

# The Role and Importance of Cognitive Symptoms in Bipolar Disorder

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## Abstract

**Objective:** Our aim was to review evidence of the role of cognitive deficits in bipolar disorder and their relationship to other factors, such as disorder variables, treatment, additional diagnoses, genetic risk, and brain imaging findings.

**Method:** Studies that examined cognitive dysfunction in bipolar disorder and its relationship to the variables of clinical, genetic, and bipolar disorder subtypes, as well as neuro-anatomical and neuro-functional evidence have been reviewed. Findings from our own studies have also been used while conducting the review.

**Results:** In bipolar disorder, deficits in executive functions, memory, and attention persist in the euthymic state. The number of episodes and the course of the disorder seem to be related to the severity of memory dysfunction and psychomotor slowness. However, symptoms of cognitive dysfunction are present at the onset of the disorder. Moreover, cognitive dysfunction has been observed in the healthy relatives of bipolar disorder patients. Cognitive dysfunction in bipolar disorder is associated with functional and possibly structural anomalies in some parts of the brain, such as the frontal and cingulate cortex. Some recent studies reported a relationship between symptoms of cognitive dysfunction and genetic variations in bipolar disorder.

**Conclusion:** Today, the presence of cognitive deficits in bipolar disorder is widely accepted; however, evidence of the neurobiological and clinical correlates of cognitive symptoms is still limited. More studies are needed to investigate the relationship between cognitive dysfunction in bipolar disorder and risk. Genetic studies are just now amending our body of knowledge. There have been many conflicting results reported by brain imaging studies. Different brain imaging approaches and genetic methods should be used with more specific cognitive and social-emotional tasks for increasing our knowledge about the nature of cognitive deficit in bipolar disorder

**Key Words:** Bipolar disorder, cognition, imaging, genetics

## INTRODUCTION

Kraepelin defined schizophrenia as a disorder in which loss of functioning is continuous and proceeded by collapse, whereas he defined manic-depressive disorder as a cyclic illness that leads to dysfunction only during the illness period. (Kraepelin, 1904). Cognitive dysfunction, apart from schizophrenia, has been featured in all disorders present in the spectrum of schizophrenia, including schizotypal personality disorder, and in the first-degree relatives of schizophrenia patients (Cadenhead et al., 1999; Gooding and Tallent, 2002; Keri and Janka, 2004; Snitz et al., 2006). In schizophrenia the severity

of cognitive symptoms is associated with loss of functioning (Bora et al., 2006b; Green, 2006) and the poor prognosis of the illness (Silverstein et al., 1994).

Although it has been for known for a long time that in bipolar disorder (BD) there may be some cognitive symptoms, with the influence of the Kraepelinian view, they were thought to be specific to BD illness periods and were perceived to be secondary to the manic and depressive symptoms, or motivational factors. In recent years data showing that cognitive dysfunction also persists in BD patients during periods of remission has come to light (Cavanagh et al., 2002; Clark et al., 2002;

Robinson et al., 2006). However, the meaning and the nature of cognitive symptoms described in BPD are still not adequate.

In this review article studies investigating executive functions, memory, psychomotor speed, and attention faculties in the euthymic state of BD, along with our own evidence, are summarized first. Then, the relationships between cognitive dysfunction, manic and depressive symptoms, and illness risk are discussed (Section 1).

Afterwards, as the result of a PUBMED search conducted with keyword combinations chosen in may 2007 (bipolar disorder, mania, neurocog\*, cog\*, neuropsych\*, MRI, PET, genet\*), studies published since 1996 that investigated the nature of cognitive dysfunction in BD were systematically reviewed (Section 2). The following criteria were incorporated into this section: (1) Application of tests designed to measure the performance in at least one of the fields of executive functions, memory, attention, and psychomotor speed; (2) to research the relationships between such performance and brain imaging, genetic data, disorder subtypes, BD risk, comorbidity, and course of illness. The dysfunction in the fields of social cognition, emotional recognition, decision-making, and general intelligence in BD were not included in this study.

The goals of this study were to review: t(1) the nature of cognitive symptoms, illness course, disorder subtypes, and treatment methods, and their relationship to substance abuse in BP, and(2) the relationships between cognitive symptoms, and brain imaging and genetic evidence.

### **Cognitive Symptoms in Bipolar Disorder**

#### **Cognitive Dysfunction in Remitted Bipolar Disorder**

##### **Memory**

One of the most important cognitive symptoms in BD during periods of remission is verbal memory dysfunction (Cavanagh et al., 2002; Bearden et al., 2001; Robinson and Ferrier, 2006). Additionally, some studies reported visual memory dysfunction (Deckersbach et al., 2004). The most frequently used assessment tools for verbal memory are the Rey Auditory Verbal Learning Test and the California Verbal Learning Test. In these tests a number of words are read to the subjects (15-16 words), which exceeds their momentary memory capacity (5-9 words), and then the subjects are asked to repeat

as many of the words as possible. This procedure is repeated several times and their performance is considered to reflect their verbal learning. After the learning stage the subjects are asked to list the words from their mind without being reminded by a list (early recollection). Then, other tests are applied; however, subjects are asked to remember these words at a later time (late recollection). Lastly, subjects are given a list composed of words that were and were not on the previous list and are asked to point out those that were on the previous list (recognition). Verbal memory dysfunction in BD patients in remission is known to be relatively evident (mid-size effect dimension). In the meta-analytic study of Robinson et al., (2006) the extent of the effect of verbal learning dysfunction (Cohen D) was 0.9, and for early and late recollection the Cohen D score was 0.7. A Cohen D score of  $\geq 0.8$  reflects a high level of dysfunction, whereas 0.5-0.8 indicates a moderate level of dysfunction. In this compilation the level of the effect indicates the severity of cognitive dysfunction in the BD group. In one of our studies, similar to these figures (with the exception of the learning value), we have come up with medium sized impairments in BD (effect sizes were: 0.56, 0.70, and 0.61 for learning, early recollection, and late recollection, respectively) (Bora et al., 2007). In our study, learning dysfunction in BD was less severe (effect size 0.74-1.06) than the measures in the 10 studies that Robinson et al. (2006) included in their meta-analysis, whereas memory measurements were very similar. This result may be due to sampling differences; for example, elapsed time since the last episode of the patients was longer in our study.

##### **Executive Functions**

Another problem that occurs during remission periods is dysfunction in executive functions. Under the heading of executive dysfunction, various cognitive dysfunctions, such as working memory (Watson et al., 2006), cognitive flexibility (Zubieta et al., 2001; Bora et al., 2005), ability to resist interference, and planning (Bearden et al., 2001; Quarashi et al., 2002; Thompson and Ferrier, 2006), which require the active participation of the frontal lobe, have been reported. The Wisconsin Card Sorting test (WCST), Stroop test, Verbal Fluency Test, and Trail-Making B test are the most utilized tests for this purpose. WCST is a test that evaluates cognitive flexibility and, to a certain extent, working memory capacity. The most frequently reported WCST scores are the number of categories completed and perseverative responses (although the instruction changes, subjects answer according to the previous instruction). The Stroop

**Table I.** Studies that investigate the effect of course of illness on cognitive functions in BD.

Study	Sample Number	Measured Cognitive Areas	Number of Depressive Periods	Number of Manic Periods	Duration of Illness
Van Gorp et al., 1998	13 BD, 12 BD + Alcohol	M, EF	–	M, EF	–
Krabbendam et al., 2000	22 BD (10 BD I, 12 BD II)	M, EF	–	–	–
Rubinsztein et al., 2000	18 BD I	EF	–	–	–
El_Badri et al. 2001	25 BD I	M, EF	–	–	–
Zubieta et al., 2001	15 BD I	EF, PS	EF	EF	–
Cavanagh et al., 2002	20 BD I	M	–	M	M
Clark et al., 2002	30 BD I	M, SA, EF	M, EF	M, SA	M,EF
Deckersbach et al. 2004	30 BD I	M	M	M	M
Martinez-Aran, 2004a	44 euthymic, 30 depressive, 34 manic BD	M, EF, PS	–	M	EF
Martinez-Aran, 2004b	40 BD I	M, EF, PS	–	M	M, PS
Clark et al., 2005	15 BD (one BD II)	SA	–	–	–
Kiessepa et al., 2005	26 BD I	M, SA, EF, PS	–	–	–
Frangou et al., 2005	44 BD I	EF	–	–	EF
Thompson et al., 2005	63 BD (9 BD II)	M, EF, PS, SA	EF	–	EF, PS
Goswami et al., 2006	37 BD	M, EF, PS	EF	EF	–
Kolur et al., 2006	30 BD	EF, SA, PS	–	–	–
Torrent et al., 2006	38 BD I, 33 BD II	M, EF, PS	–	–	M, EF, PS
Şenturk et al., 2007	28 BD I	M, EF	–	M	–
Bora et al., 2007	65 BD I	M, SA, EF, PS	PS	PS	PS

M: memory; SA: Sustained Attention; EF: executive functions; PS: psychomotor speed; (–): no relationship.

test evaluates selective attention and some of its scores, in particular the interference score, evaluate the success of inhibition of the dominant answer related to the frontal lobe. In the Trail-Making B test, subjects are asked to go to the first number to connect to the first letter of the alphabet, and then to go to the second number to be followed by the second letter and continue like this. This test is sensitive to frontal lobe functions in addition to psychomotor speed and attention. Robinson et al. (2006) calculated the extent of the effects of executive functions as follows: the completed category score in WCST as 0.62 and perseverative response score as 0.76, Stroop interference score as 0.63, and Trail-Making B test score as 0.78. In our study, we observed similarly low performance on effect size in executive functions;

the completed category score in WCST was 0.60 and perseverative response score as 0.55, Stroop interference score was 0.69, and Trail-Making B test score was 0.79 (Bora et al., 2007).

### Sustaining Attention

Another salient cognitive symptom during the euthymic state of BD is one that measured with the continuous performance tests (CPTs). During CPT a subject is asked to answer a stimulus (for example, letter A being followed by letter X) and not answer other letters. These tests have various types and the time required to complete them varies. When subjects do not answer the target stimulus it is defined as an omission error, and

**Table II.** Studies that investigate the nature of cognitive dysfunction in bipolar disorder, with brain imaging methods.

Study	Sample	Method	Result
Blumberg et al., 1999	5 manic, 6 euthymic BD, 5 HC	PET-verbal frequency	During mania: ↓ rostral and orbital Frontal activation
Sax et al., 1999	17 acute manic, 12 HC	CPT-MRI correlation	BP: CPT performance- between frontal and hippocampal volume inverse relation
So et al., 2000	26 BD (outpatients)	Neuropsychological test battery-MRI correlation	Relation between right hippocampus increased volume and cognitive dysfunction
Krabbendam et al., 2000	22 euthymic BD, 22 HC	Relation between white matter lesion and cognitive functions	No relation
Curtis et al. 2001	5 BD I, 5 SK	fMRI-verbal fluency	BD increased frontal activation
Blumberg et al., 2003	36 BD (11 manic, 10 depressive), 20 HC	fMRI-stroop	Manic BD right ventral frontal ↓, depressive left ventral frontal ↑ activation
Blumberg et al., 2003b	10 BP, 10 HC	fMRI-stroop	BD left putamen and thalamus ↑ activation
Adler et al., 2004	15 euthymic BD, 15 HC	FMRI-WM	BD, frontopolar, temporal lobe, basal ganglia and ↑ thalamus activation
Chang et al., 2004	12 BD I male (family story +), 10 HC	fMRI-spatial WM task	BD frontal cingulate, left putamen/thalamus, left DLPC increased activation
Gruber et al., 2004	11 stable BD, 10 HC	fMRI-stroop	BP ↑ DLPC activation, ↓ right singulate activation
Monks et al., 2004	12 euthymic BD I, 12 HC	fMRI-WM task	BD bilateral frontal, temporal, Parietal hypoactivation
Strakowski et al., 2004	10 euthymic BD, 10 HC	fMRI-CPT	BD ↑ limbic, paralimbic and ventrolateral PFC activation
Altshuler et al., 2005	11 manic, 13 HC	fMRI- Go- No Go	In Mania right orbitofrontal activation less prominent
Adler et al., 2005	11 BD+DEHB 15 BD	FMRI-simple attention	comorbid DEHB decreased medial frontal and cingulate activity relation
Dunn et al., 2005	9 BD, 9 HC	PET-CPT metabolism blood flow relation	No difference
Strakowski et al., 2005	16 euthymic BD, 16 HC	fMRI-Stroop	BP occipital ↑ activation, middle frontal gyrus, temporal lobe ↓ activation
Brooks et al., 2006	8 BD-depression 27 HC	PET-CPT	BD: comission-decreased DLPC activation and ommision-decreased subgenual activation relation
Deckersbach et al., 2006	8 BD, 8 HC	PET-verbal learning	Sol DLPC ↓ reduced activation
Kronhaus et al., 2006	10 remission BD, 11 HC	fMRI-stroop	BD orbital-medial PFC ↓ reduced activation
Roth et al., 2006	11 BD, 11 HC	fMRI-Stroop	BD decreased right middle and inferior frontal gyrus
Zimmermann et al., 2006	27 BD, 22 HC	MRI-executive function relation	Rostral and subgenual cingulate grey matter –WCST, white matter trace B relation
Lagopoulos et al., 2007	10 euthymic BD, 10 HC	fMRI-WM	BD frontal hypoactivation

HC: healthy control; fMRI: functional magnetic resonance imaging; DLPC: dorsolateral prefrontal cortex; PFC: prefrontal cortex; PET: positron emission tomography; WM: working memory; CPT: continuous performance test.

answering a non-target stimulus is defined as a commission error. Target-detection difficulty (omission error) is the most frequent symptom observed with CPT during the euthymic period of BD. Nevertheless, a few stud-

ies did not find any difference in CPT performance between controls and BD patients in a euthymic period (Bozikas et al., 2005). For CPT Robinson et al. (2006) calculated a common score based on omission and com-

mission errors according to the signal processing theory, and reported group differences with medium level effect sizes (Cohen D score between 0.5 and 0.6) that were smaller than verbal memory and executive functioning. According to Clark et al. (2002), target detection on CPT is the most prominent cognitive dysfunction during the euthymic period of BD. Our findings also support the view that sustained-attention difficulty is present in BD and, moreover, it shows an increase in the target answer variability. According to our findings, the magnitude of impairment in BD are; for target fixing difficulty (omission) is 0.9, for false alarms (commission) it is 0.55, and the variability score is 0.70 (Bora et al., 2007). Due to differences in score calculating methods and to different psychometric characteristics of various CPT, it is difficult to compare results. The difficulty level of various CPTs is very diverse. For example, a complicated target can become burdensome to functioning memory: however, in our opinion, effect size calculations based on signal processing theory are controversial. In this method, calculations are based both on omission and commission errors; however, during the euthymic period only target detection difficulties (increased omission errors) are observed (Clark and Goodwin, 2004). When target-detection difficulty is scored separately, a group difference with a large magnitude was reported (Clark et al., 2002; Bora et al., 2007).

### **Psychomotor Speed**

In some studies a continuation of decreased psychomotor speed during the euthymic period of BD has been reported, and Robinson et al. (2006) reported an effect size for the Trail-Making A test of 0.5. In our study the Trail-Making A test effect size was 0.65 (Bora et al., 2007).

### **Effect of the Illness Period on Cognitive Symptoms**

#### **Effect of the Manic Episode**

Number of false alarms on CPT for euthymic BD patients was reported to be the same as for normal subjects, whereas during the manic period the number of false alarms increases sharply (Bora et al. 2006). Moreover, target detection difficulties in euthymic BD patients intensify during manic periods (Clark and Goodwin, 2004; Bora et al., 2006). There are also problems observed in response inhibition evaluation tests administered during manic periods (Murphy and Sahakian, 2001). Dixon et al. (2004) showed that executive dysfunction in manic

BD patients is more severe than in depressive or euthymic BD patients. Fleck et al. (2003) recorded the same level of memory and a higher level of recognition dysfunction in manic BD patients, as compared to euthymic BD patients. Other studies report performance differences between manic and euthymic periods in adult (Martinez-Aran et al., 2004) and pediatric (Pavuluri et al., 2006) BD patients. However, it can be said that the manic period is related to more prominent frontal lobe dysfunction. Another thing to be taken into consideration is that the cognitive functions cannot be tested in most severe manic patients; therefore, in reality, cognitive dysfunction could be more severe than reported.

### **Effect of the Depressive Episode**

It is known that there is distinctive cognitive dysfunction during the depressive period of BD; however, the comparison between euthymic and depressive patients has not been studied sufficiently. Rubinsztein et al. (2006) observed dysfunction in depressed BD patients that they did not observe in euthymic patients with decision-making tests. Malhi et al. (2007) observed executive functioning and attention disorders in depressed BD patients that were not seen in euthymic patients. However, there is very little research comparing euthymic and depressive periods in BD patients and it has also been reported that euthymic patients are no different than depressive patients (Martinez-Aran et al., 2004). Some studies did not find significant difference between depression and mania (Martinez-Aran et al., 2004), whereas others report that cognitive dysfunction is less severe in depression than mania (Sweeney et al., 2000; Gruber et al., 2007). According to these last 2 studies, there is more distinctive frontal dysfunction in mania than in depression. However, cognitive symptoms specific to depression and mania in BD have not received adequate attention.

### **Effect of Sub-threshold Affective Symptoms**

BD is a psychological illness associated with frequent and sudden emotional fluctuation. Fluctuations in the mood disorder state prevail during the post depression and post manic periods. In some studies that investigated cognitive functioning euthymic period measurements were not properly defined; therefore, it is thought that the symptoms of cognitive dysfunction seen in euthymic BD patients are present because the illness period has not come to a complete end or due to the mild affective symptoms (Savitz et al., 2005). In some studies, when cognitive tests are corrected for sub-threshold affective

symptoms, less difference with respect to the control group was observed (Clark et al. 2002). Other studies have found only very small relationships between psychomotor speed (Goswami et al., 2006; Bora et al., 2007), learning and memory (Goswami et al., 2006), and attention (Frangou et al., 2005), and sub-threshold symptoms, especially depressive symptoms. In recent studies, the euthymic period has been defined more clearly and yet similar cognitive dysfunction has been recorded (Robinson et al. 2006). These results demonstrate that cognitive dysfunctions observed in euthymic BD patients can not be explained with residual symptoms of mood disorder.

### **Cognitive Functions in the Relatives of BD Diagnosed Patients**

#### **Relative Studies**

Very few studies have investigated the relationship between the presence of genetic risk for BD and cognitive dysfunctions. There is evidence that executive dysfunction (Clark et al., 2005; Frangou et al., 2005; Bora et al., 2006c) and working memory dysfunction (Ferrier et al., 2004; Bora et al., 2006c) are present in the relatives of BD patients. Frangou et al. (2005), unlike the 2 studies (Clark et al. 2005, Bora et al. 2006c) mentioned above, have found that cognitive flexibility performance was normal and asserted that only ventromedial frontal cortex dysfunction is BD's endophenotype.

One cause for the differences between these studies could be the history of psychosis in the families of BD patients. One study reported that poor cognitive flexibility test results of healthy relatives could be related to the existence of diagnosed psychotic periods of the BD patient (Bora et al., 2006c). However, due to the small sample of that study it is difficult to reach to a conclusion on this matter.

Some studies (Keri et al. 2001) have shown that the healthy relatives of BD patients could have a verbal memory disorder; however, other studies have not supported this finding (Ferrier et al., 2004; Clark et al., 2005; Bora et al., 2006c).

In some studies CPT performance of the healthy relatives of BD patients have been investigated and no significant evidence of sustained attention dysfunction in them was found (Clark et al. 2005, Bora et al. 2006c); however, this result maybe due to the small sample used in both studies.

### **Twin Studies**

Gourovitch et al. (1999) compared 7 monozygotic twins (one of each set of twins was diagnosed with BD) to 15 healthy control monozygotic twins and reported dysfunction in working memory and verbal memory in the BD twins. Kieseppa et al. (2005) compared 19 twins (one of each set of twins was diagnosed with BD) to 144 controls and found verbal dysfunction only in the female twins. Christensen et al. (2006) reported memory and language dysfunction in healthy dizygotic twins of mood disorder patients. Moreover, they reported executive dysfunction, difficulty in sustained attention, and working memory disorder in healthy monozygotic twins. As a result, relative studies have set forth that cognitive dysfunction can be evidence of genetic risk.

If the studies mentioned in the first section are to be summarized: (a) verbal memory and attention-sustaining dysfunction in BPD, have been consistently presented in euthymic patients, however the results of the studies on healthy relatives are inconsistent. This finding may indicate that verbal memory and attention disorder may be the result of illness process or on the contrary, may indicate that these deficits may be signs for the vulnerability of the underlying genotype. (b) Disorder in executive functions was found both in euthymic patients and healthy relatives. These findings points out that executive functions are one of the possible endophenotypes of bipolar disorder. However, it is necessary to show the relation of these variables to the cause of illness, neurobiological indicators and genetic of bipolar disorder.

### **Nature of Cognitive Symptoms in Bipolar Disorder**

The presence of cognitive dysfunction in euthymic state of BD show that these symptoms may be persistent features of the illness and may be connected to BD pathophysiology. Are these cognitive symptoms related to the nature of the illness, or can they be side effects of medication used for treatment? Are cognitive dysfunction symptoms present from the onset of the illness? Does the severity of these symptoms increase in time? Can the cognitive symptoms in BD, be the direct indicator of genetic risk factors of the illness? Finding answers to such questions may shed light to pathophysiology of BD.

## **Effect of Course of Illness (Table I)**

### **The Effect of Course of Illness and Number of Episodes**

There is evidence for cognitive dysfunction symptoms being more severe in bipolar patients who experience greater number of episodes (Bearden et al. 2001). Moreover, Strakowski et al. (2002) pointed out that there is prominent enlargement in ventricles in bipolar patients who experienced many episodes compared to first-episode manic patients. Such evidence suggests that bipolar disorder may have a neurodegenerative aspect or illness episodes may be neurotoxic in quality (Savitz et al., 2005).

It is already known that prominent cognitive dysfunctions are present in patients during their first episode (Albus et al., 1996). Cognitive dysfunction symptoms were also reported for the post first episode period of euthymic patients. Kolar et al. (2006) reported distinctive dysfunctions on executive functions and sustained attention in a group of patients whose illness onset is less than 5 years and who have maximum 2 illness episodes when compared to a control group. Nehra et al. (2006) could not find a difference between euthymic bipolar patients who have experienced one period or multiple periods of illness. Nevertheless, it seems that longitudinal studies are required to reach a conclusion on this matter.

### **Effect of Duration of Illness**

Many studies have shown that the length of the course of illness is related to the cognitive dysfunctions in BD. The low performance in the fields of verbal memory (Clark et al., 2002; Cavanagh et al., 2002; Deckersbach et al., 2004; Martinez-Aran, 2004), executive functions (Clark et al., 2002; Frangou et al., 2005; Thompson et al., 2005; Torrent et al., 2006), psychomotor speed (Martinez-Aran 2004, Torrent et al. 2006, Bora et al. 2007), working memory (Torrent et al. 2006) are all related to the length of the course of episodes.

### **Effect of the Number of Manic Episodes**

There is a relation between number of manic episodes and cognitive symptoms of BD. Cognitive dysfunctions in the fields of verbal memory (Van Gorp et al., 1998; Clark et al., 2002; Cavanagh et al., 2002; Deckersbach et al., 2004; Martinez-Aran, 2004), sustained attention (Clark et al., 2002), executive functions (Van Gorp et al., 1998, Zubieta et al., 2001; Goswami et al., 2006), psychomotor speed (Bora et al., 2007) are related to the number of manic episodes.

## **Effect of the Number of Depressive Episodes**

Studies have shown that there is relationship between number of depressive episodes and cognitive dysfunctions. However the severity of the relationship is weaker than the relationship of manic episodes. Findings in the fields of verbal memory (Clark et al. 2002, Deckersbach et al. 2004), executive functions (Zubieta et al. 2001, Clark et al. 2002, Thompson et al. 2005), working memory (Clark et al. 2002), non-verbal memory (Deckersbach et al. 2004), psychomotor speed (Bora et al. 2007) show that there is a relationship with the number of depressive episodes.

### **Effect of the Onset Age**

Few studies, have investigated the relationship between the onset age and cognitive symptoms. One study reports a relationship between an early onset age and verbal memory dysfunction (Bora et al., 2007). However, there is not much evidence pointing to the effect of the onset age on cognitive symptoms, unlike the length of episodes.

As a result, cognitive dysfunctions in BD are observed starting from the onset of the illness, yet become more crystallized, possibly with recurring episodes. This result supports the view that repetitive episodes have neurotoxic effect. During the recurring episodes, increased cortisol levels (Watson et al., 2004) or decreased BDNF levels (Machado-Vieira et al., 2007) may damage the structures such as the hippocampus and frontal cortex. However, it is also possible to explain these findings from a different perspective; there may be a relationship between experiencing more episodes and having severe cognitive dysfunction from the very beginning. Cross-section studies cannot exclude this probability. Moreover, there are methodological restrictions to collecting episode stories. It is expected that the depressive periods be overlooked by the manic periods in the stories received from patients and observation folders. On the contrary to schizophrenia, there is very little direct data about the time dependent changes of cognitive deficits in BD.

## **Bipolar Disorder Subtypes, Effects of Additional Diagnosis on Cognitive Symptoms**

### **Effect of Psychotic Symptoms**

Albus et al. (1996) reported that cognitive dysfunction in schizophrenia is more severe than non-psychotic diagnosed patients. In the absence of psychotic symptoms, it is thought that the psychosis history is also related to the cognitive symptoms. Martinez-Aran et al.

(2004) reported a relationship between verbal memory dysfunction and psychosis story. Glahn et al. (2006), found out a relation between working memory dysfunction and psychosis history in a combined group of euthymic and symptomatic patients. Selva et al. (2007) however, could not point out a relationship of psychosis history to cognitive symptoms in a small sampled study of euthymic and symptomatic patients. In one of our studies, we investigated the presence of a relationship between history of psychotic episodes and cognitive symptoms, with relatively big sample, where all of the samples were in remission (Bora et al. 2007). According to the evidence of this study, memory disorder and specifically cognitive flexibility disorder (WCST) were recorded only in bipolar patients who have lived psychotic periods. The cognitive dysfunctions in sustaining attention, psychomotor speed and attention constituent in prominent executive function tests (Stroop, Trail Making B) were not found relational to psychosis stories. These results show that psychosis in bipolar patients may be related to cognitive symptoms, especially frontal lobe dysfunction. However it is difficult to pass judgment on this subject at this point since alternative explanations may also be relevant. For example, it is known that the number of manic episodes is more in patients that have psychotic features, and previous results may be pointing to the idea that more manic bipolar disorder symptoms are related to more severe cognitive dysfunction. Or only in a specific group of psychotic BD patients, namely the ones with mood disorder psychotic symptoms, there may be more severe cognitive dysfunction.

### **Effect of BD Type I and II**

Very few studies have compared the cognitive abilities of BD type I and type II. Torrent et al. (2006), compares the neuropsychological performances of 33 euthymic BD II patients, 38 euthymic BD I patients and 35 healthy controls and figures out that BP II patients go through less severe cognitive dysfunctions than BD I group. In this study, it is observed that in attention and psychomotor speed dysfunctions BD II patients are equal in severity to the BD I, whereas in verbal memory and Stroop tests the performance of BD II patients were better than BD I patients and worse than the control group. In another study of the same team, verbal memory performances of BD I patients were reported as worse than BD II patients (Martinez-Aran et al., 2004). In a study investigating verbal memory in child patients, the performance of the BD II patients, unlike the BD I patients, were no different than the control group (Glahn

et al. 2005). On the other hand, Summers et al. (2006) - in contradiction with the results mentioned above- when working with a combined group (euthymic and depressive), found out that BD II patient's IQ, memory and executive function performances were worse than BD I patients. Authors have set forth the view that cognitive dysfunction in bipolar disorder is more conditional to repetitive depression. Harkavy-Friedman et al. (2006), however, compared the cognitive functions of depressive BD I and II patients who have past history of suicide attempts. They recorded differences between the two groups. BD I patients displayed lower performance on verbal fluency and BPD II patients displayed lower performance on Stroop test and reaction time. Judgment on this matter has not been made yet, and contradictory results seem to be related to the residual depressive symptoms in BPD II patients and poor matching of the samples.

### **Effect of Additional Diagnosis (Comorbidity)**

Additional diagnosis, such as anxiety disorders and attention deficit hyperactivity disorders (ADHD) are frequently encountered in BD patients. Pavuluri et al. (2006) displayed that additional ADHD diagnosis, increases the severity of executive function and attention deficits. In another small sample study of adolescent BD patients, where only ADHD accompanies the illness, there was prominent cognitive dysfunction encountered (Rucklidge, 2006). Some other studies (Doyle et al., 2005; Bearden et al., 2007) show that cognitive dysfunctions in adolescent BD patients cannot be explained with ADHD symptoms. Comorbid Obsessive-Compulsive Disorder and other anxiety disorders can also affect the cognitive functions, however there is not enough evidence on this. Deckersbach et al. (2004) found that BPD patients with various anxiety disorders have dysfunctional verbal memory performance and Bearden et al. (2007) reported a relationship between anxiety disorders in BPD and cognitive problems. In most of the older studies, the effect of comorbidity on cognitive functions was disregarded. However this topic is very important for interpretation of the results.

### **Relationship of Cognitive Symptoms to the Medication effects and Accompanying Drug Abuse**

It is likely that medication used in treatment of bipolar disorder contributes to cognitive dysfunction, such as sub-threshold mood disorder, in euthymic patients. Most of the BD diagnosed patients use lithium, anticonvulsant and antipsychotics alone or together, during the

euthymic period. Although there are studies that show that lithium may have negative effects on cognitive functions (Honig et al., 1999), some others (Stip et al., 2000; Savitz et al., 2005) do not support this view and show that lithium does not have negative effect on long-term cognitive functions. In most of the studies, BD patients using lithium do not seem to be different, in their cognitive performances, than the ones that do not use (Clark et al., 2002; Altshuler et al., 2004; Frangou et al., 2005). In one of the studies there was a reverse correlation between lithium serum level and verbal memory performance. However this relation was not enough to explain the memory dysfunction in remission (Bora et al. 2007).

The effect of anticonvulsants on cognitive functioning has been studied less. It is thought that valproic acid does not have side effects apart from moderate attention disorder (Savitz et al. 2005). In a series of events, the cognitive functions of patients were recorded to improve where lithium was cut and valproate was given to them (Stoll et al., 1996). Şentürk et al. (2007) reported no difference in cognitive functions of patients using only valproate or only lithium.

We have very little knowledge on the cognitive side effects of carbamazepine and new anticonvulsants in BD. One study compared the cognitive functions of patients diagnosed as BD who were using lithium, carbamazepine, oxcarbazepine, valproate, lamotrigine and topiramate (Gualtieri et al., 2006). According to the result of this study, oxcarbazepine and lamotrigine had minimum, topiramate had maximum cognitive side effect. Lithium was related to mid level cognitive dysfunction. However due to the cross-session nature of the study, the differences in question between the groups may be resulting from other differences.

There is some evidence that the BD patients using antipsychotics have low performance on cognitive functions. Some studies pointed out relationship between antipsychotic usage and cognitive symptoms in BD. Altshuler et al. (2004) have reported a relation between antipsychotic usage and low WCST performance. However in this study, antipsychotic usage was not explaining the cognitive dysfunction in BD by itself. Zubieta et al. (2001) have found a relation between antipsychotic usage and performance dysfunction in WCST. Frangou et al. (2005) also found out that the frontal lobe tests of patients using antipsychotic medication are worse and tied this down to the relation of dopamine to some executive functions. The usage of antipsychotics was also related to low IQ and verbal memory dysfunction (Donalson et al., 2003) and psychomotor slowness (Bearden et al., 2007). Nevertheless, there are

studies that did not report negative effect of antipsychotic usage (Pavuluri et al. 2006). Besides, as in schizophrenia, atypical antipsychotics are argued to have less negative effects on cognitive functions in BD. However data on this subject is very few. Reinares et al. (2000) having compared sub groups of euthymic BD patients that use typical antipsychotics and risperidone, reported that patients using risperidone have scored better performance in a single test (trail making B).

Studies mentioned above direct to a possible relationship of treatment to cognitive problems in BD. However these studies do not explain completely the cognitive dysfunction in remission (Savitz et al. 2005). Besides some other studies did not find any difference for cognitive functions between drug users and non-drug users (Deckersbach et al. 2004, Pavuluri et al. 2006). Besides, there are interpretation difficulties for studies, which investigate the relationship between cognitive dysfunction in bipolar disorder and drug use. The differences between drug users and non-drug users may be arising from other diverse characteristics of the groups, rather than the effect of the drugs. For example the antipsychotics given to patients with more severe pace or who are in psychotic phase can be one factor. The antipsychotic and other drugs' effect on cognitive functions during the illness have not been studied much. In one research, a relation between sedation in manic patients and target detection difficulty was set forth (Bora et al. 2006a). Usage of high doses of psychotropes may lead to aggravation of cognitive dysfunction during the manic phase. However, psychotropic drugs may correct the cognitive functions, via tranquillizing the symptoms (Gualtieri et al. 2007).

Alcohol and drug usage in BD is encountered, especially in developed countries (Chengappa et al., 2000). Alcohol and drug usage is associated with cognitive deficits and Van Gorp et al. (1998) have reported more prominent cognitive dysfunction in BD diagnosed patients. However, it does not seem possible to relate the cognitive dysfunction accompanying BD to drug usage (Savitz et al. 2005). Moreover, the similarity of data collected in countries like Turkey and India -where drug usage in BD patients is not very common- to the data coming from developed countries; supports this view (Bora et al., 2007; Gowami et al., 2006).

## **Cognitive Symptoms in Bipolar Disorder and Brain Imaging Findings (Table II)**

### **Structural Imaging Studies**

Very few studies have investigated the relationship

between cognitive symptoms in BD and structural brain imaging findings. One study has looked into the relation of white matter lesions, which is a very frequent finding in BD, with cognitive dysfunction, however could not find out any symptoms (Krabbendam et al., 2000). Zimmermann et al. (2006) have reported a relationship between decrease in the volume of frontal cingulate regions and executive dysfunction. Subgenual and rostral grey matter volume anticipates a dysfunction in WKET and rostral white and grey matter volume anticipates a Trail Making Test performance dysfunction, in BD. Sax et al. (1999) have presented a relationship between sustained attention and frontal and hippocampal anomaly, whereas So et al. (2000) have presented a relationship between increase in right hippocampus volume and cognitive dysfunction.

### Functional Imaging Studies

Functional imaging methods have been utilized more in researches studying the cognitive dysfunction in BD. In BD, the most frequently used task for activation in functional imaging studies has been Stroop test. Blumberg et al. (2003) have studied three bipolar disorder groups with euthymic, depressive and manic symptoms and healthy control's neuronal activity during Stroop test. In the left ventral prefrontal cortex of the patient group, low activation -compared to control group- has been recorded which cannot be explained by illness symptoms. Moreover, decreasing activation on the right of ventrolateral prefrontal cortex has been found in relation to mania and increase in activation on the left has been related to depression. Gruber et al. (2004) have reported decrease in the activation of frontal cingulate cortex in bipolar patients. In BPD, decrease in the ventral frontal activation during Stroop test and during other fMRI studies, both in euthymic and symptomatic patients, have been presented (Kronhaus et al., 2006; Roth et al., 2006). In euthymic bipolar patients, during Stroop test, increase of activation in dorsolateral frontal cortex, basal ganglia, thalamus and occipital cortex have been presented (Gruber et al., 2004; Strakowski et al., 2005). During manic period decrease in orbitofrontal activation have been presented during verbal fluency (Blumberg et al., 1999) and during Go-No Go test (Altshuler et al., 2005). In BD sustained attention problems have also been investigated via functional imaging methods. Strakowski et al. (2004) have reported increase in the limbic, paralimbic, ventral frontal and visual association cortex activity during CPT task, compared to healthy control group. In PET practice, Brooks et al. (2006) have reported some results in BD patients during depressive period, between CPT performance and

prefrontal cortex metabolism, which were not present in the control group. In this study, relationships were found between decreased subgenual prefrontal cortex activity and target detection difficulty and delay in answering time and between slowing down of dorsolateral prefrontal cortex metabolism and false answer mistakes. Accompanying diagnosis may effect the activation pattern observed during cognitive functions in BD. BD-DEHB comorbidity, during attention test, was found relational to decrease in ventrolateral prefrontal cortex and frontal cingulate activity and increase in posterior parietal cortex activity (Adler et al. 2005).

In euthymic period patients, during learning, there has been less increase in dorsolateral frontal cortex and hippocampus activity, compared to controls (Deckersbach et al. 2006). During working memory tasks in BD, changes in brain functioning have been reported. Some studies, have reported decrease in two sided frontal, parietal and temporal cortex activity during working memory task and decrease in supramarginal gyrus and right medial frontal cortex activity in euthymic bipolar patients (Monks et al., 2004; Lagopoulos et al., 2007). In other two studies, on the contrary, hypo-activation in frontal cingulate cortex, thalamus, basal ganglia, temporal lobe and left dorsolateral frontal cortex was reported (Adler et al. 2004, Chang et al. 2004).

If we are to summarize imaging studies, the most important finding is that there is functional and probably moderate structural disorder in the areas of brain that work under the cognitive control of emotions such as cingulate cortex and frontal lob. However the quality of the data about functional disorder are incoherent. In manic period, decrease in ventrolateral and medial frontal cortex activity is observable. In depression however, although findings are not enough increase was visible. In euthymic period, findings are more contradictory. Results of some studies, Strakowski et al. (2005), support the view that in bipolar disorder, on brain regions related to cognition there is decrease in activation, and on brain regions related to emotion there is increase in activation. Yet, in opposition to these findings, presence of euthymic orbital hypo-activation and dorsolateral hyper-activation were also presented. This case may be due to the difference in difficulty level of the tests used. The structurally dysfunctional regions of brain may be showing greater activity than normal, during simple tasks, to accomplish the task.

## Factors Affecting the Cognitive Symptoms in Bipolar disorder

Two studies pointed out to a relationship between cognitive disorder and Herpes Simplex Virus type I (HSV I) infection (Dickerson et al. 2004, Dickerson et al. 2006) in BD. Weak neurological findings have been associated with executive dysfunction in BD (Goswami et al. 2006). One study reported relationship of abnormality in dexamethasone suppression test and low performance in working memory test, which was not present in controls (Watson et al. 2006). Relationship was found between homocysteine level and cognitive disorder in BD (Dittmann et al., 2007).

## Cognitive Symptoms in Bipolar Disorder and Genetics

Two studies, reported a relationship between BDNF polymorphism and WCST performance (Rybakowski et al., 2004, 2006). According to the results of these studies Val/Val BDNF genotype carrying BD patients were more successful than the Val/Met genotype carrying ones in WKET test. In another study, genetic variation in lissencephaly critical region (chromosome 17p) that carry the LIS 1 gene and thrombocyte activating factor related gene, is found to be related to WKET perseverative errors in BD and Schizophrenia (Tabarres-Seisdedos et al., 2006). Dickerson et al. (2006), have determined COMT Val158Met genotype as a risk factor for cognitive disorder (especially for learning and remembering) in BD. Szoke et al. (2006) however, could not find a relation between COMT and NET (norepinephrine transporter) and executive functions. Few of the studies

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mentioned above, are interesting for finding relationship between genetic variations and cognitive disorder in BD. However, the relation of these findings to the etiology of bipolar disorder is controversial. It is expected to see effects of hundreds of genes, that take part for brain functions or its growth, on cognitive functions, in normals and patients; however only genetic variations that show a relation specific to cognitive symptoms of bipolar disorder can be accounted for understanding the etiology.

## CONCLUSION

Cognitive Symptoms in BD seem to be related both to the genetic tendency for the illness and the course of illness. The subtypes of bipolar disorder, additional diagnosis and to a certain extend the medication used for treatment, are among the factors that effect the cognitive dysfunction seen during the illness. Cognitive symptoms affect the functionality in a negative way. In this respect, it should be an important goal to develop treatment for cognitive dysfunction in BD. Brain imaging studies, show that the frontal lobe and cingulate cortex dysfunction can be related to BP disorder. In functional imaging studies, in different phases of the illness, utilization of tasks that are specifically related to different cognitive faculties and usage of tests that are related to socio-emotional faculties, should be a latter stage. The relation of brain's functional and structural connectivity variables to cognitive dysfunction should be set forward. Longitudinal studies and relative studies which jointly investigate neuropsychological, brain imaging, genetic and molecular biological methods carry great importance to understand the nature of the illness.

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