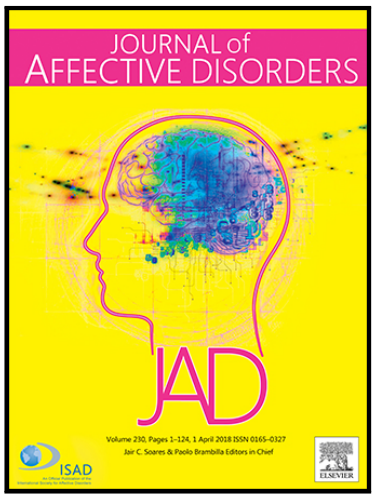


# The impact of BDNF Val66Met polymorphism on cognition in Bipolar Disorder: a review

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**Highlights**

- This review summarizes the results from genetic studies investigating BDNF cognitive modulation in BD
- BDNF Val66Met polymorphism seems to modulate cognitive functions in BD
- Val allele is associated with better cognitive performances than Met allele in adult BD
- Met allele may negatively modulate cognitive function by interacting with childhood trauma
- Met carriers also showed greater abnormalities in cognitive cerebral regions

**The impact of BDNF Val66Met polymorphism on cognition in Bipolar Disorder: a review**

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**Abstract**

**BACKGROUND:** Converging lines of evidence suggest that Brain-Derived Neurotrophic Factor (BDNF) may play a central role in the pathogenesis of Bipolar Disorder (BD), thus representing a valid biomarker of the disease. A common genetic variation in the BDNF gene, the Val66Met, is associated with reduced maturation and secretion of BDNF and therefore it has been related to specific mood, cognitive and neuroanatomical alterations in BD. However, so far, only a handful of studies have investigated the association between Val66Met polymorphism and cognitive functioning in BD.

**METHODS**: We performed a bibliographic search on PUBMED of all genetic studies investigating Val66Met modulation on cognitive performances in BD subjects. The inclusion criteria were met by nine studies, including a total amount of 897 BD subjects and 803 healthy controls.

**RESULTS**: From the analysis of the existing literature emerged that a) Val allele in BD adults, but not in BD adolescents, was associated with better performances in selective cognitive domains including executive functions, verbal learning and memory; b) Met allele may negatively modulate the association between childhood trauma and performances in memory, verbal ability and verbal fluency tasks; c) Met allele may also negatively regulate structural abnormalities in cognitive cerebral structures; d) Val/Met carriers showed greater improvements in cognitive functions compared to Val/Val and Met/Met carriers.

**LIMITATIONS:** Few genetic studies exploring the impact of Val66Met on cognition in BD.

**CONCLUSIONS**: Val66Met polymorphism likely modulates cognitive functions in BD patients with complex gene-environment interactions and through potential modulations of cerebral structures. Further and larger genetic studies are required in order to detect association between BDNF polymorphism, BDNF levels, brain abnormalities and cognition in BD.

**Keywords:** BDNF; Single-nucleotide polymorphism; Cognition; Bipolar Disorder

**Main text**

The presence of cognitive impairments among subjects affected by Bipolar Disorder (BD) in comparison to healthy individuals has been attested by several studies (Mann-Wrobel et al., 2011), especially in executive functioning, attention, visual/motor processing speed, verbal memory and verbal learning (Torres et al., 2007; Van Der Werf-Eldering et al., 2011). Interestingly, neurocognitive deficits seem to represent a trait feature of BD since cognitive alterations have been detected during all phases of the illness (Cipriani et al., 2017; Martínez-Arán et al., 2000), even during euthymia (Bostock et al., 2017; Elias et al., 2017).

Notably, these cognitive impairments could be considered a potential endophenotype of BD with high hereditability (Sagar and Pattanayak, 2017) since unaffected first degree relatives also showed a certain degree of neurocognitive dysfunction (Miskowiak et al., 2017).

For this reason, in the last decade, several studies focused their attention on the role of specific genes in the pathogenesis of BD (Menezes et al., 2018). In this regard, in accordance to the neurotrophic hypothesis of mood disorders (Sigitova et al., 2017), the Brain Neurotrophic Derived Factor (BDNF) gene was one of the most widely investigated in BD in order to attest its role as a potential biomarker of disease (Fernandes et al., 2015). BDNF is a member of the neurotrophin family, involved in cerebral plasticity including neuronal genesis, maturation and maintenance (Gómez-Palacio-Schjetnan and Escobar, 2013). Besides playing an important role in neurodevelopmental processes (Lu et al., 2014), BDNF also mediates neuronal survival during adult life, thus strongly influencing cognitive functions (Kowiański et al., 2017). Moreover, BDNF is a protein encoded by a gene located on chromosome 11 region p13-14 (Cattaneo et al., 2016) and is highly expressed in both cerebral cortex and limbic areas where it participates to memory and learning functions (Cunha, 2010). Specifically, aberrant BDNF signaling has been associated not only with BD but also with other several neuropsychiatric conditions such as major depressive disorder, anxiety disorders, schizophrenia, neurodevelopmental and eating disorders (Autry and Monteggia, 2012).

Molecular genetic studies reported that BDNF activity could be impacted by a common single nucleotide polymorphism (SNP) of BDNF gene, the Val66Met, in which a valine is replaced by a methionine at codon 66 of pro-BDNF, a pro-peptide which exerts an important function in folding and secreting the mature BDNF (Mizui et al., 2017).

Val66Met polymorphism has been associated with both reduced transport of BNDF mRNA to dendrites and decreased packaging and secretion of BDNF in neuronal cells (Baj et al., 2013). Indeed, the extracellular level of BDNF strictly depends on its activity-dependent release, which has found to be corrupted in Met carriers (Egan

et al., 2003). This impairment has been related to the presence of the Met allele in the pro-BDNF amino acid sequence which could impact its ability to be packed from Golgi apparatus into secretory vesicles and to be afterwards released into synapses (Egan et al., 2003).

It is important to note that frequency of Val66Met polymorphism exhibits significant ethnic diversities. Indeed, a recent genetic study showed that the Met allele has different frequency across general population and ranged from 0,55% for Sub-Saharan African individuals to 19,9% and 43,6% for European and Asian subjects respectively (Petryshen et al., 2010). Specifically, the homozygous genotype Met/Met seems to be rare in European populations (4%) (Shimizu et al., 2004) and more frequent in Asiatic population (23,4%) (Pivac et al., 2009). Moreover, Caucasian population showed higher frequency of Val/Val (64,2%-65%) genotype compared to Val/Met (30,5%-32,4%), while Asian population seemed to have an opposite trend, with higher Val/Met genotype frequency (45,9%) than Val/Val (30,7%) (Pivac et al., 2009; Vulturar et al., 2016).

As regards the association between Val66Met and susceptibility for BD, evidences to date are far to be conclusive. Indeed, a recent meta-analysis detected a significant association between the BDNF Val66Met and BD in Europeans (Li et al., 2016), but not in Asians (Li et al., 2016; Wang et al., 2014), while previous analyses found no association in general population (González-Castro et al., 2015).

Moreover, Val66Met polymorphism has been also associated with both cerebral and cognitive abnormalities in BD. Indeed, while a recent review associated the Val66Met risk allele with the presence of reduced hippocampal volume and activity within BD patients (Pereira et al., 2017), a previous meta-analytic review found similar decreased volume in both BD Val or Met carriers, but not among healthy subjects with the same genotypes (Harrisberger et al., 2015). Interestingly, the presence of BDNF Val66Met polymorphism in BD patients has also been investigated in relation to its potential effect on cognitive functions (Post, 2007) and an initial evidence of association has been observed in BD (Bauer et al., 2014).

In this context, this review aims at summarizing the studies elucidating the correlation between Val66Met allele and cognitive deficits in BD patients. Specifically, we performed a bibliographic search in PubMed using "*Val66Met AND Cognitive AND Bipolar Disorder*" and "*Val66Met AND Cognition AND Bipolar Disorder*" and "*BDNF AND Cognitive AND Bipolar Disorder*". We selected published studies from January 2000 until February 2018. We excluded articles that assessed other genes from BDNF. We also excluded studies in psychiatric disorders others than BD and that did not include cognitive tasks. The inclusion criteria were met by nine studies, whose methods and results are summarized in Table 1.

Among these, seven studies reported a significant correlation between BDFN SNP rs6265 and several cognitive tasks in BD patients (Aas et al., 2013; Cao et al., 2016; Lee et al., 2016; Rybakowski et al., 2006, 2003; Savitz et al., 2007; Tramontina et al., 2009), one study found a correlation but only at a trend level (Matsuo et al., 2009), while only one did not find any significant results (Zeni et al., 2013).

The cognitive performances were assessed mainly with the *Wisconsin Card Sorting Test (WCST)* (Berg, 1948), a test used to measure prefrontal lobe function, especially strategic planning and goal-directed behavior. Other tests were the N-Back Test (N-BT) to evaluate visual working memory (Kirchner, 1958) and other scales such as the Wechsler Abbreviated Scale of Intelligence (WASI) to test verbal, non-verbal and general cognitive functions (Wechsler, 1999) and the revised version of the California Verbal Learning Test (CVLT) to estimate verbal learning and declarative memory (Delis et al., 2000).

The first study was performed in 2003 by Rybakowski and colleagues (2003) who assessed executive functions in a sample of BD I patients during their euthymic or mildly/moderately depressive phase. The authors reported that the Val/Val carriers showed significant better performances in all domains of WCST compared to Val/Met carriers.

Interestingly, the same research group partially replicated these preliminary findings in a larger group of euthymic or mildly depressed BD subjects compared to patients with Schizophrenia (SZK) and healthy controls (HC) (Rybakowski et al., 2006). In this case, Val/Met and Met/Met genotypes in BD was significantly associated with worse results in three out of five tasks of the WCST. Moreover, the authors also assessed working memory functioning reporting that significant negative correlations between Val66Met polymorphism and N-back test performances were observed only in SKZ, but not in BD (Rybakowski et al., 2006).

All together these findings could be explained by the different level of cognitive processing investigated by WCST and N-back test. Indeed, while WCST mainly measures higher stages of information processing, such as mental flexibility and strategic planning, the N-Back test evaluates more primary cognitive stages, which principally depend on visual and motor coordination (Rybakowski et al., 2006). In fact, in SKZ subjects, who are known to have more severe cognitive deficits than BD (Bora, 2016), the BDNF polymorphism may be more correlated to a disruption of primary information processing, which may not yet be occurred in BD patients (Rybakowski et al., 2006).

Interestingly, subsequent studies reported that BDNF Val66Met may also have a role in modulating the association between childhood trauma and cognitive impairments in psychotic BD patients (Aas et al., 2013; Savitz et al., 2007). Specifically, Savitz and colleagues (2007) found a negative effect of childhood sexual abuse

on Memory test functioning in MET carriers not only among euthymic BD subjects, but also in their affected and unaffected relatives. Interestingly, by excluding sexual abuse from the analysis, no differences in memory tasks were found between Val and Met genotypes (Savitz et al., 2007), a result in line with the previous study by Rybakowski et al. (2006). In accordance with previous evidences (Rybakowski et al., 2006, 2003), Met carriers showed significantly worse performance on executive functions assessed through the WCST (Savitz et al., 2007)

Furthermore, Aas and colleagues (2013) assessed a mixed sample of patients with a history of childhood trauma and a diagnosis of BD I, BD II, BD Nos (not otherwise specified), Major Depressive Disorder (MDD) with mood incongruent psychotic features, SKZ spectrum disorder and other Psychoses through a standardized neuropsychological test battery, including the CVLT and other specific cognitive tests. The authors showed that Met carriers with a higher exposition to childhood physical and emotional abuse demonstrated worse cognitive performances in verbal fluency, working memory and verbal abilities, compared to Val homozygote genotype, regardless of the diagnosis (Aas et al., 2013).

Additionally, in the same study (Aas et al., 2013), a subsample of psychotic BD, SKZ and MDD patients also underwent a cerebral MRI scan. Once again, the Met genotype subjects who were exposed to more sever sexual abuse during childhood showed decreased volumes of right/left lateral ventricles and right hippocampus (Aas et al., 2013), suggesting that the pathophysiological mechanism underlying cognitive deficits in Met carriers may be also related to volumetric alterations in specific cerebral regions. This is not surprising, since ventricle enlargement and hippocampal atrophy have been associated with cognitive impairments in language, visuospatial tasks, memory and attention (Blanken et al., 2015).

Additionally, Cao and colleagues (2016) explored the effect of BDNF polymorphism on cognitive functions and cerebral volumes in a cohort of BD I and MDD patients, whether euthymic or depressed, and HC. The authors found that, within Met carriers, BD I patients had decreased hippocampal volumes compared to MDD subjects and HC (Cao et al., 2016), in partial accordance with a previous study (Aas et al., 2013). As above-mentioned, the hippocampus has a main role in cognitive functions especially in memory and spatial cognition (Schiller et al., 2015). Indeed, BD I patients carrying the Met allele also showed significant reduced memory performances measured through a revised version of CVLT, compared to both MDD subjects and HC (Cao et al., 2016).

Similarly, Matsuo et al. (2009) found a trend of association between Met genotype and the poorest memory performances among BD subjects. Additionally, a significant correlation between Met genotype and decreased anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) was stronger in BD than HC, while a gray matter volume reduction in left hippocampus was detected only in Met HC, but not in BD Met carriers

(Matsuo et al., 2009). Therefore, the Val66Met genotype among BD subjects may negatively modulate memory performances through the volumetric reduction of various cerebral areas such as hippocampus (Aas et al., 2013; Cao et al., 2016) or the ACC and the DLPFC (Matsuo et al., 2009). Indeed, also the ACC and the DLPFC detain a role in cognitive functions by promoting memory processes for remote recall and relational information respectively (Blumenfeld et al., 2011; Weible, 2013).

In contrast with all these findings, two studies reported no significant correlations between the Met genotype and cognitive dysfunctions in BD (Lee et al., 2016; Tramontina et al., 2009). Specifically, Tramontina and colleagues (2009) found that BD patients, homozygote for Val allele, performed more non-perseverative errors in WCST than Met carriers. The authors firstly attributed this surprising finding to the small sample size employed and to the presence of more synergic polymorphisms interactions in BD, which may influence the expression of specific phenotypes, such as cognitive deficits (Tramontina et al., 2009). Furthermore, the authors also suggested that non-perseverative errors may not reflect primary executive impairments, but rather a non-specific attentional dysfunction (Tramontina et al., 2009).

Moreover, Lee and colleagues (2016) performed a longitudinal investigation in a larger cohort of drug-naïve BD-I and BD-II patients. Surprisingly, they observed a correlation between plasma BDNF levels and executive functions improvements, especially in BD-I with Val/Met genotype. Indeed, while Val/Val carriers may produce higher amount of plasma BDNF, Met/Met carriers yield lower level. Therefore, it seems that a moderate BDNF plasma level, which has been associated with the Val/Met genotype (Lee et al., 2016), may better modulate cognitive improvements in BD (Govindarajan et al., 2006). However, the correlation did not survive correction for multiple comparisons (Lee et al., 2016).

Finally, only one study focused on the association between Val66Met and cognitive function in BD children and adolescents aged from 5 to 17 years old (Zeni et al., 2013). Surprisingly, the authors did not detect any significant differences in WCST results between any of BDNF genotypes (Zeni et al., 2013). The authors speculated that BDNF polymorphism may not influence yet cognitive functions in younger BD subjects (Zeni et al., 2013) given to the underway neurodevelopment of frontolimbic circuits (Yurgelun-Todd, 2007).

In conclusion, this literature review suggests a role of BDNF Val66Met polymorphism in modulating cognitive domains in BD. Indeed, we may hypothesize that the Val homozygote allele is associated with better cognitive performances in BD, especially concerning executive functions (Rybakowski et al., 2003), while Met carriers seem to worsen the cognitive performance not only in executive functions (Rybakowski et al., 2006) but also in verbal learning and memory (Cao et al., 2016; Matsuo et al., 2009) tasks. Moreover, some evidences also suggest that in adult BD patients, Met alleles may negatively regulate the association between childhood

trauma and memory (Savitz et al., 2007), verbal abilities, working memory and verbal fluency (Aas et al., 2013) performances. Additionally, it has also been suggested that they may modulate structural brain abnormalities in specific areas which are known to have a role in cognitive processes, such as hippocampus (Aas et al., 2013; Cao et al., 2016), ACC and DLPFC (Matsuo et al., 2009).

In contrast, the BDNF polymorphism seem to have no effect on neuropsychological functioning in BD adolescents, ultimately suggesting that the genetic modulation of cognition may occur only at later stages (Zeni et al., 2013). Moreover, moderate augmented secretion of BDNF, which has been related to the intermediate Val/Met genotypes, could be associated to greater enhancements of cognitive functions compared to Val/Val and Met/Met genotypes (Lee et al., 2016). Indeed, since pharmacological therapies with antidepressants and mood stabilizers may exert their beneficial effects by inducing expression of neurotrophins, such as BDNF (Grande et al., 2010), an increase response to these drugs has been documented in Val/Met carriers with mood disorders (Rybakowski et al., 2007; Yan et al., 2014).

However, all these findings should be considered in light of few important limitations. First, the above mentioned studies employed small samples and therefore their results require further replications. Second, in this review, we should also consider other potential confounding factors derived from the clinical characteristics of the patients recruited by the original studies, such as different psychopathological symptoms, duration of illness, educational level and psychotropic medications during cognitive performances. Indeed, all these clinical features are known to strongly influence cognitive functioning (Burdick et al., 2015). Finally, the potential effect of ethnic stratification on BDNF polymorphism among the studies must be also considered (Tramontina et al., 2009).

As regards BDNF polymorphism, further studies in BD are required in order to disclose its impact on cognition in BD, being aware that the genetic modulation of cognitive functions is more likely to involve interactions between several genes. Indeed, it is important to point out that the analysis of a single polymorphism represents a simplistic genetic model of a complex neuropsychological process. Therefore, it is necessary to perform longitudinal studies investigating the effect of several gene polymorphisms on cognitive function.

**Contributors**

GMM wrote the first draft of the manuscript, along with ML, GD and AP. JCS and PB contributed to revise the manuscript. All authors agreed with the final content of the manuscript.

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No conflicts of interest.

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**Table 1.** Summary of the studies described in the review.

| AUTHORS | SAMPLE | METHODOLOGY | SNPs | COGNITIVE TASK | OTHER METHODS | OTHER VARIABLES | SYMPTOMS DURING TASK | SNPs FREQUENCY IN BD | THERAPY | RESULTS IN BD GROUP |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rybakowski et al. 2003** | 54 BD-I (18 M, 36 F) | PCR as desribed by Neves-Pereira et al. | Val66 Met | WCST | /// | /// | 22 euthimic 32 midly or moderate depressed (less than 18 points on HDRS) | Val/Val = 44 Val/Met = 9 Met/Met = 1 (excluded from analysis) | 39 L 15 AD | The performance in all domains of WCST was significantly better in Val/Val compared with Val/Met |
| **Rybakowski et al. 2006** | 111 BD (37 M, 74 F) 129 SKZ (66 M, 63 F) 160 HC (66 M, 94 F) | PCR as desribed by Neves-Pereira et al. | Val66 Met | WCST N-BT | /// | /// | BD euthimic or mildly depressed | Val/Val = 81 Val/Met = 27 (include in same group) Met/Met = 3 (include in same group) | NIA | Val/Met + Met/Met performed significantly worse than Val/Val in WCST-P, WCST-CC and WCST %CONC domains. No relationship between BDNF polymorphism and N-back test. |
| **Savitz et al. 2007** | 48 BP-I 16 BP-II 44 recurrent MDD 34 single DE 65 HC 18 OD | Standard PCR methods | Val66 Met | WCST, Rey Auditory-Verbal Learning Test, Stroop Colour Word Test, Rey Comple | /// | Childhood trauma | Euthimic or relatively euthimic | Val/Val = 132 Val/Met = 72 Met/Met = 21 | NIA | Met allele was associated with a negative effect of sexual abuse on Memory performance, whereas |

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| | | | | x Figure Test,<br><br>Controlled Oral Word Association Test, Digit Span | | | | | | the Val allele has no effect. In the absence of sexual abuse, all genotypes have, on average, the same Memory score. (No longer significant interaction between BDNF and abuse after Bonferroni correction for multiple testing) |
| **Matsuo et al. 2009** | 34 BD-I<br>8 BD-II<br>42 HC | Taqman 50, with a Peltier Thermal Cycler and the ABI 7900 Sequence Detection System | Val66 Met | CVLT-II | Cerebral 1.5 MRI scan | /// | 12 depressed<br>4 manic<br>4 mixed<br>22 euthymic | Val/Val = 53<br>Val/Met = 31 | 13 unmedicated<br>22 MS<br>21 AD<br>12 AA | Val/Met BD patients performed worse on the CVLT compared to the Val/Val BD patients, but no significance was found. Val/Met BD patients showed reduced ACC and DLPC volumes |

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| | | | | | | | | | | than Val/Val BD carriers. |
| **Tramontina et al. 2009** | 64 BD-I (14 M, 50 F) | 5' nuclease Taqman allelic discrimination on ABI 7000 Sequence Detection System | Val66 Met | WCST | /// | /// | No patients with manic symptoms (YMRS > 8) some patients presented a HAM-D > 8 | Val/Val = 53 Met carriers = 29 | 59 MS 22 AA 20 TA 15 AD | Non-perseverative errors was significantly higher among patients with the Val/Val genotype. No association between BNDF genotype frequency and other WCST |
| **Aas et al. 2013** | 81 BD-I 17 BD-II 8 BD NOS 8 MDD with mood incongruent psychotic features) 99 SKZ spectrum disorder 36 other psychosis 476 HC | Affymetrix Human SNP Array 6.0 | Val66 Met | CVLT, Letter–Number Sequencing, Digit Span, Color Word Interference Test, Verbal Fluency Test, Block Design task, Matrix Reasoning from the WASI, Similarities and the Vocabul | Cerebral 1.5 T MRI scan only for a subsample | Childhood trauma | History of psychosis | Val/Val = 85 Met carriers = 29 | 113 TA + AA 22 AD 61 TA + AA + AD 53 no current medications | Significant negative correlations for Met carriers between childhood abuse and cognitive score (verbal abilities, working memory and executive function/verbal fluency), compared to Val/Val carriers. Significant negative correlations for Met carriers |

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| | | | | ary from the WASI | | | | | | between childhood abuse and smaller hippocampus and larger ventricles. |
| **Zeni et al. 2013** | 37 BD-I 7 BD-II 9 BD NOS (33 M, 20 F) (aged 5-17) | PCR as desribed by Neves-Pereira et al. | Val66 Met | WCST | /// | /// | Patients usually perform neuropsychological testing while presenting symptoms. Symptom rates or mood states did not differ between groups. | Val/Val = 40 Val/Met = 12 Met/Met = 1 | 16 MS or AA | No significant differences in WCST results between Val/Val and Val/Met + Met/Met |
| **Lee et al. 2016** | 92 BD I 263 BD II (183 M/172 F) | Modified protocol by Neves-Pereira et al. | Val66 Met | WCST CPT | BDNF plasma level | /// | HAM-D ≥ 18 | Val/Val = 80 Val/Met = 183 Met/Met = 92 | Drug naïve | Significant correlation between improvements in WCST scores and increases in plasma BDNF only in BP-I Val/Met genotypes (not surviving correction for multiple comparison) |
| **Cao et al. 2016** | 48 BD I ( 16 M, 32 F) 60 HC (21 M, | Modified protocol Gentra Pure gene blood kit | Val66 Met | Revised version of the CVLT WASI | Cerebral 1.5 T MRI scan | /// | 16 euthimic, 20 depressed at time of testing | /// | 2 L 5 AD 5 AC 1 AA 3 B | BDNF val/val patients showed similar |

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| | 39 F) | | | WTAR | | | | | 18 two or more medications 10 Drug naïve | memory performance compared with HC. BDNF met carrier BD patients showed worse memory performance compared to HC and MDD. Within BDNF met carriers, BD-I patients displayed smaller hippocampus volumes compared to HC (p=0.01) and MDD; |

**LEGEND:** AA = atypical antipsychotics; AC = anticonvulsants; ACC = Anterior cingulate cortex; AD = antidepressants; B = benzodiazepine; BD = Bipolar Disorder; BD NOS = bipolar disorder non otherwise specified; BD-I = bipolar disorder type 1; BD-II = bipolar disorder type 2; BDNF: Brain-derived neurotrophic factor; CPT = Conners' Continuous Performance Test; CVLT = California Verbal Learning Test; DE = depressive episode; DLPFC = dorsolateral prefrontal cortex; F = female; HAM-D: Hamilton Depression Rating Scale; HC = healthy controls; L = lithium; M = male; MMD = major depressive disorder; MS = mood stabilyzers; N-BT = n-back test; NIA: No Information Available; OD: Other Diagnosis; SKZ = schizophrenia; TA = typical antipsychotics; WASI = Wechsler Abbreviated Scale of Intelligence; WCST = Wisconsin Card Sorting Test; WTAR = Wechsler Test of Adult Reading; YMRS: Young Mania Rating Scale.