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White Matter Microstructural Abnormalities and Cognitive Functions Assessment in First versus Multiple episodes of Euthymic Bipolar Cases

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ABSTRACT

Background: *Recently, several studies have detected cognitive impairment and microstructural anomalies of white matter (WM) in bipolar disorder type I (BD-I). It is still unclear if these structural and cognitive anomalies in BD are progressive or static.*

Subjects and Methods: *We investigated Diffusion Tensor Imaging (DTI) derived fractional anisotropy (FA) and cognitive functions in 40 cases with euthymic BD I, who were subdivided into 20 cases with single episode and another 20 cases with multiple episodes, and were further compared with 20 healthy controls. Four tracts bilaterally (cingulum, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus) and three areas (left rostral anterior cingulate, right inferior frontal area, and right subgenual anterior cingulate) were studied. The findings were further correlated with cognitive functions (memory, executive functions, and sustained attention), which were assessed using Trail Making Test A and B, Wisconsin Card Sorting Test, Wechsler Memory Scale, and Continuous Performance Test).*

Results: *Cases with BD I either with a single episode or multiple episodes showed deficits than the control group in all the selected regions except right subgenual anterior cingulate in comparison to controls. Also, more deficits were found as regards cognitive functions.*

On the other hand, cases with many episodes had lower FA than those with a single episode regarding seven regions of interest (left and right inferior longitudinal fasciculus, left and right superior longitudinal fasciculus, left uncinate fasciculus, right cingulum, and right inferior frontal area) as well as more impairment in executive functions and sustained attention which correlated with these white matter abnormalities.

Discussion and Conclusion: *The present findings indicate that white matter microstructural abnormalities and cognitive functions deficits could serve as state and trait markers in cases with BD I. The detected abnormalities could affect the future in early diagnosis and intervention, thus facilitating functional recovery in cases with BD I.*

Keywords

DTI, Cognitive functions, Bipolar disorder, Single episode, Multiple episodes.

Introduction

Bipolar disorder (BD) has a prevalence rate of 1–3% and is typically characterized by disabling mood disorders of mania and depression [1].

Understanding the neuropathological basis of mental diseases like major depression, bipolar disorder, and schizophrenia is critical for developing effective therapies. Diffusion MRI studies adopting

the diffusion tensor imaging (DTI) model have been exceptionally efficient in finding microstructural brain defects in people with mental illness, particularly in white matter regions [2]. Numerous neurobiological defects are founded in cases with BD [3].

Recently, there is an increase in interest in the study of brain connectivity in BD I. Previous DTI studies have revealed subtle microstructural anomalies in the white matter of cases with BD, including a loss of WM network connectivity including prefrontal areas, and associative, commissural fiber tracts, and projection [4]. Thus, accumulating data from DTI research in BD implies that defective structural connectivity affects BD pathogenesis [5,6].

The majority of investigations have discovered reduced fractional anisotropy (FA) in a variety of white matter pathways [7-9], like multiple frontal and temporal areas [10,11]. Recently, a meta-analysis indicated a substantial decrease in FA in the superior longitudinal fasciculus and the left cingulum of the right BD I patient compared to the control [4].

A deeper knowledge of BD neurobiology may eventually aid in the refinement of the diagnosis and the development of novel therapies. They discovered changes in the WM microstructure in individuals with BD, as well as numerous bundles, with the biggest effects in the cingulum, in the largest multi-center DTI research of BD. Although impact sizes were small, FA was decreased in cases in the majority of ROIs [12]. Microstructural abnormalities in the white matter are often regarded as a structural indicator of BD [13].

The cognitive limitation is a hallmark of bipolar disorder, particularly in psychomotor speed, executive functions, and verbal memory [14,15]. These deficiencies affect cases with BD's social and vocational capacities, placing a considerable load on global functioning [16]. Cognitive anomalies have been found during mood episodes and have been persisted throughout remission [17,18].

Numerous investigations have established a link between the frequency of mood episodes and the severity of cognitive problems, implying underlying neurophysiological and structural alterations [19,20]. Widespread evidence of WM dysfunction in circuits is crucial for cognitive and emotional processing, which is a critical biological basis for BD psychopathology [21].

Few studies are linking DTI measurements and cognitive impairment in BD. Low FA of the uncinate fasciculus was linked to a greater number of set-shifting errors and elevated risk-taking [22].

Although these outcomes, the relationship between characteristics associated with structural changes in the brain, cognitive deficiencies, and illness chronicity in BD are still poorly understood. Additional study is required to disentangle the impact of chronic disease on the cognition and structure of the WM in cases with BD.

Based on past research, we expected that cases with BD I, both single and numerous episodes, might have a variance of white matter impairments and cognitive limitation in comparison to healthy controls, and that repeated episodes would have larger deficits than single episodes.

Subjects and Methods

Subjects

Subjects were collected from the out-patient clinics of the Institute of Psychiatry Ain shams University. The study was conducted on 40 cases with BD I during euthymic state (20 cases with single episodes and 20 cases with multiple episodes) and 20 healthy participants recruited from the employee of the Institute of Psychiatry. The study was authorized by the Faculty of Medicine Ain Shams University's Ethical Committee. All individuals provided written informed consent.

Every individual has been assessed utilizing the following semi-structured and standardized structured clinical instruments: semi-structured sheet includes family history, course of illness, information on diagnostic and clinical features, and actual and past pharmacotherapy: Structured Clinical Interview for Axis-I Disorders (SCID-I) [23]. Hamilton Depression Scale (HAM-D) with 17 items [24]; Young Mania Rating Scale (YMRS) [25] to ensure euthymic state.

Inclusion Criteria Were: (a) Age ranged between 18 and 45 (b) Males and females included (b) Diagnosis of BD type I according to (DSM-IV) criteria using SCID-I [23]. (c) Score 7 or less in both HAM-D with 17 items [24] and YMRS [26].

Exclusion Criteria Were: (a) Diagnoses of any comorbid psychiatric disorder (b) history of decompensated or severe somatic diseases, neurological diseases (cerebral vascular malformations, epilepsy, or stroke), previous head injury with loss of consciousness (for five or more minutes); (c) History of substance dependence (d) Cases taking lithium excluded because of the known neurotrophic impact of lithium treatment on the white matter of the brain [27] (e) Cases whose IQ $\leq$ 80 or received recent course (within the last three months) of Electro Convulsive Therapy (f) Left-handed; (g) The inability to undergo MR examination (metal implants, claustrophobia).

Twenty healthy controls were free of any psychiatric disorders as confirmed by the Arabic version of General Health Questionnaire (GHQ) [28,29], age ranged from 18-45, no family history of a 1st-degree relative with a psychiatric disorder, also they met the same exclusion criteria indicated for cases.

Procedures

Clinical Assessment

Cases were interviewed by a psychiatrist that was trained in this field. Regarding DSM-IV criteria, SCID-I was used to diagnose BD-I and rule out other psychiatric illnesses [23]. The Hamilton Depression Rating Scale (HAM-D) [24] and Young Mania Rating Scale (YMRS) [25] were utilized to confirm remission.

Cognitive Functions Assessment

A trained clinical psychologist performed the IQ test by the Wechsler intelligence scale for adults [26] to exclude individuals with IQ less than 80 and the cognitive functions tests including A-Wisconsin card sorting test (WCST) that enables the researchers to determine the following "frontal" lobe functions: organized searching, directing behavior toward achieving a goal, strategic planning, using environmental feedback to shift cognitive sets and modulating impulsive responding [27]. B-Wechsler Memory Scale (WMS) [30,31] was utilized to measure different memory domains. C- Continuous Performance Test (CPT) was utilized to estimate both sustained and selective attention, and D- Trail making test parts A and B [32] was utilized to test the planning, organized visual search, set-shifting, attention, and cognitive flexibility.

MRI acquisition (Diffusion tensor imaging (DTI) [33]

A 1.ST scanner was used to scan all subjects (Achiva Philips). The signal intensity was detected using an S-channel head coil. The DTI sequence was a single-shot diffusion-weighted spin-echo EPI sequence. (TR/TE, 8000/68.7 ms; applying parallel imaging [array special sensitivity encoding technique] with acceleration factor 2; matrix, 80 x 78; FOV, 22 cm; section thickness, 2 mm; 50 contiguous sections). DTI data were analyzed and processed off-line by a consultant radiologist. The DTI data was loaded into the software package that enabled us to perform seed region-of-interest selection. Regions of interests (ROIs) were placed on the suspected anatomical regions. Tractography was done to isolate the suspected tracts by tracking multiple ROIs (right and left inferior longitudinal fasciculus, right and left superior longitudinal fasciculus, right and left cingulum, right and left uncinate, left rostral anterior cingulate, right inferior frontal area, and right subgenual anterior cingulate). FA was the parameter used to compare between groups.

Statistical Analysis

The statistical tool SPSS (Statistical Package for the Social Sciences) version 25 was used to code and enter the data.

The mean and standard deviation were used to represent quantitative data, while frequency (count) and relative frequency (%) were utilized to summarize categorical data. The Mann-Whitney and Kruskal-Wallis tests were utilized to compare quantitative variables.

The Chi-square (c2) test was utilized to compare categorical data. When the anticipated frequency is less than 5, an exact test was done instead. P-values less than 0.05 were considered statistically significant.

Results

Comparison between groups as regards age and sex (Table 1)

The groups were matching as regards sex, while we found significant difference as regards age between groups with younger age of the single episode group than the multiple episodes group and the control group (p value= 0.004), while there was no significant difference between cases with multiple episodes and the control group.

Comparison between groups as regards cognitive functions (Table 2)

Cognitive functions in cases with first-episode and multiple-episode were affected in a statistically significant manner in comparison to the controls as regards: Trail making test part B (TMT B) with ($p< 0.001$), the higher commission of errors ($p=0.036$), and elevated omission of errors ($p < 0.001$) in continuous performance test ($p<0.001$), lower number of category completed (p value=0.017) and a higher number of perseverative errors (p value=<0.001) in Wisconsin card sorting test, and lastly all subtests of Wechsler Memory with $p < 0.001$.

In addition, cases with multiple episodes were affected compared to controls in a statistically significant manner regarding Trail Making Test Part A (TMT A) with $p=0.026$.

Multiple episode cases were affected more than the first episode regarding trail-making test part B, elevated omission of errors in CPT, and higher preservative in WCST.

There were no differences between multiple and first-episode cases regarding TMTA, the commission of errors in CPT, conceptual level of WCST, and all subtests of Wechsler Memory.

Comparison between Groups As Regards DTI Findings

Regarding the comparison between the control group and the cases' groups, we found statistically significant deficits that reflected lower FA values of (left and right inferior longitudinal fasciculus, left and right superior longitudinal fasciculus, left and right uncinate fasciculus, right and left cingulum, left rostral anterior cingulate, and right inferior frontal area), while no statistically significant difference was found among groups as regards right subgenual anterior cingulate.

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Single episode group versus multiple-episode group revealed a statistically significant deficit in the multiple-episode group than single episode group in all seven regions of interest (left and right inferior longitudinal fasciculus, left and right superior longitudinal fasciculus, right cingulum, left uncinate fasciculus, and right inferior frontal area). The single episode group had statistically significant lower FA of the right uncinate fasciculus, left cingulum, and left rostral anterior cingulate than the multiple episode group. Finally, there was no statistically significant difference among groups as regards right subgenual anterior cingulate (Figure 1 and 2).

Correlation between DTI Findings and Cognitive Functions in the Cases' Group

Correlations between DTI findings and cognitive functions in cases groups (both single episode group and multiple-episode group as one group) revealed a negative correlation between FA of right SLF and number of omission errors (subtest of continuous performance test) (p value= 0.029), negative correlation between FA of right ILF and trail making test part B(p value=0.045), negative correlation between FA of right Uncinate fasciculus and trail making test part A (p value=0.010), positive correlation between FA of left uncinate fasciculus and category completed (WCST subtest (p value=0.029) and verbal memory (p value=0.042), positive correlation between FA of the left cingulum and verbal memory (p value=0.048), positive correlation between FA of left rostral anterior cingulate and verbal memory (p value=0.002).

	Demographic data	Single episode BD (n=20)	Multiple episode BD (n=20)	Control (n=20)	F/x2#	p-value
Age (years)	Mean ± SD	24.05 ± 5.29	31.05 ± 7.39a	30.35 ± 8.11a	6.012	0.004*
	Range	17-37	18-45	20-45		
Sex	Male	12 (60%)	13 (65%)	12 (60%)	0.141#	0.932
	Female	8 (40%)	7 (35%)	8 (40%)		

Table 1: Comparison between Groups As Regards Age and Sex.
F-One Way Analysis of Variance; #x2: Chi-square test p-value>0.05 NS; *p-value <0.05 S.
Post HOC test: a: significant difference with single episode b: significant difference with multiple episodes.

	Cognitive Functions	Single episode BD (n=20)	Multiple episode BD (n=20)	Control (n=20)	ANOVA	p-value
Trail making test B	Mean ± SD	63.35 ± 16.45	70.65 ± 29.41	52.25 ± 13.42b	11.360	<0.001**
	Range	65-250	115-240	60-200		
Commission errors	Mean ± SD	13.55 ± 5.03	13.20 ± 8.01	9.05 ± 4.12ab	3.531	0.036*
	Range	6-27	5-33	4-17		
Omission errors	Mean ± SD	18.75 ± 11.84	50.10 ± 63.87a	3.20 ± 4.34ab	8.080	<0.001**
	Range	2-38	3-247	0-15		
Wisconsin Card Sorting Test (WCST)						
Categories completed	Mean ± SD	5.20 ± 1.24	5.10 ± 1.33	6.00 ± 0.00ab	4.403	0.017*
	Range	2-6	2-6	6-6		
Conceptual level	Mean ± SD	66.25 ± 15.79	64.35 ± 13.93	66.45 ± 4.71	0.173	0.841
	Range	26-88	29-84	60-72		
Perseverative errors	Mean ± SD	66.25 ± 15.79	64.35 ± 13.93	66.45 ± 4.71	8.468	<0.001**
	Range	26-88	29-84	60-72		
Wechsler Memory Scale (WMS)						
General memory	Mean ± SD	50.65 ± 13.57	54.85 ± 17.99	76.25 ± 8.05ab	19.749	<0.001**
	Range	29-80	29-101	62-89		
Verbal memory	Mean ± SD	80.25 ± 6.03	84.00 ± 16.54	100.90 ± 10.97ab	16.874	<0.001**
	Range	69-94	62-126	85-117		
Visual memory	Mean ± SD	30.90 ± 12.87	30.95 ± 12.13	42.50 ± 11.30ab	6.084	0.004*
	Range	15-62	12-54	20-60		
Attention	Mean ± SD	61.60 ± 12.65	66.20 ± 15.05	81.05 ± 11.73ab	11.826	<0.001**
	Range	42-81	48-102	50-100		
Recall	Mean ± SD	56.05 ± 13.71	52.55 ± 16.35	70.80 ± 13.56ab	8.809	<0.001**
	Range	30-91	17-75	35-87		

Table 2: Comparison between Groups As Regards Cognitive Functions.
F-One Way Analysis of Variance
p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS
Post HOC test: a: significant difference with single episode b: significant difference with multiple episodes.

	DTI findings: Fractional Anisotropy (FA)	Single episode BD (n=20)	Multiple episodes BD (n=20)	Control (n=20)	ANOVA	p-value
Right superior longitudinal fasciculus	Mean ± SD	0.469 ± 0.033	0.452 ± 0.043	0.531 ± 0.050ab	18.797	<0.001**
	Range	0.365-0.504	0.400-0.533	0.471-0.668		
Left superior longitudinal fasciculus	Mean ± SD	0.487 ± 0.028	0.461 ± 0.052 a	0.513 ± 0.032ab	9.131	<0.001**
	Range	0.404-0.532	0.329-0.548	0.463-0.575		
Right inferior longitudinal fasciculus	Mean ± SD	0.484 ± 0.026	0.465 ± 0.054 a	0.518 ± 0.043ab	8.033	<0.001**
	Range	0.394-0.514	0.365-0.530	0.459-0.601		
Left inferior longitudinal fasciculus	Mean ± SD	0.485 ± 0.054	0.464 ± 0.062 a	0.521 ± 0.041ab	5.935	0.005*
	Range	0.290-0.545	0.338-0.542	0.427-0.583		
Right uncinate fasciculus	Mean ± SD	0.439 ± 0.035	0.452 ± 0.035 a	0.492 ± 0.037ab	12.257	<0.001**
	Range	0.362-0.483	0.411-0.539	0.449-0.597		
Left uncinate fasciculus	Mean ± SD	0.485 ± 0.022	0.448 ± 0.043 a	0.502 ± 0.037ab	12.394	<0.001**
	Range	0.432-0.519	0.337-0.517	0.455-0.600		
Right cingulum	Mean ± SD	0.514 ± 0.037	0.474 ± 0.039 a	0.522 ± 0.047ab	7.785	<0.001**
	Range	0.428-0.569	0.412-0.561	0.436-0.613		
Left cingulum	Mean ± SD	0.529 ± 0.058	0.457 ± 0.046 a	0.555 ± 0.047ab	20.259	<0.001**
	Range	0.369-0.612	0.413-0.571	0.466-0.621		
Right inferior frontal area	Mean ± SD	0.415 ± 0.084	0.393 ± 0.071 a	0.463 ± 0.068ab	4.580	0.014*
	Range	0.269-0.597	0.301-0.579	0.369-0.597		
Left rostral anterior cingulate	Mean ± SD	0.429 ± 0.103	0.454 ± 0.054 a	0.512 ± 0.056ab	6.537	0.003*
	Range	0.234-0.583	0.335-0.537	0.439-0.623		
Right subgenual anterior cingulate	Mean ± SD	0.401 ± 0.082	0.409 ± 0.062	0.421 ± 0.093	0.293	0.747
	Range	0.266-0.590	0.296-0.502	0.302-0.597		

Table 3: Comparison between groups as regards DTI findings.
F-One Way Analysis of Variance; **p-value <0.001 HS
Post HOC test:
a: significant difference with a single episode; b: significant difference with multiple episodes.

Figure 1

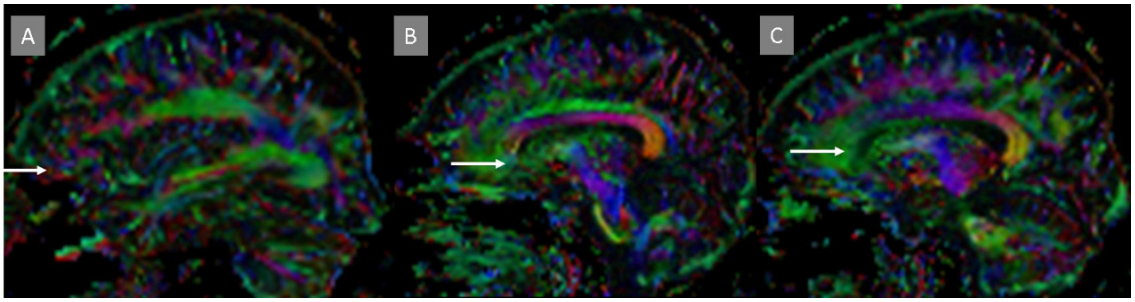
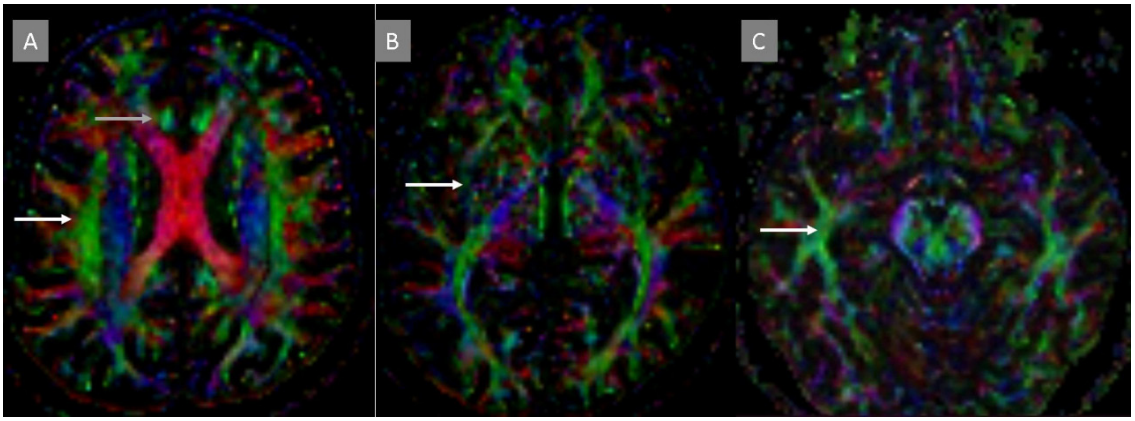


Figure 2



		Right SLF	Left SLF	Right ILF	Left ILF	Right uncinate	Left uncinate	Right cingulum	Left cingulum	Right inf. frontal	Left ROST ant cingulate	Right subgenual ant cingulate
Trail making test A	R	-0.051	-0.118	0.229	-0.055	-0.403	0.075	0.115	0.035	-0.056	-0.088	0.192
	p-value	0.753	0.467	0.156	0.737	0.010*	0.644	0.479	0.832	0.733	0.587	0.234
Trail making test B	R	0.103	0.100	-0.319	0.189	-0.216	0.146	0.261	0.223	-0.267	-0.077	0.023
	p-value	0.528	0.540	0.045*	0.243	0.181	0.369	0.104	0.167	0.095	0.636	0.887
Wisconsin card sorting test												
Category completed	R	-0.085	0.022	0.084	-0.147	-0.273	0.345	0.127	0.077	0.053	-0.111	-0.217
	p-value	0.604	0.893	0.607	0.364	0.088	0.029*	0.433	0.635	0.743	0.495	0.178
Conceptual level	R	-0.021	0.102	-0.168	-0.228	-0.140	0.215	0.177	-0.053	0.174	-0.069	-0.172
	p-value	0.898	0.533	0.302	0.156	0.390	0.184	0.274	0.748	0.283	0.673	0.288
Conceptual level %	R	-0.135	0.144	0.036	-0.025	-0.121	0.262	0.062	0.103	0.107	-0.172	-0.169
	p-value	0.407	0.376	0.826	0.877	0.459	0.102	0.705	0.525	0.512	0.288	0.296
Perseverative errors	R	0.253	0.074	0.156	0.007	-0.082	0.240	0.081	0.275	-0.115	-0.016	-0.015
	p-value	0.115	0.649	0.336	0.964	0.616	0.136	0.619	0.086	0.480	0.920	0.925
Continuous performance test												
Commission errors	R	-0.027	-0.280	0.006	-0.158	0.000	-0.172	0.035	-0.163	0.142	-0.155	-0.016
	p-value	0.867	0.080	0.972	0.330	0.998	0.290	0.828	0.316	0.383	0.340	0.920
Omission errors	R	-0.346	0.066	0.009	-0.024	-0.050	0.124	0.095	0.142	-0.177	-0.160	0.012
	p-value	0.029*	0.685	0.957	0.884	0.762	0.445	0.560	0.383	0.275	0.325	0.940
Wechsler memory test												
General memory	R	0.070	0.256	-0.244	0.328	0.181	0.251	0.168	0.254	0.174	0.381	-0.061
	p-value	0.666	0.111	0.129	0.039	0.265	0.118	0.299	0.114	0.282	0.015	0.709
Verbal memory	R	0.025	0.101	-0.055	0.106	-0.008	0.323	0.328	0.312	0.279	0.469	-0.259
	p-value	0.879	0.533	0.736	0.515	0.961	0.042*	0.039	0.048*	0.081	0.002*	0.107
Visual memory	R	-0.221	0.131	-0.229	0.023	-0.012	0.340	-0.124	0.186	-0.052	0.034	-0.067
	p-value	0.170	0.420	0.155	0.890	0.941	0.032	0.447	0.251	0.749	0.835	0.681
Attention	R	-0.182	-0.129	-0.120	0.055	-0.034	-0.154	-0.015	-0.109	0.109	-0.071	-0.040
	p-value	0.261	0.427	0.462	0.735	0.833	0.344	0.925	0.503	0.505	0.662	0.806
Recall	R	-0.261	0.031	0.006	-0.045	0.035	0.091	0.087	0.019	-0.119	-0.035	-0.048
	p-value	0.104	0.849	0.972	0.784	0.832	0.578	0.592	0.909	0.466	0.828	0.767

Table 4: Correlation between DTI Findings and Cognitive Functions in the Cases Group.
t-Pearson Correlation Coefficient; p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS.

Discussion

Although the availability of effective pharmacological and non-pharmacological treatments, many cases with BD remain symptomatic. Advances in our understanding of the neurobiology of BD may aid in the development of novel therapeutic targets and biomarkers for early detection, prognosis, and therapy response in BD [34].

Cognitive dysfunction is a hallmark of bipolar I disorder (BD-I), with abnormalities in verbal learning, executive functioning, and memory observable in both acutely symptomatic and remitted cases [35,36].

Previous research has proposed that microstructural alterations in the white matter of frontal-subcortical circuits result in a disconnection syndrome between the subcortical and frontal areas. These network changes are related to clinical symptoms of BD, implying that DTI is a promising method for exploring the neuropathological underpinnings of BD [37].

So, in our study, we examined white matter integrity using the DTI (ROI technique) in cases with BD Type I after a single episode and multiple episodes relative to healthy controls. We also correlated the findings of DTI with cognitive function tests.

Comparison between Groups As Regards Cognitive Functions

There is growing recognition that people with BD-I frequently experience lasting cognitive abnormalities, even when they are euthymic. The majority of investigations on bipolar individuals in remission have consistently found abnormalities in various cognitive domains.

In agreement with our study, several studies found sustained attention impairment in bipolar cases during euthymia [38-40].

Additionally, [39,41] shown that decreased executive function is the most frequently reported neurocognitive deficiency in euthymic BD cases.

Verbal memory is an episodic memory that is reported to affect people with BD (Cognitive dysfunction in bipolar disorder : a guide for clinicians - Ohio Valley University, n.d.). Additionally, [42] discovered that cases with BD performed badly on the verbal memory subtest of the WMS-R when compared to controls. Numerous investigations have revealed a recall memory deficit in persons with euthymic bipolar disease [43-45].

In this work, cases with BD who had numerous episodes of remission behaved worse in attention and executive function than those who had a single episode. Neuropsychological impairments have been associated with many disease episodes and a more serious illness course in euthymic bipolar individuals. This relationship has been viewed as indicative of a progressive disease process.

This work revealed impaired memory functions among both groups of cases compared to the control group assessed by the WMS-R scale. In contrast, we found no significant difference between the single episode and multiple episodes groups.

Previous studies indicated that the number of episodes associated negatively with the executive functions, that reflects the progression of the illness and its negative effect on cognitive functions [35,46].

Our results add to previous research investigating the abnormalities of white matter in BD. We found a significant deficit in the cases' group (both with a single episode or many episodes) than the control group in all selected regions except the right subgenual anterior cingulate.

As with our findings, a review of DTI in cases with BD revealed a consistent reduction in FA, particularly in the fronto-limbic tracts and corpus callosum [47]. Hence, DTI reports have revealed consistent anomalies in areas linked with emotional regulation and structures that interhemi-spherically integrate these areas.

As regards cingulum, in agreement with our results, several studies revealed a significant deficit in this important and main pathway of the limbic system in cases with BD [12, 21,22,47,50].

The majority of research found that regions included in emotion processing, like the association tracts, and commissural had lower FA values [45,51]. The latter include the UF [21,51-53] and the cingulum [46,54].

The results of lower FA levels correlate to the BD definition as a disconnect syndrome [7].

Concerning the association tracts, multiple investigations have found impaired WM connectivity in cases with BD, with the majority demonstrating cingulum impairment [45,46,55] and the UF [45,52,56]. The cingulum is a complex fiber-system that forms the major component of the total limbic network with UF fibers of connection between the anterior temporal lobe, and medial prefrontal cortex, such as the amygdala. These areas are largely associated with BD pathophysiology [9].

In bipolar disease, it is prevalent to find lower FA of white matter tracts connecting prefrontal cortical areas with anterior limbic structures in the control of emotions, the anterior corpus callosum, alterations in temporal white matter, the superior longitudinal fasciculus, the uncinate fasciculus, and cingulum regions [57].

In a white frontal tracts study, such as the corpus callosum, the cingulum, the inferior fronto-occipital fasciculus, and the uncinate fasciculus, [58] have replicated outcomes in the cingulum bundle of euthymic BD1 cases with reduced FA. However, in the right hemisphere rather than on the left, as observed in [22].

In the precentral, medial frontal, occipital worlds, and lower parietal, [59] reported elevated FA values. Increased FA in left uncinated fasciculus (UF) and left optical radiation and right thalamic radiation were observed by [51].

To present, total DTI results in BD have lowered, increased, or no FA differences between healthy controls and cases [60,61]. Inconsistency between findings is thought to represent changes in data collecting procedures and patient variables between DTI investigations [62]. Most studies include heterogeneous samples in different moods of BD cases mixing individuals [63], that could be correlated with varied activation of neural networks [64] and different WM DTI patterns [65]. The single episode group had statistically significant lower FA than the multiple episodes group regarding right uncinate fasciculus, left cingulum, and left rostral anterior cingulate.

This result was not expected and is not per the remainder of our results. Currently, we do not have a conclusive explanation for this discrepancy. One possible explanation is the confusing impact of antipsychotic and mood stabilizers drugs, because all cases were receiving therapy, and medications have varying impacts on the brain structure.

Evidently, research indicates that structural brain abnormalities and cognitive impairment are not always present at the outset of disease, but become more apparent with chronicity and recurrent episodes [23,66,67]. Additionally, neuroprogression appears to be associated with the cumulative consequences of increased oxidative stress, immunological malfunctioning, mitochondrial malfunction, neurotrophic support breakdown, and cellular resilience impairment [68,69]. Hypothesized that many episodes might result in persistent changes in neural activity, resulting in an increased risk of relapse and a weaker adherence to therapy [70].

Antipsychotics of the first and second generations are expected to have an influence on WM integrity, regardless of the fact that their impacts vary significantly between investigations, ranging from promyelinating effects to decreased WM integrity [23,65].

Earlier research has suggested that microstructural anomalies in the WM of frontal-subcortical networks results in a state of disconnection between the frontal and subcortical regions. These findings demonstrate a direct relationship between executive cognitive functioning and impaired WM microstructural integrity of the fronto-limbic circuits in individuals with remitted BD and add to the growing body of evidence for the neuronal damage that underpins the disease's residual symptomatology [37].

These aspects of cognitive decline appear to be highly correlated with WM and brain connection degeneration [39,71,72].

According to some research, recurrent bouts of BD are connected with increased cognitive disruption. It has been hypothesized that subsequent bouts produce minor damages to brain regions, resulting in cognitive and neurological impairment seen in BD, particularly following many episodes.

The research relating cognitive deficits to indications of illness severity and progression is not always consistent.

Each indicated the critical nature of these areas' integrity in relation to various cognitive activities, as we discovered.

These results of diminished white matter integrity and cognitive impairments in multi-episode BD compared to single episode BD may suggest increasing neuronal damage caused by BD. Numerous hypotheses exist to account for the genesis of this progressive damage, which may include constitutive modifications (metaplastic changes and synaptic tagging) as well as allostatic changes [69,71]. The impact of psychotropic medications on brain structure is still conflicting; whereas lithium is possibly neuroprotective and not linked to brain volume damage [74,75], early evidence from animal and human studies [76,77] indicate that atypical antipsychotic usage linked to brain volume loss. Because all cases received antipsychotic medication at many stages of illness and were using an antipsychotics combination and mood stabilizers, we could not conduct a subgroup analysis to adjust the drug effects.

Lately, a neuro inflammatory element has been associated with the pathogenesis of several mental diseases [78], which provides a logical explanation for the presence of WM lesions in individuals with BD [79]. Notably, WM is more susceptible to BD's inflammatory neurotoxic effects. The cognitive deterioration which happens during the disease course appears to be related, at least in part, to susceptibility to the inflammatory toxic consequences [80].

The disruption of neuronal connection caused by myelin sheath deterioration, the cause of which is unclear, is thought to play a significant role in the neurobiology of BD [81]. In conclusion, there is confirmation of extensive abnormalities in BD cases, implying a progressive loss of brain connection across various networks.

Ethical Approval

The nature of this work was discussed with each participant, and written informed consent was taken from all participants before participating in the study. The Ethics Committee approved this study of Ain Shams University Hospital after a very clear statement that provided information on the following points; study rationale, participation in this work was completely voluntary and free, participation in the work had no direct benefit to the participant, although the information obtained can be utilized for the benefit of other cases, they may be withdrawn at any time without giving any justification and without affecting their care service, and the findings of the work may be used for publishing. However, the identities of the cases would be completely secret.

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