Journal of Affective Disorders 132 (2011) 344–355

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Neuroimaging-based markers of bipolar disorder: Evidence from two meta-analyses

Josselin Houenou [a,b,c,d], Juliane Frommberger [e], Soufiane Carde [b], Manuela Glasbrenner [e], Carsten Diener [e], Marion Leboyer [a,b,c], Michèle Wessa [e,*]

[a] INSERM, U 955, IMRB, Department of Medical Genomic, Psychiatry Genetic Team, University Paris Est-Créteil, Creteil, F-94000, France
[b] AP-HP, Henri Mondor-Albert Chenevier Hospitals, Department of Psychiatry, Creteil, F-94000, France
[c] Fondation FondaMental, French National Science Foundation, France
[d] LNAO, CEA I2BM NeuroSpin, Gif-Sur-Yvette, France
[e] Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Mannheim, Germany

ARTICLE INFO

Article history:
Received 19 June 2010
Received in revised form 14 February 2011
Accepted 3 March 2011
Available online 5 April 2011

Keywords:
Bipolar disorder
Voxel-based morphometry
Functional magnetic resonance imaging
Emotion
Grey matter

ABSTRACT

Background: Bipolar disorder (BD) is often misdiagnosed or tardily detected, leading to inadequate treatment and devastating consequences. The identification of objective biomarkers, such as functional and structural brain abnormalities of BD might improve diagnosis and help elucidate its pathophysiology.
Methods: To identify neurobiological markers of BD, two meta-analyses, one of functional neuroimaging studies related to emotional processing and a second of structural whole-brain neuroimaging studies in BD were conducted in the present study. Conducting a literature search on studies published up to September 2009 we identified 28 studies that were eligible for the meta-analyses: 13 functional magnetic resonance imaging studies, related to emotional processing and 15 structural imaging studies using whole-brain voxel-based morphometry. Only studies comparing patients with bipolar disorder to healthy controls were considered. Data were extracted or converted to a single anatomical reference (Talairach space). The activation likelihood estimation technique was used to assess the voxel-wise correspondence of results between studies.
Results: In patients with BD, decreased activation and diminution of gray matter were identified in a cortical-cognitive brain network that has been associated with the regulation of emotions. By contrast, patients with BD exhibited increased activation in ventral limbic brain regions that mediate the experience of emotions and generation of emotional responses. The present study provides evidence for functional and anatomical alterations in BD in brain networks associated with the experience and regulation of emotions.
Conclusions: These alterations support previously proposed neurobiological models of BD and might represent valid neurobiological markers of the disorder. The specificity of these results to unipolar depression remains to be explored.

1. Introduction

Bipolar disorder (BD) is the sixth largest cause of disability-adjusted life years (Murray and Lopez, 1996) and its prevalence worldwide is at least 1% (Merikangas et al., 2007). This high prevalence is associated with under-recognition (Hirschfeld et al., 2003) and delayed diagnosis leading to inadequate treatment, huge medical costs and high rates of comorbidity (Keck et al., 2008). As a consequence, there is a clear need to improve diagnostic tools and to identify objective biomarkers. Specific functional and structural brain abnormalities underlying cognitive and emotional trait impairments that are present during both acute episodes

* Corresponding author at: Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Square J5, 68159 Mannheim, Germany. Tel.: +49 621 1703 6008; fax: +49 621 1703 6305.
E-mail address: michele.wessa@zi-mannheim.de (M. Wessa).

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doi:10.1016/j.jad.2011.03.016

and remission have been proposed as promising candidates for biomarkers of bipolar disorders (Phillips and Vieta, 2007; Singh and Rose, 2009).

One of the characteristic impairments of BD is abnormal emotional liability reflected by extreme fluctuations in mood and emotions, and heightened emotional reactivity during all phases of the illness (Henry et al., 2003; Henry et al., 2008). The diagnostic criteria for BD, including euphoria, irritability and depression, suggest that not only is emotional reactivity increased but also that the capacity to regulate emotional states is impaired in these patients. On a neurobiological level, excessive emotional reactivity and difficulties in regulating emotions in patients with BD has been proposed by some investigators to result from an imbalance between a functionally hyperactive ventral-limbic pathway and a functionally hypoactive cortical-cognitive pathway (Blumberg et al., 2002; Phillips et al., 2003; Phillips et al., 2008). The ventral-limbic pathway involves the orbitofrontal cortex (OFC), the subgenual cingulate cortex (SGC), the amygdala and the hippocampus. By contrast, deficient emotion regulation is thought to be mediated by a network of brain regions including the dorsolateral prefrontal cortex (dlPFC), the dorsal ACC (dACC), the posterior cingulate cortex (PCC) and the precuneus. Consequently prefrontal and cingulate systems may exert weaker than normal inhibitory control of subcortical structures (Ochsner and Gross, 2005; Strakowski et al., 2005) resulting in impaired emotion regulation. As the ventrolateral prefrontal cortex (vlPFC; Brodmann Area (BA) 45/47) plays an important role in the regulation of emotional states (Kalisch, 2009; Kanske et al., 2010) it has been included in the cortical-cognitive rather than the ventral-limbic path in more recent models of BD (Phillips et al., 2008). These neurobiological models of BD overlap with models for major depression (MD) as introduced by Mayberg (1997; 2003). The models differ, however, in the assumption that the suggested neurobiological alterations mediate a general emotional hyperactivity, i.e. to positive and negative stimuli, whereas for MD this is only expected for negative stimuli. Yet, the specificity of neurobiological alterations has still to be investigated and unfortunately most studies did not use or analyze positive and negative stimuli separately.

In line with the above described neurobiological models of BD, greater than normal activation in ventral-limbic brain structures has indeed been demonstrated in symptomatic and remitted patients with BD, particularly in response to emotional stimuli (Strakowski et al., 2005; Wessa and Linke, 2009). There is also empirical evidence of hypoactivation of cortical-cognitive prefrontal and parietal regions in these patients (Wessa and Linke, 2009), although the relevant findings are inconsistent.

Interestingly, structural neural abnormalities corresponding to these observed functional neural alterations have been described. A recent review (Savitz and Drevets, 2009) and meta-analysis (Arnone et al., 2009) suggest that the prefrontal lobe in general and cortical-cognitive network components such as the dlPFC, in particular, are smaller in BD patients. Diverse findings have been reported for ventral-limbic structures with increased amygdala volume, normal size of the hippocampus and smaller than normal gray matter content in the orbitofrontal cortex, the SGC and the rostral ACC (Hajek et al., 2009; Savitz et al., 2009).

Overall, findings from functional and structural neuroimaging studies of BD seem to support the neurobiological model and the pattern of abnormalities described may thus be a core feature, or biomarker, of bipolar disorder. However, this conclusion is weakened by the inconsistency of empirical findings that may be linked to heterogeneity across studies. Furthermore, most neuroimaging studies of BD are underpowered, with a high risk of type II error (Kempton et al., 2008), leading to false negative findings. On the other hand, false positives may occur from studies undertaking too many statistical comparisons. One methodological approach to at least partly overcome these problems is to use meta-analysis, a method searching for communalities across different studies investigating patients with diverse clinical features (e.g., mood state) and using disparate methodologies. For the purpose of neuroimaging studies in BD this means to search for neurobiological abnormalities common to different samples of patients and using different methodologies.

Meta-analytic tools are now available for functional and structural neuroimaging studies (e.g., Anatomical Likelihood Estimation (ALE)) (Turkeltaub et al., 2002; Laird et al., 2005a; Laird et al., 2005b; Eickhoff et al., 2009) and as the meta-analytic approach explores the generalizability of findings (Rosenthal and DiMatteo, 2001), meta-analyses of neuroimaging data now allow the identification of findings common to several MRI studies without subjective bias. Additionally, meta-analytic tools for neuroimaging data make brain localizations in different studies comparable by transforming them into a single common stereotactic space (Talairach) and using a single terminology. In the last few years, several studies have used the ALE approach to identify functional brain networks underlying diverse executive functions (Minzenberg et al., 2009) and diverse emotional tasks (Fusar-Poli et al., 2009) as well as aberrant neural networks in different mental disorders (obsessive compulsive disorder: Rotge et al., 2010; schizophrenia: Li et al., 2009). No meta-analysis of functional alterations associated with emotional processing has been conducted in bipolar disorder, despite abnormal emotional reactivity appearing to be a core feature of the disease.

Most meta-analyses addressing structural changes have focused on particular regions of interest (ROI) (McDonald et al., 2004; Kempton et al., 2008; Arnone et al., 2009), such as the amygdala; the ALE approach has recently been used to analyze whole-brain voxel-wise differences in gray matter volume (voxel-based morphometry (VBM)) in adult and pediatric bipolar disorder (Ellison-Wright and Bullmore, 2010).

We describe here a meta-analytic approach to looking for functional and structural cerebral biomarkers of bipolar disorder by combining results from functional magnetic resonance imaging (fMRI) studies related to emotional processing and whole-brain VBM studies of gray matter. We used the same ALE strategy for two parallel meta-analyses in adult patients with BD, one addressing functional, the other structural gray matter changes in order to ease comparison of results from both meta-analyses. For the same reason, we restricted the structural meta-analysis to the gray matter. We only included studies of adult patients as neurodevelopment during the adolescence influences the neural modifications in bipolar disorder (Blumberg et al., 2004). We hypothesized