left IFG compared to healthy subjects. Interestingly, they also showed that only offspring had decreased modulation in the ACC for the implicit condition compared to siblings.

A study targeted anticipation and feedback of reward and loss during a monetary incentive task in children of BDP and controls (Singh MK et al., 2014). UR showed decreased activation in the pregenual cingulate cortex during loss anticipation, and increased in the left inferior frontal gyrus when receiving feedback of reward. UR showed increased connectivity between pregenual cingulate cortex and right ventrolateral frontal gyrus during anticipation of loss, and weaker connectivity during reward processing. Therefore, high-risk children presented some degree of disturbed prefrontal function during reward processing, although no differences were found at the behavioral level.

Inhibition function has been tested in children, both suffering from BD and at risk for it (the siblings or offspring of adult bipolar patients), using a change-signal task (Kim et al., 2012). They found no behavioral differences between groups, but UR showed increased activity in two regions of the vlPFC, one region of the inferior parietal gyrus, and two left cerebellar regions during successful changes. For unsuccessful changes, BDP showed elevated activation of sgACC compared to UR and HC. Comparison of the successful vs unsuccessful

changes revealed greater activation of the right vlPFC in BDP and UR. This was not better explained by offspring or sibling status, medication, or comorbid ADHD.

Again, similarly to adult studies, and although no study so far exactly replicated the findings of another, we see that the same regions are involved: amygdala/PHG, ventrolateral PFC/IFG and pre/subgenual ACC. We can also notice that the direction of the change seems to have a relationship with the valence of the stimuli, although the precise associations are not clear yet.

Discussion

We have here summarized the functional neuroimaging findings currently available in relatives of patients with BD, considered an at-risk population. The overall pattern when examining the most valid and comparable results (fMRI whole-brain differences between UR and matched HC during cognitive or emotional tasks) shows results comparable with the current literature on BD. The most robust results resulting from whole-brain analyses, such as changes in the frontal gyrus, the insula, the amygdala, and the parietal cortex are summarized in Table 3. We chose to regroup those regions based on coordinates rather than anatomical labels that are not always consistent, and this is displayed in Figure 1. Nonetheless, the synthesis of these studies still requires excessive simplification. Indeed, the lack of reproducibility studies and the existence of multiple methodological approaches prevent definitive conclusions.

These common regions found both in the literature for bipolar patients and in this review for high-risk population include the inferior/ventrolateral frontal gyrus, the medial frontal cortex/ACC, limbic-related areas and the parietal cortex, that have all been involved in meta-analyses comparing bipolar patients to controls (Chen et al., 2011; Delvecchio et al., 2012; Houenou et al., 2011; Kupferschmidt and Zakzanis, 2011). It is not totally consistent with the meta-analysis on high-risk young subjects, which reported differences in dlPFC,

cerebellum, insular cortex and inferior parietal lobule (Lee et al., 2014). However this particular study applied Activation Likelihood Estimation (ALE) to studies including mainly pediatric populations. The broader study of Fusar-Poli et al. (Fusar-Poli et al., 2012) found association between at risk group and activation in medial and superior frontal cortex, as well as the insula. These perturbed activations in specific regions, found both in at-risk population and patients, are candidate vulnerability markers.

Insula activation seems consistently altered in relatives of patients with BD, although in the current review the direction of the activation varies. For example, inside the same task, the insula showed reverse activation for different conditions (Sepede et al., 2012). However, hyperactivation of the insula correlates with cyclothymia and might predict the development of depression in relatives (Whalley et al., 2013).

More consistent is the hyperactivation of the amygdala in emotional paradigms (Olsavsky et al., 2012; Whalley et al., 2011). ROI studies also consistently show increased amygdala activity in tasks such as implicit emotional recognition, emotion regulation, and reversal learning (Kanske et al., 2015; Linke et al., 2012; Surguladze et al., 2010). Hyperactivation of the amygdala in BD is usually taken for granted in neurobiological models (Blond et al., 2012; Frey et al., 2013; Langan and McDonald, 2009; Phillips et al., 2008; Phillips and Swartz, 2014; Strakowski, 2012; Townsend and Altshuler, 2012; Wessa et al., 2014), confirmed by whole brain meta-analyses (Chen et al., 2011; Delvecchio et al., 2012; Houenou et al., 2011; Kupferschmidt and Zakzanis, 2011). This activation often extends into the parahippocampal gyrus (Lee et al., 2014). The inclusion of tasks with emotion processing and affective cues (Strakowski, 2012) seems an important favoring factor although the exact specificity of processes eliciting amygdala hyperactivation as a trait marker of bipolar disorder remains unclear, since cognitive tasks also seem to modulate this activation in high-

risk subjects (Linke et al., 2012). One could argue that reversal learning tasks also include a reward component, hence a form of emotional processing (Wessa et al., 2014).

Therefore, the results reported here confirm once again that limbic activity, and in particular that of the amygdala, is a core component of the disease and might represent a vulnerability trait, although psychological processes and mood states have to be considered as well (Hariri, 2012; Wessa et al., 2014).

Regarding frontal cortices, deficits in the activation of the left inferior frontal gyrus during processing of emotional negative stimuli (Roberts et al., 2013) and reward (Singh MK et al., 2014) reinforce the hypothesis of a deficit of cognitive control (Delvecchio et al., 2012). This is also supported by the results of a study using a ROI approach in a similar region on the right side (Ladouceur et al., 2013) and studies in patients (Brotman et al., 2014; Favre et al., 2013; Hajek et al., 2013). However, laterality is not consistent. Moreover, a region found in one of the whole brain analyses shows hyperactivation during a cognitive task in healthy relatives (Kim et al., 2012) and similar ROIs also show hyperactivation for working memory task and happy faces conditions (Ladouceur et al., 2013; Thermenos et al., 2010). In addition, greater activation of this region interpreted as greater inefficiency is associated with Met158 genotype and affective disease expression (Lelli-Chiesa et al., 2011). It is worth noting that the ventrolateral PFC region found hyperactivated by Kim et al. (2012) presents the same coordinates as the one found deactivated in meta-analyses of patients (Chen et al., 2011; Houenou et al., 2011), where modulation is also stronger for negative facial expressions (Delvecchio et al., 2012). One explanation could be a compensatory overactivation in UR (Frangou, 2012), and maybe in some categories of patients as well, when a relatively simple cognitive control is required. This compensatory mechanism could be overloaded for negative stimuli processing for example. Therefore, the exact role of ventrolateral IFG (BA47,

sometimes referred as orbitofrontal cortex as well) in BD and the subsequent role of inhibition deficit as endophenotype for the disease needs to be studied (Frey et al., 2013). Its pattern is probably more complex than a simple trait-like hypoactivation.

The same pattern of altered activation in high-risk subjects emerges for a more anterior region, the fronto-polar cortex. Whole-brain studies show increased activation for executive functions and positive stimuli (Brotman et al., 2014; Drapier et al., 2008) but hypoactivation for negative stimuli (Brotman et al., 2014). A ROI approach of this region shows hyperactivation during a WM task for both high-risk subjects and controls compared to patients (Thermenos et al., 2010). This might again be interpreted as a compensatory mechanism, of which the efficacy depends on attentional demand, as demonstrated in bipolar patients during a difficult N-back task (Jogia et al., 2012). Again, the efficacy of this mechanism could be overwhelmed by negative emotional processing (Diler et al., 2013). Another explanation might be that hypoactivation of this region arises latter in the process and represent a consequence of the disease. Further research to disentangle the effect of emotion and attention on frontal activity is needed in bipolar disorder patients and unaffected relatives in order to better understand the relationship to the disease.

Another expected finding in these high risk populations is the modulation of the medial prefrontal cortex, both in the dorsal (Surguladze et al., 2010) and the anterior (Allin et al., 2010) ACC. Dorsal ACC is expected to show hypoactivity in bipolar disorder patients, consistent with diminished cognitive control (Phillips et al., 2008). Here it rather showed hyperactivation when judging faces with implicit emotional processing, which can also be understood as a compensatory mechanism in at risk subjects.

The ventral medial prefrontal cortex, or the anterior para-limbic regions, are involved in the pathophysiology of BD, in particular in regard to its connection with the amygdala (Blond et al., 2012; Price and Drevets, 2012). Interestingly, the vmPFC has been found to best

differentiate between relatives and controls in pattern recognition analyses (Mourão-Miranda et al., 2012) and is part of the DMN, that itself shows alterations in bipolar patients (Torrisi et al., 2013; Vargas et al., 2013) and relatives (Khadka et al., 2013; Meda et al., 2012). Resting state alterations in the vmPFC might be specific to BD compared to schizophrenia (Ongür et al., 2010). Alterations in the vmPFC have been proposed as one of the initial signs of degradation in BD and worsen as the disease develops (Savitz et al., 2014). The vmPFC or the medial OFC did not appear in whole-brain analyses of first-degree relatives of patients with BD, however ROI analyses showed hyperactivation of medial OFC in relatives (Linke et al., 2012), compatible with the motivational dysregulation model (Wessa et al., 2014). However these results are also the opposite of those found in siblings of bipolar patients during sad mood induction as assessed by PET (Krüger et al., 2006), where the medial OFC displayed low activity in both siblings and patients.

The absence of alteration of the dorsolateral prefrontal cortex in high-risk subjects compared to healthy controls in this review is surprising. This finding might point towards the hypothesis of initial limbic and possibly medial-ventrolateral prefrontal dysfunctions, with hypoactivation of dlPFC regions arising as a consequence or a scar of the disease. However, although hypoactivations of this region have repeatedly been identified in bipolar patients (e.g. Mullin et al., 2012), most recent models focus on the ventrolateral and medial prefrontal cortices (Phillips and Swartz, 2014; Strakowski et al., 2012), as confirmed by this review.

Methodological limitations

First of all, most of the studies made no difference between inclusion of offspring or first-degree relatives of bipolar patients, although this can be very different conceptually, ranging from at-risk subjects to resilient subjects. Second of all, there is a great variability of age ranges represented amongst the various study participants. Given that grey matter undergoes

important developmental changes over the course of time, this further confounds any comparisons (Raznahan et al., 2011). Thirdly, the exclusion criteria applied to offspring participants varied from the most stringent measures, enforcing a total absence of psychiatric disorder (e.g. Kanske et al., 2013), to having no exclusions criteria at all (e.g. Roberts et al., 2013). Since the offspring of bipolar patients presenting subsyndromal or full other psychiatric symptoms are actually more likely to develop the disease (Duffy et al., 2010), selecting "hypernormal" offspring might reduce sensibility to vulnerability. Moreover, thorough examination of mental status of control subjects' parents was not always correctly reported.

Future studies performed on more homogenous groups should allow researchers to perform meta-analyses of interest. Another limitation is that many of the studies analyzed, which do find the same type of results, were in fact produced by the same groups, for e.g. (Whalley et al., 2013, 2012a, 2012b, 2011). Finally, future research should take care to apply more standardized reporting of brain areas, in particular the frontal gyrus, relying on brain coordinates that will allow meta-analyses.

Conclusion

In conclusion, this qualitative review of fMRI studies including first-degree relatives of bipolar patients support the current neural models of BD (Phillips and Swartz, 2014; Strakowski, 2012). More specifically, the same regions implicated in the pathophysiology of the disease, such as the inferior frontal gyrus (vlPFC, fronto-polar cortex), the medial PFC, limbic area and in particular amygdala, as well as the parietal lobe present altered activations in unaffected first-degree relatives of bipolar patients, as compared to controls. However, the disparity of cognitive tasks and samples makes it difficult to identify a specific pattern for high-risk subjects. Additional research is still required in order to ascertain the balance

between the modulation of activation due to compensatory mechanisms, functional inefficiency or true trait phenomenon, in the light of specific functional processes.

Conflict of interest

None of the authors of this manuscript report biomedical financial interest or any other potential conflicts of interest.

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Tables captions:

Table 1: Main characteristics of the 25 fMRI studies using a cognitive/emotional task and including unaffected relatives of bipolar disorder patients (ASRM: Altman Self-Rating Mania scale; BDI: Beck Depression Inventory; BPRS: Brief Psychiatric Rating Scale; CALS: Child Affect Liability Scale; CDI: Children's Depression Inventory; CDRS: Child Depression Rating Scale; CERQ: Cognitive Emotion Regulation Questionnaire; CGAS: Clinical Global Assessment Scale; DASS: Depression Anxiety and Stress Scale; DIGS: Diagnostic Interview for Genetic Studies; FIGS: Family Interview for Genetic Studies; GAF: Global Assessment of Functioning; HAMD: Hamilton Depression Scale; ISS: Internal State Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major Depressive Disorder; MFQ: Mood and Feelings Questionnaire; MWTB: Mehrfachwahl-Wortschatz-Intelligenztest; NART: National Adult Reading Test; PARS: Pediatric Anxiety Rating Score; POMS: Profile of Mood State; SADS: Schedule for Affective Disorders and Schizophrenia; SANS/SAPS: Scale for the assessment of negative symptoms and positive symptoms; SCARED: Screen for Childhood Anxiety and Related Disorders; SCL-90-R: Symptom Checklist; TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego-auto questionnaire; UR: Unaffected Relatives; WAIS: Wechsler Adult Intelligence Scale; WASI: Wechsler Abbreviated Scale of Intelligence; YMRS: Young Mania Rating Scale)

Table 2: Main findings of the fMRI 25 studies using a cognitive/emotional task and including unaffected relatives of bipolar disorder patients (AR: Affected Relatives; BDP: Bipolar Disorder Patients; CPT: Continuous Performance Test; dlPFC: dorsolateral Prefrontal Cortex; HC: Healthy Controls; IFG: Inferior Frontal Gyrus; IPL: Inferior Parietal Lobule; mPFC: medial Prefrontal Cortex; OFC: Orbitofrontal Cortex; PCC: Posterior Cingulate Cortex; PHG: Parahippocampal Gyrus; ROI: Region-of-Interest; UR: Unaffected Relatives; vACC; ventral Anterior Cingulate Cortex; vlPFC: ventrolateral Prefrontal Cortex; WBA: Whole-Brain Analysis)

Table 3: Synthesis of main findings from whole brain fMRI analyses, comparing unaffected relatives (UR) of bipolar patients to healthy controls (HC). (ACC: Anterior Cingulate Cortex; MNI: Montreal Neurological Institute; dmPFC: dorsomedial Prefrontal Cortex; PCC: Posterior Cingulate Cortex; PHG: Parahippocampal Gyrus; WM: working memory). Alphabetical labels correspond to Figure 1.

Figure 1: Anatomical disposition of the main findings reported in Table 3. MNI coordinates as reported in Table 3. Yellow: increased activation, right hemisphere; Red: increased activation, left hemisphere; Light blue: decreased activation, right hemisphere. Dark blue: decreased activation, left hemisphere; Alphabetical labels correspondence in Table 3.

Table(s)

First author, year of publication	Bipolar Disorder Patients (BDP)	Healthy Controls (HC)	Relatives (UR and others)	Diagnosis Criteria	Supplementary questionaires
Drapier *et al* . 2008	Bipolar I Disorder, n = 20 (11 female), Age (mean) = 42.7	n = 20 (10 female), Age (mean) = 41.9	First-degree relatives (4 parents, 10 sibling and 6 offspring), n = 20 (8 female), Age (mean) = 43	SADS - Lifetime Version, FIGS	BDI, ASRM
Thermenos *et al* . 2010	Bipolar Disorder, n = 19 (8 female), Age (mean) = 41.1	n = 19 (10 female), Age (mean) = 39.2	First-degree relatives, n= 18 (10 female), Age (mean) = 36.3	SCID-IV, FIGS, Diagnostic Interview Schedule for DSM-IV	SANS/SAPS, POMS
Costafreda *et al* . 2009	Bipolar Disorder, n = 28 (16 female), Age (mean) = 40.0	n = 48 (23 female), Age (mean) = 37.4	Monozygotic twins, n = 7 (6 female), Age (mean) = 39.4	Maudsley Familiy Study: SADS-Lifetime version, FIGS	Annett scale, WASI, NART, SANS/SAPS, BDI, ASRM, HAMD, YMRS
Allin *et al* . 2010	Bipolar I Disorder, n = 18 (11 female), Age (mean) = 39.2	n = 19 (9 female), Age (mean) = 39.9	First-degree relatives, n = 19 (8 female), Age (mean) = 40.5	SADS - Lifetime Version	BDI, ASRM
Surguladze *et al* . 2010	Bipolar I Disorder, n = 20 (11 female), Age (mean) = 42.7	n = 20 (10 female), Age (mean) = 41.9	First-degree relatives, n = 20 (8 female), Age (mean) = 43	SADS - Lifetime Version, FIGS	BDI, ASRM
Lelli-Chiesa *et al* . 2011	Bipolar Disorder, n = 40 (21 female), Age (mean) = 44.0	n = 50 (24 female), Age(mean) = 34.9	First-degree relatives, n = 25 (10 female), Age (mean) = 34.9 ; First-degree relatives with MDD (n = 15) or anxiety disorder (n = 7) , n = 22 (14 female), Age (mean) = 32.5	SCID I and II, FIGS	WAIS-R, GAF, HAMD, YMRS, BPRS
Pompei *et al* . 2011	Bipolar I Disorder, n = 39 (20 female), Age (mean) = 39.43	n = 48 (23 female), Age (mean) = 36.33	First-degree relatives, n = 25 (12 female), Age (mean) = 35.0 ; First-degree MDD relatives, n = 14 (9 female), Age (mean) = 31.2	SCID I, FIGS	WAIS-R, HAMD, YMRS, BPRS
Pompei *et al* . 2011	Bipolar I Disorder, n = 39 (20 female), Age (mean) = 39.43	n = 48 (23 female), Age (mean) = 36.33	First-degree relatives, n = 25 (12 female), Age (mean) = 35.0 ; First-degree MDD relatives, n = 14 (9 female), Age (mean) = 31.2	SCID I, FIGS	WAIS-R, HAMD, YMRS, BPRS
Whalley *et al* . 2011	_	n = 70 (38 female), Age (mean) = 20.89	First-degree/second-degree relatives of Bipolar I Disorder, n = 93 (48 female), Age (mean) = 21.01	SCID or OPCRIT	TEMPS-A, YMRS, HAMD
Whalley *et al* . 2011	_	n = 75 (42 female), Age (mean) = 20.76	First-degree/second-degree relatives of Bipolar I Disorder, n = 81 (41 female), Age (mean) = 21.375	SCID or OPCRIT	TEMPS-A, NART, YMRS, HAMD
Kim *et al.* 2012	Pediatric Bipolar Disorder, n = 28 (16 female), Age (mean)=14.37	n = 21 (8 female), Age (mean)=13.8	sibling of "narrow phenotype" children or offspring of BDP type I or II, n=13 (7female), Age (mean) =13.9	K-SADS-PL, SCID or DIGS (parents)	WASI, CDRS, YMRS
Mourão-Miranda *et al* . 2012	_	n = 16 (9 female), Age (mean) = 15.3	Offspring of BDP, n = 16 (9 female), Age (mean) = 14.8	K-SADS-PL, SCDI-I, family history-research diagnostic criteria	MFQ, SCARED, CALS
Linke *et al* . 2012	Bipolar I Disorder, n = 19 (11 female), Age (mean) = 45	sample 1 (matched to patients): n = 19 (11 female), Age (mean) = 45 ; sample 2 (matched to UR): n = 22 (11 female), Age (mean) = 28	First-degree relatives (13 offspring and 9 siblings) of BDP type I, n = 22 (11 female), Age (mean) = 28	SCID-I	Culture Fair Intelligence Test, HAMD, YMRS, BDI
Olsavsky *et al* . 2012	Bipolar Disorder, n = 32 (15 female), Age (mean) = 14.7	n = 56 (30 female), Age (mean) = 14.0	At risk sibling and offspring of BDP, n = 13 (6 female), Age (mean) = 14.0	K-SADS-PL (offspring) and SCID-I/P or DIGS (BDP)	WASI, YMRS, CDRS, PARS
Whalley *et al* . 2012	_	n = 81 (44 female), Age (mean) = 21.08	First-degree/second-degree relatives of Bipolar I Disorder, n = 90 (45 female), Age (mean) = 21.24	SCID (not said explicitly in the text - refered to diagnosis to patients along with OPCRIT)	NART
Sepede *et al* . 2012	Bipolar I Disorder, n = 24 (14 female), Age (mean) = 34.8	n = 24 (16 female), Age (mean) = 32.5	First-degree relatives of BDP type I (12 offspring and 10 siblings), n = 22 (15 female), Age (mean) = 31.5	SCID I and II	Edinburgh Handedness Inventory, WAIS, HAMD, YMRS
Roberts *et al* . 2013	_	n = 49 (32 female), Age (mean) = 23.2	First-degree relatives (33 offpring and 14 siblings) of BDP type I (n = 37) or II (n = 10), n = 47 (25 female), Age (mean) = 24.6	K-SADS-BP, DIGS, FIGS	WASI, DASS, ASRM, ISS, CDI, MADRS, BDRS, YMRS
Whalley *et al* . 2013	_	n = 58 (33 female), Age (mean) = 20.78	First-degree/second-degree relatives of Bipolar I Disorder, n = 78 (36 female), Age (mean) = 21.12 ; First-degree MDD relatives of BD patients type I, n = 20 (12 female), Age (mean) = 20.59	SCID or OPCRIT	TEMPS-A, NEO-Five Factor Inventory, YMRS, HAMD
Ladouceur *et al* . 2013	_	n = 15 (11 female), Age (mean) = 13.8	Offspring of BDP type I or type II, n = 16 (7 female), Age (mean) = 14.2	K-SADS-PL	WASI, Holingshead Four-Factor Index, Edinburgh Handedness Inventory, Stony Brook Symptom Inventory, MFQ-L, CALS, SCARED
Kanske et al. 2013	Bipolar I Disorder, n = 22 (14 female), Age (mean) = 39.4	sample 1 (matched to patients): n = 22 (12 female), Age (mean) = 40.5; sample 2 (matched to UR): n = 17 (8 female), Age (mean) = 35.9	First-degree relatives (5 siblings, 4 offspring and 8 parents), n = 17 (8 female), Age (mean) = 36.6	SCID	YMRS, HAMD, BDI
Erk *et al* . 2014	_	n = 110 (62 female), Age (mean) = 32.7	First-degree relatives, n = 59 (36 female), Age (mean) = 31.8	SCID /medical record	MWTB, SCL-90-R, STAI-T, BDI
Brotman *et al* . 2014	Bipolar Disorder, n = 20 (13 female), Age (mean) = 15.6	n = 29 (13 female), Age (mean) = 14.9	Offspring and/or siblings of BD patients, n = 15 (6 female), Age (mean) = 14.5	K-SADS-Present and Lifetime Version	WASI, YMRS, CDRS, CGAS
Singh *et al.* 2014	_	n = 25 (15 female), Age (mean) = 11.8	Offspring of BDP type I, n = 20 (13 female), Age (mean) = 12.7	WASH-U-KSADS, KSAD-PL	YMRS, CDRS-r, Multidimensional Anxiety Scale for Children, CGAS, Barratt Impulsiveness Scale, Revised Dimensions of Temperament Survey
Tseng *et al.* 2014	Bipolar Disorder, n = 27 (12 female), Age (mean) = 14.4	n = 37 (21 female), Age (mean) = 14.7	Offspring and/or siblings of BD patients, n = 13 (5 female), Age (mean) = 13.7	KSADS-PL for patients	WASI, YMRS, CDRS, PARS, CGAS
Kanske et al. 2015	Bipolar Disorder, n = 22 (14 female), Age (mean) = 39.4	sample 1 (matched to patients): n = 22 (12 female), Age (mean) = 40.5; sample 2 (matched to UR): n = 17 (8 female), Age (mean) = 35.9	First-degree relatives (5 siblings, 4 offspring and 8 parents), n = 17 (8 female), Age (mean) = 36.7	SCID	YMRS, HAMD, BDI, CERQ

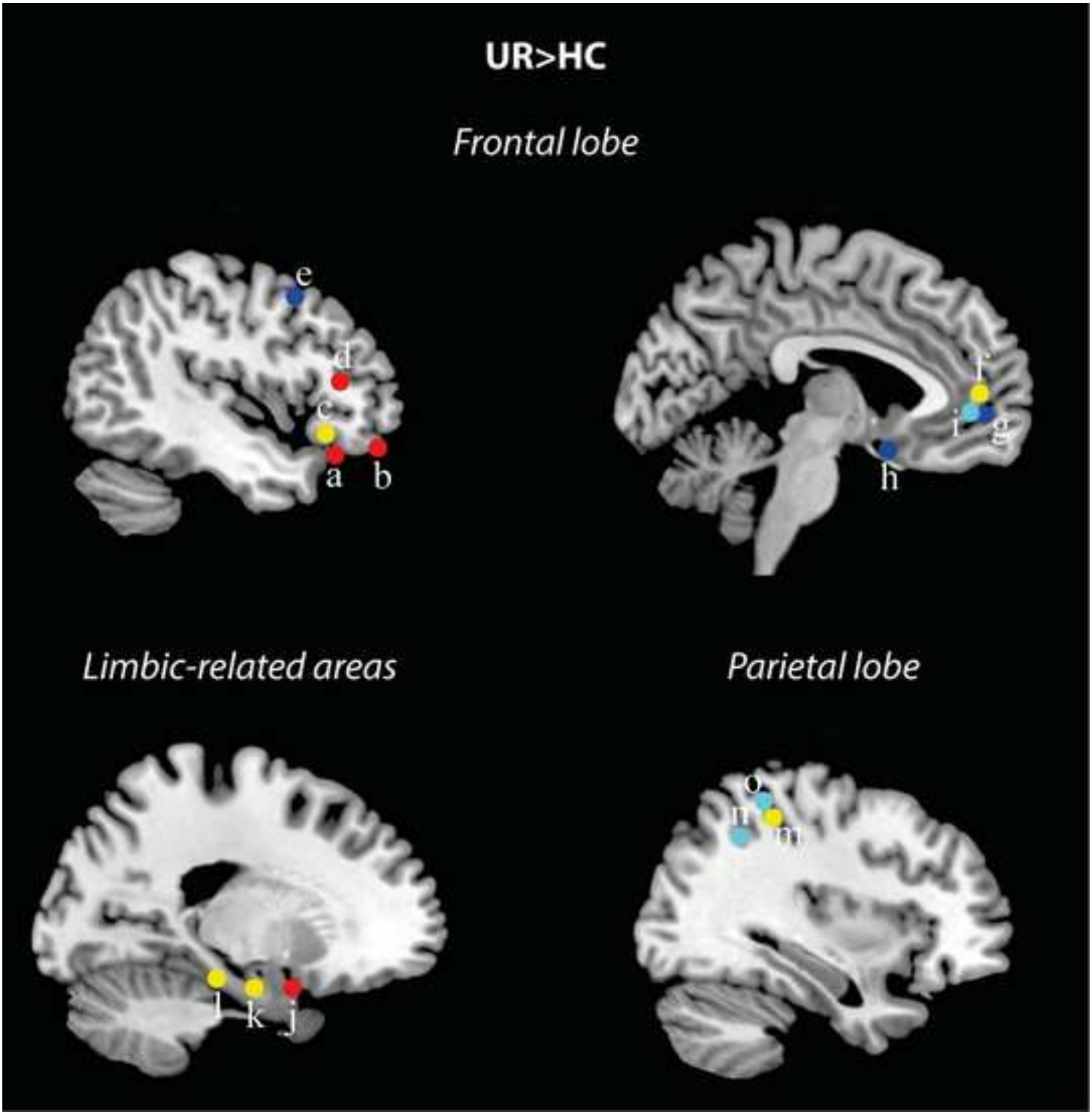
Table(s)

First author, year of publication	Task	Additional Methodology / DNA genotyping	Technique	Results
Drapier *et al* . 2008	N-back working memory task (1-back, 2-back and 3-back)	_	fMRI (1.5 T) WBA	UR > HC: ↑ left fronto-polar cortex (2-back)
Thermenos *et al* . 2010	CPT-X task (0-back) and N-back working memory task (2-back)	_	fMRI (1.5 T) ROI	UR>HC: ↑left ant. Insula, left OFC/inf frontal gyrus (BA 47), right sup. parietal cortex
Costafreda *et al* . 2009	Verbal fluency task	_	fMRI (1.5 T) ROI	BDP & UR = HC: BA 44/45 (inf. frontal cortex)
Allin *et al* . 2010	Verbal fluency task	_	fMRI (1.5 T) WBA	BDP & UR > HC: ↑retrosplenial/PCC (both conditions); UR>HC: ↑precuneus, ↓left fronto-temporal cortex (easy condition) ; ↓mPFC (hard condition) ;
Surguladze *et al* . 2010	implicit emotional faces recognition (happy or fearful)	_	fMRI (1.5 T) WBA and ROI	BDP & UR > HC: ↑mPFC, left putamen (happy, fearful); ↑amygdala (ROI, happy)
Lelli-Chiesa *et al* . 2011	Sad facial affect discrimination task	COMT Met158VAL genotyping	fMRI (1.5 T) ROI	Met/Met: AR>BDP>UR>HC: ↑ right vlPFC
Pompei *et al* . 2011	Stroop Colour Word Test		fMRI (1.5 T) WBA	BDP & UR & AR > HC: ↓sup. + inf. parietal lobules;
Pompei *et al* . 2011	Stroop Colour Word Test	Psycho-Physiological Interaction (PPI)	fMRI (1.5 T) ROI for PPI (vlPFC)	UR > HC: ↓connectivity vlPFC- vACC; vlPFC-insula; ↑connectivity vlPFC - dlPFC
Whalley *et al* . 2011	Hayling sentence completion test (verbal initiation section)	_	fMRI (1.5 T) WBA	UR>HC: ↑left amygdala (correlation difficulty)
Whalley *et al* . 2011	Hayling sentence completion test (verbal initiation section)	Diacylglycerol Kinase Eta (DGKH)	fMRI (1.5 T) WBA	UR with RISK haplotype > UR heterozygote: left medial frontal, left precuneus, right PHG, ACC and PCC
Kim *et al.* 2012	Change Task (adapted from stop-sigmal)		fMRI(3T) WBA and ROI	UR>HC and BD: ↑ right vlPFC; UR &BDP > HC: ↑right IPL, right caudate
Mourão-Miranda *et al* . 2012	Emotional face gender labeling	Pattern classification (Gaussian Process Classifiers)	fMRI (3 T) WBA	vmPFC, sup. temporal sulcus best differenciate
Linke *et al* . 2012	Reversal Learning Task	_	fMRI (3 T) ROI	UR>HC: ↑right amygdala (reward, rule reversal), mOFC (same + punishment);
Olsavsky *et al* . 2012	Emotional task	_	fMRI (3 T) WBA and ROI	BDP & UR > HC: ↑right amygdala (ROI, fearful faces); UR >BDP>HC: ↑right PHG/amygdala (whole-brain, fearful faces)
Whalley *et al* . 2012	Hayling sentence completion test	microRNA MIRI37 SNP (G/T) genotyping	fMRI (1.5 T) WBA	UR=HC: no significant difference
Sepede *et al* . 2012	Continuous Performance Test (CPT)	_	fMRI (1.5 T) ROI	UR > BDP &HC: ↓PCC, ↑bilat. inf. parietal lobule, left insula (correct target condition) ; UR & BDP > HC : ↑middle cing. cortex, insula (BDP>UR>HC in left insula) (incorrect target condition)
Roberts *et al* . 2013	Emotional Go/No-Go task	_	fMRI (3T) WBA	UR > HC: ↓left IFG (inhibition fearful faces);
Whalley *et al* . 2013	Hayling sentence completion test (verbal initiation section)	longitudinal follow-up (2 years)	fMRI (1.5T) WBA	relatives who developped MDD: ↑ bilat. insula
Ladouceur *et al* . 2013	Emotional face 0-back and 2-back working memory task	Psycho-Physiological Interaction (PPI)	fMRI (3T) ROI	UR>HC: ↑right vlPFC (happy faces distractors), ↓right vlPFC (fearful faces distractors); UR: modulation connectivity vlPFC-amygdala
Kanske et al. 2013	Mental calculation coupled to emotional distractors	_	fMRI (3T) WBA	UR=HC: no significant difference
Erk *et al* . 2014	Episodic Memory task	CACNA1C genotyping	fMRI (3T) WBA	UR & HC with risk allele > HC without risk allele: ↓bilat. hippocampus, subgenual cortex
Brotman *et al* . 2014	Parametric face paradigm	_	fMRI (3T) WBA and ROI	BDP & UR >HC: ↓amygdala modulation (angry faces, ROI); ↓ left IFG (angry faces, whole-brain); UR>HC: ↓left IFG (happy faces, explicit) and ↑left IFG (happy faces, implicit)
Singh *et al.* 2014	Monetary incentive delay task	Psycho-Physiological Interaction (PPI)	fMRI (3T) WBA and ROI	UR>HC : ↓ pregenual cortex, anticipation of loss vs anticipation of reward ; ↑ left lateral OFC, reward feedback; UR: less connectivity bewteen pregenual cingulate and right vlPFC
Tseng *et al.* 2014	Face memory task		fMRI (3T) WBA	UR > HC >BDP: ↑right PHG; UR & BDP < HC: ↓ middle frontal gyrus
Kanske et al. 2015	emotion regulation task (view/reapraisal/distraction with mental calculations)	Psycho-Physiological Interaction (PPI)	fMRI (3T) ROI	UR + BDP > controls: ↑ amygdala (impaired down-regulation during reappraisal), positively correlated with connectivity with OFC

Table(s)

UR > HC, whole-brain analyses fMRI		
frontal lobe	MNI coordinates (x,y,z)	
inferior / ventrolateral frontal gyrus	left: -21 11 -17	↓ inhibition fearful faces (Roberts et al. 2013, **h**)
	right: 45 25 -8	↑ successful change (Kim et al. 2012, **c**)
	left: -45 29 -19	↑ reward feedback (Singh et al. 2014, **a**)
left middle frontal gyrus	-42 12 48	↓ successfully recalled faces (Tseng et al. 2014, **e**)
left fronto polar cortex	-43 47 -16 to -30 66 6	↑ WM (Drapier et al. 2008, **b**)
	-49 31 10	↑ happy faces ↓angry faces (Brotman et al. 2014, **d**)
medial frontal cortex	ACC/dmPFC: 2 50 7	↑ implicit faces (Surguladze et al. 2010, **f**)
	ACC/mPFC: -7 52 -2	↓ verbal fluency (Allin et al. 2010, **g**)
	pregenual ACC: 10 46 -1	↓ anticipation of loss >anticipation reward (Singh et al. 2014, **i**)
limbic-related areas		
amygdala	right: 24 -26 -18	↑ emotional faces (Olsavsky et al. 2012, **l**)
	left: -28 6 -22	↑ difficulty Hayling task (Whalley et al. 2011, **j**)
PHG	right: 12 -10 -22	↑ successfully recalled faces (Tseng et al. 2014, **k**)
parietal lobe		
right superior parietal cortex	27 -42 57	↓ Stroop (Pompei et al. 2011b, **n**)
right inferior parietal cortex	41 -38 50	↑ successful change (Kim et al. 2012, **m**)
	34 – 52 42	↓ Stroop (Pompei et al. 2011b, **o**)

Figure


UR>HC
Frontal lobe
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