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Review

The relationship between genetic risk variants with brain structure and function in bipolar disorder: A systematic review of genetic-neuroimaging studies

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ABSTRACT

Genetic-neuroimaging paradigms could provide insights regarding the pathophysiology of bipolar disorder (BD). Nevertheless, findings have been inconsistent across studies. A systematic review of gene-imaging studies involving individuals with BD was conducted across electronic major databases from inception until January 9th, 2017. Forty-four studies met eligibility criteria (N = 2122 BD participants). Twenty-six gene variants were investigated across candidate gene studies and 4 studies used a genome-wide association approach. Replicated evidence (i.e. in > 2 studies) suggests that individuals with BD carrying the BDNF Val66Met risk allele could have reduced hippocampal volumes compared to non-carriers. This review underscores the potential of gene-neuroimaging paradigms to provide mechanistic insights for BD. However, this systematic review found a single replicated finding. Suggestions to improve the reproducibility of this emerging field are provided, including the adoption of a trans-diagnostic approach.

Abbreviations: AC, anterior cingulum; ACE, adverse childhood experiences; ACG, anterior cingulate gyrus; ALIC, anterior limb of internal capsule; ANK3, ankyrin 3; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; BOLD, blood oxygen level dependent; CACNA1C, calcium voltage-gated channel subunit alpha1C; CC, corpus callosum; CCb, corpus callosumbody; CCg, corpus callosum genu; CG, cingulate gyrus; CNP, 2′,3′-cyclic-nucleotide 3′-phosphodiesterase; COMT, catechol-*O*-methyltransferase; CR, corona radiata; CST, corticospinal tract; DAAO, d-amino acid oxidase; DAOA, d-amino acid oxidase actiqvator; DGKH, diacylglycerol kinase eta; DISC1, disrupted in schizophrenia 1; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; DOK5, docking protein 5; DTI, diffusion tensor imaging; EAAT2, excitatory amino-acid transporter 2; ERBB2, Erb-B2 receptor tyrosine kinase 2; FA, fractional anisotropy; FM, forceps major; fMRI, functional MRI; FG, fusiform gyrus; FOF, fronto-occipital fasciculus; GABA, gamma-amino butyric acid; GALNT7, polypeptide *N*-acetylgalactosaminyltransferase 7; GI, gyrification index; GM, grey matter; GP, globus pallidus; GRIN2B, glutamate ionotropic receptor NMDA type subunit 2B; GSK-3β, glycogen synthase kinase 3 beta; GWAS, genome-wide association study; HAP, risk haplotype at the 5′ end of the NRG1 gene; HCs, healthy controls; ICP, inferior cerebellar peduncle; L-1β, interleukin-1 betal; IPL, inferior parietal lobule; IOG, inferior occipital gyrus; LV, lateral ventricles; LF, longitudinal fasciculus; MA, minor allele; MCP, middle cerebellar peduncle; MD, mean diffusivity; MOG, myelin oligodendrocyte glycoprotein; mPFC, medial prefrontal cortexm; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; NA, nucleus accumbens (NAc); NMDA, *N*-methyl-D-aspartate; NRG1, neuregulin 1; ODZ4, teneurin transmembrane protein 4; OFC, orbitofrontal cortex; PCG, posterior cingulate gyrus; PF, prefrontal region; PFC, prefrontal cortex; PGR, polygenic risk score; PHG, parahippocampal gyrus; RD, radial diffusivity; SZ, schizophrenia; 5-HTTLPR, serotonin-transporter-linked polymorphic region; SNP, single nucleotide polymorphism; SYNE1, spectrin repeat containing nuclear envelope protein 1; SREBF1, sterol regulatory element-binding transcription factor 1; SREBF2, sterol regulatory element-binding transcription factor 2; STG, superior temporal gyrus; TBSSBD, tract-based spatial statistics; TNF, tumor necrosis factor; TP, temporal pole; TR, thalamic radiation; UF, uncinate fasciculus; VBM, voxel-based morphometry; vlPFC, ventrolateral prefrontal cortex; WM, white matter; ZNF804A, zinc finger protein 804A

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1. Introduction

Bipolar disorder (BD) may affect approximately 2.4% of the population worldwide, and is associated with significant disability and elevated mortality rates compared to the general population (Grande et al., 2016; Hayes et al., 2015; Merikangas et al., 2011). The pathophysiology of BD has not been completely elucidated, and the current state of knowledge on putative mechanisms underpinning different clinical features and illness trajectories is limited (Craddock and Sklar, 2013; Hasler and Wolf, 2015). Several lines of evidence indicate that hereditary factors play a relevant role in the patho-etiology of BD, with phenotypic concordance rates ranging from 40 to 70% in monozygotic twins, and 8–10% in first-degree relatives (FDRs) (Kerner, 2014; Smoller and Finn, 2003). Genome-wide significant loci for BD have emerged from *meta*-analyses of GWAS, while loci near the *TRANK1*, *ANK3, ODZ4, CACNA1C*, and *NCAN* genes had at least one additional replication (Goes, 2016; Green et al., 2013; Muhleisen et al., 2014). A recent GWAS identified two additional novel loci associated with bipolar disorder i.e. an inter-genic region on 9p21.3 and markers within *ERBB2* (Hou et al., 2016). In addition, the *CACNA1C* gene differed in expression in the prefrontal cortex of patients with BD compared to controls (Nurnberger et al., 2014). However, identified genome-wide significant signals seem to explain a low proportion of phenotypic variance of BD (Goes, 2016), and a polygenic risk score accounts for only 3% of its phenotypic variance (Group, 2011). It has been proposed that the effects of risk genes for BD could be larger and more evident on intermediate phenotypes neurobiologically linked to the disorder, thus providing an impetus to the emergence of 'gene imaging' studies in the literature (Bigos and Weinberger, 2010; Gurung and Prata, 2015; Ivleva et al., 2010).

Precise mechanisms through which genetic variations may influence neural pathways accounting for the phenotypic heterogeneity of BD are yet to be established. Significant efforts have been conducted to identify phenotypic characteristics that are thought to lie more proximal to the genetic factors (i.e. endophenotypes) with the aim that this approach would aid in the identification of biological mechanisms of BD (Gottesman and Gould, 2003; Kurnianingsih et al., 2011). In this context, a large body of literature indicates that BD is associated with significant functional and structural neuroimaging alterations (Kempton et al., 2011; Kupferschmidt and Zakzanis, 2011). Furthermore, *meta*-analytic evidence indicates that functional and structural neuroimaging abnormalities may be evidence in individuals at-risk for BD (Fusar-Poli et al., 2012), and a recent systematic review indicates that functional and structural neuroimaging abnormalities are also evident in healthy FDRs of patients with BD (Piguet et al., 2015). Altogether this literature provides support to the view that subtler functional and structural neuroimaging abnormalities in at-risk individuals could represent vulnerability markers of BD. 'Imaging genetics' has emerged as a field with an underlying rationale that genetic variations that confer risk to mental disorders may exhibit higher penetrance at such brain functional/structural alterations than at the more distal psychopathological/behavioral levels (Hashimoto et al., 2015; Rasetti and Weinberger, 2011). Hence, an ever-increasing number of studies has attempted to investigate the associations between genetic variations expected to play a pathophysiological role in BD and structural and functional neuroimaging abnormalities. However, different age groups, neuroimaging modalities, treatment-related effects and investigated genes (or polygenic risk scores) are potential confounders which might have contributed to the heterogeneity of studies so far (Kurnianingsih et al., 2011). To overcome such a strong heterogeneity a systematic review of 'neuroimaging genetics' studies which considered genes which have been previously found to reach genome-wide significance in schizophrenia and BD was conducted (Gurung and Prata, 2015; Lee et al., 2012). However, this previous systematic review considered studies performed solely in healthy individuals, while only seven studies performed in samples with BD were included (Gurung and Prata, 2015). A comprehensive systematic overview focusing on 'imaging genetics' specifically in people with BD is currently lacking.

Therefore, our systematic review aims to provide a comprehensive and up-dated synthesis of all available 'imaging genetics' literature in BD. Both structural and functional magnetic resonance imaging studies will be considered. Our goal was two-fold: (1) to summarize and facilitate the integration of findings in this evolving field; and (2) to provide an illustrative structural and functional brain map of significant BD-associated gene risk variants, which are expected to be linked to brain regions with known alterations in BD.

2. Methods

A systematic literature search of genetic variations and functional and structural magnetic resonance imaging (MRI) studies in BD was conducted. We followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement (Moher et al., 2010), using an *a priori* defined but unpublished protocol.

2.1. Search strategy

The EMBASE, PubMed/MEDLINE and PsycINFO electronic databases were searched from inception up to January 9th, 2017. The following search string was used: (bipolar disorder OR mania OR bipolar depression) AND (structural magnetic resonance OR functional magnetic resonance OR fMRI OR BOLD fMRI OR magnetic resonance imaging OR magnetic resonance neuroimaging OR tractography) AND (SNPs OR single nucleotide polymorphism OR haplotypes OR gene expression OR gene OR genetic score OR genetic* OR methylome OR epigenetic* OR genome OR transcriptome OR polymorphism OR genetic polymorphism OR genome wide OR genome-wide). In addition, the reference lists of eligible articles were hand searched to identify additional eligible References

2.2. Eligibility criteria

The articles included in this review fulfilled the following criteria: (1) human studies with participants at any age with a diagnosis of type I BD (BD-I), type II BD (BD-II), or BD not otherwise specified (BD-NOS) using standard diagnostic criteria (DSM-IV, ICD-10 or Research Diagnostic Criteria regardless of the current mood state (euthymic, manic or depressed); (2) combined investigations of genetic factors and brain imaging protocols (structural or functional). The included articles had to investigate imaging-genetic associations of BD patients that were carriers of high-risk alleles compared to either healthy controls (HC) and/or BD patients who were non-carriers of the investigated risk alleles. No language restrictions were applied. Studies that reported a sub-analysis of a well-defined sample of participants with BD within a broad mood disorder group were also eligible.

Animal and *post-mortem* studies, case series, literature reviews, conference papers, meeting abstracts or *meta*-analyses were excluded. Studies which included samples with mixed diagnoses were excluded, unless data for participants with BD were separately provided. Articles that used imaging methods other than structural or functional MRI (e.g., magnetic resonance spectroscopy or positron emission tomography) were also excluded.

2.3. Study selection

Two investigators (LPP and BPF) independently screened the titles and abstracts of retrieved references for eligibility. Next, the full-texts of the selected references were obtained, and the same authors independently reviewed each article for final inclusion in this systematic review. Disagreements were resolved through consensus. Whenever a consensus could not be achieved, a third author (CAK) made the final