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Cognitive Dysfunction in Euthymic Adolescents with Bipolar Disorder: Is There Any Deficit in Their Visual Memory?

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Abstract

Background: Various cognitive dysfunctions are reported in children and adolescents with bipolar disorder (BD) in manic, depressed, and euthymic phases. Among these deficits, the findings related to visual memory are more inconsistent.
Objective: Given the limitations and inconsistencies, we aimed to compare visual memory in the euthymic phase of BD with a typically developing group.
Methods: Thirty 11 to 18 year old inpatients with bipolar manic episode were compared with 30 normal youths regarding their visual memory. The Kiddie schedule for affective disorders and Schizophrenia-Present and lifetime were used to confirm the diagnosis and comorbidities. Conners Parent Rating Scale (CPRS), Young Mania Rating Scale (YMRS), Children Depression Inventory (CDI), and Raven's Progressive Matrices (RPM) were conducted to evaluate attention-deficit hyperactivity, manic, depressed symptoms, and IQ respectively. Paired Associates Learning (PAL) and Pattern Recognition Memory (PRM) taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were used to assess visual memory for both groups. Adolescents with BD performed these tasks when entered the euthymic phase of the disorder.
Results: The 2 groups did not have any differences in their age, gender, and IQ. Most PAL and PRM scores were poorer (nonsignificant) in the BD group compared with the TD participants. The PRM mean correct latency score was higher in the BD individuals with ADHD compared with both the non-ADHD and the Typically Developing (TD) adolescents (P = 0.01 and P = 0.02, respectively).
Conclusions: Youths with euthymic phase of BD suffer from some visual memory problems. These deficits may be related to comorbid attention deficit hyperactivity disorder.

Keywords: Adolescent, Bipolar, Euthymia, Visual Memory

1. Background

Neurocognitive functioning is an important field in bipolar disorder (BD). A systematic review by Malhi, Ivanovski, and Szekeres (2004) revealed that the principal impaired cognitive domains in adults with BD were executive functioning, attention, and memory (1). Cross sectional comparisons of different mood phases against healthy individuals delineate the overall BD state-specific deficits, however, the commonality found in different BD phases suggests a sharing neurocognitive mechanism compromise which can be seen as a persistent neuropsychological deficit in euthymia. A large body of literature suggests that cognitive dysfunction can be ascribed as an endophenotype in adults suffering from BD and their relatives (2). Among the cognitive deficits found, verbal memory and learning as well as working memory were proposed as the most suitable endophenotypes for BD.

There are also studies on neurocognitive profile of children and adolescents with BD. Frias, Palma, and Farriols (2014) conducted a systematic review in pediatric BD and found impairment in verbal and visual-spatial memory (3), processing speed, working memory, and social cognition. As reported in adults with BD, some studies conducted on children and adolescents have found that cognitive function deficits are trait-like problems in youths with BD and continue even in the euthymic phase of the disorder. For example, Pavuluri, Henry and Devineni (2006) found impairments in attention (4), executive functioning, working memory, and verbal learning domains in pediatric BD compared with healthy condition, regardless of disorder status or pharmacologic intervention. Schenkel et al. (2012) indicated that verbal learning and memory deficits were more common in youths with BD-I and BD-II compared

with healthy individuals and could be considered as cognitive endophenotypes for pediatric BD (5).

Among the various impaired cognitive functions in children and adolescents with BD including verbal memory, attention, executive functioning, and working memory, the findings related to visual memory are more inconsistent. Lera-Miguel, Andres-Perpina, and Fatjo-Vilas, (2014) tracked neurocognitive changes in a group of treated adolescents with BD for 2 years (6). Visual memory as well as verbal memory, executive functioning, and working memory impairment were stable in patients versus healthy controls. Julia J. Rucklidge (2006) studied neuropsychological functioning of adolescents with BD, compared to a control group, and found the working memory domain as the only dysfunction that discriminated the 2 groups (7).

2. Objective

Given the limitation and inconsistencies regarding the visual memory deficit as a trait-dependent marker in youths with BD, we aimed at comparing visual memory in a group of inpatient adolescents with BD in the euthymic phase of the disorder with a typically developing group.

3. Materials and Methods

3.1. Participants and Procedure

In a case control study, a consecutive sampling method was used to enroll the clinical group during 2013 and 2014. The clinical participants consisted of thirty 11 to 18 year old adolescents (9 males and 21 females) admitted to the child and adolescent ward at Roozbeh psychiatry hospital. They were all diagnosed by board-certified child and adolescent psychiatrists as having BD, acute manic or mixed episode according to the DSM-IV-TR criteria.

To confirm the diagnosis and evaluate the comorbidities, the Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime -Persian Version (K-SADS-PL-PV) were used. The Children Depression Inventory (CDI), and the Young Mania Rating Scale (YMRS) were completed to assess the depressive and manic symptoms severity. The participants with depressed phase were excluded from the study. To consider the common comorbidity of BD with attention-deficit hyperactivity disorder in youths, the Conners' Parent Rating Scale (CPRS) was used to evaluate the severity of related problems. The adolescents with IQ lower than 90 and any major neurologic or psychiatric disorders including learning disorders were excluded.

After 2 to 3 weeks of receiving the medications, the participants completed the YMRS again. The YMRS total score less than 8 was considered as the manic/mixed episode that had been controlled. In the euthymic phase, the adolescents were ready to cooperate with neurocognitive testing. The Paired Associates Learning (PAL) and the Pattern Recognition Memory (PRM) tasks from the Cambridge neuropsychological test automated battery (CANTAB) were used to evaluate the visual memory. These tests were administered at the neurocognitive laboratory of Roozbeh hospital.

The control group included 30 IQ and age- matched volunteer typically developing (TD) students (14 males and 16 females) recruited from the mainstream schools in central parts of Tehran. After providing consent forms, the adolescents and their parents participated in the study. The adolescents did not have any history of psychiatric problems; however, the Children Symptoms Inventory (CSI-4) was completed by the parents to exclude any psychiatric disorders in their adolescents. The students' IQ was calculated using the Raven Progressive Matrices test. Then, the students were invited to the Roozbeh neurocognitive lab to do the PAL and PRM tasks.

Each of the K-SADS-PL, RPM, and CANTAB tests were performed by 3 separate experienced psychologists. The YMRS, CDI, CSI-4, and CPRS were managed by the first author as her thesis to obtain the MD degree. Because the clinical group stayed at the ward, wearing special uniforms and the TD participants came from outside based on preplanned appointments, the assessors were aware of the case or control status of the participants.

The study was approved by the ethics committee of Tehran University of Medical Sciences. Written consent forms were received from both adolescents and their parents.

3.2. Measures

3.2.1. The kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version-Persian Version

The K-SADS-PL-PV is a semi structured diagnostic interview which assesses current, past, and lifetime diagnostic status in 6 to 18 year-old youths (8). The psychometric properties of the Persian version has been reported as good or excellent for most psychiatric disorders (9).

3.3. Children Depression Inventory (CDI)

The CDI is a self-report inventory with 27 items and evaluates depressive symptoms in 7 to 17 year-old children. The alpha reliability coefficient ranged from 0.71 to 0.86 (10). A study on Iranian children reported its test-retest reliability and internal consistency as 0.8 and 0.89, respectively (11).

3.4. Young Mania Rating Scale (YMRS)

This 11- item scale evaluates manic symptoms based on the patient report and therapist's observation over the pre-

vious 48 hours and the information derived from the clinical interview. The validity coefficient of 0.41 to 0.85 and reliability coefficient of 0.88 to 0.9 have been reported (12). The YMRS showed acceptable validity and reliability in Iran (13).

3.5. Conners' Parent Rating Scale (CPRS)

The scale assesses attention deficit-hyperactivity disorder (ADHD) and related behavior problems in 3 to 17 year-olds. The CPRS could discriminate a clinical group of Iranian children diagnosed with ADHD from nonaffected individuals ($P < 0.001$).

3.6. Raven's Progressive Matrices (RPM)

RPM (Raven and Court 1996) is a well-known worldwide measure for nonverbal intelligence and perceptual reasoning. The standardized norms for 5 to 18 year-old Iranian children and adolescents are available (14).

3.7. Cambridge Neuropsychological Test Automated Battery (CANTAB)

Two visual memory tasks were used from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Retrieved from www.cantab.com on 10, 11, and 2009):

1. Paired Associates Learning (PAL): In this test, some boxes are displayed on the screen and opened in a randomized order. One or more of the boxes will contain a pattern. The patterns are then displayed one by one in the middle of the screen. The participant is instructed to touch the box where the pattern was originally located. There are different stages in which the number of patterns increased up to 8. Error occurs when the participant selects a box not containing the target stimulus.

2. Pattern Recognition Memory (PRM): This test has 2 phases. In the first phase, the participant is presented with a series of 12 colored visual patterns for 3 seconds. The examinee needs to memorize these patterns. In the second phase, 12 paired novel and old patterns are presented in which the participant is required to choose between a pattern they have already seen and a novel pattern.

This test is scored using 2 indices: (a) mean correct latency; (b) number correct.

3.8. Statistical Analysis

Data were analyzed using descriptive statistics, independent t test, analysis of variance (ANOVA), and Bonferroni correction methods.

4. Results

The 2 groups were not significantly different in their age, gender, and IQ. The mean age was 15.3 (1.4) and 16.2 (1.5) years in the BD and TD groups, respectively. The mean of IQ was 106 (11.9) in the BD and 107.7 (11.1) in the TD group.

Among the BD group, 40% (N = 12) were diagnosed as having ADHD, and 70% had subclinical symptoms of depression.

The results of the 2 visual memory tests of CANTAB including Paired Associates Learning (PAL) and Pattern Recognition Memory (PRM) are demonstrated in the below. below. Although all subtests scores were poorer in the BD group compared to the TD participants, we did not find any significant differences between the 2 groups.

To compare the TD group and BD individuals with and without ADHD in visual memory, ANOVA was used. We found a significant difference between the 2 groups only in PRM mean correct latency (Table 3). A Bonferroni post hoc analysis showed that the PRM scores ($P = 1$) was not significantly different between the non-ADHD and TD adolescents. However, the PRM mean correct latency score was higher in the BD individuals with ADHD compared to both the non-ADHD and the TD adolescents. With respect to the PAL scores, the only significant difference was related to total errors (2 shapes) mean scores ($P = 0.03$). These mean scores (and standard deviations) in the TD, non-ADHD, and ADHD groups were 0.03 (0.18), 0.50 (1.15), and 0.0 (0.0) respectively. The results of the post hoc analysis did not show any significant differences.

5. Discussion

The present study was conducted to evaluate the visual memory as a trait dependent variable in adolescents with bipolar disorders (BD) compared with a group of healthy adolescents. The Paired Associates Learning (PAL) and Pattern Recognition Memory (PRM) subtests of CANTAB were administered to inpatient adolescents with bipolar mixed/manic episode when they entered into the euthymic phase of the disorder. The individuals with BD performed poorer than the TD group on all tests stages, but the differences in mean subtests scores were not significant.

Regarding impaired visual memory in BD, there is greater evidence in adults compared to youths. In a study comparing 4 groups of adults diagnosed as manic, mixed, or depressed bipolar disorder with healthy individuals (15), all BD participants had lower percent correct scores in PRM test. Murphy et al. (2001) also found longer response latencies in BD individuals compared to the control group (16). Sparding et al. (2015) used the Rey complex figure test and showed that working memory, verbal, and visual

Table 1. Comparison of Visual Memory Based on the Paired Associates Learning (PAL) Mean Scores Between the Bipolar and Typically Developing Groups

PAL indices scores	TD Group	BD Group	Significance	PAL Indices Scores (Continue)	TD Group	BD Group	Significance
First trial memory score	20.5 + 3.8	9.8 + 3.2	0.4	Total errors adjusted	9.1 + 8.2	10.9 + 9.4	0.4
Mean errors to success	1 + 1.1	1.3 + 1.1	0.4	Total trials	11.3 + 2.2	12.4 + 2.3	0.2
Mean trials to success	1.3 + 0.2	1.4 + 0.3	0.2	Total trials (adjusted)	11.3 + 2.2	11.5 + 3.2	0.7
Number of patterns reached	8	8	-	Total errors (1 shape)	0	0	-
Number of patterns succeeded on	8	8	-	Total errors (2 shapes)	0.03 + 0.1	0.3 + 0.9	0.1
Stages completed	8	8	-	Total errors (3 shapes)	0.5 + 1	1 + 1.5	0.1
Stages completed on first trial	6.1 + 0.7	5.8 + 0.7	0.1	Total errors (6 shapes)	3 + 3.2	2.6 + 2.8	0.6
Total errors	9.1 + 8.2	10.9 + 9.4	0.4	Total errors (8 shapes)	5.5 + 6.2	7.2 + 7.1	0.3

Table 2. Comparison of Visual Memory Based on the Pattern Recognition Memory (PRM) Mean Scores Between the Bipolar and Typically Developing Groups

PRM Scores	TD Group	BD Group	Significance
Mean correct latency	2076 + 506	2237.4 + 651	0.2
Number correct	21.6 + 1.7	21.3 + 1.9	0.5
Percent correct	90 + 7.3	88.8 + 8.1	0.5

memory were impaired in adults with bipolar I and II compared to the control group (17). These findings were similar in euthymic state of BD. For instance, Lera-Miguel, Andres-Perpina and Fatjo-Vilas (2014) found impaired working, verbal, and visual memory in adults with BD after a 2-year period of remission (6). Okasha et al. (2014) compared 60 BD adults in euthymic phase with 30 normal participants using the WCST, CPT, and WAIS (18). They confirmed visual memory deficit in the BD individuals. Forcada et al. (2015) found that visual memory index was one of the predictive factors of cognitive and psychosocial functioning in euthymic bipolar adults (19).

Evidence (Kyte et al. 2006) shows that impairments in neuropsychological performance have more similarities than differences between youths and adults with BD (20). These neurocognitive similarities may suggest a vulnerability to pediatric BD in contrast to the assumption that individuals with BD experience progressive brain functioning changes as they respond to episodes. In a meta-analysis of studies on neurocognitive performance of youths with BD, Joseph, Frazier, and Youngstrom, (2008) found the largest effect size for verbal memory measures (d - 0.77), which was consistent with the neurocognitive deficits data in adults with BD (21, 22). However, the difference was moderate for visual memory (d - 0.51) and visual perceptual skills (d - 0.48) domains.

The findings in our study were consistent with some studies, suggesting that the differences between the BD youths and the control group in some cognitive dysfunctions including visual memory depend on attention deficit hyperactivity disorder (ADHD) comorbidity, not the BD itself. We observed significantly lower PRM mean correct latency in the TD group compared to the BD adolescents only when they had comorbid ADHD. This latency was significantly higher in the ADHD group compared with the non-ADHD adolescents. Pavuluri et al. (2006) found significant higher impairment in neuropsychological functioning in the pediatric BD group with ADHD compared with the group without ADHD on attention, executive function, and visual memory domains (23). However, the BD group compared to the healthy individuals, had much more significant impairment in working memory and verbal memory composites regardless of ADHD comorbidity. Frias, Palma, and Farriols (2014) also found greater verbal/visual-spatial memory, processing speed, working memory, and social cognition impairments in youths with acute mood episode, BD Type I, and/or ADHD comorbidity (3). Pavuluri, West and Hill (2009) conducted a 3-year longitudinal study of neurocognitive functioning in a group of medication receiving youths with BD compared to a TD group (24). At baseline, they found a developmental delay in executive function, attention, verbal memory, visual memory, visuospatial perception, and working memory in BD individuals. In the year third year, impairment in all assessed domains were obvious, however, a slower rate of improvement was only observed in executive function and verbal memory. Moreover, the attention domain was still impaired in youths with BD and comorbid ADHD who were treated with stimulants. They concluded that attention problems in pediatric BD may be different from the ADHD-related attention deficit. Moreover, it seems that in youths with BD, impairment in some cognitive domains, including visual memory, have less evidence than the more studied domains of verbal memory and executive functioning. The existing adult functional neuroimaging in BD sup-

Table 3. ANOVA Results to Compare PRM Scores for the Typically Developing Adolescents, BD Group with and Without ADHD

PRM Scores	TD Group		BD Group Without ADHD		BD Group Without ADHD		Significance
	Mean	SD	Mean	SD	Mean	SD	P
Mean correct latency	2076.88	506.49	1998.95	585.93	2505.20	595.52	0.01
Number correct	21.60	1.75	21.72	1.56	20.66	2.30	0.25
Percent correct	90.03	7.33	90.47	6.52	86.32	9.95	0.29

ports the abnormalities in the caudal and rostral ventral prefrontal cortex as the state and trait-related changes, respectively, as well as fronto-limbic changes found in adolescents and adults with BD (25-28).

Finally, the literature on neurocognitive profile of children and adolescents with BD suggest the following points: (1) There are some differences in youths neurocognition compared to adults, which can be due to developmental CNS characteristics, course of the disorder, or the effects of medication; (2) The neurocognitive functioning of youths with BD is affected by other psychiatric comorbidities, especially ADHD, and should be considered when interpreting the data; (3) The special cognitive profile seen in pediatric BD may exist before the onset of mood changes and can be ascribed as an endocogniphenotype; and (4) Cognitive impairment will continue even after symptoms remission and put youths at risk of academic and psychosocial problems. However, most studies on BD cognitive domains were cross sectional, had small sample size, used different cognitive subsystems and instruments, and did not exclude the effects of medications or comorbidities. Therefore, it is acceptable to find inconsistency in cognitive problems when studying children and adolescents with BD.

5.1. Limitations and Suggestions

This was the first study in Iran to evaluate visual memory characteristics in adolescents with euthymic BD. We confirmed the diagnoses using the semi-structured interview. Moreover, we administered a computer-based, language-free neuro-cognitive battery. We did not evaluate the adolescents in the manic phase as they could not cooperate due to their acute symptoms. As a result, we could not compare cognitive functioning in manic and euthymic phase and did not exclude the effects of prescribed medication. Moreover, due to the small sample size, assessing the effects of comorbid ADHD may not be generalized. Therefore, studies with greater sample size, comparing different states of the disorder, using functional imaging, and using a longitudinal design are needed to reach more accurate results. Research on cognitive resources and remediation are also essential to provide prevention and rehabilitation strategies and protocols appropriate for high-risk and suffering youths.

5.2. Conclusions

Children and adolescents with different phases of bipolar disorder suffer from various cognitive dysfunctions including visual memory. These deficits may be related to comorbid psychiatric conditions such as ADHD.

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Footnotes

Authors' Contribution: Zahra Shahrivar and Mehdi Tehrani-Doost conceived and designed the evaluation. Hoda Bakhtiari collected the clinical data. Zahra Shahrivar and Mehdi Tehrani-Doost interpreted the clinical data. Zahra Shahrivar drafted the manuscript. Elham Shirazi revised it critically for important intellectual content. Hoda Bakhtiari and Javad Mahmoudi Gharai performed the statistical analysis. Mehdi Tehrani-Doost did the administrative, technical, and material support. Zahra Shahrivar and Mehdi Tehrani-Doost supervised the study. All authors read and approve the final manuscript

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