Journal of Affective Disorders 195 (2016) 199–214

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review article

Can neuroimaging disentangle bipolar disorder?

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ARTICLE INFO

Article history:
Received 11 August 2015
Received in revised form
2 January 2016
Accepted 24 January 2016
Available online 9 February 2016

Keywords:
Bipolar disorder
Heterogeneity
Neuroimaging
MRI
Sub-types
Dimension

ABSTRACT

Background: Bipolar disorder heterogeneity is large, leading to difficulties in identifying neuropathophysiological and etiological mechanisms and hindering the formation of clinically homogeneous patient groups in clinical trials. Identifying markers of clinically more homogeneous groups would help disentangle BD heterogeneity. Neuroimaging may aid in identifying such groups by highlighting specific biomarkers of BD subtypes or clinical dimensions.
Methods: We performed a systematic literature search of the neuroimaging literature assessing biomarkers of relevant BD phenotypes (type-I vs. II, presence vs. absence of psychotic features, suicidal behavior and impulsivity, rapid cycling, good vs. poor medication response, age at onset, cognitive performance and circadian abnormalities).
Results: Consistent biomarkers were associated with suicidal behavior, i.e. frontal/anterior alterations (prefrontal and cingulate grey matter, prefrontal white matter) in patients with a history of suicide attempts; and with cognitive performance, i.e. involvement of frontal and temporal regions, superior and inferior longitudinal fasciculus, right thalamic radiation, and corpus callosum in executive dysfunctions. For the other dimensions and sub-types studied, no consistent biomarkers were identified.
Limitations: Studies were heterogeneous both in methodology and outcome.
Conclusions: Though theoretically promising, neuroimaging has not yet proven capable of disentangling subtypes and dimensions of bipolar disorder, due to high between-study heterogeneity. We issue recommendations for future studies.

Contents

Abbreviations: AAO, age at illness onset; ACC, anterior cingulate cortex; BD, bipolar disorder; BP, bipolar patients; BP-I/II, bipolar patients type I/II; CC, corpus callosum; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; EOBP, early-onset bipolar patients; FA, fractional anisotropy; fMRI, functional MRI; GM, grey matter; IOBP, intermediate-onset bipolar patients; LOBP, late-onset bipolar patients; LSI, local sulcal indices; MPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; PET, positron emission tomography; PF, psychotic features; PPC, posterior parietal cortex; SA, suicide attempts; SPECT, single photon emission computed tomography; SZ, schizophrenia; sMRI, structural MRI; VLPFC, ventrolateral prefrontal cortex; VPFC, ventral prefrontal cortex; WM, white matter; WMH, white matter hyperintensities

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http://dx.doi.org/10.1016/j.jad.2016.01.039
0165-0327/

1. Introduction

Current definitions of bipolar disorder (BD) reflect a clinically and etiologically heterogeneous entity, covering complex and heterogeneous phenotypes (Hägele et al., 2015; Hasler and Wolf, 2015). This may explain the difficulties in forming clinically homogeneous patient groups in clinical trials, leading to only partial effectiveness of current psychotropic treatments and to difficulties identifying neuropathophysiological mechanisms or genetic factors underlying BD (Cuthbert and Insel, 2013).

Although the etiology of BD remains largely uncertain, a growing body of literature seeks to highlight specific biomarkers of this disorder. A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Frey et al., 2013). Awareness of these biomarkers would help clinicians understand underlying neuropathophysiological processes corresponding to neural circuit abnormalities (Hägele et al., 2015; Insel et al., 2010; Phillips and Kupfer, 2013).

Neuroimaging, and specifically magnetic resonance imaging (MRI) shows promise in the search for these biomarkers. However, because results of MRI studies comparing patients with BD and healthy subjects are inconsistent, they have not led to a clear picture of the neuropathophysiological processes underlying BD (Phillips and Kupfer, 2013; Selvaraj et al., 2012). Studies including clinically more homogeneous subject groups would aid in deciphering BD heterogeneity, but require innovative approaches to identify these subgroups of patients (Houenou et al., 2015). Two approaches that would help achieve this goal are dimensional clinical assessment and clearly defined sub-typing of BD.

One approach, a dimensional clinical assessment of BD, is useful because for one given clinical syndrome, patients with the same diagnosis (e.g., bipolar depression) may have opposite symptoms (e.g., increased or decreased appetite; insomnia or hypersomnia; psychomotor retardation or agitation…). This phenomenon leads to the formation of heterogeneous groups of patients (Casey et al., 2013). A dimensional approach, such as the Research Domain Criteria (RDoC) project proposed by the US National Institute of Mental Health, may help to solve this issue by overstepping the boundaries between different diagnostic categories to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures." (http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml).

Another approach is to sub-categorize BD into clinically defined sub-types. Although the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) defines several categories of BD (type I or II, presence or absence of psychotic features and with or without rapid cycling), many others could be identified, including the presence or absence of suicide attempts, differences in age at onset and predominant polarity (Henry and Etain, 2010; Houenou et al., 2015). However, even if these classifications have phenomenological relevance, we do not know at this time if any are biologically relevant. Nor is it clear if they could increase specificity in neuroimaging data and thus help identify the neuropathophysiological mechanisms underlying BD. Working toward answering these questions, we aim to perform a review of the current literature, which attempts to identify such neuroimaging-based potential biomarkers of relevant BD phenotype.

2. Methods

One challenge we faced was to define the "core" clinical dimensions and sub-categories related to specific neuroanatomical or functional markers in BD (Houenou et al., 2015). Based on the literature and main models of BD (Phillips and Kupfer, 2013; Houenou et al., 2015), we selected sub-types and clinical dimensions commonly used in epidemiological and clinical studies. This resulted in six sub-types: history of psychotic features (PF), type (I or II), rapid cycling, history of suicide attempts (SA), response to medication and age at illness onset (AAO-early, intermediate or late); and three dimensions: impulsivity, circadian rhythm abnormalities and cognitive performance.

After defining the sub-groups and clinical dimensions, we searched the online PubMed database for relevant literature. We reviewed English-language studies published before July 2015, using systematic combinations of the keywords "neuroimaging", and "bipolar", with each dimension or sub-type. Studies considered for inclusion used a neuroimaging tool, specifically structural magnetic resonance imaging (sMRI), functional MRI (fMRI), diffusion tensor imaging (DTI), single photon emission computed tomography (SPECT) or positron emission tomography (PET) and compared bipolar patients (BP) according to the different subtypes or along different dimensional levels. We also checked these articles' reference lists and considered literature reviews. Our method resulted in two types of studies considered, those using a categorical approach (e.g., brain volumes of patients with versus without rapid-cycling), and those using a dimensional approach (e.g., correlation between brain volumes and impulsivity score of patients with BD).

Once we identified the relevant literature, we checked that, in their analysis and interpretation, each took into account the variables most likely to cause bias in neuroimaging (i.e. age, sex; mood state, consumption of substances status, illness duration and psychotropic medication status). For white matter hyperintensities (WMH) and DTI studies, we specifically checked whether they controlled for cardiovascular risk factors. These risks are associated with WMH in the general population (Murray et al., 2005) and so may particularly affect DTI results (Jones et al., 1999).

3. Results

Overall, we identified 63 studies that fit our inclusion criteria. Tables 1–6 show detailed results of each study, that we also summarized in Figs. 1–6. For each, we specify neuroimaging technique, neuroimaging approach (e.g. whole brain or regions of interest) when relevant, methodology and main results with effect sizes if available. We also comment on potential methodological