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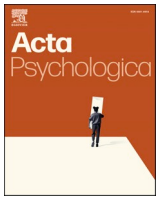

Verbal learning, working memory, and attention/vigilance may be candidate phenotypes of bipolar II depression in Chinese Han nationality

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ABSTRACT

Objectives: Bipolar II depression (BD-II) is a subtype of bipolar disorder with recurrent depressive, manic, and frequent depressive episodes as the main clinical manifestations. This study aimed to compare the cognitive function of patients with BD-II with those of healthy siblings and controls to explore the internal phenotype of BD-II in the field of cognitive function.

Methods: 66 BD-II patients, 58 healthy siblings, and 55 healthy controls were assessed with the Trail Making Test (TMT), Digit Symbol Coding Test (DSCT), Category Fluency, Hopkins Verbal Learning Test-Revised (HVLTR), Brief Visuospatial Memory Test-Revised (BVMT-R), Wechsler Memory Scale 3rd ed. Spatial Span Subtest (WMS-III SS), Neuropsychological Assessment Battery Mazes (NABM), Continuous Performance Test, and Identical Pairs (CPT-IP).

Results: Patients with BD-II showed cognitive deficits in visual learning, reasoning and problem solving, verbal learning, attention/vigilance, working memory, and speed of processing. Healthy siblings showed cognitive deficits in reasoning and problem solving, verbal learning, attention/vigilance, working memory, and speed of processing. Substantial differences were observed among the three groups in reasoning and problem solving.

Conclusions: Verbal learning, working memory, and attention/vigilance may be potential endophenotypes that can be used to identify BD-II among Han Chinese in the early stage.

1. Introduction

Bipolar disorder (BD) is a mood disorder characterized by periodic fluctuations in thinking, emotion, and behavior; BD includes manic and depressive episodes that vary in frequency, degree, and duration (Miller et al., 2014). According to the degree of mania, BD can be divided into bipolar I and II. Bipolar I disorder refers to severe depression, mania, or mixed episodes; bipolar II disorder refers to severe depression and manic episodes with no history of mania or mixed episodes. BD reportedly affects more than 1% of the global population and is one of the leading causes of disability in young people (Grande et al., 2016). Some surveys have shown that the suicide rate of patients with BD is 20–30 times higher than that of the healthy population. Ultimately, 6%–7% of patients with BD choose suicide (Plans et al., 2019). A study analyzed patients with self-injury and suicidal behavior in mental hospitals. In addition, It found that the most common clinical diagnosis was affective disorder, accounting for 41.8% (Tanimoto et al., 2018), and that patients with bipolar disorder had the highest rate of suicidal ideation up to 60%, 52% of whom had at least one self-injury behavior (Chen et al., 2014; Weintraub et al., 2017). BD usually begins at around age 20; the earlier the onset is, the worse the prognosis will be (Carvalho et al., 2020). For many people with bipolar II disorder, the first cause of concern is usually depression, which lasts much longer over the course of the illness than manic episodes. In The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), the depressive episode of patients with bipolar II disorder has the same diagnostic criteria as Major Depressive Disorder; thus, BD might be misdiagnosed as depression (Chen et al., 2019; Phillips & Kupfer, 2013). Approximately 40% of patients with BD have been misdiagnosed as unipolar depression, with an average misdiagnosis time ranging from5.7 to 7.5 years, and misdiagnosed patients often misuse antidepressants (Tomasik et al., 2021). Therefore, early and correct identification has a great

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significance to the prognosis of patients with BD.

Cognitive impairment is among the core symptoms of BD and is an important feature of BD's development course that is usually separate from emotional symptoms (Solé et al., 2017). Impairment of cognitive function affects social function. Having stable emotional symptoms does not mean that patients' functions have returned to normal. Thus, the cognitive function of patients with BD needs to be the focus of research. An "endophenotype" refers to an internal and intermediate phenotype that fills the gap between distal genes and disease expression (Bearden et al., 2020). It provides a means to identify and measure the "upstream" characteristics of invisible clinical manifestations and the "downstream" biological consequences of distal genes (Zarringhalam et al., 2018). Endophenotypes are included in but are not limited to cognitive neuroscience, neuropsychology, neurobiology, and biochemistry (Sizoo et al., 2015; Yardeni et al., 2021). Endophenotypic studies have been used in BD research; cognitive impairment may be one of the endophenotypes of BD (Guglielmo et al., 2021).

Studies on the cognitive function of BD are imperfect. They are limited by samples and test methods. Thus, the conclusions of previous research are not consistent and focus on the direct comparative study between patients with BD and healthy controls (HC). We supposed that the cognitive impairment related to BD may exist in patients with bipolar II depression (BD-II) and their healthy siblings (HS) among Han Chinese. Therefore, in the present study, patients with BD-II, their HS and HC were included. Recognized cognitive testing tools were used to explore the characteristics of cognitive impairment of BD-II and to explore its possibility as an intra-phenotype of BD-II.

2. Material and methods

2.1. Participants

BD-II group: patients with BD-II were treated in the Department of Psychosomatic Medicine, The First Affiliated Hospital of ** University from January 2019 to December 2020. The admission criteria were as follows: (1) met the diagnostic criteria of DSM-5 BD; (2) 17–55 years old; (3) 24 items of Hamilton Depression scale (HAMD24) $\geq$ 20; (4) Young Mania Rating Scale (YMRS) $<$ 6; (5) primary school education; (6) Han nationality, right-handed; and (7) voluntarily participated and signed the informed consent form. The exclusion criteria were as follows: (1) nervous system disease or brain trauma; (2) immune system disease; (3) obsessive-compulsive disorder; (4) schizophrenia; and (5) intellectual disability. All the patients in the group were diagnosed by two psychiatrists, including one psychiatrist with the professional title of deputy high school or above. The patients were diagnosed again and screened for inclusion into the group through a relevant psychological evaluation. A total of 66 cases were enrolled in this group.

Healthy sibling group: siblings of BD group. The inclusion criteria were as follows: (1) physically healthy and no history of mental illness; (2) 17–55 years old; (3) HAMD24 $<$ 8; (4) YMRS $<$6; (5) Han nationality, right-handed; (6) primary school education or above; and (7) voluntarily participated and signed the informed consent form. The exclusion criteria were as follows: (1) nervous system diseases or brain trauma; (2) immune system diseases; and (3) substance abuse. A total of 58 cases were enrolled in this group.

Healthy control group: healthy people recruited by means of leaflets and Internet introduction from January 2019 to December 2020. The admission criteria were as follows: (1) physically healthy with no history of mental illness; (2) 17–55 years old; (3) HAMD24 $<$ 8; (4) YMRS score $<$ 6; (5) Han nationality, right-handed; (6) primary school education or above; and (7) voluntarily participated and signed the informed consent form. Exclusion criteria were as follows: (1) personal and familial history of mental illness; (2) nervous system disease or brain trauma; (3) immune system disease; and (4) substance abuse. A total of 55 cases were enrolled in this group.

To rule out the effects of drugs on cognitive function, the study included all first-episode and untreated patients. All the subjects were tested by the same trained psychology graduate student from 9:00 am to 11:00 am daily in a quiet and comfortable psychological evaluation room. This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University, and all the subjects signed the informed consent form.

2.2. Measures

The functions of all subjects in the cognitive areas of speed of processing, verbal learning, visual learning, reasoning and problem solving, working memory, and attention/vigilance were evaluated using the following tests. (1) Speed of processing: a. Trail Making Test (TMT), in which numbers were connected in order from small to large; b. Digit Symbol Coding Test (DSCT), the symbol of each number pair was written within a specified period of time; c. Category Fluency, the subject was asked to say as many animal names as possible within the specified time. (2) Verbal learning: Hopkins Verbal Learning Test-Revised (HVLTR), in which the subjects were shown 12 words, after which they were immediately asked to recall as many words as possible. The total number of words recalled correctly was recorded. (3) Visual learning: Brief Visuospatial Memory Test-Revised (BVMT-R), in which the subjects were shown six geometric patterns for 10 s, after which they were required to draw visual patterns on a blank piece of paper. (4) Reasoning and problem solving: Neuropsychological Assessment Battery Mazes (NABM), in which the subjects were required to complete the maze test within a specified time and were scored according to the requirements. (5) Working memory: Wechsler Memory Scale 3rd ed. Spatial Span Subtest (WMS-III SS), in which the subject's non-verbal working memory was assessed by testing the ability to remember the location of modules tapped by a series of operators. (6) Attention/vigilance: Continuous Performance Test and Identical Pairs (CPT-IP); in the continuous operation test of the same pairing, when a series of multiple numbers (2, 3, and 4 digits) were presented on the computer for a short time, two stimuli in the same line were pressed simultaneously. The reaction time and accuracy were recorded. The original scores obtained in all cognitive tests were converted into T scores through the Chinese norm formula.

2.3. Statistical analysis

The data were statistically analyzed by SPSS26.0 software, and all indicators (clinical data and cognitive function test) were tested for homogeneity of Levene variance. One-way ANOVA was used to test the T scores of the three groups. According to the homogeneity of variance, Fisher minimum significant difference or Tamhane test was selected for post-comparison. Sensitivity analysis showed that the results of the analysis using the original and T scores were the same.

3. Results

3.1. Comparison of general data and clinical characteristics of the subjects

Table 1 shows that no significant differences were found in sex, age, and years of education among the three groups ($P > 0.05$). The score comparison, effect value, and confidence interval of the three groups in six cognitive areas are shown in Tables 2 and 3. Fig. 1 directly shows the cognitive situation of the three groups.

Note−BD-II: patients with Bipolar II depression; HS: healthy siblings; HC: healthy controls; BVMT-R: Brief Visuospatial Memory Test-Revised; NABM: Neuropsychological Assessment Battery Mazes; HVLTR: Hopkins Verbal Learning Test-Revised; CPT-IP: Continuous Performance Test-Identical Pairs; WMS-III SS: Wechsler Memory Scale 3rd ed. Spatial Span Subtest; DSCT: Digit Symbol Coding Test; TMT: Trail Making Test.

Table 1
Demographic characteristics for each group.

	BD-II (N = 66)	HS (N = 58)	HC (N = 55)	P-value	F/χ^2
	Mean ± SD	Mean ± SD	Mean ± SD		
Years of education (years)	11.9 ± 2.3	11.6 ± 2.2	11.6 ± 2.3	0.355	0.702
Age (years)	24.5 ± 6.3	24.0.2 ± 6.4	25.5 ± 7.8	0.564	0.575
Gender	(n, %)	(n, %)	(n, %)	0.212	3.101
Male	29 (43.9)	33 (56.9)	23 (41.8)		
Female	37 (56.1)	25 (43.1)	32 (58.2)		

Note−BD-II: patients with Bipolar II depression; HS: healthy siblings; HC: healthy controls.

Table 2
Scores for each item.

Items	BD-II (N = 66)	HS (N = 58)	HC (N = 55)	BD-II vs HS	BD-II vs HC	HS vs HC
	Mean ± SD	Mean ± SD	Mean ± SD	P-value	P-value	P-value
Visual Learning	46.8 ± 7.3	50.0 ± 7.6	52.5 ± 8.4	0.022	<0.001	0.089
BVMTR	46.8 ± 7.3	50.0 ± 7.6	52.5 ± 8.4	0.022	<0.001	0.089
Reasoning and Problem Solving	43.5 ± 8.6	46.4 ± 8.3	60.9 ± 8.1	0.050	<0.001	<0.001
NABM	43.2 ± 8.5	46.4 ± 8.3	60.9 ± 8.1	0.030	<0.001	<0.001
Verbal Learning	42.4 ± 8.8	45.2 ± 8.1	51.4 ± 8.8	0.067	<0.001	<0.001
HVLTR	42.4 ± 8.8	45.2 ± 8.1	51.3 ± 8.8	0.069	<0.001	<0.001
Attention/ Vigilance	33.8 ± 10.8	35.1 ± 10.0	43.4 ± 9.7	0.476	<0.001	<0.001
CPT-IP	34.0 ± 11.0	35.1 ± 10.0	43.4 ± 9.7	0.548	<0.001	<0.001
Working Memory	34.8 ± 9.7	37.9 ± 10.3	48.0 ± 7.9	0.076	<0.001	<0.001
WMS-III SS	34.8 ± 9.7	37.9 ± 10.3	48.0 ± 7.9	0.072	<0.001	<0.001
Speed of Processing	41.2 ± 9.7	46.6 ± 7.5	50.4 ± 12.2	0.002	<0.001	0.047
Category Fluency	48.8 ± 9.8	50.7 ± 8.8	53.9 ± 9.4	0.268	0.004	0.073
DSCT	41.0 ± 12.1	46.7 ± 11.9	47.7 ± 14.7	0.014	0.005	0.702
TMT	39.8 ± 8.2	44.4 ± 9.5	49.5 ± 13.8	0.011	<0.001	0.078

3.2. T-scores for each item

Table 2 shows that no significant difference was found in the scores for verbal learning, working memory, and attention/vigilance between the BD-II and the HS groups, but significant differences were found in other cognitive areas. The BD-II group scores were significantly lower than those of the HS group. In all six areas of measurement, namely, verbal learning, visual learning, speed of processing, attention/vigilance, working memory, and reasoning and problem solving, the BD-II group scores were lower than those of the HC group ($p < 0.05$). No significant difference was found between the HS and HC groups, except in visual learning. In all other cognitive areas, the scores of the HS group were lower than those of the HC group ($p < 0.05$). Therefore, according to the definition of endophenotype (Ozcan et al., 2016), verbal learning, working memory, and attention/vigilance were candidate phenotypes of BD-II.

4. Discussion

In this study, the scores of patients with BD-II were significantly lower than those of HC in multiple neuropsycho-logical tests, which suggested that BD-II affects patients' cognitive function. Cognitive deficits exist in multiple domains, such as verbal learning, visual learning, speed of processing, attention/vigilance, working memory, and reasoning and problem solving, which was consistent with previous studies on the cognitive function in patients with BD (Cusi et al., 2010; Ha et al., 2012). We also found neurocognitive deficits in the HS of patients with BD-II. The HS showed poor performance in tests of reasoning and problem solving, verbal learning, attention/vigilance, working memory, and speed of processing, in which areas of cognitive impairment detected in patients with BD-II were included. The patients who participated in the study had their first attack or did not take any medication, thereby ruling out the potential effect of drugs on the patient's cognitive function. The cognitive domain score of the selected HC group was not significantly different from that of the Chinese standard sample. The results of our study were verified by comparing with the standard sample (Zhang et al., 2019).

The CPT-IP score of the BD-II group was lower than that of the HC group, which may be due to the negative effect of bipolar depression on attention. The CPT-IP score of first-degree relatives was lower than that of HC group, which may indicate that first-degree relatives have pathogenic potential. The working memory, verbal learning, and visual learning scores of the BD-II group were significantly lower than those of the HC group, which confirmed that BD-II could impair an individual's memory. However, the scores of the HS group were different from those of the BD-II group, which showed that no significant difference was found in the scores of verbal learning and working memory between the HS and BD-II groups. However, the visual learning scores of the HS group were higher than those of the BD-II group, which confirmed that different physiological and working mechanisms exist among visual, language, and working memories (Shipstead et al., 2014). The TMT and DSCT BD-II group scores were significantly lower than those of the HS and HC groups. No significant difference was found in the TMT and DSCT scores between the HS and HC groups. In terms of Category Fluency, the score of the BD-II group was lower than that of the HC group, whereas the score of the HS group was not significantly different from those of the BD-II and HC groups. The three tests of TMT, DSCT, and Category Fluency constituted the field of processing speed. Significant differences existed in the processing speed of the three groups.

Significant differences existed in reasoning and problem solving among the three groups. A certain degree of cognitive impairment was confirmed in the BD-II and HS groups, and the scores for each cognitive domain in the HS group were between those of the BD-II and the HC groups. Compared with HC, some differences existed in the cognitive function among the relatives of patients with BD-II. Variations in genetics, growth environment, and educational conditions may be the reasons for these differences. Significant differences were found in verbal learning, working memory, and attention/vigilance between the BD-II and the HC groups. The scores of the HS group in the above three areas were intermediate to those of the BD-II and the HC groups. The differences were not significant when compared with the BD-II group but were significant when compared with the HC group. Therefore, verbal learning, working memory, and attention/vigilance are possible endophenotypes of BD-II.

Cognitive impairment and brain structural abnormalities have been found in patients with BD (Bourne et al., 2013; Van Rheenen et al., 2020). The present study found that the cognitive impairment of patients with BD-II can be detected through their verbal learning, visual learning, processing speed, attention/vigilance, working memory, and reasoning and problem solving. This finding was consistent with the results of previous studies on cognitive function in patients with BD (Burdick et al., 2011; Liu et al., 2019). Patients with BD-II show impairment in verbal learning function and working memory (Ha et al.,

Table 3
ESs and 95% confidence intervals (CIs) of neurocognitive test variables between subgroups.

Items	BD-II vs HS			BD-II vs HC			HS vs HC		
	ES	SE	95%CI	ES	SE	95%CI	ES	SE	95%CI
Visual Learning	−0.43	1.40	(−5.98,-0.48)	−0.72	1.42	(−8.51,-2.93)	−0.31	1.46	(−5.37,-0.38)
BVMTR	−0.43	1.40	(−5.98,-0.48)	−0.72	1.42	(−8.51,-2.93)	−0.31	1.46	(−5.37,-0.38)
Reasoning and Problem Solving	−0.34	1.51	(−5.96,0.00)	−2.08	1.53	(−20.48,-14.44)	−1.77	1.58	(−17.59,-11.36)
NABM	−0.38	1.50	(−6.25,-0.32)	−2.13	1.52	(−20.77,-14.75)	−1.77	1.31	(−17.58,-11.38)
Verbal Learning	−0.33	1.54	(−5.89,0.20)	−1.02	1.57	(−12.07,-5.90)	−0.73	1.61	(−9.32,-2.96)
HVLTR	−0.33	1.54	(−5.88,0.22)	−1.02	1.57	(−12.01,-5.82)	−0.72	1.61	(−9.27,-2.90)
Attention/Vigilance	−0.12	1.84	(−4.94,2.31)	−0.94	1.86	(−13.34,-5.99)	−0.84	1.92	(−12.14,-4.56)
CPT-IP	−0.10	1.85	(−4.77,2.54)	−0.91	1.88	(−13.18,-5.76)	−0.84	1.94	(−12.18,-4.52)
Working Memory	−0.31	1.69	(−6.35,0.32)	−1.49	1.71	(−16.50,-9.73)	−1.10	1.77	(−13.59,-6.61)
WMS-III SS	−0.31	1.69	(−6.39,0.28)	−1.49	1.71	(−16.54,-9.78)	−1.10	1.77	(−13.59,-6.61)
Speed of Processing	−0.62	1.79	(−9.01,-1.96)	−0.83	1.81	(−12.81,-5.65)	−0.38	1.87	(−7.43,-0.06)
Category Fluency	−0.20	1.69	(−5.21,1.46)	−0.53	1.71	(−8.44,-1.68)	−0.35	1.77	(−6.67,0.30)
DSCT	−0.47	2.32	(−10.35,-1.19)	−0.50	2.35	(−11.35,-2.06)	−0.07	2.43	(−5.72,3.86)
TMT	−0.52	1.61	(−8.65,-0.87)	−0.85	2.11	(−14.94,-4.64)	−0.43	2.23	(−10.46,0.40)

Note−BD-II: patients with Bipolar II depression; HS: healthy siblings; HC: healthy controls; CI: confidence intervals; ESs: effect sizes (Cohen's d); SE: standard error; BVMT-R: Brief Visuospatial Memory Test-Revised; NABM: Neuropsychological Assessment Battery Mazes; HVLTR: Hopkins Verbal Learning Test-Revised; CPT-IP: Continuous Performance Test-Identical Pairs; WMS-III SS: Wechsler Memory Scale 3rd ed. Spatial Span Subtest; DSCT: Digit Symbol Coding Test; TMT: Trail Making Test.

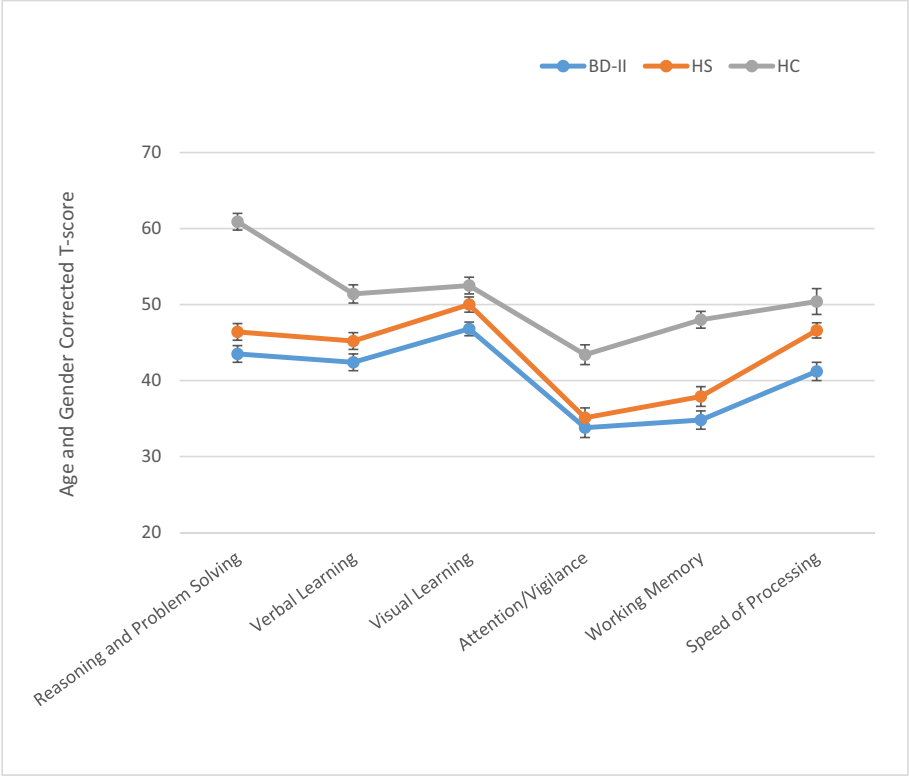

Fig. 1. Note−BD-II: patients with Bipolar II depression; HS: healthy siblings; HC: healthy controls; the line segment on each node represents the range of standard error.

2012; Pirkola et al., 2005), suggesting that the ability to process language information is impaired in patients with depression. The brain has a reduced capacity for information storage, refreshing, and processing. Patients with bipolar disorder have impaired working memory, which may be related to glutamate neurotransmission disorder in the brain. Some studies have shown that glutamate neurotransmission disorder seems to be the neurobiological basis for cognitive flexibility. Magnetic resonance studies have shown that glutamate in the prefrontal cortex of patients with depression decreases before taking antidepressants, and the activation and increase of glutamate may enhance individuals' working memory (De Berardis et al., 2018). In addition, glutamate neurotransmission disorder may also be related to suicidal cognitive bias in patients with affective disorder, so ketamine can be effective in reducing their suicidal ideation (Orsolini et al., 2020). Laura et al. (Rodríguez et al., 2012) found that patients with BD I and II showed worse performance in most memory measures, including semantic memory, recall, and recognition, compared with normal controls. The verbal and working memory scores in the HS group were lower than those in the HC group. This finding was consistent with the results of Ferrier and Bora (Bora et al., 2008; Nicol Ferrier et al., 2004). A review of young BD patients revealed significant attention deficit during the first episode (Bo et al., 2017). The abovementioned studies supported

our results very well.

Some studies investigated the relationship between functional network integrity and cognitive impairment. Compared with healthy people, the overall efficiency of cingulate cortical network in BD was significantly lower (Sheffield et al., 2017). In working memory, memory coding, and attention persistence tests, the activity of the lateral and dorsal cognitive control areas of the prefrontal lobe is abnormal in patients with BD, whereas the activity of the dorsal prefrontal lobe determines the level of cognitive function. The decrease of dorsal activity of the prefrontal lobe is related to cognitive function impairment (Kessing & Miskowiak, 2018). In addition, peripheral inflammation may also be related to cognitive impairment in patients with BD; c-reactive protein (CRP), interleukin (IL)-1 receptor antagonist, IL-6, and tumor necrosis factor-α (TNF- α) and their receptors may play a role in the development of cognitive impairment in BD (Misiak et al., 2018).

This study had several limitations. First, although the cognitive field of measurement was comprehensive, limitations in the evaluation of cognitive function existed in some dimensions. The maze subtest examined the field of reasoning and problem solving, which was an executive function dimension. In the future, we can add other cognitive assessment tools, such as Stroop, or more comprehensively evaluate the specific dimensions of cognitive impairment in patients with BD. Second, the results of the cognitive test were affected by the state of the test and the surrounding environment. Third, this study did not explore the relationship between BD severity and cognitive function. In addition, the interpretation of the results may be limited to the sampling range and size of this study. Finally, this study is a cross-sectional study. Therefore, longitudinal follow-up observation was not performed. In the future, image genetic analysis can be added to comprehensively analyze the characteristics and mechanisms of cognitive impairment in BD from the perspective of cognitive function interaction of gene "brain function" to achieve accurate cognitive intervention therapy and to promote the overall functional rehabilitation of patients.

5. Conclusions

In conclusion, this study demonstrates that patients with BD-II not taking the medicine, generally have cognitive impairment as well as some in their HS. It turned out that verbal learning, working memory, and attention may be potential endophenotypes to identify BD-II among Han Chinese in the early stage.

CRediT authorship contribution statement

Zhizhong Hu: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. Maorong Hu: Writing - original draft, Writing - review & editing, Data curation, Formal analysis, Funding acquisition, Investigation. Xin Yuan: Data curation, Formal analysis, Investigation. Huijuan Yu: Data curation, Formal analysis, Investigation. Yanyan Zhang: Data curation, Formal analysis, Investigation. Zihang Lu: Investigation, Methodology, Visualization. Jinyuan Chen: Data curation, Formal analysis, Project administration, Resources.

Declaration of competing interest

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