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Review article

The search for neuroimaging and cognitive endophenotypes: A critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder

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ABSTRACT

The phenomenology and underlying pathophysiology of bipolar disorder (BD) are heterogeneous. The identification of putative endophenotypes for BD can aid in the investigation of unique patho-etiological pathways, which may lead to the development of personalised preventative and therapeutic approaches for this multi-faceted disorder. We included original studies involving unaffected first-degree relatives of BD patients (URs) and a healthy control (HC) comparison group with no first-degree family history of mental disorders, investigating: 'cold' and 'hot' cognition and functional and structural neuroimaging. Seventy-seven cross-sectional studies met the inclusion criteria. The present review revealed that URs in comparison with HCs showed: (i) widespread deficits in verbal memory, sustained attention, and executive function; (ii) abnormalities in the reactivity to and regulation of emotional information along with aberrant reward processing, and heightened attentional interference by emotional stimuli; and (iii) less consistency in the findings regarding structural and resting state neuroimaging, and electrophysiological measures.

Contents

Abbreviations: ACC, anterior cingulate cortex; CPT, continuous performance task; dlPFC, dorsolateral prefrontal cortex; DSM, the Diagnostic and Statistical Manual of Mental Disorders; DTI, diffusion tensor imaging; EEG, electroencephalogram; ERP, event-related potential; HC, healthy controls; ICD, the International Classification of Diseases; mOFC, medial orbito-frontal cortex; mPFC, medial prefrontal cortex; omPFC, orbito-medial prefrontal cortex; SC, Schizophrenia; SCWT, Stroop Colour Word Task; TMT, Trail making task; UD, unipolar depression; UR, healthy, unaffected first-degree relatives of patients with BD; vACC, ventral anterior cingulate cortex; VBM, voxel based morphology; VLPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefronal cortex; WAIS, Wechsler Adult Intelligence Scale; WM, working memory; WMH, white matter hyper intensities; WMS, Wechsler Memory Scale.

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1. Introduction

Bipolar disorder (BD) is a common chronic illness that is characterised by extreme mood fluctuations and substantial cognitive impairment (Goodwin and Jamison, 2007; Grande et al., 2016). Although compelling evidence indicates that BD is associated with a high degree of heritability (e.g., Goes, 2016; Kieseppä et al., 2004; McGuffin et al., 2003), its exact pathophysiology remains elusive and involves a complex set of gene-environment interactions (Uher, 2014). Replication of genome wide association studies have proven to be difficult due to the complexity of the disorder, differences in diagnostic criteria, methodological challenges, and possible patho-etiological heterogeneity (Gatt et al., 2015; Kerner, 2015; McCarroll et al., 2014), although notably a recent study identified some putative biological pathways involved in the genetic predisposition to BD (e.g., hormonal regulation, calcium cannels; see Nurnberger et al., 2014). Endophenotypes are disease-associated traits that are highly heritable, associated with the illness, independent of the clinical state, and found in non-affected family members to a greater extent than in the general population (Gershon and Goldin, 1986; Gottesman and Gould, 2003; Leboyer et al., 1998). The past decades, the field has witnessed an intensive research effort in to putative endophenotypes for BD, which may improve the understanding of disease heterogeneity through biological validation and phenotype stratification (Hasler et al., 2006; Kerner, 2015).

The search for candidate endophenotypes for BD has revealed substantial evidence for trait-related abnormalities across several neurocognitive domains (Balanza-Martinez et al., 2008) and neuroimaging measures (Hozer and Houenou, 2016; Wu et al., 2016). However, studies in unaffected relatives (URs) of BD patients have produced less uniform evidence for changes in neurocognitive function and neuroimaging measures. It is therefore crucial to evaluate which abnormalities are most consistently exhibited in genetically predisposed individuals to identify the most promising candidate endophenotypes for BD. These efforts may lead to identification of the most consistent biological pathways in BD.

Cognitive deficits are candidate endophenotypes of BD (e.g., Bora et al., 2009b; Glahn et al., 2010). These include disturbances in both 'cold' (i.e., non-emotional) and 'hot' (i.e., emotion-laden) cognition (Roiser and Sahakian, 2013). Trait-related deficits in 'cold' cognition have been repeatedly reported in individuals with BD across several neurocognitive domains, particularly within verbal memory and executive function (Bourne et al., 2013; Robinson et al., 2006; Torres et al., 2007), as well as in their unaffected relatives (Arts et al., 2008; Balanza-Martinez et al., 2008). Although changes in the processing of emotional information and emotional regulation are core abnormalities in mood disorders (Miskowiak and Carvalho, 2014; Phillips et al., 2008), these aspects of 'hot' cognition have only recently become a focus of scientific investigation in URs of patients with mood disorders. These studies suggest that emotion dysregulation is not only present in BD during acute mood episodes (Almeida and Phillips, 2013; Phillips et al., 2008) and in remission (Townsend et al., 2013), but also occur in genetically predisposed individuals (Heissler et al., 2014; Kanske et al., 2015).

Functional and structural imaging studies of BD have revealed fronto-limbic functional abnormalities (Chen et al., 2011a; Strakowski et al., 2012; Strakowski et al., 2005) coupled with structural changes, such as lateral ventricle enlargement (Arnone et al., 2009; Kempton et al., 2008; McDonald et al., 2004). However, little research has been conducted on URs of patients with BD (Mathias de Almeida et al., 2013). Functional neuroimaging studies of resting state activity in the prefrontal cortex, anterior cingulate cortex, and mesolimbic structures that subserve processing of emotionally-laden stimuli and emotion regulation show promise in revealing putative brain-based endophenotypes (Phillips and Vieta, 2007; Vargas et al., 2013). Indeed, aberrant neural response seems to be a more sensitive assay of abnormal brain function than overt behavioural or subjective measures (Haas et al., 2007). Nevertheless, the search for neuroimaging endophenotypes and a precise neuroimaging biosignature for BD has revealed discrepant findings (Phillips and Swartz, 2014) due to small and heterogeneous samples and different methodological approaches (Phillips and Kupfer, 2013).