The characteristic of cognitive impairments in patients with bipolar II depression and its association with N-acetyl aspartate of the prefrontal white matter

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Background: Cognitive deficit is acknowledged as a core feature of clinical manifestations of bipolar disorder (BD). However, the underlying mechanism of cognitive impairment in bipolar II depression has remained uncertain. We aim to determine the association of cognitive impairments with biochemical metabolism using proton magnetic resonance spectroscopy (^{1}H-MRS) and a battery of neuropsychological testing.

Methods: The current study was designed to assess four cognitive domains in a sample of 110 patients with bipolar II depression and 110 healthy controls, using a battery of 6 cognitive tests, including the Digit Symbol Substitution Test (DSST), Wisconsin Cart Sorting Test (WCST), Trail Making Test Part B (TMT-B), Digit Span Test (DST), TMT-part A (TMT-A) and Verbal Fluency Test (VFT). Metabolite levels were obtained in the following brain regions of interest: bilateral prefrontal white matter (PWM), bilateral anterior cingulate cortex (ACC), bilateral lenticular nucleus (LN), and bilateral thalamus. N-acetyl aspartate (NAA)/creatine (Cr) and choline-containing compounds (Cho)/Cr ratios are analyzed.

Results: Patients with bipolar II depression performed significantly worse on DSST (score), TMT (completion time), DSB (score), and VFT (valid word number) when compared with healthy controls. In the bilateral PWM, NAA/Cr ratios in the PWM were significantly reduced (bilaterally) than those in healthy controls. Correlation analysis was conducted with data from patients with bipolar II depression, we found that the NAA/Cr ratio of the left PWM was positively correlated with the score of DS and DSB, and the NAA/Cr ratio of the right PWM was negatively correlated with the completion time of TMT-B.

Conclusions: Our findings suggested that psychomotor speed, executive function, working memory, and verbal fluency are impaired in patients with BD II depression. Hypoactivity NAA/Cr in bilateral PWM may be associated with BD II depression's pathophysiology and results in cognitive dysfunction.

Keywords: Bipolar disorder (BD); cognitive function; proton magnetic resonance spectroscopy (^{1}H-MRS); N-acetyl aspartate (NAA); prefrontal white matter (PWM)

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Introduction

Bipolar disorder (BD) is considered one of the most common and most disabling chronic mood disorders, a distinguished type I and type II for a manic or hypomanic episode. Patients with BD experiencing depression episodes result in more severe psychosocial impairment compared to BD type I (1). Meanwhile, bipolar II depression and major depressive disorder may share similar cognitive domain deficits and brain function alterations (2-4), resulting in a similar clinical profile, making the differential diagnosis a challenge.

Cognitive impairment is considered a core feature of BD. Typically, processing speed, executive function, attention, and working memory are characteristic markers for BD (5,6). Cognitive dysfunction was reported as a prodromal marker that existed before mood symptoms and occurred in euthymic episodes and healthy relatives of BD (7-9). However, BD type I and BD type II are pathophysiological different, which is still controversial. Prior studies have noted cognitive deficits in bipolar II depression (4,10) and their first-degree relatives (11), suggesting that cognitive deficits may improve performance as a promising candidate endophenotype of bipolar II depression (12). However, the neural mechanism of cognitive dysfunction in bipolar II depression is still unknown.

Neuroimaging can supply insight into the possible pathogenesis of cognitive deficits. For example, the prefrontal lobe, anterior cingulate cortex (ACC), and thalamus are involved in working memory, attention, and executive function in BD patients (13-18). Proton magnetic resonance spectroscopy (^{1}H-MRS) is a technique that can be performed to measure brain metabolic abnormalities in vivo, including N-acetyl aspartate (NAA), choline-containing compounds (Cho), and creatine (Cr). Although there are a growing number of studies examining the metabolic levels and their alteration after treatment in patients with bipolar II depression (3,8,19-21), limited studies investigated the association of cognitive impairments with brain biochemistry in bipolar II depression. In previous studies about bipolar II depression, the NAA/Cr ratio in the left lenticular nucleus (LN) and thalamus was found to be correlated with executive dysfunction (8,10), and the altered biochemical of ACC has a close relationship with attention and executive function (15,16). However, earlier studies only focused on a specific part of cognitive function with a small sample size of patients. Future comprehensive research of biochemical metabolism and its related-cognitive deficit with a large sample is needed.

We examined four cognitive domains (psychomotor speed, executive function, attention/working memory, and verbal fluency) and biochemical metabolites in prefrontal white matter (PWM), ACC, thalamus, and LN of non-late-life and treatment-naïve patients with bipolar II depression. We are interested in the relationship between cognitive impairments and abnormal biochemical metabolism in bipolar II depression. We hypothesized that the deficits of four cognitive domains and abnormal biochemical metabolism could be found in patients with bipolar II depression, and cognitive deficits may correlate with the abnormal biochemistry. Furthermore, cognitive deficits may correlate with the PWM, ACC, LN, and thalamus' abnormal biochemistry.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7098).

Methods

Participants and clinical assessment

From July 2013 to September 2017, 110 out- or in-patients with bipolar II disorder during a depressive episode were recruited from the psychiatry department, First Affiliated Hospital of Jinan University, Guangzhou, China. We limited the age range of all participants to 18–45 years. In this study, BD type II is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorder IV (DSM-IV). The diagnostic assessment was performed using the Structured Clinical Interview for DSM-IV (SCID) Patient Edition and has never taken medication. Two experienced clinical psychiatrists (Y.J. and S.Z) performed a clinical diagnosis. The current study used 30% of the data reported in our previous studies (4,8,10).

The clinical state of each patient was assessed by using the Young Mania Rating Scale (YMRS) and 24-item Hamilton Depression Rating Scale (24-item HDRS) during the two days before the cognitive assessment and magnetic resonance imaging (MRI) scan. The inclusive criteria were a 24-item HDRS total score >21 and a YMRS total score <7 for BD II depression patients. Exclusion criteria: any other current psychiatric disorder, pregnancy and any contraindication to MRI scanning, alcohol or other substance dependence or abuse (current or past), the presence of a current (or history) organic medical illness, brain injury, or another neurological disease, current (or history) use of any form treatment, including psychotherapy, psychotropic medication or electroconvulsive therapy.

One hundred ten healthy controls matched by age, sex, and education level were recruited from the local community by advertisements. The healthy controls were screened using the SCID non-patient edition. The inclusive criteria were healthy volunteers, and a 24-item HDRS total score <7 and a YMRS total score <7. Exclusion criteria included any active or history of neurological and psychiatric illness, a family history of psychiatric illness in first-degree relatives.

All participants were Chinese Han people and right-handed. All participants were asked to sign a written informed consent following a full written and verbal explanation of the study. The study was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (No. 2016/030), China, and conducted following the Declaration of Helsinki (as revised in 2013).

Neurocognitive assessment

Each participant was examined individually by the same neuropsychologist, trained to administer and score the battery of tests that span four cognitive domains.

Psychomotor speed

Digit Symbol Substitution Test (DSST) measures psychomotor speed, a subtest of the Wechsler Adult Intelligence Scale-Revised by China (WAIS-RC). DSST was performed to calculate the raw score.

Executive function

The Wisconsin Cart Sorting Test (WCST) was performed to calculate the number of total errors (TE) and the number of categories completed (CC).

Trail Making Test-part B (TMT-B) was performed to calculate the completion time.

Attention/working memory

Digit Span Test (DST) was performed by all participants to assess the attention/working memory, including Digit Span Forwards (DSF) and Digit Span Backwards (DSB). Correct responses on the DSF and DSB were calculated.

TMT-part A (TMT-A) was performed to calculate the completion time.

Verbal fluency

Verbal Fluency Test (VFT) was performed to calculate the valid words. Participants were given 60sec to name as many animals as possible.

MRI data acquisition and preprocessing

All participants received MRI and ^{1}H-MRS scanning within two days of initial contact. All MRI data were obtained on a General Electric (GE) Discovery MR750 3.0T system equipped with an 8-channel phased-array head coil. To confirm the absence of brain signals and structural abnormalities, including brain tumors, vascular diseases, and other brain diseases, routine axial T_1-weighted fluid attenuation inversion recovery (T_1 FLAIR) and fast spin echo T_2-weighted MR images were obtained. The following parameters were used to acquire MRI: T_1 FLAIR [repetition time (TR)/echo-time (TE) =1,750/24 ms, numbers of excitation (NEX) = 1,240×240 mm field of view (FOV), 320×256 matrix, 5 mm slice thickness, 1.5 mm gap, acquisition time =1 min and 22 s], fast spin echo T_2-weighted MR images (TR/TE =8,400/145 ms, NEX =1,240×240 mm FOV, 256×256 matrix, 5 mm slice thickness, 1.5 mm gap, acquisition time = 2 min and 15 s).

We used the 2D multivoxel technique to obtain the spectrum. The anatomic localization was acquired using axial T2-weighted MR images with the following parameters: TR/TE =3,500/102 ms, NEX = 2,240×240 mm FOV, 256×256 matrices, 5 mm slice thickness with no gap, acquisition time = 1min and 45 s. The volume of interest (VOI), including 49 nominal voxels (7.5×7.5×10 mm^3), was positioned in the PWM, ACC, LN, and thalamus (*Figure 1A,B,C,D*). ^{1}H-MRS with a single section of 2D multi-voxel was performed using a point resolved spectroscopy sequence (PRESS) with chemically selective suppression (CHESS) water suppression. The acquisition parameters were as follows: TR/TE =1,000/144 ms, NEX =1,180×180 mm FOV, 240×240 matrix, 10 mm slice thickness, 7.5×7.5×10 mm^3 nominal voxel size. The total acquisition time for ^{1}H-MRS was 10 min and 56 s.

Then, saturation bands were placed outside the VOI to minimize lipid contamination from the scalp. We conduct automatic pre-scanning before each spectroscopic scan for achieving an optimal full width at half-maximum of 10 Hz. As a quality standard, we exclude spectra with a line width better than 10 Hz or water suppression above 98%.

Voxel placements for spectroscopy were performed by an experienced radiologist, who was blinded to each participant's diagnosis. The GE Advantage Workstation AW4.2_07 FuncTool analyzed the spectral dataset. NAA/Cr and Cho/Cr ratios were used for the analysis of brain

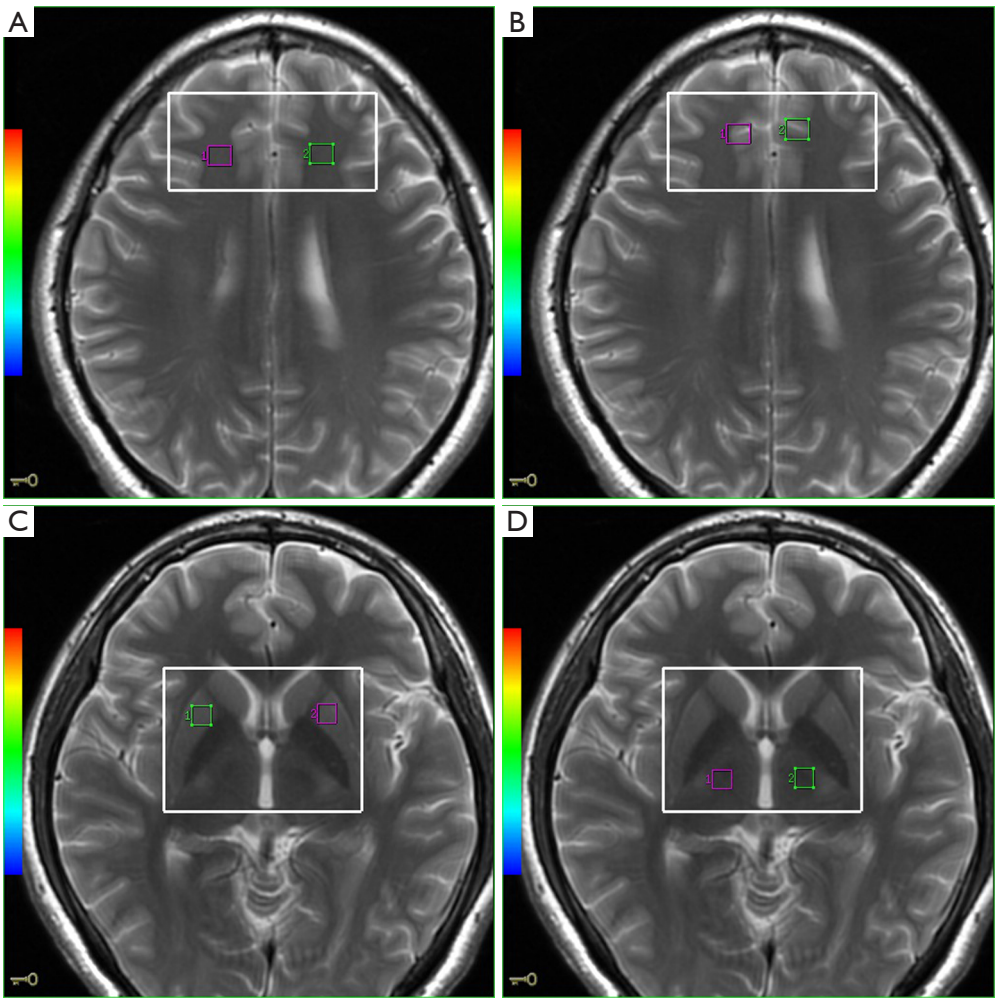

Figure 1 Magnetic resonance image (MRI) scan of a healthy control subject showing the location of magnetic resonance spectroscopy (MRS) of the volume of interest (VOI) placed in the left and right prefrontal white matter (PWM) (A), anterior cingulate cortex (ACC) (B), lenticular nucleus (LN) (C) and thalamus (D). The large white boxes represent the VOIs for MRS acquisition, and two small boxes depict the individual VOIs of bilateral PWM, ACC, LN, and thalamus for spectral analysis. For each subject, the ROI size was identical in the left and right brain regions using the mirror symmetry tools from the FuncTool software.

biochemical changes.

Statistical analysis

SPSS 21.0 software conducted all data analyses (SPSS, Chicago, IL, USA). All variables were evaluated for normality of distribution by mean of the Kolmogorov-Smirnov goodness-of-fit test. Clinical, demographic data (except gender), cognitive variables, and metabolite ratios between the two groups were performed by independent two-sample *t*-test (normal variable) and Mann-Whitney U test (skewed variables). Sex distribution in the group was compared using the Chi-squared test. All the statistical tests were two-tailed, and a P value of less than 0.05 was considered statistically significant. Additionally, we applied a Bonferroni correction to adjust α for multiple comparisons; the adjusted critical p value would be the significance level (α=0.05) divided by the total number of comparisons per type of analysis. And P<0.00208 (0.05/24) was considered significant.

Effect sizes (ESs) (Cohen's D) were computed to weigh the degree of cognitive deficits. The computed formula: (mean value of patient group – mean value of controls)/ standard deviation of controls. Cognitive impairment was

Table 1 Demographics and clinical data of bipolar II depression and healthy control

	Bipolar II depression patients	Healthy controls	χ^2 or t	P value
Number of subjects	110	110	–	–
Age (year), mean ± SD [range]	23.94±7.84 [18–45]	22.93±7.71 [18–45]	–0.962	0.337[a]
Gender (male/female)	53/57	49/61	1.217	0.544[b]
Education (year)	12.68±2.68	13.95±2.12	2.134	0.155[a]
Age of onset (year)	19.90±8.13	–	–	–
Duration of illness (month)	49.15±53.46	–	–	–
Number of episodes	2.81±1.29	–	–	–
Number of hypomanic episodes	1.21±0.55	–	–	–
Number of depressive episodes	1.59±0.93	–	–	–
Psychotic features	21	–	–	–
Family history	28	–	–	–
24-item HDRS score	24.56±7.74	3.91±3.65	–24.278	0.000[a*]
YMRS score	3.91±6.65	0.27±0.74	24.883	0.000[a*]

[a], independent sample *t*-test; [b], χ^2 test; *, P<0.05 significant. BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

classified as mild deficit (0.2< ES <0.5), moderate deficit (0.5< ES <0.8), and severe deficit (ES >0.8).

The multiple linear regression was conducted with NAA/Cr, Cho/Cr ratios as the independent variables, and cognitive variables serving as the dependent variables in patients with bipolar II depression. Using the forward likelihood ratio, the probability of F entering ≤ is 0.100, and the probability of F removing ≥ is 0.150. The significance level of the final model maintenance variable was ≤0.05.

Results

Sociodemographic and clinical data

Sociodemographic and clinical data of all participants are summarized in *Table 1*. No significant differences were observed in age, gender, and education level between the two groups.

Group differences of cognitive function

Figure 2 shows the comparison of cognitive function indices between the two groups. However, with the healthy control group, patients with bipolar II depression showed significantly worse on TMT-B (completion time) (*Figure 2B*), DSB (score) (*Figure 2C*), DSST (score) (*Figure 2E*) and VFT (valid word number) (*Figure 2F*) (*z*=–6.149, P=0.000; *z*=–3.930, P=0.000; *z*=–3.074, P=0.002; t=–4.379, P=0.000). According to the ESs, the DSST (score) (ES =–0.98) exhibited severe deficits, the TMT-B (completion time) (ES =0.79) and VFT (valid words number) (ES =–0.66) exhibited moderate deficits, and the DSB (score) (ES =–0.45) exhibited mild deficit. No significant differences of WCST (CC and TE number) (*Figure 2A*), DSF (score) (*Figure 2C*) and TMT-A (completion time) (*Figure 2D*) were found in the two groups.

Group differences of biochemical metabolite ratios

Figures 3 and 4 show the comparisons of biochemical metabolite ratios (NAA/Cr and Cho/Cr) in the four cerebral VOIs between patients with bipolar II depression and healthy controls. Compared to healthy controls, patients with bipolar II depression showed significantly lower NAA/Cr in the bilateral PWM (*Figure 3*) (t=–7.532, P=0.000; t=–7.132, P=0.000), but did not differ significantly in Cho/Cr ratios of bilateral PWM (*Figure 3A*). We found there were no significant differences in the other neuro-metabolite ratios of the left and right ACC, LN, and thalamus between the two groups (*Figure 4*).

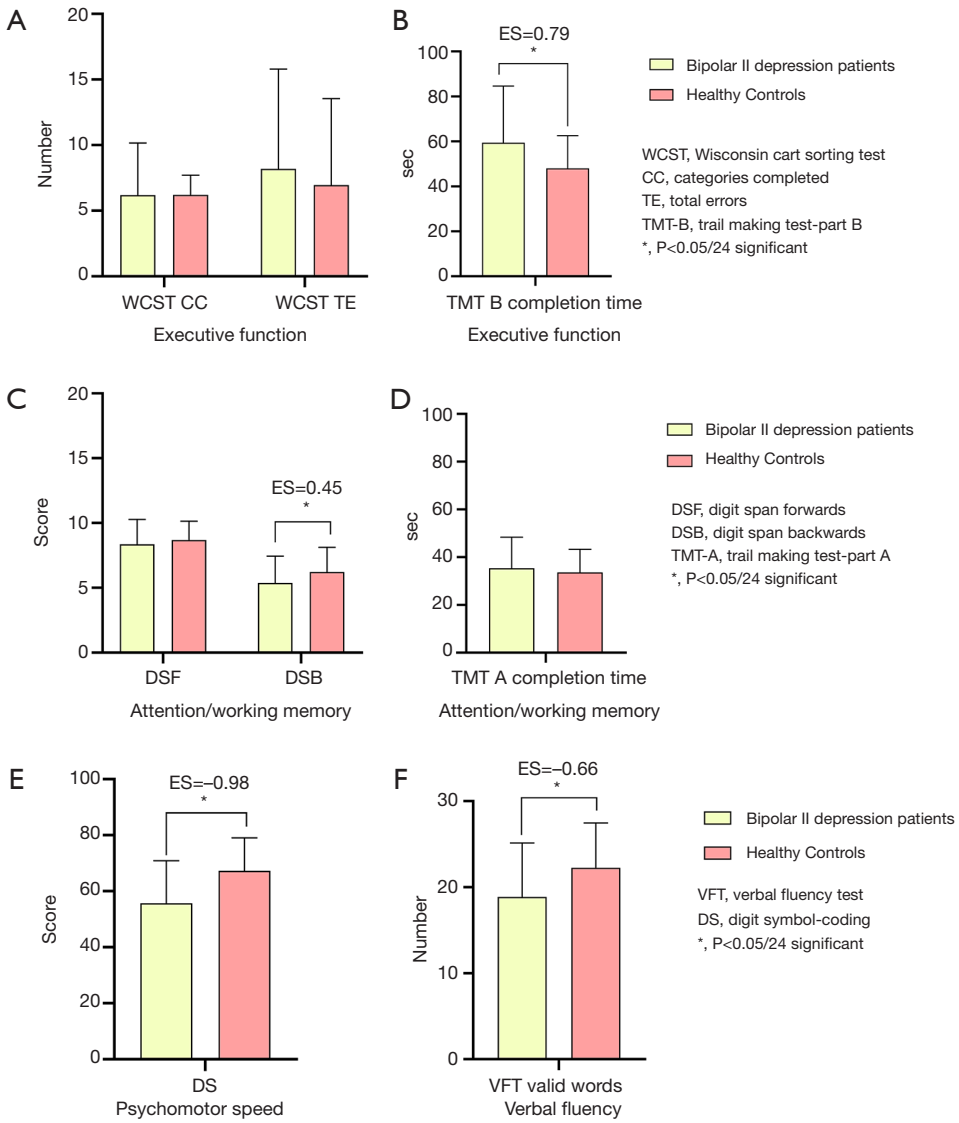

Figure 2 Comparisons of cognitive function indices between bipolar II depression and healthy control. (A) and (B) show the results of executive function performance, (C) and (D) show the results of attention and working memory, (E) shows the result of psychomotor speed, and (F) shows the result of verbal fluency. Only the number of VFT valid words was compared using the Mann-Whitney U test; other cognitive variables were compared using an independent two-sample *t*-test. WCST, Wisconsin cart sorting test; CC, categories completed; TE, total errors; TMT-B, trail making test-part B; DSF, digit span forwards; DSB, digit span backwards; TMT-A, trail making test-part A; VFT, verbal fluency test; DS, digit symbol-coding. *, P<0.05/24 significant.

Correlations between abnormal ^{1}H-MRI indices and cognitive indices

Table 2 shows the linear regression analyses of abnormal cognitive function indices and biochemical metabolite ratios in bipolar II depression patients. NAA/Crratio of the left PWM was positively correlated with the score of DS (t=3.095, P=0.003) and DSB (t=3.040, P=0.003), and NAA/Crratio of the right PWM was negatively correlated with the completion time of TMT-B (t=–2.968, P=0.004).

Discussion

The present comprehensive research aims to identify the characteristics of cognitive deficit and neuro-metabolism alterations in a large patient sample with bipolar II

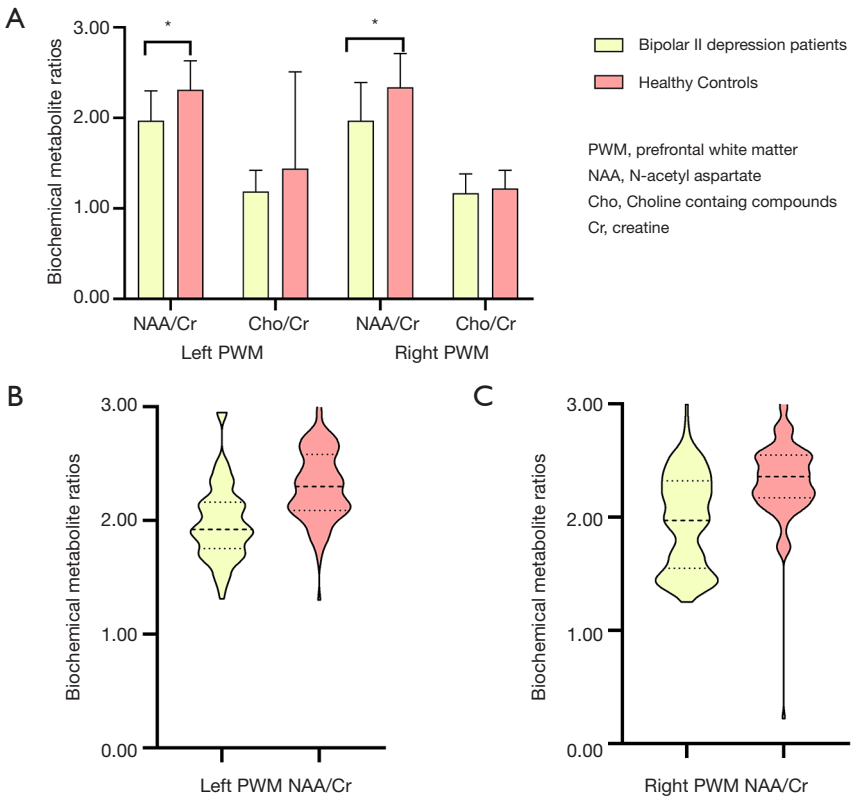

Figure 3 Comparisons of biochemical metabolite ratios in the prefrontal white matter (PWM) between bipolar II depression and healthy control. (A) shows the results of N-acetyl aspartate (NAA)/creatine (Cr), choline-containing compounds (Cho)/Cr ratios of the bilateral PWM. (B) and (C) show the results of the NAA/Cr ratio of the left and right PWM. Only the Cho/Cr ratio of the left PWM was compared by using the Mann-Whitney U test; other biochemical metabolite ratios were compared by using an independent two-sample *t*-test. *, P<0.05/24 significant.

depression who have never taken medications. We also explore associations between targeted metabolite levels and cognitive performance. The main findings for bipolar II depression in the current study are the following: (I) worse performance on DSST, TMT-B, DSB, and VFT; (II) decreased NAA/Cr in the bilateral PWM; (III) a positive correlation between abnormal NAA/Cr of the left PWM and the score of DSST and DSB, negative correlation between abnormal NAA/Cr of the right PWM, and the completion time of TMT-B.

Neuro-metabolic abnormalities within the frontal lobe in BD have been implicated in many imaging studies. A lower NAA/Cr ratio was found in the bilateral PWM of bipolar II depression when compared with healthy controls, in agreement with previous studies (3,8). However, normal NAA concentration in the frontal lobe was reported in another study (22). The decreased NAA/Cr ratio is considered to reflect dysfunctional neurons, decreased number, the density of neurons, or mitochondrial function impairment, and increased NAA has been described as improved neuronal function and viability with the response to therapy (23). According to our results, bipolar II depression patients may have a neuronal loss or mitochondrial function impairment in the bilateral PWM. Lower NAA/Cr ratios of bilateral PWM are related to poorer cognitive functions in patients with bipolar II depression, suggesting that PWM's abnormal neuro-metabolism may involve more subtle illness-specific cognitive deficits.

The severe deficit in psychomotor speed was found in bipolar II depression, positively correlated with decreased NAA/Cr of the left PWM, suggesting that the left PWM dysfunction was positively correlated with a deficit in psychomotor speed. Psychomotor speed deficits may

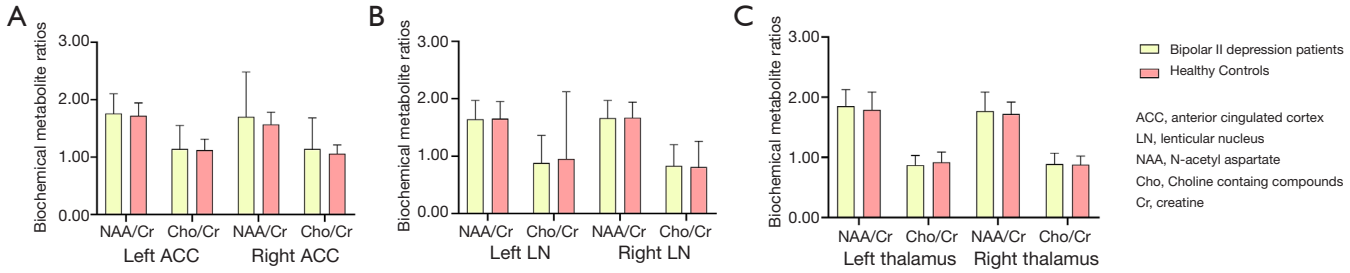

Figure 4 Comparisons of biochemical metabolite ratios in the anterior cingulated cortex (ACC), lenticular nucleus (LN), and thalamus between bipolar II depression and healthy control. (A) shows the results of N-acetyl aspartate (NAA)/creatine (Cr), choline-containing compounds (Cho)/Cr ratios of the bilateral ACC, (B) shows the result of NAA/Cr, Cho/Cr ratios of the bilateral LN, and (C) show the result of NAA/Cr, Cho/Cr ratios of the bilateral thalamus. NAA/Cr, Cho/Cr ratios of the right ACC, and Cho/Cr ratios of the left and right LN were compared by using the Mann-Whitney U test; other biochemical metabolite ratios were compared by using an independent two-sample *t*-test.

Table 2 The linear regression analyses between abnormal cognitive function indices and biochemical metabolite ratios in bipolar II depression patients (n=110)

	Unstandardized coefficients		Standardized coefficients Beta	*t*	P value	R^2	R_{adj}^2
	B	Std. Error					
Score of DSST							
Constant	38.557	7.701		5.007	0.000		
NAA/Cr ratio of left PWM	10.836	3.501	0.293	3.095	0.003*	0.086	0.077
TMT-B completion time (s)							
Constant	76.946	9.099		8.457	0.000		
NAA/Cr ratio of right PWM	–12.091	4.073	–0.281	–2.968	0.004*	0.079	0.070
Score of DSB							
Constant	2.723	1.102		2.472	0.015		
NAA/Cr ratio of left PWM	1.524	0.501	0.288	3.040	0.003*	0.083	0.074

*, P<0.05 significant. BD, bipolar disorder; DSST, digit symbol substitution test; TMT-B, trail making test-part B; DSB, digit span backward; PWM, prefrontal white matter; NAA, N-acetyl aspartate; Cr, creatine.

be a potential endophenotypic index for BD since it has been found in BD patients and their first-degree relatives (24,25). Moreover, psychomotor speed was an underlying variable that implicitly affected visual memory, performance, working memory, verbal fluency, and cognitive flexibility (26). Slower psychomotor speed was considered related to the smaller gray matter volume in the bilateral prefrontal region. However, better psychomotor speed was generally considered related to larger gray matter volumes in the bilateral prefrontal lobe, bilaterally hippocampus, and left superior temporal gyrus in normal controls (26). Psychomotor speed was associated with degree centrality abnormalities of the temporal lobe in early BD patients (27). Furthermore, a positive relationship between the inferior temporal surface area and psychomotor speed was reported in BD (28).

DSB was used to measure working memory, and DSF and TMT-A were used to measure attention. A mild deficit of working memory was found in bipolar II depression, consistent with the previous study (29). Working memory's efficient functioning depends on inhibitory processes, limiting the access of information into working memory, and updating the contents of working memory by removing irrelevant information. Healthy relatives of BD performed less accurately and required additional time in working memory tasks (30). Additionally, decreased working

memory also existed in BD patients at the remission phase, suggesting that working memory deficit was not only a phenomenon of mood but a consequence of enduring brain dysfunction (31). In this study, we found evidence that working memory deficit in bipolar II depression could be accounted for by the generalized NAA/Cr ratio decrease of the left PWM. Working memory is one central function of the prefrontal cortex. Previous studies have identified aberrant activity in the prefrontal cortex during working memory performance (30,32,33). Specifically, one study reported that working memory-related dorsolateral prefrontal cortex (DLPFC) activity in remitted patients with BD was modulated by the catechol-O-methyltransferase (COMT) Val158Met genotype (34). Greater ACC activation during working memory tasks is found in bipolar II depression, which may distinguish between unipolar and bipolar depression (35). However, no evidence of a relationship between working memory and ACC biochemical metabolism was detected in our study. An explanation for this might be that we investigated the biochemical metabolism at a resting state rather than during a working memory task.

A moderate deficit of executive function was found in bipolar II depression in the current study, which also found in their unaffected first-degree relatives (6,36,37). Executive dysfunction may occur in the early stages of bipolar II depression and may remain during remission (8). Positive relationships between executive function and NAA levels of the LN and ACC were reported in bipolar II depression (8,38), and a negative relationship between increased volume in the right caudate and poorer performance of executive function was reported in BD type I patients at remission phase (37). In this study, a negative relationship between executive dysfunction and abnormal NAA/Crratio in the right PWM was found in bipolar II depression. According to our results, abnormal NAA/Crratio in the right PWM may be a crucial factor underlying executive function impairments in bipolar II depression.

Verbal fluency is a higher executive function, a series of cognitive processes necessary to control and regulate lower-level processing and goal-directed behavior. In this study, a moderate deficit of verbal fluency was found in bipolar II depression. Significant improvements in verbal fluency were found in patients with BD after cognitive therapy (39). Increased activation in the ACC during the verbal fluency task has been reported in patients with BD (40). Hypoactivation of the prefrontal cortex and hyperactivation of the bilateral precuneus were also found during verbal fluency tasks in euthymic patients with BD (41,42). The pattern of response to verbal fluency is highly diagnostic for schizophrenia and distinct from BD (40). Another important finding was that verbal fluency deficits were associated with the reduced white matter integrity in the left inferior frontal-occipital fasciculus and the forceps minor in BD (43). Verbal fluency may be related to the prefrontal lobe function (44), presumed to be correlated with the PWM's abnormal biochemistry. However, no relationship between verbal fluency and neuro-metabolism of the PWM was found in bipolar II depression in this study.

The association between cognitive deficits and brain biochemistry in bipolar II depression was investigated in this study. The findings of this study are promising, but some limitations must be noted. Firstly, only acute episode patients with bipolar II depression were recruited in this current study, with no euthymic episode or manic/hypomanic episode patients and their first-degree relatives, it is still not clear whether the association between cognitive dysfunction and neuro-metabolism was specific to the depression episode or shared by all episodes of BD. Secondly, all patients carried on with follow-up for two years after inclusion in this study. If patients had presented a manic episode during the observation period, he would exclude from the analysis, but some patients still do not show manic or hypomanic episodes. Thirdly, we investigated the biochemical metabolism in resting state rather than cognitive functional tasks, including working memory tasks and verbal fluency tasks. However, the neuro-biochemical changes during cognitive tasks associated with bipolar II depression have yet to be explored. Fourthly, a semi-quantitative analysis was performed in this study, using Cr as an internal reference. However, the accuracy of Cr as a standard is controversial. Subsequent studies with absolute measures could revalidate this finding. Finally, previous studies have reported the association between cognitive function and gene polymorphism (45) or gene expression in BD (46,47). Further studies are needed to investigate whether the dysfunction is related to bipolar II depression's genetic risk.

Conclusions

Our study's main findings are partially consistent with earlier studies showing cognitive impairments in bipolar II depression. There are positive correlations between abnormal NAA/Cr of the left PWM and the score of DSST and DSB and a negative correlation between abnormal

NAA/Crof the right PWM and the completion time of TMT-B. Our findings suggested that psychomotor speed, executive function, working memory, and verbal fluency are impaired in BD II depression patients. Also, hypoactivity NAA/Cr in bilateral PWM may be associated with the pathophysiology of bipolar II depression and results in cognitive dysfunction. These findings may improve our understanding of cognitive impairments, neural pathogenesis, and supply a marker for the early identification of bipolar II depression.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7098). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All participants were Chinese Han people and right-handed. All participants were asked to sign a written informed consent following a full written and verbal explanation of the study. The study was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (No. 2016/030), China, and conducted following the Declaration of Helsinki (as revised in 2013).

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