Original Article

Gene Polymorphisms of Cognitive Function in Patients with Bipolar Disorder: A Systematic Review and Meta-analysis

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Abstract

Objectives: Evidence showed that the etiology of cognitive impairment in bipolar disorder (BD) is related to genetic susceptibility. But results from many studies evaluating the association between candidate genes and cognitive function in BD are inconsistent. To define the effect of risk target single-nucleotide polymorphisms (SNPs) on the association of cognition in BD, we did a systematic review and meta-analysis to study the risk genetic variants. **Methods:** A search for literature was conducted through online databases updated as of October 2018. Recruited studies were compared for cognitive difference in BD patients with certain gene polymorphisms. **Results:** Meta-analyses were conducted, for two SNPs of target genes including brain-derived neurotrophic factor (rs6265) and calcium channel, voltage-dependent, L type, alpha 1C subunit (rs1006737), in the recruited seven studies. Quantitative analysis showed no significance in the association between the polymorphisms of rs6265 or rs1006737 with global intelligence quotient or rs6265 with Wisconsin Card Sorting test in BD. **Conclusion:** Our results implied that the cognitive impairment in patients with BD might not be explained by a SNP in current evidence. We suggest that further studies with larger sample size and deeper phenotype are needed to elucidate the relevance of gene variant model contributed to the susceptibility of cognitive dysfunction in patients with BD.

Key words: genetic variants, global intelligence quotient, single-nucleotide polymorphism, Wisconsin Card Sorting test
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Introduction

Bipolar disorder (BD) is a disabling illness due to its early onset, severity, and chronicity. BD is among the top 10 causes of years lost due to disability according to a report in the Global Burden of Disease in 2000 [1]. In addition, population growth and aging are leading to an increase in the burden of disease and prevalence over time [1]. The clinical pictures of chronic BD are recurrent episodes of mania and depression interspaced by periods of euthymia and associated with impairments in different aspects of daily living [2]. Cognitive dysfunction is a common and robust feature of schizophrenia, and this pattern of cognitive deficits can overlap in some BD patients with less severe form [3]. The significance of these cognitive deficits in BP is not consistent in studies. Furthermore, BD can impact negatively on social functioning and be responsible for the poor interepisode recovery or quality of life seen in a high proportion of patients [4, 5]. Therefore, to investigate the etiology for cognitive impairment in BD patients is important, and further improving the prognosis of BD is worthwhile. Current evidence showed that most patients with BD show cognitive impairment to some extent, even during euthymic state [6]. Moreover, some neurocognitive deficits are present not only in the early stage of the illness, but also in premorbid phase [7].

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Although the cause of cognitive impairment in BD is not well understood, its association with genetic susceptibility can be expected as the heritability of BD has been estimated to be around 80%–85% [8]. In addition, genetic modeling studies of twins and siblings further showed that neuropsychological deficits are both in patients with BD and in their unaffected relatives, describing that certain cognitive functions, as endophenotypes for BD, have strong heritability [9]. Those affected aspects of neurocognitive function include verbal recall and learning, processing speed, working and facial memory, selective attention, as well as response inhibition [9].

Many studies have evaluated associations between candidate genes and cognitive processes in BD, and proposed some theoretical mechanisms to explain how those genes act on cognition, but their results are inconsistent and without unified outcome measurements between studies [10]. For example, the most frequently studied genes include calcium channel, voltage-dependent, L type, alpha 1C subunit (*CACNA1C*) [11], and brain-derived neurotrophic factor (*BDNF*) [12], others which are related to dopamine regulation, such as dopamine receptor gene 1 (*DRD1*) [13], catechol-O-methyl transferase (*COMT*) [14] or homeobox transcription factor 1 alpha gene (*LMX1A*) [15], and neuregulin 1 gene (*NRG1*) [16]. In addition, the range of cognitive measurements varies from studies to studies as general intelligence quotient (IQ) to specific cognitive domains. Recent studies also have suggested several candidates for the multiple genes of small effect that are assumed to underlie genetic risk for complex neuropsychiatric disorders and also phenotype as cognition. Therefore, we intended in this study to do a systematic review and meta-analysis to study the effects of risk genetic variants from candidate gene association studies.

Methods

Search strategy and inclusion criteria

The PubMed, PsycInfo, and Embase databases were searched to the end of October 2018 using combinations of the terms "bipolar disorder" and "cognition," or "processing speed," "working memory," "attention/vigilance," "verbal learning," "visual learning," "reasoning and problem solving," "executive function," and "gene(s) and MESH term." The keywords for the above cognitive domains were suggested by the International Society of Bipolar Disorder Consensus 2010. References cited in articles on studies were also examined to identify potential additional studies that might not be collected in the first attempt of search.

We determined all eligible studies using the following inclusion criteria: (a) being published in a peer-reviewed journal, (b) having detailed description of the sample tested, (c) providing genetic polymorphism information in BD patients, and (d) comparing cognitive differences between BD patients with major allele of certain gene polymorphisms and those with minor allele one. The authors of those studies were contacted for additional information if uncertainty existed about whether their data met our inclusion criteria, or if we needed additional data which were not contained in the published original report. We excluded studies if no cognitive data were reported or if an overlap of reported data was identified between articles.

This study was exploring secondary data of published papers, and was exempt for further review by the institutional review board of the Taipei City Hospital (protocol number = TCHIRB-10812018-W and date of exemption = January 7, 2020) without requirement of collecting any signed written consents from the study participants).

Selection of genotypes and phenotypes

The initial assessed studies regarding the genotype included single-nucleotide polymorphisms (SNPs) belonging to 19 genes – *SNX7* (sorting nexin 7), *BDNF*, *DISC1* (disrupted in schizophrenia 1), *MMP9* (matrix metallopeptidase 9), *CACNA1C* (calcium channel, voltage-dependent, L type, alpha 1C subunit), *DGKH* (diacylglycerol kinase eta), *CHRNA7* (cholinergic receptor nicotinic alpha 7 subunit), *GGT7* (gamma-glutamyltransferase), *APOE* (apolipoprotein E), *COMT* (catechol-O-methyl transferase), *NET* (norepinephrine transporter), *ANK3* (ankyrin 3), *NRN1* (neuritin 1), *DRD1* (dopamine receptor D1), *serotonin*, *LMX1A* (homeobox transcription factor 1 alpha), *NRG* (neuregulin), *EAAT* (excitatory amino acid transporter), and *MsrA* (methionine sulfoxide reductase A) in 38 studies. Of the 19 unique genes reported, 5 genes in 25 studies were extracted because three or more studies existed in the same candidate gene research, including *BDNF*, *CACNA1C*, *APOE*, *COMT*, and *ANK3*. We further excluded *APOE* studies because of lack of overlapping SNP loci between studies.

Phenotypes of cognitive measures were not limited in the initial search process to any kinds of neurocognitive tests. In this condition, two approaches were considered: (a) assessing studies evaluating the same cognitive test, or (b) assessing studies evaluating the same cognitive domain, irrespective of the test. The second approach was not pursued due to the lack of consensus for categorizing cognitive symptoms into cognitive domains. In addition, considering the large variety of cognitive tests used as end points in the reviewed studies, collapsing these into domain-specific groups would introduce a validity bias, as different cognitive tests measure different cognitive abilities, even within the same cognitive domain. Moreover, because certain individual tests would qualify to be assigned to different cognitive domains, this would introduce uncertainty when interpreting the results. To overcome several of these problems, we chose the first approach evaluating studies with a common cognitive test as less validity bias.

According to the selection of genotypes and phenotypes for the comparison within BD patients, we could only extract studies with same tests with available raw data information. After having contacted authors for primary data for pooling, we quantitatively analyzed seven studies into our meta-analysis. Using this criterion, the outcomes of Wisconsin Card Sorting Test (WCST) and global IQ score were chosen in the meta-analysis: *BDNF* rs6265 in association with IQ and WCST in four studies and *CACNA1C* rs1006737 in association with IQ in three

studies. Due to failure of getting the primary data in studies for *COMT* and *ANK3*, we preserved only two studies, respectively, and therefore not presented as quantitatively analysis. Figure 1 shows the systematic review and selection process.

Data extraction and quality assessment

Data were independently extracted by two authors, and discrepancies were resolved by consent after discussion. Where data were reported in a format that did not allow inclusion in the meta-analysis, the authors were contacted directly and asked if willing to release data in the appropriate format. For each study, the extracted data included first author, year of publication, reported ethnicity, diagnosis and mood status, average age of sample, and mean with standard deviation for each cognitive variable by genotype groups. *BDNF* and *CACNA1C* genotypes were grouped according to the presence or absence of the minor allele (Val/Val vs. Val/Met or Met/Met). Where cognitive data were available from more than one occasion, the scores used were from the first assessment only. To assess the methodological quality of eligible studies, we used the Newcastle–Ottawa Quality Assessment Scale for Case–Control Studies (NOS) [17]. The NOS is a freely available eight-item scale with a version for assessing the quality of case–control studies in meta-analysis. This scale evaluates the domains of selection, comparability, and exposure. One star is allocated when a feature of quality is present up to a maximum of 9 (the comparability domain can score up to two stars); studies awarded 7 or more stars would be considered a high-quality study.

Statistical analysis

Data were initially analyzed within a fixed-effects framework. A fixed-effects framework assumes that the effect of genotype is constant across studies, and between-study variation is considered to be due to chance or random variation. The assumption was checked using Chi-square test of goodness of fit for homogeneity but showed heterogeneity representing by value of tau-squared. Therefore, a random-effects framework was used. Random-effects models are more conservative than fixed-effects models and generate a wider confidence interval (CI). The significance of the pooled effects size was determined using mean score in raw cognitive tests. Instead of standardized mean difference, we used raw mean score with more advantage for interpretation meaning as the pooling studies used the same cognitive test (IQ and WCST) in our meta-analysis. We did not do funnel plots and Egger test because potential publication bias is highly suggested due to the poor response rate from individual study authors and also limited number of included studies.

All statistical analyses of this meta-analysis were done by R software version 3.6.1 (https://www.r-project.org/). The

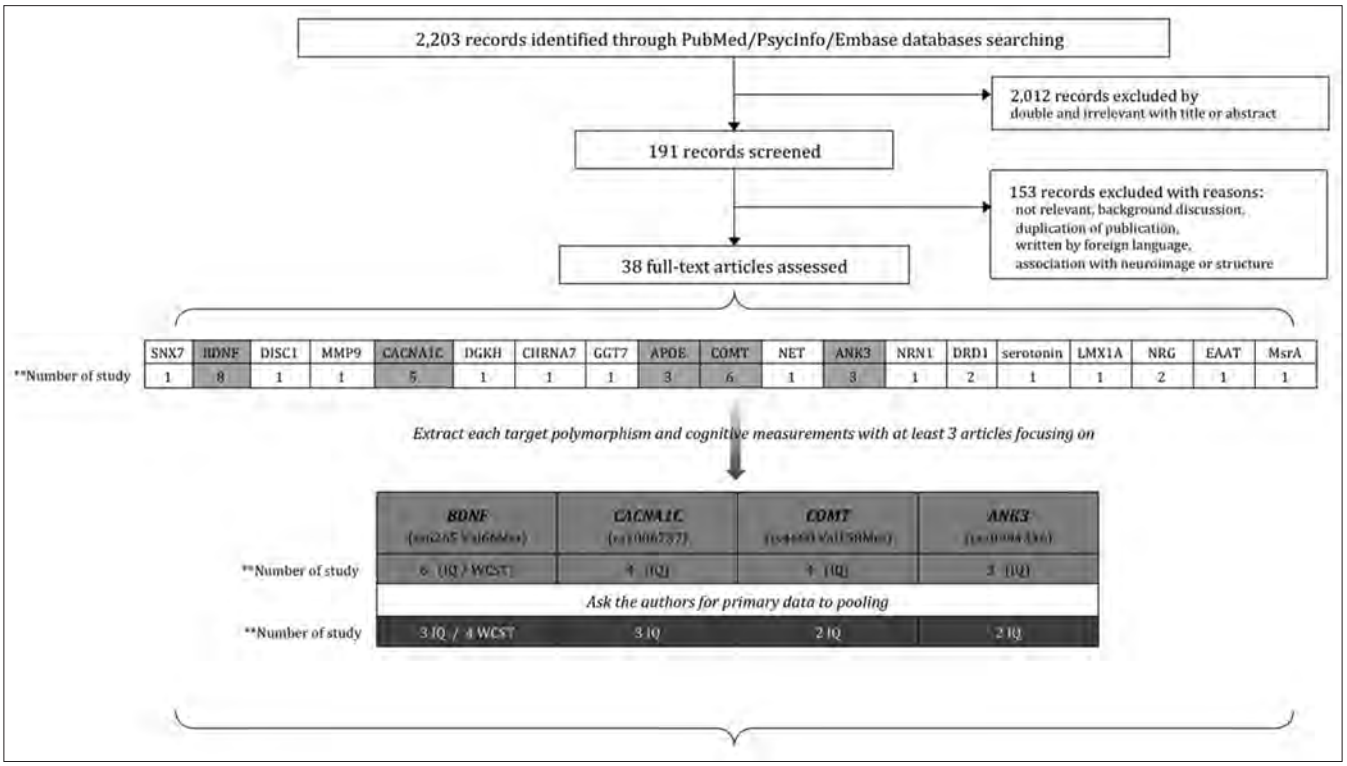

Figure 1. Flowchart of selection process in the meta-analyses. *SNX7*, sorting nexin 7; *BDNF,* brain-derived neurotrophic factor; *DISC1,* disrupted in schizophrenia 1; *MMP9*, matrix metallopeptidase 9; *CACNA1C*, calcium channel, voltage-dependent, L type, alpha 1C subunit, *DGKH,* diacylglycerol kinase eta; *CHRNA7,* cholinergic receptor nicotinic alpha 7 subunit; *GGT7,* gamma-glutamyltransferase; *APOE*, apolipoprotein E; *COMT*, catechol-O-methyl transferase; *NET,* norepinephrine transporter; *ANK3*, ankyrin 3; *NRN1*, neuritin 1; *DRD1*, dopamine receptor D1; *LMX1A*, homeobox transcription factor 1 alpha; *NRG*, neuregulin; *EAAT*, excitatory amino acid transporter; *MsrA*, methionine sulfoxide reductase A; IQ, intelligence quotient; *WCST*, Wisconsin Card Sorting Test.

differences between groups were considered significant if $p < 0.05$.

Results

Characteristics of included studies

The final dataset of three studies comprised 226 independent samples in cognitive data as IQ was reported by *BDNF* Val66Met polymorphism. Among those studies, the average age of the patients was around 40 years, except the object of the study of Zeni et al. [18] having children and adolescents. Meanwhile, we pooled four studies that comprised 276 independent samples with *BDNF* Val66Met polymorphism assessing cognitive performance using WCST to our meta-analysis. Two of those studies [12, 19] with slightly larger mean age of patients (around the age of 45 years) showed a positive association with risk Met allele, rather than the rest of studies. The final dataset of the three studies comprised 306 independent samples having cognitive data as IQ with *CACNA1C* rs1006737 genotype, and only one of the study samples is from Asian population [20].

Two studies that comprised 216 independent samples with *COMT* Val158Met (rs4680) polymorphism assessing cognitive performance by IQ found inconsistent results. Soeiro-de-Souza et al. [21] reported a significant association between the risk Met allele and cognitive dysfunction. But Wirgenes et al. [22] only confirmed a significant association with schizophrenia, but did not provide the exact cognitive measurement data associated with BD. As *ANK3* has been identified as a risk factor for BD, two studies published in 2011 and 2014, which comprised 95 independent samples with *ANK3* rs10994336 genotype, assessed the genetic impact on IQ performance in BD. The results failed to prove the significance in the association between rs10994336 and cognitive dysfunction with possible limitation of small sample sizes. In summary, further investigations that link *ANK3* variants to endophenotype of BD are required. Table 1 summarizes the 11 studies.

Meta-analysis of association results

We pooled seven studies into our meta-analysis (Figure 1). Four studies were *BDNF* (rs6265) for association with IQ and WCST. Three studies were *CACNA1C* (rs1006737) for association with IQ.

Associations between intelligence quotient and brain-derived neurotrophic factor and calcium channel, voltage-dependent, L type, alpha 1C subunit

We analyzed the *BDNF* rs6265 polymorphism in the association of IQ performance in BD patients (Figure 2a). Three studies, comprising 226 independent samples, contributed to the study data for the meta-analysis. Random-effects analysis indicated no evidence of difference (mean difference = 0.09, 95% CI = −3.54–3.72, $Z = 0.05$, nonsignificance). As for the variant of *CACNA1C* rs100673, three studies comprising 306 independent samples contributed to the study data for the meta-analysis. As shown in Figure 2b, random-effects analysis showed no significant difference of IQ performance between the groups (mean difference = 1.66, 95% CI = −1.04–4.37, $Z = 1.21$, nonsignificance).

Associations between Wisconsin Card Sorting Test and brain-derived neurotrophic factor

The WCST, a neurocognitive test, addressing the function connected with prefrontal lobe activity, could reflect the inability across various function domains, including the percentage of perseverative errors (WCST-P), the percentage of nonperseverative errors (WCST-NP), the number of

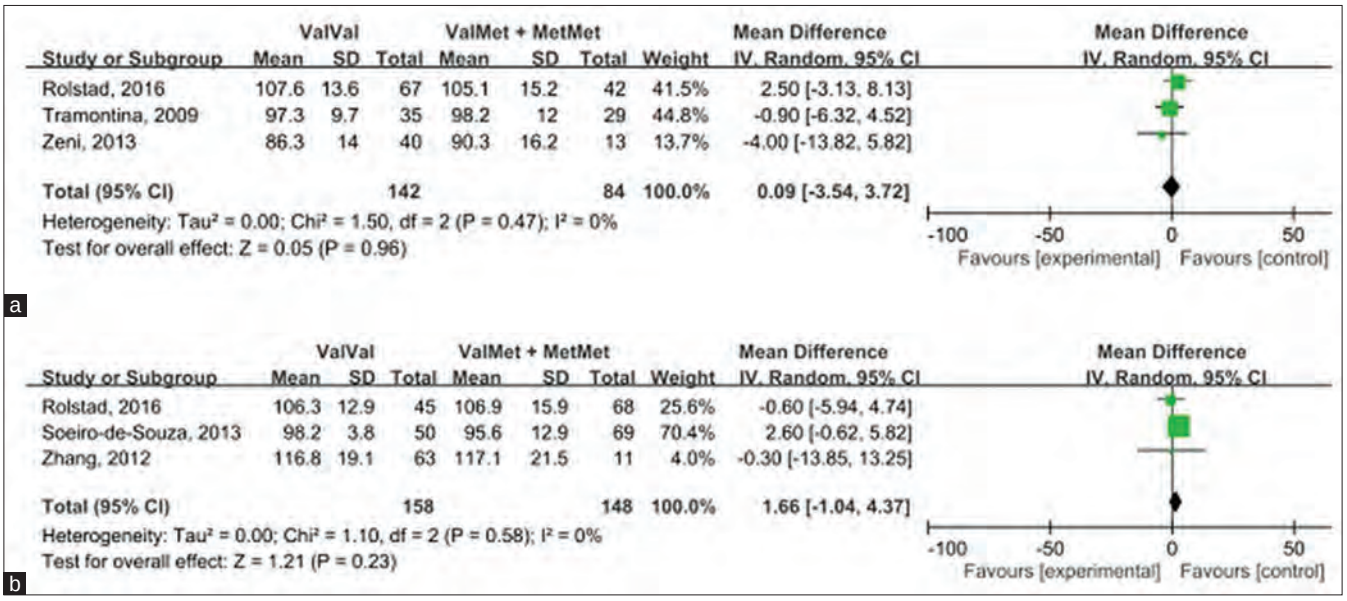

Figure 2. Forest plots of association between *BDNF rs6265*/*CACNA1C rs1006737* polymorphisms and IQ in bipolar patients. (a) IQ difference in *BDNF* genotype (rs6265). (b) IQ difference in *CACNA1C* genotype (rs1006737). *BDNF,* brain-derived neurotrophic factor; *CACNA1C,* calcium channel, voltage-dependent, L type, alpha 1C subunit; IQ, intelligence quotient; CI, confidence interval.

Table 1. Characteristics of the studies in the current meta-analyses

Genotype	First author, year	Ethnicity	Mood status	Sample	Average age of sample	Cognitive variables	Mean with SD for each variable		Result Risk SNP	Risk of bias*
							Val/Val	Val/Met + Met/Met		
BDNF (rs6265)	Rolstad et al., 2016	Swedish	*Unavailable*	114 (BD) 104 (control)	37.9 ± 12.8 (BD)	IQ	107.6; 13.6 (67)	106.0; 14.7 (38) + 96.2; 17.1 (4) = 105.1; 15.2 (42)	NS	Selection*** Comparability** Exposure***
	Zeni et al., 2013	Caucasian	*Unavailable*	53	11.90 ± 2.61 (Val/Val) 10.07 ± 3.01 (Val/Met)	IQ	86.27; 14 (40)	90.25; 16.2 (13)	NS	Selection** Comparability** Exposure***
						WCST			NS	
						P	20.39; 10.95 (38)	18.90; 10.64 (10)		
						NP	22.37; 12.24 (38)	24.50; 12.68 (10)		
						CC	3; 1.98 (38)	3.6; 2.01 (10)		
						CONC	44.15; 20.36 (38)	44.61; 24.05 (10)		
						CAT	34.07; 35.67 (38)	25.5; 18.22 (10)		
	Tramontina et al., 2009	Caucasian	Euthymic or depressive	64	42.3 ± 11.1	IQ	97.3; 9.7 (35)	98.2; 12.0 (29)	NS	Selection*** Comparability* Exposure***
						WCST			NS	
						P	30.9; 18.3 (35)	30.3; 21.1 (29)		
						NP	25.5; 17.8 (35)	16.7; 11.8 (29)		
						CC	2.5; 2.1 (35)	3.6; 2.4 (29)		
						CONC	40.4; 24.2 (35)	47.7; 24.8 (29)		
	Rybakowski et al., 2006	Poland	Euthymic or depressive	129 (SZ) 111 (BD) 160 (control)	27.1 ± 9.6 (SZ) 43.4 ± 13.7 (BD) 32.9 ± 11.5 (control)	WCST			Significant with Met	Selection** Comparability* Exposure***
						P	10.6; 4.5 (81)	15.0; 11.0 (30)		
						NP	9.8; 4.9 (81)	11.3; 9.5 (30)		
						CC	5.8; 0.5 (81)	5.2; 1.6 (30)		
						CONC	75.8; 10.7 (81)	67.7; 20.4 (30)		
						CAT	16.5; 8.6 (81)	24.3; 26.2 (30)		
	Rybakowski et al., 2003	Poland	22 euthymic 32 depressive	54	46	WCST			Significant with Met	Selection** Comparability* Exposure***
						P	10.5; 5.0 (44)	17.0; 15.6 (9)		
						NP	9.8; 5.5 (44)	15.9; 15.2 (9)		
						CC	5.8; 0.6 (44)	4.6; 2.4 (9)		
						CONC	75.3; 11.9 (44)	59.1; 25.9 (9)		
						CAT	17.8; 9.6 (44)	40.1; 39.3 (9)		
CACNA1C (rs1006737)	Rolstad et al., 2016	Swedish	*unavailable*	114 (BD) 104 (control)	37.9 ± 12.8 (BD)	IQ	106.3; 12.9 (45)	107.7; 16.7 (54) + 103.6; 12.1 (14) = 106.9; 15.9 (68)	NS	Selection*** Comparability** Exposure***
	Soeiro-de-Souza et al., 2013	Unavailable	37 euthymic, 39 manic, 33 depressive	109 (BD) 96 (control)	29.9 ± 6.42 (Val/Val) 29.78 ± 8.94 (Val/Met) 31.91 ± 10.01 (Met/Met)	IQ	98.16; 3.75 (50)	98.07; 11.89 (54) + 86.64; 12.49 (15) = 95.6; 12.9 (69)	Significant with Met/Met	Selection*** Comparability* Exposure***

Contd...

Table 1. Contd...

Genotype	First author, year	Ethnicity	Mood status	Sample	Average age of sample	Cognitive variables	Mean with SD for each variable		Result Risk SNP	Risk of bias*
							Val/Val	Val/Met + Met/Met		
	Zhang et al., 2012	Chinese	Unavailable	318 (SZ) 401 (control) 74 (BD)	27.94 ± 7.89 (SZ) 22.43 ± 6.30 (control) 27.08 ± 8.28 (BD)	IQ	116.75; 19.07 (63)	117.09; 21.46 (11)	NS	Selection*** Comparability* Exposure**
Genotype	First author, year	Ethnicity	Mood status	Sample	Average age of sample	Cognitive variables	Mean with SD for each variable		Result Risk SNP	Risk of bias*
							Val/Val + Val/Met	Met/Met		
COMT (rs4680)	Soeiro-de-Souza et al., 2012	Unavailable	22 manic, 21 mixed, 29 depressive	72 (BD) 76 (control)	28.2 ± 5.4 (BD) 23.4 ± 3.3 (control)	IQ	96.61; 12.66 (54)	64.00; 1.41 (18)	Significant with Met/Met	Selection*** Comparability* Exposure***
	Wirgenes et al., 2010	Unavailable	Unavailable	171 (SZ) 144 (BD) 340 (control)	33.7 ± 9.6 (SZ) 37.1 ± 11.7 (BD) 34.92 ± 10.1 (control)	IQ	Nonavailable	Nonavailable		
Genotype	First author, year	Ethnicity	Mood status	Sample	Average age of sample	Cognitive variables	Mean with SD for each variable		Result Risk SNP	Risk of bias*
							CC	CT + TT		
ANK3 (rs10994336)	Hori et al., 2014	Japanese	Euthymic	49 (BD) 633 (control)	48 ± 15.1 (BD) 45.7 ± 16.2 (control)	IQ	102.57; 16.63 (21)	103.76; 13.28 (25) 111.67; 2.08 (3)	NS	Selection*** Comparability** Exposure***
	Ruberto et al., 2011	British	Euthymic	46 (BD) 73 (relative) 67 (control)	43.88 ± 10.68 (BD) 32.94 ± 11.64 (relative) 36.20 ± 13.17 (control)	IQ	117.71; 18.07 (39)	121.71; 16.27 (7)	NS	Selection**** Comparability* Exposure***

*Assess with Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies. SNP, single-nucleotide polymorphism; *BDNF*, brain-derived neurotrophic factor; *CACNA1C*, calcium channel, voltage-dependent, L type, alpha 1C subunit; *COMT*, catechol-O-methyl transferase; *ANK3*, ankyrin 3; SZ, schizophrenia; BD, bipolar disorder; NS, not significant; SD, standard deviation; IQ, intelligence quotient; WCST, Wisconsin Card Sorting Test; P, perseverative errors; NP, nonperseverative errors; CC, completed corrected categories; CONC, conceptual level responses; WCST-CAT, first category

correctly completed categories (WCST-CC), the percentage of conceptual-level responses (WCST-CONC), and the set to the first category (WCST-CAT).

Four studies, comprising 276 independent samples, contributed to the study data for the meta-analysis of the former four domains [12,18,23,24]. Random-effects analysis indicated no evidence of difference between the Val/Val allele to the Val/Met and Met/Met group in the results of WCST-P, WCST-NP, WCST-CC, and WCST-CONC (Figure 3a-d). Among those four studies, only three studies, comprising 212 independent samples, obtained the result of WCST-CAT, and the random-effects model also showed no significant difference between Val/Val and those with minor allele one (Figure 3e).

Discussion

Family, twin, and adoption studies have demonstrated evidence for the importance of genetic factors in BD [25]. BD and schizophrenia share the cognitive dysfunction endophenotype [15]; by comparison, studies focusing on genetic susceptibility for cognitive impairment in BD are unclear. In the present study using meta-analyses, we did a systemic overview of the association between gene polymorphisms and the cognitive function in patients with BD. We used four selected genes (*BDNF*, *CACNA1C*, *COMT*, and *ANK3*) with four SNPs (rs6265, rs1006737, rs4680, and rs10994336) to identify the association between the genetic factors and cognitive impairment. Before this study, *COMT* and *ANK3* have not been included in quantitative analysis due to lack of sufficient raw data. In our meta-analyses, we could not identify the significant difference between the former two SNPs in IQ or WCST in BD (Figures 2 and 3).

Given that BDNF has been shown to be a potent modulator of synaptic transmission and plasticity in the central nervous system [12], its association with cognitive processes as memory and learning could be implicated. Recent studies showed that serum BDNF levels are negatively correlated with the severity of manic and depressive symptoms, suggesting that peripheral BDNF measures can play a rôle as a biomarker in BD [23]. Previously, many studies demonstrated that abnormal hippocampal activity assayed with functional magnetic resonance imaging is associated with Met allele of rs6265, a polymorphism of BDNF gene [26], that BD patients with poorer neuropsychological functioning have decreased hippocampal volume [27], implying that Val66Met polymorphism might be a susceptible gene for cognitive dysfunction in BD. Similarly, calcium influx through L-type voltage-gated calcium channels participates in many transmembrane signaling pathways, therefore variations in calcium channel activity can affect signal transduction and brain circuitry. Some previous studies already indicated that the intracellular calcium signaling and homeostatic regulation is associated with the pathophysiology and pharmacology of BD [28], and addressed that the polymorphism of the calcium channel, voltage-dependent, L type, alpha 1C subunit (*CACNA1C*) risk Met allele influences brain morphology and also modulates both brain function and cognitive performance [11]. Except rs1006737, many candidate SNPs for *CACNA1C* still exist to be associated with cognitive impairment in BD [29]. Up to now, several studies have revealed inconsistent results, suggesting that further studies are required to elucidate not only the rôle of *BDNF* and *CACNA1C* in the interaction between the neural development and the process of mental disorder, but also its genetic mechanism in diverse ethnic populations.

Dopamine dysregulation hypothesis explains how antipsychotic agents work for treating schizophrenia and manic symptoms of BD; besides, dopamine is also a key neurotransmitter in the brain with an important rôle for regulating cognition and attention [30-32]. Therefore, polymorphisms in the catechol-O-methyl transferase (*COMT*) gene, an enzyme of the catecholaminergic neurotransmitters norepinephrine and dopamine, such as rs165599, have been reported to influence the executive aspects of verbal memory [14], and rs4680 has shown a negative association with cognitive dysfunction in the domains of execution, memory, verbal fluency, and intelligence tests during manic and mixed episodes [11]. Ankyrin 3 gene, encoding the ankyrin G protein, a scaffolding protein located at the neuronal axon initial segments and the nodes of Ranvier, which is involved in action potential generation using clustering sodium gated channels, is another risk gene identified in genome-wide association studies of BD [33]. An SNP of *ANK3*, rs10994336, has been reviewed to establish the association with sustained attention [34], ventral prefrontal cortical activation, and visual-prefrontal effective connectivity in BD [35]. Although the definite pathogenesis of BD with cognition decline has not been found, those mentioned above point out the current theory as a hypothetical underlying mechanism.

Our present review and meta-analysis are a preliminary attempt to extract the effect of risk target SNP on the association of cognition in patients with BD. As genetic factors play an important rôle in the etiology of BD, the common phenotype along with this mood disorder, cognitive impairment, should be inclusive. Nevertheless, none of these four candidate SNPs were found to be with strong or significant evidence in our analyses (Figures 2 and 3). Therefore, the possibility of their influence on neurocognition in patients with BD still needs to be clarified. Our systematic review showed that no available data existed to investigate all domains of cognition and the deficits may be inconsistent within the domains in cognitive tests. Whether these are discrete areas exist to impair or to reflect an underlying single more basic cognitive abnormality (e.g., psychomotor speed or working memory) is not yet clear. In addition, no longitudinal studies existed to contain in our recruited findings, and those studies usually had small sample size (with patients' number being around 50–150). Differences in medication variables or mood scales between assessment moments could not be controlled and may have influenced the results.

The etiology of BD is complex, and the possible existence of dynamic interaction between disease progression and neurobiology of cognitive function may exist is clear. The heterogeneity of cognitive dysfunction could be the reason

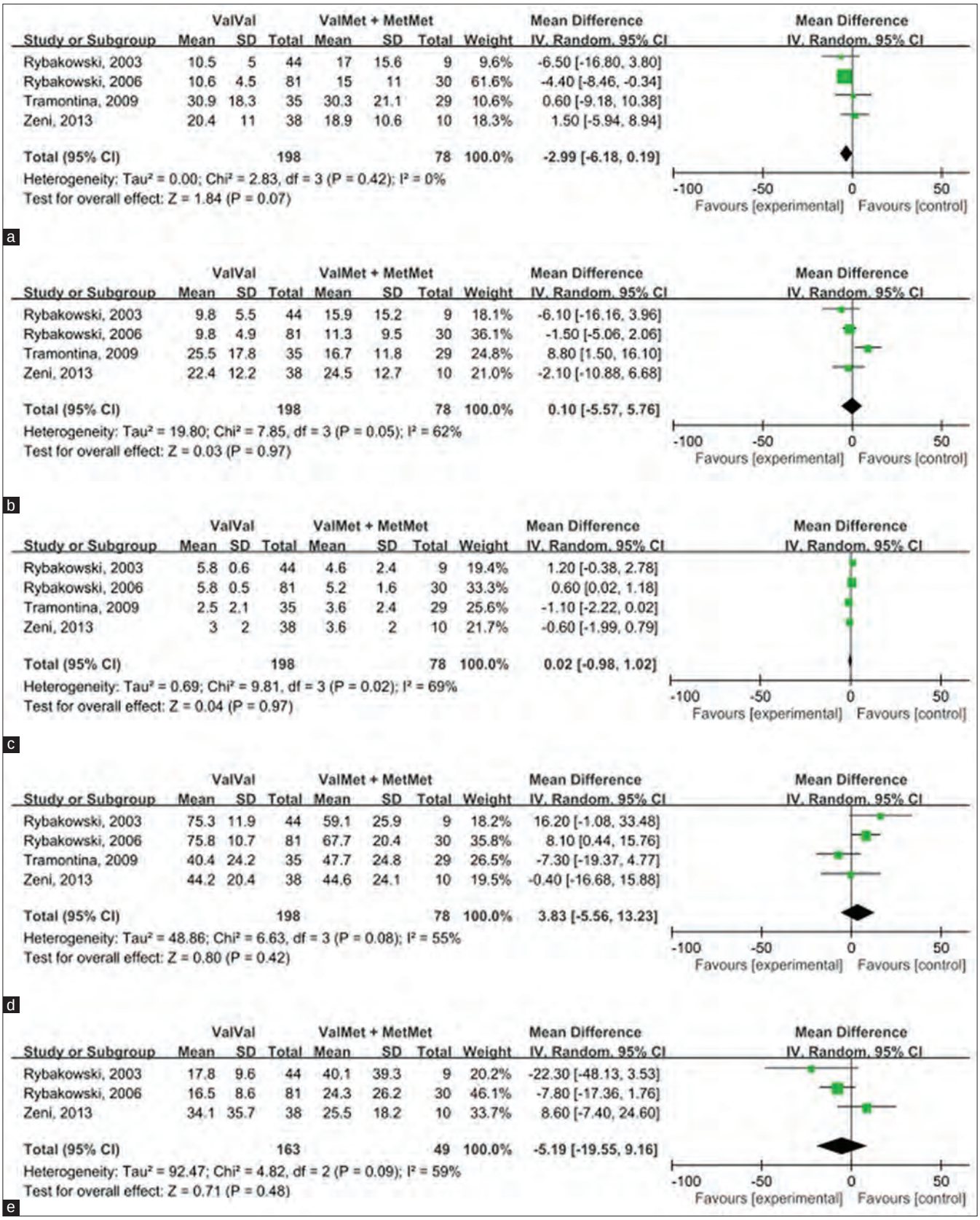

Figure 3. Forest plots of association between WCST results and bipolar patients with *BDNF* rs6265 polymorphism. (a) WCST-P difference in *BDNF* genotype (rs6265). (b) WCST-NP difference in *BDNF* genotype (rs6265). (c) WCST-CC difference in *BDNF* genotype (rs6265). (d) WCST-CONC difference in *BDNF* genotype (rs6265). (e) WCST-CAT difference in *BDNF* genotype (rs6265). *BDNF*, brain-derived neurotrophic factor; WCST, Wisconsin Card Sorting Test; WCST-P, perseverative errors; WCST-NP, nonperseverative errors; WCST-CC, completed corrected categories; WCST-CONC, conceptual-level responses; WCST-CAT, first category; CI, confidence interval.

that the cognitive function in patients with BD is hard to be explained through several SNPs shown in our study. Another reason underlying our findings may be the lack of power as these genetic effects are likely to be subtle. Current evidence implying the common disease with a common variant model in complex diseases such as psychiatry disorders is consistent [36]. But one study showed the trend that the block design approached between four SNPs has been associated with BD, indicating a potential genetic overlap between two of them [37]. Therefore, pooling or larger association studies on deeply phenotyped samples may in future provide a promising approach to investigate the effects and mechanisms of genetic risk variants in cognitive function in patients with BD.

Study limitations

The readers are warned against overinterpreting our study results because this study has four limitations:

- We studied only relatively well-studied polymorphic variants in candidate genes and included the measurement of cognitive tests merely.
- Studies reported in the literature may be subject to publication biases in which positive studies are more likely to be published, and this situation may unduly influence the inferences drawn in summarizing the findings.
- We had small number of existing studies.
- Different mood statuses, onset age of mental illness, and psychotropic agent effect on cognitive performance, are difficult to adjust for those heterogeneity.

Summary

Further studies are warranted to overcome the heterogeneities of cognitive performance in BD and to elucidate the relevance of gene variant model contributed to the susceptibility of cognitive dysfunction in patients with BD.

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Conflicts of Interest

All authors declare no potential conflicts of interest in writing this report.

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