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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

decision regarding inclusion. The agreement between the two raters was high (83.7%).

2.4. Data extraction

Two authors (LPP and BPF) independently extracted the data of selected papers using a standardized spreadsheet. The following variables were recorded: first author, year of publication, sample size, age of participants, % of females, diagnostic criteria for BD, genetic assessment (name of the gene, method, SNP and allele groups), imaging methods and procedures, the experimental paradigm (in case of fMRI), MRI regions of interest (ROI) and the results of the association between the genetic variants and each ROI. Whenever the sample contained BD patients as part of a broader sample that included other psychiatric diagnoses, only data and associations of the BD group was extracted. The agreement between the two raters was 89.6%.

2.5. Data synthesis

Due to the anticipated heterogeneity and paucity of homogenous studies, meta-analysis of included studies was not feasible. Thus, we synthesized the included studies with a best evidence synthesis. First, we considered structural imaging studies and candidate genes and GWAS relationships. Second, we considered the relationship between functional imaging studies and candidate genes and GWAS studies. We considered evidence to be replicated or consistent when a relationship was evident between 2 studies between a candidate gene/GWAS and a particular structural and/or functional neuroimaging abnormality.

3. Results

3.1. Search results

The literature search found 873 records, and 9 additional references were found through searching the reference lists of included articles. After the removal of duplicates, 632 unique references were screened. Five hundred and seventy-one references were excluded after title/abstract screening. Of the 61 full-texts assessed, 17 were excluded due to: (1) not an original study (k = 2); (2) no data for BD participant was provided (k = 9), (3) not investigating samples with BD (k = 1), (4) no genetic measure (k = 1), (5) using other neuroimaging method not specified in the inclusion criteria (k = 2), (6) not investigating genetic-imaging associations in BD (k = 1) or (7) article not available (k = 1). Therefore, forty-four genetic-neuroimaging studies met inclusion criteria for this qualitative systematic review. Fig. 1 presents the flowchart of study selection. The studies excluded during full-text review and reasons for exclusion are presented in Supplementary Table S1 that accompanies the online version of this article.

3.2. Overview of included studies

All included studies are described in Tables 1 and 2 (structural MRI, k = 28) and Tables 3 and 4 (fMRI, k = 16). Forty studies investigated 26 candidate risk genes for BD and 4 studies used a genome-wide significance analysis. The studies altogether included 2122 participants with BD [BD group; age = 38.6 ± 13.6 years (mean ± SD); 56.6% female] and 2389 healthy participants (HC group; age = 35.9 ± 12.4 years (mean ± SD); 53.0% female). All studies included only adult samples except for three studies that included only pediatric samples (Barzman et al., 2014; Liu et al., 2010; Zeni et al., 2016). Twenty-eight studies investigated structural changes using either VBM or DTI, and 16 studies used functional MRI to investigate changes in brain activity associated. The functional studies were based on several tasks, including emotional processing of faces (k = 8), Posner emotional task (k = 1), verbal fluency tasks (k = 4), and working memory (k = 2). Emotional tasks included contrasts of the task-related activity and baseline, and within neutral and affective content. The other tasks compared task-related activity with baseline.

3.3. Structural imaging studies

3.3.1. Candidate genes

Twenty-six studies investigated associations of 19 candidate genes with structural imaging data (see Table 1 for studies using VBM and Table 2 for studies using DTI). Except for the study by Zeni et al. (2016), all other studies included an adult sample. Eighteen studies investigated structural measures [total/regional brain volumes, cortical thickness and white matter (WM) integrity] using VBM, 6 studies focused on DTI metrics [e.g. fractional anisotropy (FA)] and 2 studies used both methods. The most frequently investigated genes were *BDNF* (5 studies, all VBM), *CACNA1C* (5 studies, 4 VBM and 1 DTI), *ANK3* (3 studies, 1 VBM and 2 VBM/DTI combined), *5-HTTLPR* (3 studies, 2 VBM and 1 DTI), *ZNF804A* (3 studies, 1 VBM and 2 DTI), and *GSK-3β* (2 studies, 1 VBM and 1 DTI) (Tables 1 and 2). The remaining genes (*EAAT2*, *DGKH*, *NRG1*, *HAP*, *CNP*, *MOG*, *IL-1B*, *ODZ4*, *SYNE1*, *DAOA, GRIN2B, SREBF1* and *SREBF2*) were investigated by a single study.

Six studies included only participants with BD (i.e. carriers vs. non-carriers of genetic risk variants) (Benedetti et al., 2013; Benedetti et al., 2015a,b; Benedetti et al., 2014; Poletti et al., 2016; Poletti et al., 2014). Three of those studies investigated *5-HTTLPR* (Benedetti et al., 2015a), *GSK-3β* (Benedetti et al., 2013) or *SREBF1/2* (Poletti et al., 2016) using DTI. Benedetti et al. (2015a) found that carriers of the *5-HTTLPR* S (i.e., short) allele had increased radial and mean diffusivity in several brain white matter tracts, including the cingulum gyrus, corpus callosum (body and genum) and corona radiata compared to non-carriers. Significant increases in axial diffusivity measures were observed in carriers of the less active GSK3-β rs334558*C gene-promoter variant in 70 participants with an index bipolar depressive episode across several white matter fiber tracts (Benedetti et al., 2013). Interestingly, lithium treatment (which inhibits GSK-3β) was also associated with similar changes in axial diffusivity, which points to a better integrity of axon and myelin sheaths (Benedetti et al., 2013). Poletti et al. (2016) found that carriers of the *SREBF2* rs1052717 polymorphism A/A genotype had increased radial diffusivity and reduced FA compared to G carriers in the cingulum, corpus callosum, superior and inferior longitudinal fasciculi, and anterior thalamic radiation. The remaining 3 studies investigated variations in the *5-HTTLPR* (Benedetti et al., 2014), *GSK-3β* (Benedetti et al., 2015b) or *EAAT2* (Poletti et al., 2014) genes using VBM. All three studies did not verify any significant genetic-imaging associations in BD.

The other 19 studies included a HC comparison group. Fourteen of these studies found significant associations of brain structural changes and genetic variants, in both grey and white matter. These included associations of the *BDNF* (k = 4), *5-HTTLPR* (k = 1), *CACNAC1* (k = 1), *DGKH* (k = 1), *NRG1* and HAP_{ICE} haplotype (k = 1), *IL-1β* (k = 1) with brain volumes using VBM, and also *ANK3* (k = 2), *5-HTTLPR* (k = 1), *GSK-3β* (k = 1) and *GRIN2 B* (k = 1) with white matter integrity using DTI. See section 3.5.1 for details.

3.3.2. Genome-wide association studies

Two studies used Genome-Wide Association Studies (GWAS) to identify genes associated with BD, and then investigated associations with structural changes using VBM (Bakken et al., 2011; Oertel-Knochel et al., 2015) (Table 1). Oertel-Knochel et al. (2015) investigated 7 SNPs obtained from a GWAS study in SZ (*MIR137*, *CCDC68*, *CNNM2*, *NT5C2*, *MMP16*, *CSMD1* and *PCGEM1*) to identify genetic variants associated with structural brain changes across the psychosis spectrum. No statistically significant association was observed for the group that included only participants with BD. Bakken et al. (2011) examined associations of 597,198 SNPs with average cortical thickness using the PLINK analytic tool (Purcell et al., 2007) to fit an additive linear model with minor allele counts, sex, age and diagnosis, using a conservative

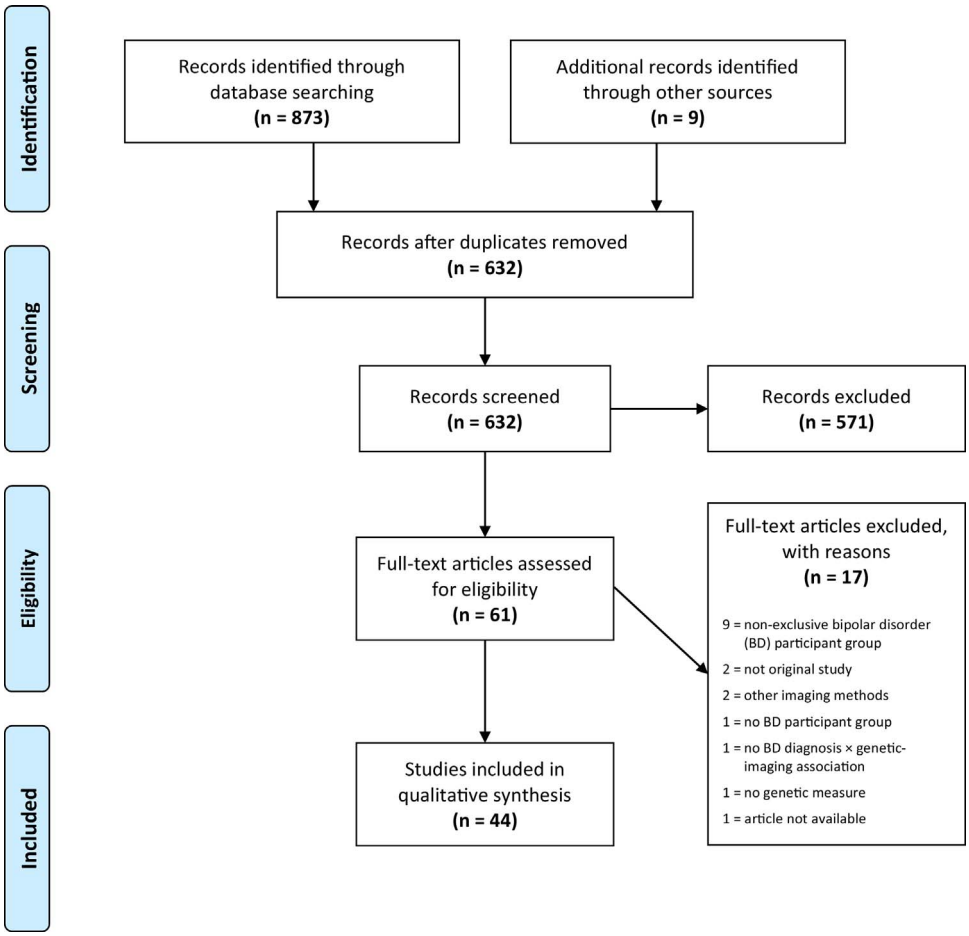

Fig. 1. PRISMA flowchart of the study selection process.

Bonferroni correction for genome-wide significance. No statistically significant imaging-genetic associations were found in the BD group.

3.4. Functional imaging studies

3.4.1. Candidate genes

Fifteen studies investigated associations of variations in 11 candidate genes and blood oxygen level dependent (BOLD) fMRI. The most frequently investigated genes were *CACNA1C* (4 studies) and *ANK3, DAAO* and *DISC1* (2 studies each) (Tables 3 and 4). The remaining genes (*TNF*, *G72*, *BclI*, *COMT*, *DOK5*, 5-*HTTLPR* and *NRG1*) were investigated in a single study.

Barzman et al. (2014) investigated a small sample of pediatric BD patients, and found that the expression of 11 TNF-related genes in peripheral blood mononuclear cells of participants with BD significantly correlated with activation of the amygdala or anterior cingulate gyrus during the affective Posner task.

All other studies included only adults, and included a HC group for comparison. Eight of these studies found significant gene × brain activity associations in BD patients. The CACNAC1 gene was associated with increased amygdala activation in the face recognition paradigm (k = 2). The ANK3 gene was associated with increased activity in the cingulate cortex during a working memory task (k = 1). Both the *ANK3* and *CACNAC1* genes were associated with reduced activation of the vlPFC during the emotional facial processing task (k = 1). The DISC1 gene was associated with decreased activation of the IPL and left CG during a verbal initiation and sentence completion task (k = 1). Also in a verbal fluency paradigm, the DAOA (k = 1) genotype was associated with a greater deactivation of the let precuneus in BD patients, while the NRG1 genotype was associated with increased activation of the right posterior OFC. Finally, the 5-HTTPLPR was associated with lower ventral anterior CG activity during emotional processing of faces (k = 1). See section 3.5.2 for details.

3.4.2. Genome-wide association studies

Liu et al. (2010) investigated a sample of adolescents with BD and HCs of similar age. These authors performed a GWAS, and found that the rs2023454 SNP of the *DOK5* gene was associated with right amygdala activation under contrast to hostility faces although no significant differences between and within BD and HC samples were observed. Dima et al. (2016) calculated a polygenic risk score (PGR) from genes that were associated with BD in a GWAS. Although the PGR was associated with changes in brain activity during a facial processing task and a working memory task in both the BD and HC groups, no statistically significant differences emerged between the two groups or within the BD group as a function of the PGR.

3.5. Significant genetic-neuroimaging associations in BD

The statistically significant associations reported across genetic-neuroimaging studies using candidate genes are shown in Table 5. In addition, a brief synopsis of possible biological functions of gene products is provided.

3.5.1. Structural VBM and DTI studies

Statistically significant structural neuroimaging alterations in BD

Table 1
Studies investigating the association of genetic polymorphisms and brain structure in BD using voxel based morphometry (VBM) in magnetic resonance imaging (MRI).

Author	Gene	Subjects, n	Genetic Polymorphisms, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Cao et al. (2016)	*BDNF*	BD, 48	Met carriers, 13	32 (66.6)	41.0 ± 12.6	MRI 1.5T	**Yes**	BD patients carrying the *BDNF* met allele had smaller hippocampal volumes compared to HCs.
		HC, 60	Met carriers, 19	39 (65.0)	40.5 ± 12.9	VBM ROIs: Hippocampal cortical/ subcortical volume		
Zeni et al. (2016)	*BDNF*	BD, 29	Val/Val, 19	11 (57.8)	14.8 ± 2.2	MRI	**No†**	No significant differences between BD patients and HCs in left or right hippocampal volumes.
	rs6265		Met carriers, 10	3 (30.0)	11.8 ± 2.5	VBM		
		HC, 22	Val/Val, 12	3 (25.0)	12.7 ± 2.6	ROI: Hippocampal cortical volume		
			Met carriers, 10	5 (50.0)	13.4 ± 3.4			
Chepenik et al. (2009)	*BDNF*	BD, 20	Val/Val, 12	11 (55.0)	21–56***	MRI 1.5T	**Yes**	Both hippocampal volumes were significantly smaller in participants with BD compared to HCs, and the *BDNF* met allele was associated with smaller hippocampal volumes in both diagnostic groups.
			Val/Met, 7 Met/Met, 1			VBM		
		HC, 18	Val/Val, 12	12 (66.6)	18–58***	ROI: Hippocampal cortical volume		
			Val/Met, 8					
Mirakhur et al. (2009)	*BDNF*	BD, 18	One or more Met alleles, 6	10 (55.5)	38.4 ± 8.4	MRI 1.5T	**Yes**	Individuals with BD carrying one or more *BDNF* met alleles showed greater losses in GI, an effect that correlated with GM loss in the left hemisphere
		HC, 18	One or more Met alleles, 4	9 (50.0)	36.7 ± 13.2	VBM Cortical volume, gyrification index		
Matsuo et al. (2009)	*BDNF*	BD, 42	Val/Val, 24	19 (79.1)	36.1 ± 9.3	MRI 1.5T	**Yes**	Anterior CG GM volumes significantly smaller in Val/Met BD compared to Val/Val BD Smaller left dlPFC GM volumes in Val/Met compared to Val/Val subjects within BD and HC groups.
			Val/Met, 18	14 (77.8)	35.2 ± 9.7	VBM		
		HC, 42	Val/Val, 29	19 (65.5)	35.4 ± 10.5	ROIs: dlPFC, ACG, and hippocampus GM volumes		
			Val/Met, 13	8 (61.5)	34.2 ± 10.4			
Benedetti et al. (2014)	*5-HTTLPR*	BD, 136	L/L, 45	32 (71.1)	45.9 ± 10.9	MRI 3.0T	**No**	Exposure to early stress correlated with GM volumes in the right prefrontal cortex (Brodmann area 46) in S carriers only.
			L/S, 68	42 (61.7)	46.1 ± 12.2	VBM		
			S/S, 23	19 (82.6)	48.5 ± 13.6	ROI: Hippocampal GM		
Scherk et al. (2009b)	*5-HTTLPR*	BD, 37	L/L, 8	4 (50.0)	39.8 ± 14.1	MRI 1.5T	**Yes**	S carriers showed a relatively increased volume of the right amygdala compared to homozygous L-allele carriers irrespective of diagnostic status.
			S carriers, 29	15 (51.7)	45.1 ± 11.8	VBM		
		HC, 37	L/L, 18	15 (83.3)	39.6 ± 15.1	ROI: Amygdala GM volume		
			S carriers, 19	7 (36.8)	42.3 ± 10.8			
Wolf et al. (2014)	*CACNA1C*	BD, 28	A/A + A/G, 16	6 (37.5)	43.9 ± 13.0	MRI 1.5T	**No†**	The authors found that the amygdala volume was influenced by *CACNA1C* genotype in BD but did not reach statistical significance.
			G/G, 12	7 (58.3)		VBM		
		HC, 16	A/A + A/G, 8	4 (50.0)	33.7 ± 13.4	ROI: Amygdala GM volume		
			G/G, 8 (rs1006737)	6 (75.0)				
Soeiro-de-Souza	*CACNA1C*	BD, 39	Met/Met, 4	24 (61.5)	32.9 ± 10.9	MRI 3.0T	**No†**	The *CACNA1C* genotype had no significant influence on

(continued on next page)

Table 1 *(continued)*

Author	Gene	Subjects, n	Genetic Polymorphisms, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
et al. (2012)								amygdala or hippocampus volumes in either groups.
			Val/Met, 20 Val/Val, 15			VBM ROI: Amygdala and hippocampal GM volumes		
		HC, 40	Met/Met, 3 Val/Met, 15 Val/Val, 22	20 (50.0)	25.9 ± 5.8			
Perrier et al. (2011)	*CACNA1C*	BD, 41	A/A + A/G, 24	10 (41.6)	44.4 ± 12.3	MRI 1.5T	**Yes**	BD patients carrying the risk allele had smaller left putamen than healthy controls.
	Rs1006737		G/G, 17	11 (64.7)	44.1 ± 11.5	VBM		
		HC, 50	A/A + A/G, 22	7 (31.8)	35.6 ± 12.7	ROI: Basal ganglia, hypothalamus and amygdala GM volumes		
			G/G, 28	16 (57.1)	34.4 ± 13.7			
Benedetti et al. (2015b)	GSK-3*β*	BD, 150	A/A, 62	40 (64.5)	46.2 ± 11.5	MRI 3.0T	**No**	*GSK-3β* rs334558*G carriers and the long-term administration of lithium were synergistically associated with increased GM volumes in the right frontal lobe, including the boundaries of subgenual and OFC.
			A/G, 68	14 (20.5)	44.9 ± 11.6	VBM		
			G/G, 20	14 (70.0)	46.9 ± 10.8	Whole-brain GM volume		
Poletti et al. (2014)	*EAAT2*	BD, 86	G/G, 14	56 (65.1)	46.4 ± 12.7	MRI 3.0T	**No**	The effect of SLC1A2–181A > C revealed itself only among patients exposed to lower levels of ACE, with T/T homozygotes showing the lowest and G/G the highest hippocampal GM volume.
			G/T, 43 T/T, 29		45.3 ± 11.0 45.0 ± 12.6	VBM ROI: Hippocampal GM volume		
Kittel-Schneider et al. (2015)	*DGKH*	BD, 30	No GAT, 15	9 (60.0)	42.1 ± 12.4	MRI 1.5T	Yes	There was a significant association of the *DGKH* risk haplotype with increased left amygdala volume in BD, but not in HCs.
			> = 1 GAT, 15	6 (40.0)	45.8 ± 12.4	VBM		
		HC, 18	No GAT, 13	10 (76.9)	31.0 ± 11.3	ROI: Amygdala GM volume		
			> = 1 GAT, 5	2 (40.0)	39.4 ± 15.5			
Cannon et al. (2012)	NRG1	BD, 33	T/T, 9	6 (67.0)	37.0 ± 11.0	MRI 1.5T	**Yes**	The NRG1 SNP and the HAP_{ICE} haplotype were associated with abnormal WM volume in the BD group in the fornix, cingulum and PHG circuit
			C carriers, 18	11 (61.0)	42.0 ± 11.0	VBM		NRG1 (SNP8NRG221533): C carriers > T/T in CG/PHG, splenium and anterior CC
	HAP		Arh1, 8	5 (63.0)	44.0 ± 11.0	Whole-brain WM volume		HAP_{ICE} haplotype: Arh0 < Arh1 in Fornix, caudate, posterior CG
			Arh0, 23	14 (61.0)	41.0 ± 12.0			MOG (rs2857766): HC G/G > C carriers in CST, MCP, ICP
	CNP		G/G, 16	10 (63.0)	40.0 ± ± 12.0			
			A carriers, 14	9 (64.0)	41.0 ± 12.0			
	MOG		G/G, 19	13 (68.0)	41.0 ± 12.0			
			C carriers, 11	6 (55.0)	40.0 ± 10.0			
	NRG1	HC, 39	T/T, 10	8 (80.0)	44.0 ± 15.0			
			C carriers, 27	11 (41.0)	40.0 ± 15.0			
	HAP		Arh1, 11	4 (34.0)	36.0 ± 13.0			
			Arh0, 26	15 (58.0)	43.0 ± 16.0			
	CNP		G/G, 21	9 (43.0)	39.0 ± 14.0			
			A carriers, 16	8 (50.0)	45.0 ± 17.0			
	MOG		G/G, 21	10 (48.0)	45.0 ± 12.0			
			C carriers, 15	7 (47.0)	34.0 ± 16.0			

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Table 1 *(continued)*

Author	Gene	Subjects, n	Genetic Polymorphisms, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Papiol et al. (2008)	*IL-1β*	BD, 20	Non carriers, 8	10 (50.0)	43.4 ± 11.7	MRI 1.5T	**Yes**	A -511C/T polymorphism (rs16944) of IL-1β gene was associated with whole-brain and left dlPFC GM deficits in BD patients.
			Allele*2 carriers, 20			VBM		
		HC, 45	Not reported	21 (46.6)	29.4 ± 9.0	Whole-brain WM and GM volumes; ROIs: dlPFC GM, STG GM, hippocampus GM and LV		
Tesli et al. (2013)	*ANK3*	BD, 121	ANK3 (rs9804190,	71 (58.6)	35.8 ± 11.5	MRI 1.5T	**No**	There were no significant associations between risk SNPs and structural brain alterations in BD.
	CACNA1C	HC, 219	rs10994336 rs10994397	102 (46.5)	35.9 ± 9.7	VBM		
	ODZ4 *SYNE1*		rs1938526)** CACNA1C (rs1006737, rs4765913)** ODZ4 (rs12576775, rs2175420)** SYNE1 (rs9371601)**			Whole-brain GM volume		
Zuliani et al. (2009)	*DAOA*	BD, 38	M23 CC, 10	7 (70.0)	38.9 ± 11.0	MRI 1.5T	**Yes**	Both M23 and M24 were associated with reductions of GM density within left TP (CC < CT < TT) in the BD group. M23 was also associated with reductions in right amygdala GM density.
			M23 CT, 16	7 (43.7)	41.1 ± 11.4	VBM		
			M23 TT, 12	5 (41.6)	37.5 ± 7.7	Whole-brain;		
			M24 AA, 10	7 (70.0)	41.7 ± 10.9	ROIs: temporal lobe and amygdala-hippocampal complex GM volumes		
			M24 AT, 18	7 (38.8)	40.5 ± 11.1			
			M24 TT, 9	4 (44.4)	37.1 ± 7.8			
		HC, 81	M23 CC, 25	12 (48.0)	34.4 ± 10.3			
			M23 CT, 38	17 (44.7)	35.0 ± 11.6			
			M23 TT, 18	10 (55.5)	32.6 ± 8.5			
			M24 AA, 26	13 (50.0)	34.5 ± 10.4			
			M24 AT, 38	16 (42.1)	35.0 ± 11.6			
			M24 TT, 17	10 (58.8)	33.3 ± 8.8			
Bergmann et al. (2013)	*ZNF804A*	BD, 85	rs13393271, 81	43 (53.0)	36.1 ± 11.0	MRI 1.5 T	**No††**	There were no associations between any of the SNPs and cortical thickness measures in HC or BD groups.
			rs359878, 85			VBM		
		HC, 152	rs13393271, 148 rs359878, 151	73 (48.0)	35.9 ± 9.6	Whole-brain cortical thickness		
Oertel-Knochel et al. (2015)	7 risk SZ SNPs from a GWAS	BD, 20	MIR137 (rs1625579)	11 (55.0)	39.0 ± 12.1	MRI 3.0 T	**No**	Increased additive genetic risk for SZ was associated with reduced white matter volume in a group of participants consisting of healthy individuals, SZ first-degree relatives, SZ patients and BD patients, but not in diagnostic groups separately.
		HC, 38	CCDC68 (rs12966547) CNNM2 (rs7914558) NT5C2 (rs111915801) MMP16 (rs7004633) CSMD1 (rs10503253)	20 (52.6)	37.1 ± 11.1	VBM Whole-brain WM volume		

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Table 1 *(continued)*

Author	Gene	Subjects, n	Genetic Polymorphisms, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Bakken et al. (2011)	GWAS	BD, 97 HC, 181	PCGEM1 (rs17662626)** None	53 (55.0) 87 (48.0)	35.7 ± 11.1 35.9 ± 9.5	MRI 1.5T VBM Whole-brain cortical thickness	**No**	No SNP associations were genome-wide significant in the BD group.

* Risk between BD carriers of the risk allele and healthy controls or BD non-carriers of the risk allele. Significant interactions considering only clinical symptoms scores or medication use were not considered.
** Frequencies or N not reported.
*** Mean and SD not reported.
† Small sample size was considered a limitation in the original report.
†† Limitations were not reported.

patients were associated with genetic variations of the *BDNF*, *5-HTTLPR*, *CACNA1C*, *DGKH*, *NRG1*, *IL-1β*, *ANK3*, and *GRIN2 B* genes (Table 5). Nevertheless, there was a lack of replicated evidence.

Two studies provided evidence that BD patients who carry the Met allele of the BDNF gene may present several structural alterations encompassing several brain areas namely the left and right hippocampus (Cao et al., 2016; Chepenik et al., 2009). A four-year prospective study found that individuals BD participants who were carriers of one or more BDNF Met alleles had significantly greater losses in gyrification indexes, an effect that correlated with gray matter loss in the left hemisphere (Mirakhur et al., 2009). Matsuo et al. (2009) observed smaller bilateral anterior cingulate gyrus volumes in BD patients with Val/Met compared to those with Val/Val BDNF genotypes, while in both the BD and HC groups participants with the Val/Met BDNF genotype had smaller left and right gray matter volumes of the dorsolateral prefrontal cortex.

Increased volumes of the left amygdala were observed in carriers of the S allele of the 5-*HTTLPR* gene both in BD and HC groups (Scherk et al., 2009a).

Genetic variations in the *CACNA1C* genes were not associated with significant structural changes in three VBM studies (Soeiro-de-Souza et al., 2012; Tesli et al., 2013; Wolf et al., 2014), whereas Perrier et al. (2011) found that euthymic BD patients carrying the *CACNA1C* rs1006737 risk allele had a smaller volume of the left putamen compared HCs.

A significantly increased volume of the left amygdala was associated with the *DGKH* haplotype (rs994856/rs9525580/rs9525584 GAT) in 30 euthymic patients with type I BD but not in HCs (Kittel-Schneider et al., 2015). The risk genotype (TT) of the *NRG1* SNP8NRG221533 was associated with reduced white matter volumes in the fornix, cingulum and para-hippocampal gyrus in a type I BD sample (Cannon et al., 2012). In the same study, BD participants carrying one or two copies of the HAP_{ICE} haplotypes of the *NRG1* gene had greater white matter volume than those carrying none in the fornix, caudate and cingulum (Cannon et al., 2012). Papiol et al. (2008) found that a −511C/T SNP (rs16944) of the IL-1β gene was associated with whole-brain and left dlPFC gray matter deficits in a sample of 20 participants with BD in a VBM study. Two studies found that distinct variations of the ANK3 gene were associated with DTI findings (reduced FA) compatible with widespread white matter deficits in several brain regions, such as the forceps minor, the uncinate fasciculus, the anterior cingulate gyrus, the dorsolateral frontal cortex, the left temporoparietal WM, and in posterior dorsomedial WM (Lippard et al., 2016; Ota et al., 2016). Finally, compared to the G allele of the *GRIN2 B* gene, brain FA values were significantly lower in BD patients with risk T allele in left and right frontal regions, left parietal region, left and right occipital regions and the left cingulate gyrus (Kuswanto et al., 2013).

3.5.2. *fMRI studies*

Functional neuroimaging alterations were associated with genetic variations in the *CACNA1C*, *ANK3*, *DISC1*, *TNF*, *DAOA*, *5-HTTLPR* and *NRG1* genes (Table 5).

The most frequent regions with functional alterations significantly associated with genetic variations in BD were: (1) the right anterior CG (ACG), where variation in the *ANK3* and *TNF* genes were associated with greater activation in working memory tasks (*ANK3*) or Posner task (*TNF*), whereas the *5-HTTLPR* S allele was significantly associated with lower activation during an emotional processing task; (2) the left ACG, where polymorphisms in the *TNF* gene were associated with increased activation and the *5-HTTLPR* S allele with decreased activation during emotional processing tasks; (3) left amygdala, where variation in the *CACNA1C* and *TNF* genes were associated with greater activation during emotional processing tasks; (4) left CG, where polymorphisms in *DISC1* were associated with lower activation during a verbal fluency task; (5) left para-hippocampal gyrus, where *ANK3* polymorphisms were associated with greater activation; and during a working memory

Table 2
Studies investigating the association of genetic polymorphisms and brain structure in BD using diffusion tensor imaging (DTI) in magnetic resonance imaging (MRI).

Author	Gene	Subjects, n	Genetic Polymorphisms, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Diffusion Tensor Imaging (DTI) and VBM								
Ota et al. (2016)	*ANK3*	BD, 43	C/C, 24	8 (33.3)	40.8 ± 9.9	MRI 1.5T	**Yes (DTI)**	Decreased FA was found in the forceps minor in non-T-allele BD patients compared with the T-carrier BD group.
	rs10761482		T carriers, 19	13 (68.4)	35.9 ± 7.9	DTI/VBM		No main effect of genetic variations were found on the GM volume and the genotype-by-diagnosis interaction.
		HC, 229	C/C, 133	94 (70.6)	45.8 ± ± ± 15.8	Whole-brain GM volume and WM FA		
			T carriers, 96	74 (77.0)	45.3 ± 15.6			
Lippard et al. (2016)	*ANK3*	BD, 90	C/C, 52	35 (67.0)	27.5 ± 12.2	MRI 3.0 T	**Yes (DTI)**	BD subjects carrying the T (risk) allele showed decreased FA compared with other subgroups, independent of age within the UF.Compared with BD CC homozygotes, BD T-carriers had lower FA in the UF and anterior CG bilaterally, indorsomedial frontal WM, in left temporoparietal WM and in posterior dorsomedial WM, among others.
	rs9804190		T carriers, 38	26 (68.0)	26.5 ± 11.1	DTI/VBM		
		HC, 97	C/C, 56	28 (50.0)	23.9 ± 9.0	Whole-brain analysis		
			T carriers, 41	23 (53.0)	28.6 ± 12.9	ROIs: amygdala and OFC GM; whole-brain and UF FA		
DTI								
Benedetti et al. (2015a)	*5-HTTLPR*	140, BD	L/L, 47	32 (68.0)	46.4 ± 20.7	MRI 3.0T	Yes	S carriers showed significantly increased radial and mean diffusivity in several brain WM tracts (right posterior CG, left anterior CG, CCb, CCg and right posterior CR)
			S carriers, 93	36 (38.7)	30.3 ± 10.2	DTI Whole-brain analysis		
Benedetti et al. (2013)	GSK-3β	70, BD	T/T, 26	19 (73.0)	45.7 ± 11.8	MRI 3.0T	Yes	The rs334558*C carriers and the long-term use of lithium were associated with increased axial diffusivity in several WM fiber tracts (CC, FM, anterior CG and posterior CG bilaterally, including its hippocampal part, left superior and inferior LF, left inferior FOF, left posterior TR, bilateral superior and posterior CR, and bilateral CST).
			C carriers, 44	31 (70.0)	45.7 ± 11.4	DTI Whole-brain analysis		
Kuswanto et al. (2013)	GRIN2B	BD, 14	G/G, 1	4 (18.1)	36.9 ± 12.2	MRI 3.0T	Yes	Compared to G allele, brain FA values were significantly lower in BD patients carrying the T allele in bilateral frontal regions, left parietal region, left occipital region, right occipital region and left CG.
			G/T, 2 T/T, 11			DTI Whole-brain analysis		
		HC, 22	G/G, 3 G/T, 5 T/T, 14	11 (50.0)	32.7 ± 12.3			
Mallas et al. (2016a)	*CACNA1C*	BD, 43	A/A, 15	25 (58.1)	41.1 ± 12.3	MRI 1.5T	**No†**	There was no significant main effect of the CACNA1C genotype on FA. In BD patients, the ZNF804A rs1344706 risk genotype increased the magnitude of the effect of the CACNA1C risk genotype, but the association was no longer significant after controlling for age.
	rs1006737		A/G, 15 G/G 13			DTI Whole-brain analysis		
		HC, 124	A/A, 17 A/G, 51 G/G, 56	57 (46.0)	35.8 ± 13.4			
Mallas et al. (2016b)	*ZNF804A*	BD, 43	A/A, 19	25 (58.1)	41.0 ± 12.3	MRI 1.5T	**No**	No areas with a significant diagnosis by genotype interaction were found.

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Table 2 *(continued)*

Author	Gene	Subjects, n	Genetic Polymorphisms, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
	rs1344706		A/C, 16			DTI		
			C/C, 8			Whole-brain analysis		
		HC, 124	A/A, 59	57 (46.0)	35.7 ± 13.4			
			A/C, 51					
			C/C, 14					
Poletti et al. (2016)	*SREBF1*	BD, 93	A/A, 10	5 (50.0)	44.8 ± 13.8	MRI 3.0T	**Yes**	No effect on DTI measures of WM integrity was observed for SREBF 1 polymorphism. The SREBF2 rs1052717 polymorphism A/A genotype had increased radial diffusivity compared to A/G and G/G, and the A/A genotype had reduced FA compared to G carriers in cingulum, corpus callosum, superior and inferior longitudinal fasciculi, and anterior thalamic radiation.
	rs11868035		A/G, 45	29 (64.4)	46.1 ± 12.1	DTI		
			G/G, 38	28 (73.7)	43.8 ± 9.2	Whole-brain analysis		
	SREBF2		A/A, 27	19 (70.4)	43.8 ± 12.1			
	rs1052717		A/G, 39	25 (64.1)	45.7 ± 11.3			
			G/G, 27	18 (66.7)	45.3 ± 10.3			

* Risk between BD carriers of the risk allele and healthy controls or BD non-carriers of the risk allele. Significant interactions considering only clinical symptoms scores or medication use were not considered.
† Sample size was not mentioned as a limitation in the original report.

task; and (6) the left vlPFC, where variations in both *CACNA1C* and 5-*HTTLPR* genes were associated with greater activation during emotional processing tasks.

The fMRI paradigms that were most frequently used across functional neuroimaging studies with statistically significant genetic-imaging findings were emotional faces task (8 studies) and the verbal fluency test (2 studies). Three studies found associations of the *CACNA1C* risk allele A with an increase in activation of either left or right amygdala (Jogia et al., 2011; Tesli et al., 2013), and a hypoactivation of the vlPFC (Dima et al., 2013; Jogia et al., 2011), with one study reported both alterations (Jogia et al., 2011) in the emotional faces task. The remaining studies found decreased activation of the vlPFC in association with the *ANK3* rs10994336 polymorphism risk allele T (Delvecchio et al., 2015) or a decreased activation of the ventral anterior cingulate gyrus related to the 5HTTLPR S risk allele (Shah et al., 2009). Studies that employed the verbal fluency test were inconsistent regarding both genetic variations and activated ROIs (Mechelli et al., 2012; Mechelli et al., 2008).

3.5.3. Illustrative brain map of significant replicated gene-neuroimaging findings

Fig. 2 summarized replicated gene-imaging findings in BD patients in comparison to healthy controls. A difference was considered statistically significant ($p < 0.05$) only if the neuroimaging findings of BD patients carrying the risk allele were different from the HCs or BD subjects not carrying the risk allele (i.e., a gene x diagnosis interaction). Two fMRI studies found that individuals with BD carrying the A variant of the *CACNA1C* Rs1006737 polymorphism had decreased activity in the right dorsal ventrolateral prefrontal cortex during the emotional faces paradigm. However, samples across those two investigations appeared to overlap (Dima et al., 2013; Jogia et al., 2011), and thus this association was not regarded as a true replication. Furthermore, two VBM studies found that subjects BD who were carriers of the Met allele of the BDNF Val66Met polymorphism had decreased volumes of the left and right hippocampi (Cao et al., 2016; Chepenik et al., 2009).

3.6. Methodological considerations

The minority of included studies enrolled only euthymic BD participants (k = 10; 22.7%), while the mood status of participants with BD was clearly described in 21 (47.7%) studies. Twenty studies (45.5%) controlled results for the effects of medication or otherwise included only drug-free BD participants, while most included studies controlled findings for multiple comparisons (k = 33; 75.0%). A healthy control group was included in 36 (81.8%) studies. The median (IQR) sample sizes for VBM, DTI and fMRI studies were 80 (72–84), 153.5 (87.25–172) and 80.5 (69.5–87.25). A whole-brain analysis was conducted in 15 (34.0%) studies, while 18 (40.9%) studies performed only a priori defined ROI-based analyses, and 4 (9.1%) studies carried out both types of analyses. Twenty-eight studies used a 1.5T magnetic field, 13 studies used 3.0T, 1 study 4.0T and 2 did not specify the magnetic field of the scanner.

4. Discussion

The aim of this systematic review was to assess the extant literature reporting 'imaging genetics' findings in BD. We included both structural and functional MRI studies. The most frequently reported genes (at least 2 studies) with statistically significant neuroimaging alterations in BD patients were *CACNA1C*, *ANK3*, *BDNF*, *5-HTTLPR*, *NRG1* and *DAOA*. Of those genes, loci close to the *CACNA1C* and *ANK3* genes have reached genome-wide significant associations with BD, and associations were replicated in at least one independent dataset (Goes, 2016). To our knowledge this effort represents the largest evidence-based synthesis to date of this field.

Table 3
Studies investigating the association of genetic polymorphisms and brain activity in BD using functional magnetic resonance imaging (fMRI) during emotional tasks.

Author	Gene	Subjects	Genetic Polymorphism, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Tesli et al. (2013)	CACNA1C	BD, 66	A/A + A/G, 34	18 (52.9)	34.2 ± 10.0	fMRI 1.5T	**Yes**	Carriers of the risk allele had increased activation in the left amygdala in the BD group.
			G/G, 32	20 (62.5)	35.5 ± 11.4	Emotional stimuli (negative faces) paradigm)		
		HC, 123	A/A + A/G, 71	31 (43.7)	34.0 ± 7.8	ROI: Bilateral amygdala		
			G/G, 52	23 (44.2)	35.3 ± 10.4			
Radua et al. (2013)	*CACNA1C*	BD, 20	Rs1006737 GG, AG and AA	8 (40.0)	43.0 ± 14.0	fMRI (Tesla not reported)	No††	MTG out-degree connectivity gradually decreased with the number of CACNA1C risk alleles (GG < AG < AA) in BD and HC groups.
		HC, 20	Letter to the editor, N not reported	10 (50.0)	42.0 ± 12.0	Fearful faces		
						ROIs: MFG, left putamen and left amygdala		
Jogia et al. (2011)	*CACNA1C*	BD, 41	GG, 17	21 (51.2)	44.3 ± 11.9	fMRI 1.5T	Yes	Independent of diagnostic group, the right amygdala showed greater activation during fear-face recognition relative to neutral faces in AA/AG compared to GG individuals. The right vlPFC expressed reduced activation in individuals with the high-risk allele compared with those with the low-risk variant in BD patients.
			AG, 19			Facial affect recognition task (fearful vs neutral faces)		
			AA, 5			ROIs: PFC, ACG, amygdala and hippocampus		
		HC, 50	GG, 28	23 (46.0)	34.9 ± 13.2			
			AG, 18					
			AA, 4					
Dima et al. (2013)	*CACNA1C*	BD, 41	A/A + A/G, 17	11 (64.7)	44.4 ± 12.3	fMRI 1.5T	**Yes**	BD carriers of either genetic risk variant exhibited pronounced reduction in vlPFC activation compared to HCs.
			G/G, 24	10 (41.6)	44.1 ± 11.6	Facial affect paradigm		
		HC, 46	A/A + A/G, 25	9 (36.0)	36.3 ± 10.4	ROIs: IOG, FG, amygdala, vlPFC and whole-brain analysis		
			G/G, 21	9 (42.8)	38.1 ± 13.4			
	ANK3	BD, 41	T/T + C/T, 16	7 (43.7)	42.0 ± ± 10.7			
			C/C, 25	14 (56.0)	43.3 ± 2.3			
		HC, 46	T/T + C/T, 14	7 (50.0)	40.6 ± 12.2			
			C/C, 32	14 (43.7)	39.3 ± 12.3			
Barzman et al. (2014)	*TNF*	BD, 10	TNF gene expression levels, 10	5 (50.0)	15.0 ± 1.0	fMRI 4.0T	**Yes**	Expression of 11 TNF-related genes were significantly correlated with activation of amygdala or anterior CG during the affective Posner Task.
						Posner Task (Selective attention task to negative emotions)		
						Whole-brain analysis		
Lelli-Chiesa et al. (2011)	*COMT*	BD, 40	Val/Val, 11	21 (52.5)	44.0 ± 11.9	fMRI 1.5T	**No††**	No significant diagnosis × genotype interaction was detected in the BD group.
			Val/Met + Met/Met, 29			Sad facial affect discrimination task		
		HC, 50	Val/Val, 15	24 (48.0)	34.9 ± 13.2	ROIs: Amygdala and ventral PFC		
			Val/Met + Met/Met, 35					

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Table 3 *(continued)*

Author	Gene	Subjects	Genetic Polymorphism, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Liu et al. (2010)	GWAS	BD, 39	rs2023454 SNP DOK5 gene	24	15.0 ± 2.8	fMRI 3.0T	**No†**	No significant main effect of diagnosis and no significant diagnosis × genotype interaction was detected. In both the BD and HC samples the rs2023454 SNP of the DOK5 gene was significantly associated with right amygdala activation under the hostility contrast.
		HC, 29		18	13.0 ± 2.9	Face-processing paradigm ROI: Amygdala		
Shah et al. (2009)	*5-HTTLPR*	BD, 30	L/L, 10	7 (70.0)	36.9 ± 16.9	fMRI 3.0T	**Yes**	During fear and happy face processing, ventral ACG activation was significantly lower in the BD compared to the HC group, and in S carriers compared to L/L individuals within both HC and BD groups
			S carriers, 20	13 (65.0)	29.4 ± 11.0	Emotional face paradigm		
		HC, 48	L/L, 14	6 (42.8)	26.1 ± 9.3			
			S carriers, 34	22 (64.7)	29.1 ± 10.3	ROI: Ventral ACG		
Dima et al. (2016)	Polygenic risk score (GWAS)**	BD, 41	0.37 (0.04)	21 (51.2)	44.3 ± 11.9	fMRI 1.5T	**No**	The PGR was associated with task-related changes in the BOLD signal in both the BD and HC groups. No significant correlation between the PGR score and the signal changes observed in BD patients during the facial affect paradigm was found (increased activation of ACG and decreased activation of the right superior frontal gyrus). In the 2-back task, no effect of group was noted and no correlation of the PGR score and group was observed in the task-related activation.
		HC, 46	0.32 (0.06)	21 (45.7)	40.3 ± 13.2	Facial affect paradigm; 2-back task Whole-brain analysis		

* Comparisons between BD carriers of the risk allele and healthy controls or BD non-carriers of the risk allele. Significant interactions considering only clinical symptoms scores or medication use were not considered.

** Polygenic risk score (PGR) is calculated in each individual by aggregating variation across GWAS loci nominally associated with BD into a quantitative score (Dima and Breen, 2015). The study used a PGR based on 16,691 SNPs with $p < 0.1$. It is presented as mean (SD).

† Sample size was considered a limitation in the original report.

†† Sample size was not mentioned as a limitation in the original report.

Table 4
Studies investigating the association of genetic polymorphisms and brain activity in BD using functional magnetic resonance imaging (fMRI) during verbal and working memory tasks.

Author	Gene	Subjects	Genetic Polymorphism, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
Delvecchio et al. (2015)	*ANK3*	BD, 41	T/T + C/T, 16	7 (43.7)	42.0 ± 10.7	fMRI 1.5T	**Yes**	For the ANK3 rs10994336, the risk T-allele was associated with increased activation in the right ACG and left PCG in BD patients compared to HCs.
			C/C, 25	14 (56.0)	43.3 ± 12.3	N-back task		For the ANK3 rs9804190, the risk C-allele homozygotes showed increased activation in right ACG in BD patients compared to HCs.
			(Rs10994336)			Whole-brain analysis		
			C/C, 21	13 (61.9)	43.5 ± 12.5			
			T/T + C/T, 20	9 (45.0)	44.8 ± 9.5			
			(Rs9810490)					
		HC, 46	T/T + C/T, 14	7 (50.0)	40.6 ± 12.2			
			C/C, 32	14 (43.7)	39.3 ± 12.3			
			(Rs10994336)					
			C/C, 28	14 (50.0)	40.1 ± 13.2			
			T/T + C/T, 18	8 (44.4)	40.1 ± 11.9			
			(Rs9810490)					
Prata et al. (2011)	*DISC1*	BD, 35	Ser/Ser, 17	11 (61.1)	38.1 ± 13.3	fMRI 1.5T	**No**	No significant effect of Cys704Ser was detected.
			Cys Carriers, 18	10 (55.5)	40.9 ± 11.2	Verbal fluency		
		HC, 53	Ser/Ser, 26	12 (46.1)	31.7 ± 11.1	ROIs: Left middle/superior frontal gyrus and whole-brain analysis		
			Cys Carriers, 27	15 (55.5)	37.8 ± 9.9			
Chakirova et al. (2011)	*DISC1*	BD, 36	T/T, 16	14 (38.8)	39.3 ± 10.8	fMRI 1.5T	**Yes**	Decreased activation in BD carriers of SNP rs821633 in the right IPL and left CG compared to non-carriers.
			C/C + C/T, 20			Verbal initiation and Sentence completion tasks		
		HC, 34	T/T, 16	25 (75.7)	37.3 ± 12.1	Whole-brain analysis		
			C/C + C/T, 18					
			(rs821633)					
Mechelli et al. (2012)	*DAOA*	BD, 33	A/A, 10	7 (70.0)	34.6 ± 13.1	fMRI	**Yes**	DAOA AA genotype was associated with greater deactivation (i.e. repetition > verbal fluency) during task performance than the AG/GG genotype in patients with BD, but not in HC in left precuneus. There were no regions showing a significant diagnosis by DAAO genotype interaction.
	(rs746187)		A/G + G/G, 23	15 (65.2)	39.2 ± 11.7	1.5T		
		HC, 47	A/A, 22	11 (50.0)	32.9 ± 8.2	Verbal fluency paradigm		
			A/G + G/G, 25	12 (48.0)	34.8 ± 11.8	Whole-brain analysis		
			T/T, 27	14 (51.8)	34.5 ± 10.3			
	DAAO		T/G + G/G, 20	9 (45.0)	33.2 ± 10.3			
	(rs2111902)		T/T, 16	10 (62.5)	39.1 ± ± ± ± 11.0			
			T/G + G/G, 17	11 (64.7)	38.5 ± 12.0			
Papagni et al. (2011)	*DAAO*	BD, 33	C/C, 19	11 (57.8)	40.1 ± 12.2	fMRI 1.5T Verbal fluency paradigm	**No**	No significant effects of diagnosis or of genotype in comparisons involving BD patients.
			C/T + T/T, 14	9 (64.2)	37.0 ± 11.9	Whole-brain analysis		
		HC, 48	C/C, 29	14 (48.2)	34.9 ± 10.5			
			C/T + T/T, 19	10 (52.6)	33.5 ± 10.9			
Ham et al. (2016)	*Bcl*I	BD, 26	G/G, 11	11 (100.0)	29.6 ± 8.5	fMRI 3.0T	**No†**	No significant main effects of genotype, diagnosis or reward condition involving BD patients solely.
			C carriers, 15	10 (66.6)	33.6 ± 9.0	Reward test paradigm		
		HC, 32	G/G, 18	12 (66.6)	34.5 ± 4.7	Whole-brain analysis		
			C carriers, 14	10 (71.4)	32.5 ± 6.0			
Mechelli et al. (2008)	NRG1	BD, 29	T/T, 16	12 (75.0)	35.1 ± 12.6	fMRI 1.5T	**Yes**	The high-risk variant of NRG1 was associated with greater deactivation in the left precuneus in both HC and BD. Right posterior

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Table 4 *(continued)*

Author	Gene	Subjects	Genetic Polymorphism, n	Gender, female, n (%)	Age, years, mean ± SD	Methods	Statistically significant difference?*	Main findings
								OFC expressed increased activation in individuals with the high-risk variant in the BD group.
			C/T, 13	8 (61.5)	41.1 ± 9.8	Verbal fluency task		
		HC, 45	T/T, 25	12 (48.0)	35.7 ± 9.7	Whole-brain analysis		
			C/T, 20	12 (60.0)	34.6 ± 12.2			

†Sample size was considered a methodological limitation in the original report.
†† Sample size was not mentioned as a limitation in the original report.
*Comparisons between BD carriers of the risk allele and healthy controls or BD non-carriers of the risk allele. Significant interactions considering only clinical symptoms scores or medication use were not considered.

Our findings suggest that the effects of genetic variants on intermediate neuroimaging phenotypes could be independent (i.e., pleiotropic) of effects on the clinical phenotype per se (Gottesman and Gould, 2003), which is consistent with the view that an endophenotypic approach may aid in the search of biological pathways underpinning heterogeneous mental disorders like BD (Miskowiak et al., 2016). The findings reviewed herein may at least partly explain that although at the population level BD is associated with a significant degree of both "cold" and "hot" (i.e., emotion-laden) (Miskowiak and Carvalho, 2014; Roiser et al., 2009) cognitive deficits, recent *meta*-analyses point to a significant degree of heterogeneity (Bora and Pantelis, 2016; Bortolato et al., 2015; Bourne et al., 2013). Nevertheless, a certain degree of uncertainty lies on the precise pathways which could be influenced by those gene products with relevance to the underlying neurobiology of subsets of individuals with BD. Furthermore, one cannot exclude the possibility that those risk genetic variants are not inherently causal, but instead may be passed in linkage disequilibrium with causative ones. We observed that although several candidate gene studies reported significant associations with structural/functional neuroimaging findings, whilst the few studies that followed a GWAS methodology did not report statistically significant findings (Bakken et al., 2011; Liu et al., 2010; Oertel-Knochel et al., 2015). Evidence indicates that the literature on structural and functional neuroimaging studies could be limited by an excess of significance bias (i.e., there is an excess of statistically significant findings), which may undermine the reproducibility of the field as a whole (Fusar-Poli et al., 2014; Ioannidis et al., 2014). In addition, a selective reporting of outcomes (i.e., only those genes with statistically significant findings are reported) could result in a type I error (Ioannidis et al., 2014). Moreover, sample sizes varied across studies, and due to the few studies available it is difficult to estimate the statistical power of individual studies. This aspect may also undermine the reproducibility of gene-imaging studies as discussed in detail elsewhere (Carter et al., 2016). Therefore, we focused our discussion on candidate genes with at least two statistically significant findings. Furthermore, we contextualized the main findings of our review with data derived from the preclinical and neuropsychological literature.

4.1. The CACNA1C gene

The *CACNA1C* gene encodes the L-type voltage-dependent calcium channel 1C subunit, and at least two GWAS have implicated its rs1006737 SNP as a risk variant associated with BD (Sklar et al., 2008). This association has been consistently replicated since then (Goes, 2016). Notwithstanding Perrier et al. (2011) observed a significantly reduced volume of the left putamen in a sample of BD patients carrying the rs1006737 SNP risk allele compared to HCs. However, two subsequent VBM studies failed to replicate those findings (Soeiro-de-Souza et al., 2012; Wolf et al., 2014).

Significant within-group differences were observed in BD who were carriers of the risk allele of the *CACNA1C* gene after recognition of negative/fearful faces (compared to neutral faces) in the facial affect recognition task. For example, carriers of the risk allele had a higher activation of the left amygdala in one study (Tesli et al., 2013), while another study found higher activation of the amygdala bilaterally in the same task (Jogia et al., 2011). Furthermore, two studies found an hyperactivation of the left ventrolateral prefrontal cortex in the same experimental paradigm (Dima et al., 2013; Jogia et al., 2011). Nevertheless, another study did not report significant functional brain abnormalities related to this risk allele in the facial emotion recognition task (Radua et al., 2013). Methodological differences across studies may explain those discrepant findings. For example, Radua et al. (2013) did not explicitly exclude BD participants with co-occurring somatic and mental disorders. Furthermore, there was an overlap in samples included in the studies carried out by Jogia et al. (2011) and Dima et al. (2013). Ou et al. (2015) postulated that the lack of significant differences in neuroimaging studies between participants with BD and

Table 5
Summary of findings of reported genes and statistically significant differences between BD patients with high-risk genetic polymorphisms and healthy controls (HCs).

Gene	Name	Function	Reported Polymorphisms	N of studies	Polymorphism with positive results	Method	Neuroimaging finding		Functional paradigm or DTI parameter used
							Increased	Decreased	
CACNA1C	L-type calcium channel α1C subunit	Voltage-dependent Ca2+ channels rapidly increase intracellular Ca2+ concentration after depolarization, initiating a host of responses, including neurotransmitter release and changes in gene expression (Gargus, 2009)	rs1006737, G to A	4	Rs1006737 (Risk allele A)	VBM		L Putamen (v)	
					Rs1006737 (Risk allele A)	fMRI	L Amygdala (f)		Emotional face task
					Rs1006737 (Risk allele A)	fMRI	R Amygdala (f)	R vlPFC (f)	Emotional face task
					Rs1006737 (Risk allele A)	fMRI		R vlPFC/ L vlPFC (f)	Emotional face task
ANK3	Ankyrin 3	Encodes ankyrin 3, a large protein involved in coordinated assembly of ion transporters and cell adhesion molecules at axon initial segments and nodes of Ranvier in myelinated nerves (Linke et al., 2011)	rs10994336 rs9804190 rs10761482	4	rs10761482 (cytosine [C] / thymine [T]; (risk allele C)	DTI		R Forceps minor/ L Forceps minor	FA
					rs9804190 (T carriers [risk])	DTI		R UF/ L UF/ R Dorsal ACG/ L Dorsal ACG/ L Temporoparietal region/ L Dorsal CG/ L Parietooccipital region/ R Parietal region WM	FA
					rs10994336 (risk allele T)	fMRI	R ACG/ L PCG (f)	R vlPFC/ L vlPFC (f)	N-back task
					rs9804190, risk allele C)	fMRI	R ACG (f)		N-back task
					rs10994336; risk allele T	fMRI			Emotional face task
BDNF	Brain-derived neurotrophic factor	Small protein of the neurotrophin family that regulates various brain functions; it has been implicated in modulation of hippocampal plasticity and hippocampal-dependent memory (Lu and Gottschalk, 2000)	Val66Met (rs6265)	3	Met carriers	VBM		R Hippocampus/ L Hippocampus	
					Met carriers	VBM		R Hippocampus/ L Hippocampus	
					Met carriers	VBM		R ACG/L ACG/ L dlPFC	
5-HTTLPR	Serotonin transporter polymorphism	Polymorphism in the upstream regulatory region of the gene – a 44-bp deletion/insertion (5-HTTLPR) located at the 5′-flanking regulatory region of the gene coding for the serotonin transporter (SLC6A4) on chromosome 17q11.2. In vitro studies evidenced that the basal activity of the long (l) variant was more than twice that of the short (s) form of the 5-HTTLPR, suggesting that serotonin transporter gene transcription is modulated by variants of the 5-	Long (l) and short (s) variants (risk)	3	s carriers	VBM	R Amygdala (v)		

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Table 5 *(continued)*

Gene	Name	Function	Reported Polymorphisms	N of studies	Polymorphism with positive results	Method	Neuroimaging finding		Functional paradigm or DTI parameter used
							Increased	Decreased	
		HTTLPR with the s allele corresponding to low serotonin uptake activity (Heils et al., 1996)							
					s carriers	DTI	R PCG/ L ACG/CCb/ CCg/ R posterior CR		RD and MD
					s carriers	fMRI		R Ventral ACG/ L Ventral ACG	Emotional face task
NRG1	Neuregulin-1	Encodes a family of signaling proteins in various tissues of the body with NRG1 expression being highest in the brain. In the nervous system, NRG1 proteins have been implicated in numerous functions, including neuronal migration, synapse formation and receptor expression as well as myelination by regulating oligodendrocyte proliferation and differentiation (Winterer et al., 2008)	SNP8NRG243177 (rs6994992) SNP8NRG221533 (rs35753505)	2	SNP8NRG221533 (rs35753505) C carriers (high risk)	VBM	L CG/ L PHG/CCs/ ACC		
					SNP8NRG221533 (rs35753505) C carriers (high risk)	fMRI	R posterior OFC		Verbal fluency task
G72	D-amino acid oxidase activator	G72 has been associated with modulation of NMDA receptor function and with regulation of mitochondrial function and dendritic branching (Zuliani et al., 2009)	SNPs M23C/T and M24A/T	2	M23 and M24 T carriers	VBM		L TP/ R Amygdala	
			SNP rs746187A/G		SNP rs746187 A/A	fMRI		L Precuneus	Verbal fluency
DISC1	Disrupted-in-schizophrenia 1	Expressed predominantly within the hippocampus and codes for a protein with a globular N-terminus domain, a coiled C-terminus domain, and several coiled-coil domains. The functional role of DISC1 is largely unknown, but these distinct domains allow DISC1 protein to interact with both centrosomal and cytoskeletal proteins as well as with membrane associated and signal transduction proteins (Callicott et al., 2005)	Various risk variants (rs1538979, rs821577, rs821633, rs821616 [Ser704Cys], rs6675281 [Leu607Phe] and rs1411771) (Chakirova et al., 2011)	1	rs821633, risk allele C	fMRI		R IPL/ L CG	Verbal initiation and Sentence completion tasks
DGKH	Diacylglycerol kinase eta (DGKη)	The DGKη enzime plays an important role in the inositol triphosphate second messenger pathway by catalyzing the metabolism of diacylglycerol (DAG) to phosphatidic acid. DAG is an activator of many isoforms of protein kinase C (PKC). Therefore, DGKH regulates the activity of PKC isoforms which play a key role in various signaling pathways (Kittel-Schneider et al., 2015)	Risk haplotypes (rs9315885, rs1012053, rs1170191, TAC), risk haplotype (rs994856/ rs9525580/ rs9525584 GAT) and/or risk polymorphisms in DGKH (rs994856, rs9525580, rs9525584, rs9315885)	1	rs994856/ rs9525580/ rs9525584 GAT (risk haplotype)	VBM	L Amygdala		
HAP$_{ICE}$	NRG1 HAPICE	It is a core haplotype of NRG1	Arh0 (no copies of the haplotype): no	1	Arh1: risk	VBM	R Fornix/ L Caudate/		

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Table 5 *(continued)*

Gene	Name	Function	Reported Polymorphisms	N of studies	Polymorphism with positive results	Method	Neuroimaging finding		Functional paradigm or DTI parameter used
							Increased	Decreased	
	(deCODE) haplotype	consisting of five SNPs and two microsatellites (Cannon et al., 2012)	risk Arh1 (1 or 2 copies of the haplotype): risk				L PCG		
IL-1β	Interleukin-1 beta	Encodes for interleukin-1 beta (IL-1β), pro-inflammatory cytokine which has an important role in the induction of the dopaminergic phenotype in mesencephalic neuronal precursors as well as in the regulation of dendrite growth in developing cortical neurons (Papiol et al., 2008)	–511 AvaI polymorphic site (rs16944) of IL-1B gene. Allele*1 (511C) of IL-1B gene completes an AvaI restriction site, while allele*2 (511T) gives an intact product	1	Allele*2 carriers	VBM		L dlPFC	
GRIN2B	NMDA receptor subunit 2B	Encodes the NR2B subunit of the NMDA glutamate receptor. This subunit is expressed in the cortical and medial temporal parts of the brain, striatum, and olfactory bulb (Kuswanto et al., 2013)	Risk variant rs890 G/T	1	T allele	DTI	R Frontal region/ L Frontal region/ L Parietal region/ L Occipital region/ R Occipital region/ L CG		FA
TNF	Tumor necrosis factor	Encodes Tumor necrosis factor-alpha (TNFα), a cytokine involved in both systemic and neuro-inflammation and in the acute phase reaction, and may influence neuronal and neurochemical processes associated with aggression in preclinical and clinical studies (Barzman et al., 2014)	TNF family genes expression (Barzman et al., 2014)	1	TNF family genes expression levels (11)	fMRI	R ACG/ L ACG/ L amygdala		Posner Task (Frustrative non-reward task)

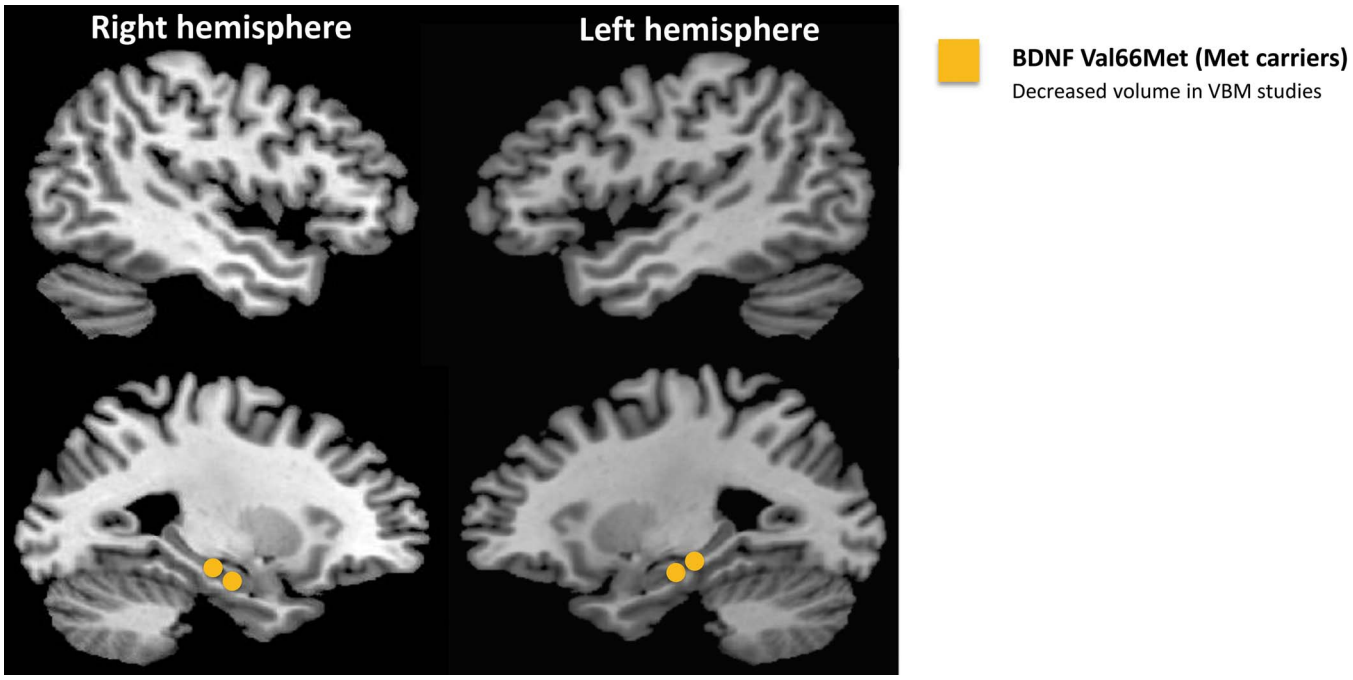

Fig. 2. Brain map representing the approximate locations of replicated gene-neuroimaging findings in BD patients compared to healthy control groups. VBM studies (k = 2) found decreased volumes of the left and right hippocampi in carriers of the Met allele of the *BDNF* Val66Met polymorphism (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

HCs as a function of the *CACNA1C* risk allele could be due to differences in the prevalence of cardiovascular risk factors. Therefore, differences in eligibility criteria across studies may at least in part explain contrasting results across studies. Nevertheless, those functional brain abnormalities as a function of the presence of the AA/AG *CACNA1C* risk alleles are consistent with the neuropsychological literature. Hence although less unanimous than the neuroimaging literature, BD patients who carry those risk alleles may score poorer on speed of processing and digit span tests compared to non-carriers (consistent with a lower efficiency of the left ventrolateral prefrontal cortex). In addition, carriers of the risk allele may display impaired recognition of emotional faces (disgust, sadness, happiness, and anger) [see Ou et al. (2015) for a review].

4.2. The ANK3 gene

The *ANK3* gene codes for Ankyrin G, a protein which may be involved in the stabilization and localization of ion channels and cell adhesion molecules to nodes of Ranvier and initial segments of axon (Gasser et al., 2012). Furthermore, an elegant preclinical study found a lack of voltage-gated sodium channels in GABAergic parvalbumin interneurons in mice deficient of exon 1b of the *ANK3* (Lopez et al., 2016). Consistently, mice exhibited an *ANK3* gene dose-dependent phenotype characterized by manic-like behavior, epilepsy, and sudden death (Lopez et al., 2016). In addition, Ankyrin G has been implicated in neurodevelopment, and in the onset of myelination (Ching et al., 1999), and also in the regulation of neurogenesis (Durak et al., 2015; Leussis et al., 2012).

Replicated findings indicate that different risk alleles of the *ANK3* gene may impact white matter structure in BD. For example, BD patients who were carriers of the risk allele rs10761482 SNP had decreased FA in the forceps minor (Ota et al., 2016), while BD patients who were carriers of the risk allele of the rs9804190 had decreased FA in the uncinate fasciculus and the cingulate gyrus bilaterally among other regions compared to CC homozygotes (Lippard et al., 2016). These findings are consistent with a recent meta-analysis of DTI studies in BD which evidences widespread white matter in this illness compared to controls (Nortje et al., 2013). Greater widespread abnormalities in individuals with BD carrying risk variants of the *ANK3* gene also provide support for a putative role of Ankyrin G in myelination. In addition, risk alleles of this gene could lead to accelerated brain aging in BD (Rizzo et al., 2014). Furthermore, the risk C-allele of rs10761482 SNP was significantly associated with worse performance on verbal comprehension, logical memory and processing speed in BD patients in one study (Hori et al., 2014), while another study found that the risk allele of the rs10994336 SNP was associated with reduced sensitivity in target detection and increased errors of commission during sustained attention in both patients with BD and HCs (Ruberto et al., 2011). Altogether, these data suggest that different risk alleles of the *ANK3* gene could have a deleterious effect on WM structure in BD, which could be related to neurocognitive deficits. This hypothesis is further supported by a study that found that the risk allele of the rs10994336 SNP was associated with hyperactivation of the right anterior cingulate cortex and left posterior cingulate cortex in patients with BD compared to HCs in the N-back test, which measures executive function (Delvecchio et al., 2015).

4.3. The BDNF gene

The brain-derived neurotrophic factor (*BDNF*) gene is located on chromosome 11p14.1. The BDNF protein is a member of the neurotrophin superfamily, which supports neuronal survival, neural differentiation during development, and has been implicated in the regulation of activity dependent-synaptic plasticity in mature neurons (Duman and Monteggia, 2006; Hempstead, 2015). This neurotrophin is abundantly expressed in the hippocampus (Duman and Monteggia, 2006). The BDNF rs6265 SNP has been frequently investigated and an alteration at nucleotide 196 (G/A) which produces a Val66Met substitution (Notaras et al., 2015a). This SNP may result in a diminished cellular trafficking and packaging of the mature BDNF protein into the secretory vesicles, thus reducing depolarization-induced release of this neurotrophin (Notaras et al., 2015a). Furthermore, carriers of this risk SNP could produce the Met BDNF prodomain in larger amounts, with may have opposing effects (i.e., a negative impact in

neuron architecture remodeling) via an activation of the p75 and sortilin-related VPS10 domain containing receptor 2 (SorCS2) receptors (Hempstead, 2015). Consistently, this systematic review found replicated evidence that carriers of the BDNF met allele exhibit smaller hippocampal volumes (Cao et al., 2016; Chepenik et al., 2009). In one study BD carriers of this risk allele presented smaller hippocampal volumes compared to HCs (Cao et al., 2016), whereas in carriers of the Met allele had smaller hippocampus regardless of diagnostic group (i.e., BD or HC) (Chepenik et al., 2009). Zeni et al. (2016) studied a sample of pediatric patients with BD, and found that the Met allele of the BDNF gene had no influence on hippocampal volumes. A potential explanation for this finding is that this SNP could influence hippocampal volume over time as suggested by a previous study (McIntosh et al., 2007). A previous meta-analysis found that neuropsychiatric patients with either the Val/Val genotype or Met-carriers had significantly smaller hippocampal volumes compared to HCs with the same genotypes (Harrisberger et al., 2015). Therefore, it is possible that the Met risk allele could mediate within group differences in BD samples, but not differences between participants with BD and HCs.

A recent meta-analysis suggests that the *BDNF* Val66Met SNP is not associated with BD (Gonzalez-Castro et al., 2015), although this association could be significant in European populations (Li et al., 2016). This highlights that the effects of the Met allele of the *BDNF* gene could be more readily demonstrated at the neuroimaging or neuropsychological level than at the diagnostic level. Hence, several studies suggest that individuals with BD carrying the Met allele could have worse cognitive function in several domains including memory (Cao et al., 2016; Rybakowski et al., 2003; Rybakowski et al., 2006; Tramontina et al., 2009), although this association has not been unanimously demonstrated across studies (Rolstad et al., 2016; Rosa et al., 2014). These discrepancies may be related to the influence of concomitant medication (Grande et al., 2014). Furthermore, the involvement of BDNF in the pathophysiology of BD is supported by a recent meta-analysis which found that peripheral levels of this protein could be a biomarker of illness activity (Fernandes et al., 2015). Finally, preclinical evidence points to a role for BDNF in BD (de Souza Gomes et al., 2015; Macedo et al., 2012).

4.4. The 5-HTTLPR gene

A functional polymorphism (*5-HTTLPR*) in the promoter of serotonin transporter gene (*SLC6A4*) has been described in 1996 (Lesch et al., 1996). Since then, the impact of this polymorphism in a range of mental disorders and intermediate phenotypes have been a focus of substantial research efforts [see Jonassen and Landro (2014) for a review]. In addition, evidence suggests that methylation of the serotonin transporter gene may provide an epigenetic marker of exposure to life adversities (Provenzi et al., 2016). Notwithstanding the *5-HTTLPR* polymorphism does not seem to affect the methylation status of the *SLC6A4* gene, preliminary evidence suggests a possible interaction of methylation status and the short (S) allele in the development of stress-related mood disorders (Olsson et al., 2010).

Benedetti et al. (2014) observed that the S allele of the *5-HTTLPR* mediated the effect of early life stress on gray matter volumes in the right prefrontal cortex in a sample with BD. Furthermore, the S allele was also associated with higher right amygdala volumes in both patients with BD and HCs. Notwithstanding a previous meta-analysis suggests that the S allele could lead to amygdala hyperactivation in emotional paradigms (Murphy et al., 2013), our systematic review did not find a study to replicate this finding in BD. Nevertheless, one study found that S carriers had lower ventral anterior cingulate cortex activation compared to L/L participants during processing of happy and fear faces; this effect was evident in both the HC and BD groups (Shah et al., 2009). Clearly effects of the 'S' *5-HTTLPR* on intermediate phenotypes in BD deserve further investigation.

4.5. The NRG1 gene

Evidence indicates that neuregulin 1 and its cognate receptor ErB4 play significant roles in the regulation of synaptic transmission, myelin formation, and neuronal and glial cell survival (Mei and Nave, 2014). Although variations in *NRG1* gene were initially associated with schizophrenia [see Mostaid et al. (2016) for a review], subsequent studies pointed to a possible association with BD (Cao et al., 2014; Georgieva et al., 2008; Green et al., 2005; Gutierrez-Fernandez et al., 2014), notwithstanding this findings has not been supported thus far by GWAS (Goes, 2016). In keeping with this view, a study found aberrant cleavage of the neuregulin 1 in the *post mortem* hippocampus of individuals with BD (Marballi et al., 2012). We found evidence that a risk *NRG1* SNP (SNP8NRG221533) and its HAP_{ICE} haplotype was associated with greater white matter in the fornix, cingulum, parahippocampal gyrus, and the corpus callosum (Cannon et al., 2012). In addition, a functional neuroimaging study found that individuals with BD carrying the high-risk SNP (rs35753505) of the *NRG1* gene displayed hyperactivation of the right posterior orbitofrontal cortex compared to non-carriers (Mechelli et al., 2012). Clearly the impact of high-risk variants of the *NRG1* gene on structural and functional brain abnormalities in individuals with BD require further study.

4.6. Limitations

The findings of this systematic review should be interpreted within its limitations. First, the methodological quality of included studies varied. For example, the mood state of participants with BD varied across studies. In addition, some studies did not include a HC group, while few studies did not control results for multiple comparisons. Second, several confounding variables should be considered (e.g., differences in length of illness, number of previous affective episodes, and exposure to mood stabilizing medications). For example, it has been suggested that hippocampal volumes in BD may vary as a function of the number of affective episodes in a subset of patients with neuroprogressive forms of the illness (Cao et al., 2017; Lim et al., 2013). Furthermore, the large majority of studies included in this systematic review enrolled adult samples. For example, a meta-analysis indicates that hyperactivation of the amygdala across emotional face recognition fMRI studies is more evident in BD-youths than among BD-adults (Wegbreit et al., 2014). Third, although our findings indicate that the effects of genetic variants in the risk of BD may be more readily reflected as at the brain structure/function level than in the disease per se, this notion has been challenged by some experts. For example, Flint and Munafo (2007) provides *meta*-analytic evidence that the effect sizes of illness-related genetic variants on intermediate phenotypes may not necessarily be larger than the ones observed for the illness phenotype. Fourth, we included structural and functional MRI studies, but not other imaging tools (e.g., positron emission tomography). Fifth, although we found promising replicated findings, several significant associations deserve replication. For example, converging evidence from both preclinical and GWAS studies have implicated ANK3 as a putative risk gene for BD, while recent gene imaging studies offered promising initial results (Lippard et al., 2016). In addition, the reproducibility of this field deserves careful examination (Carter et al., 2016). Sixth, the use of pre-defined ROI-based analyses could bias some of the converging findings of this review. For example, the study by Chepenik et al. (2009) in which the Met allele of the BDNF Val66Met polymorphism was associated with bilateral hippocampi reduction in individuals with BD restricted their analyses to this brain structure.

4.7. Implications

This systematic review open several research implications. It has been increasingly recognized that neurobiological abnormalities span

conventional diagnostic categories in psychiatry. This fact motivated the NIMH to launch the Research Domain Criteria (RDoC) initiative (Cuthbert and Insel, 2013), with an attempt to provide a complimentary research classification system for mental disorders built upon dimensions of neurobiology and observable behavior, and moving towards precision psychiatry (Fernandes et al., 2017; Vieta, 2015). Consistent with this assumption several genetic risk variants seem to overlap across major mental disorders (Gatt et al., 2015). Furthermore, a recent study investigated a large panel of brain-based biomarkers and included participants across the psychotic spectrum (schizophrenia, schizoaffective disorder, and BD), and found three distinct psychotic biotypes that did not respect diagnostic categories (Clementz et al., 2016). Consistently, the only replicated finding observed in this review is also apparent in similar studies involving schizophrenia samples. For example, the Val66Met BDNF polymorphism has also been associated with reduced hippocampi volume in schizophrenia (Notaras et al., 2015b), while a recent systematic review found that several putative risk genes for both BD and schizophrenia may influence brain structure and function in healthy control samples (Gurung and Prata, 2015). Therefore, future efforts to replicate the findings of this systematic review could include participants with different diagnostic categories, and a better control of potential confounding variables (e.g. concomitant medication and substance use. In addition, the *a priori* publication of research protocols in the field of 'imaging genetics' could improve its reproducibility and reduce the risk of selective outcome reporting (Carter et al., 2016).

5. Conclusion

This review synthesis indicates that the 'gene-imaging' research paradigm may aid in the identification of intermediate phenotypes, and therefore could provide more consistent biological mechanistic insights for BD. Variants in the *CACNA1C*, *ANK3, and BDNF* genes yielded the most consistent findings thus far, by applying neuroimaging paradigms to GWAS-emerging candidate genes. Future research efforts should include samples with different diagnostic categories, and the development of collaborative consortia with a priori published protocols could enhance the impact of future efforts. However, highly robust findings are unlikely if the only source of candidate genes are GWAS and gene polymorphisms, and neuroimaging studies are particularly difficult in bipolar patients because of the influence of complex medication regimes.

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Contributors

LPP, CAK and AFC designed the protocol and searched the literature. LPP and BPF screened the studies and extracted the data. LPP, CAK and AFC analyzed the data. LPP, CAK, RTS and AFC wrote the first draft of the manuscript. MS, BPF, MF, RMV, KWM, EV, NV and BS contributed to the interpretation and discussion of the findings, and to the writing of the manuscript. All authors have read and approved the final version of this manuscript for submission. All authors have participated sufficiently in the work to take responsibility for its content.

Conflict of interest

The authors declare no conflicts of interest that could influence this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.05.002.

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