Clinical Determinants of Cognitive Dysfunctions and Cognitive Endophenotypes in Bipolar Disorder

Murat İlhan Atagün[1,2], Özlem Devrim Balaban[1], Kürşat Altınbaş[2], Sema Yeşilyurt[3], Devran Tan[4]

[1]Psychiatrist, 12. Psychiatry Clinic, [2]Psychiatrist, Raşit Tahsin Mood Center, Outpatient Unit, [3]Psychiatrist, Psychotic Disorders Outpatient Unit, Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, İstanbul [4]Assistant Prof. Dr., Maltepe University Medical School, Department of Psychiatry

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ÖZET

İki uçlu bozuklukta bilişsel işlev bozukluklarının klinik belirleyicileri ve bilişsel ara fenotipler

Bilişsel işlev bozuklukları iki uçlu bozukluğun klinik düzelme dönemlerinde dahi hastaları etkilemektedir. Başta sözel öğrenme, sözel bellek ve yürütücü işlev bozuklukları olmak üzere faal bellek, dikkat, dikkati sürdürme ve işlem hızı iki uçlu bozuklukta öne çıkan alt bilişsel alanlardır. Sözel öğrenme ve sözel bellek hastaların yanında birinci derece akrabalarda da en fazla etkilenmiş işlevler olduklarından hastalıkla ilgili bir özellik olabilir, dolayısıyla bilişsel ara fenotip kavramına en uygun aday gibi görünmektedirler. Psikotik hastalık dönemlerinin olup olmaması, geçirilen hastalık dönemi tip ve sayıları, hastalığın başlangıç yaşı ve hastalık süresi bilişsel kayıpları etkilediği belirlenmiş klinik parametrelerdir. İki uçlu bozuklukların erken başlangıçlı formları, tip II bozukluk, yaşlılık ve komorbidite varlığı durumlarında bilişsel işlevlerin nasıl etkilendiği ile ilgili sınırlı sayıda araştırma bulunmaktadır. Ayrıca ilaçların bilişsel işlevleri kalitatif ve kantitatif olarak nasıl etkilediği ile ilgili yeterli ve tutarlı kanıt bulunmamaktadır. Hastaların birinci derece akrabalarında bilişsel kayıpların görülmesi ve kayıpların ailesel benzerlik göstermesi bilişsel işlevler için kalıtım göstergesi olabilir, bu nedenle araştırmaların desenlenmesinde genetik modellerin dikkate alınması önemli veriler sağlayabilir.

Anahtar kelimeler: İki Uçlu Bozukluk, bilişsel işlev bozuklukları, ara fenotip, klinik belirleyiciler

ABSTRACT

Clinic determinents of cognitive dysfunctions and cognitive endophenotypes in bipolar disorder

Cognitive dysfunctions influence patients with bipolar disorder even when they are clinically remitted. Verbal learning, verbal memory and executive functions foremost, working memory, (sustained) attention and processing speed are substantial cognitive domains in bipolar disorder. Dysfuntions in verbal learning and memory might be observed in first degree relatives as well; and thus seem to be best candidates for the cognitive endophenotype concept. Prior psychotic episodes, numbers and types of episodes, age of illness onset and duration of illness are clinical parameters seem to influence cognitive functions. There are relatively limited numbers of researches about cognitive dysfunctions in early onset forms, old age, type II disorder and comorbidity aspects of bipolar disorders. Results from the researches regarding qualitative and quantitative effects of medications on cognition are inconsistent. Cognitive deficits of first degree relatives and familial resemblance of deficits might be indicators of heritability of cognitive functions, therefore taking genetic models into account in designs of researches may provide considerable data.

Key words: Bipolar Disorder, cognitive dysfunctions, endophenotype, clinic determinents

Address reprint requests to:
Dr. Murat İlhan Atagün, Bakırköy Prof. Dr. Mazhar Osman Mental and Nervous Disease Training and Research Hospital, Raşit Tahsin Mood Center, Outpatient Unit. 34747 Zuhuratbaba, Bakırköy, İstanbul - Turkey

Phone: +90-212-543-6565/1106

Fax: +90-212-660-3222

E-mail address:
muratilhanatagun@gmail.com

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INTRODUCTION

Cognitive dysfunctions can be seen at any stage of bipolar disorder (BD) (1-3), however become more evident at acute mood episodes (2,4-7). Emil Kraepelin said that there is improvement between the acute episodes and cognitive losses recover with clinical remission. In the last 20 years, new evidence cumulated that cognitive losses can also be detected in clinical remission (euthymia) periods (6,8). In this context, cognitive dysfunction cannot be entirely explained by the mood changes. Likewise, in a meta-analysis of studies which cognitive functions were evaluated in euthymic phase, most evident dysfunctions were found

Table 1: Cognitive deficits observed in the euthymic phase of bipolar disorder

Cognitive Funcitons	Study
Executive functions	Ferrier et al. (18), El Badri et al. (19)
Verbal memory	van Gorp et al. (20), Altshuler et al. (21)
Verbal learning	Zubieta et al. (22)
Attention span	Clark et al. (8), Wilder-Willis et al. (23)
Working memory	Ferrier et al. (18)
Visuao-spatial memory	Rubinsztein et al. (24)
Declarative memory	Thompson et al. (25); van Gorp et al. (20)
Problem solving	Scott et al. (26)
Process speed	Tham et al. (27)

Table 2: Studies which executive functions were investigated in bipolar disorder

Araştırma	Görev	Bulgu
Frangou et al., 2005 (29)	Wisconsin Card Sorting Test	No difference was found between euthymic bipolar patients (n=44) and healthy controls (n=44).
Martinez-Aran et al, 2004 (6)	Wisconsin Card Sorting Test	More perseverative errors were found with depressive (n=30), manic and hypomanic (n=44) and euthymic (n=44) bipolar patients compared to healthy controls
Altshuler et al, 2004 (21)	Wisconsin Card Sorting Test	More perseverative errors were found with euthymic bipolar patients (n=40) compared to healthy controls (n=22).
Zubieta et al, 2001 (22)	Wisconsin Card Sorting Test	More perseverative errors were found with euthymic bipolar patients (n=15) compared to healthy controls (n=15) and they gave less correct answers.
Clark et al, 2002 (8)	London Tower Test	No difference was found between euthymic bipolar patients (n=30) and healthy controls (n=30).
Rubinsztein et al, 2000 (24)	London Tower Test	Euthymic bipolar patients (n=18)could give correct answers in longer time compared to healthy controls (n=18).
Thompson et al, 2005 (25)	London Tower Test	Euthymic bipolar patients (n=63) made more moves and could complete in longer time compared to healthy controls (n=63).

in executive and in verbal learning areas. However, areas like verbal memory, abstract thinking, attention processing, response inhibition and psychomotor speed were also found defective (9). In another meta-analysis, moderate dysfunction was found in verbal memory, attention, processing speed and executive function (10). In the meta-analysis of Arts et al. (11), which of these dysfunctions can be a candidate endophenotype was investigated. Verbal memory and executive dysfunction can be detected in milder forms in the families so that these were the best candidate endophenotypes . In their 2-years follow-up study, Mur et al. (12) found that neurocognitive test performance of euthymic bipolar patients were found to be lower compared to healthy volunteers (Table 1).

Current neuroscience models propose that cognitive processes are managed by neuronal networks scattered to various brain regions rather than a single brain region (13). In these networks, most popular approach was regional specialization in these networks, i.e. different levels of responsibility of different regions in data processing (14). According to this theory, specific brain regions (15) and even specific neuron groups (16, 17) may be related with a distinct cognitive process. Sub-cognitive domains which became foremost in current studies are executive functions, working memory, verbal learning, verbal memory, attention, vigilance and process speed.

Main Sub-Cognitive Domains in Bipolar Disorder

1. Executive Functions

Wisconsin card sorting test, block design, London tower test, verbal and non-verbal problem solving tasks, Stroop test, trail making tests, verbal fluency and figure fluency tests and various gambling tasks are some of the tests utilized for testing executive function. Problem solving and reasoning are also considered as executive

function and (based on factor analysis) it was suggested that they can help to seperate working memory from executive functions (28). Studies which executive functions of bipolar patients were investigated was shown in Table 2.

Inconsistency of the findings was interpreted as not all but part of the executive functions were disturbed. Perseverative errors in Wisconsin card sorting test may be considered as reduced cognitive flexibility (6,22,30). Wisconsin card sorting test performance was disturbed before disease started in the high risk group of children (31). However, number of episodes (22) and duration of illness (6) also found to affect test performance.

2. Working Memory

Working memory can be defined as required and temporary storage possibilities, which are needed to increase the neuronal response between the real event and its mental representation. It builds the infrastructure of "higher" cognitive processes like judgement, planning, language and abstract thinking (32,33). Baddeley (34,35) suggested an organization for working memory having 3 components: Central executive component (provides the distribution of information retrieved in memory to the final process regions) and two slave systems, articulating cycle and visual-spatial note book (they provide maintenance of the mental representation of verbal and visual information). Rubinsztein et al. (24) found that euthymic patients poorly performed in remembering the geometric shapes and spatial locations in CANTAB computerized cognitive test battery. Thompson et al. (25) found deficits in spatial memory and disorder in relevant learning (episodical memory) with the same battery. Findings about the visual spatial memory are contradictory. Rubinsztein et al. (24) reported that there is a relationship between visual working memory and hospital days. Thompson et al. (25) found a relationship between total hospitalization numbers and spatial working memory. Similarly, Frangou et al. (29) reported that increased duration of illness also affects executive functions, however, there are also opposite data (36,37).

3. Verbal Learning and Memory

Most consistent findings about the cognitive deficits in bipolar disorder are the ones from the verbal memory tests (4,6,20,21,37-43). First degree relatives who were not affected by the disease were also performed badly at verbal memory tests (44,45). Executive functions are directly related to learning and memory problems and learning and memory problems in bipolar disorder can be related with this. Deckersbach et al. tested this (41) and concluded that impairment can be related with semantic clustering. However, in another study it was concluded that problem in the learning strategy can be related with coding (38). Bipolar patients performed badly in episodic memory tests in the acute episodes (46,47). Martinez-Arán et al. (48) suggested that delayed verbal recall is the best cognitive criterium to predict psychosocial functionality in the global evaluation of functionality. In the same study, verbal cognitive deterioration in areas like memory and executive functions are related with lower functionality.

4. Attention and Vigilance

Stroop, Dichotic Listening, Continous Performance Test (CPT) and SPAN are tests which can be used to investigate attention processes. It can easily be observed in routine clinical settings that bipolar patients can not concentrate for longer time periods and their attention can easily be reduced. There is a substantial number of studies showing that manic symptoms can affect Continous Performance Test (CPT) (49-55). Clark ve Goodwin (51) reported that manic patients make errors at discriminating target impulses at CPT and false alarms began to increase; however, euthymic bipolar patients make errors only at discriminating target impulses. This test was utilized in the studies published by other groups and similar results were reported (39, 51, 56). There are studies which showed that duration of illness and severity are inversely correlated with attention processes (51, 57, 58) and there are also studies which could not concluded at the same results (59). Reasons for these confusing results may be due to attention process deficits starting with or before the disease in a

small proportion of patients.

5. Process Speed

Digit-symbol exchange, Trail Making and Stroop are among tests which can used for measuring process speed. If process speed is a parameter as the consequence of different brain regions working in coordination then cognitive slowing can be an important criterium for evaluating neuronal competence. Digit-symbol exchange (25) and trail making tests A and B (18, 27, 60) were found to be defective in euthymic patients. Cognitive slowing was found in bipolar disorder, depression (46, 61), hypomania and mania (39, 46, 61, 62). There are studies which found correlation between process speed (6, 25) and duration of illness (27). Clark et al. (8) found that process speed slows in patients who do not take medication (n=11) and for this reason suggested that reduction in process speed is not related with treatment in their small size study.

Relationship between Clinical Factors and Cognitive Functions

There is evidence showing cognitive deficits affect functionality more than sub-syndromal symptoms (6, 48). It was showed that number of previous episodes (especially mania), number of hospitalizations, presence of psychotic symptoms and total duration of illness affects cognitive functions (memory, attention, abstraction etc.) negatively (6, 22, 63). In a study done in early-onset bipolar patients, even though short time passed between illness onset and evaluation and not too many mood periods have been experienced, deficits detected in adults are also present in childhood bipolar disorder (64). Bora et al. (65) reviewed 45 studies and reported a correlation between age of onset and verbal memory deficit and psychomotor slowing. Joseph et al. (66) reviewed studies on cognitive functions in childhood bipolar disorders and reported that most consistent findings were at verbal memory, attention, executive functions and working memory like in adults. Martino et al. (67) compared 20 elderly euthymic patients whom have mean 28 years disease duration with age, gender, education and premorbid IQ matched 20 healthy volunteers. Significant differences were found in sub-tests in verbal memory, psychomotor speed and executive functions and results were not reported different from the young population. These findings are consistent with Young et al. (68).

Torrent et al. (69) investigated the presence of cognitive deficits in type II bipolar disorder. Cognitive deficits mainly in verbal learning and executive functions were found in type II which is less severe than type I. Authors noted this does not mean that type II disorder is not a milder disease.

In the study of Glahn et al. (36) done in euthymic and symptomatic mixed patient groups, presence of previous psychotic episodes found to negatively affect cognitive functions (working memory). Bora et al. (70) showed the relationship between the history of psychotic episode and memory and cognitive flexibility impairment in their relatively big sample and totally composed of euthymic patients.

In a study which investigated the impact of gender on cognitive functions in bipolar disorder, performance of male patients were found to be worse than female ones (46). There are few studies on the impact of comorbidity on cognitive dysfunction in bipolar disorder. Van Gorp et al. (71) reported that executive functions of the alcohol addicts were impaired compared to healthy controls. Impact of comorbid disorders (as attention deficit hyperactivity disorder, substance and alcohol addiction, anxiety disorders) with bipolar disorder on the cognitive deficits are subjects waiting to be evaluated.

Effects of Medications on Cognitive Functions

It was previously thought that mood stabilizers do not have any significant effect on cognitive performance (72). However, in the meta-analysis of Wingo et al. (73) which 12 studies in the literature were analysed, 276 lithium using and 263 non-lithium using patients were compared and it was found that verbal memory and verbal learning have been negatively affected in the lithium group. In a recent study, cognitive performances of 20 lithium-using, 20 non-lithium using and 20

healthy volunteers were compared (74). Verbal memory performances of all bipolar patients were found worse than healthy volunteers regardless of medication use. No difference was found between the medication using and non-using groups and this interpreted as lithium not negatively affecting cognitive functions. Rybakowski et al. (75) grouped patients as good responders (n=12), partly responders (n=26) and non-responders to lithium and compared them with patients' first degree relatives and healthy volunteers. Non-responders to lithium performed worse in Wisconsin card sorting test compared to good responders, first degree relatives performed worse than healthy controls. In the meta-analysis of Wingo et al. patients were divided into two groups: lithium using and non-lithium using. It can be observed that non-lithium using patients were not without treatment. Şentürk et al. (76) compared verbal memory and executive functions of patients using lithium as monotherapy (n=17) and valproate as monotherapy (n=11) with healthy volunteers (n=29) by using Wechsler Memory Scale and Wisconsin card sorting test and found that performance of lithium and valproate groups were similar but both of their performance were lower than healthy controls. In the comprehensive review of Bora et al. (65), it was reported that medications are related with psychomotor slowing.

Information on the effects of first generation antipsychotics and benzodiazepines are based on clinical observations. In bipolar disorder which chronobiology is importantComparative studies needed considering the impact of treatment on cognitive functions. However, there are some ethical obstacles. In a recent review by Balanzá-Martinez et al. (77) a novel method was proposed by having medication sensitive patients investigated to obtain important data.

Difficulties of investigating the relatiosnship between medications and cognitive disorders can be listed as follows: There is a substantial amount of variation related with dose and type of treatment. Polypharmacy became like a rule rather than an exception in bipolar disorder. Data from medication-free or monotherahy subgroups of milder patients - should not be adjusted to the universe of more severe patients. Another methodological problem is successive accumulation of neurocognitive side effects of treatments or contribution of neurotoxicity of drug interactions from combination treatments to cognitive deficits and the impossibility of examining this currently. On the other hand Goldberg and Chengappa (78) proposed that cognitive dysfunction can be part of the disease or of iatrogenic origin.

A Candidate Endophenotype: Cognitive Loss

There is robust evidence from twin, adoption and family studies which shows that bipolar disorder has a strong genetic component and heritability of bipolar disorder was found 80% (79). However, due to its complex, polygenic nature and partial penetrance, its genetic inheritance has not been fully explained (80,81).

It was suggested that endophenotypes which mean endophenotypes are better indicators of genetic tendency. Gottesman ve Gould (82) proposed some criteria for symptoms and signs which can be suggested as endophenotypes. Two important criteria were added due to their relevance with the disease, heritability and co-segregating in families which the disease is clustered:

I. It should be independent from the clinical condition and can also be shown in clinically improved patients;

II. It should be observed in relatives whom were not affected compared to general population.

Determining endophenotypes is important due to following reasons:

i. They may make the genetic linkage stuides easier and accelerate them;

ii. They may make it possible to predict which individulas will develop bipolar disorder in the future;

iii. They may provide early diagnosis and intervention possibilities;

iv. They may be utilized to develop sub-types.

There are several convincing studies showing that cognitive dysfunctions are strong endophenotype candidates in schizophrenia (83-85). However, there is not enough evidence for bipolar disorder yet. In their recent publication of Bora et al. (65), they reviewed researches which evaluated euthymic patients (45

studies and 1423 patients) and their first-degree relatives (17 studies, 443 participants). It was reported that attention deficit, response inhibition, executive functions and verbal memory deficits were observed both in patients (medium-to-high impact magnitude) and relatives (small-to-medium impact magnitude), deterioration in process speed, visual memory and verbal fluency were only observed in patients.

Cognitive deficits in first-degree relatives whom were not affected by the disease suggest possible neurodevelopmental processes of genetic origin. Several studies were done in first-degree relatives of two-sided probands but inconsistent results were obtained (39,44,86). However, in a meta-analysis, statistically significant deficits with a medium-impact factor (Cohen's db: 0.5) in executive functions and verbal memory were found (11). In their systematic review, Balanzá-Martínez et al. (87) found deficits in sub-cognitive domains of verbal learning and memory (6 out of 11 studies), working memory (3 out of 9 studies), psychomotor speed (2 out of 8 studies) and attention (2 put of 8 studies) and they concluded that there is not adequate data. Frantom et al. (88) reported that tests which are most sensitive to cognitive endophenotypes were digit-symbol and block design tests.

Relatively limited losses in patients' relatives suggest that cognitive deficits seen in patients may be due to disease-related factors such as chronic course of the disease, mood episodes, side effects of the treatment and psychiatric comorbidity (89) and this shows that neurodevelopmental process has a little role in the etiopathogenesis of cognitive deficits.

There are several studies done with the relatives of the bipolar type I patients. There are few studies done with the relatives of the bipolar type II patients and when compared with the relatives of the type I bipolar patients, similar but less severe cognitive deficits were reported (44, 90, 91). This finding is in concordance with the presence of less severe cognitive deficits in type II bipolar patients compared to type I patients (69,92).

Determining endophenotypes is possible with combining information from research areas such as cognitive, neuroimaging and genetics (93-95). Tests which are sensitive to learning, memory and executive functions are similar from test functions point of view (93). Verbal learning, memory and working memory are processed in pre- and medial frontal areas and these regions are in close relation with bipolar pathophysiology (96, 97). Similar changes observed in non-affected relatives of patients (94, 95) show that there may be a tendency to emotional and cognitive disorders. Decrease in volume of white and grey matters of ventral striatum and anterior cingulate cortex were observed in patients' relatives (98). Changes in the prefrontal cortex of patients which are independent of mood is thought to be an indicator of the sensitivity to continous pathology (99).

It has been suggested that cognitive impairment may be familial or has genetic origin (100). Cognitive losses may be due to genetic and environmental factors of various degrees. Familial similarity of cognitive loss may be an inheritance indicator of cognitive functions (101) and because of this; genetic should be considered in designing research. Heritability has been shown in some cognitive deficits (56,102) but has not been evaluated in bipolar disorder in detail(103). Investigating cognitive functions in families with bipolar patients by genetic transference methods is important to test whether cognitive functions can be endophenotypes or not.

CONCLUSION

Executive dysfunction is generally not fulminant in bipolar disorder and different functions were affected with various severity. However, determining the degree of impairment in different executive functions can be done by developing current tests, studies done with bigger samples and investigating the underlying neuroanatomy. Dysfunction of tracts between prefrontal areas and other brain regions can explain both executive dysfunctions and affective findings such as disinhibition, impulsivity and attention deficit.

The type and degree of cognitive impairment affected by mood episodes, what extent can this impairment be explained by the mood, , impact of the course of disease on cognitive functions, contribution

of comorbidity and lastly the cognitive effects of the medications used are main topics that should comprehensively evaluated.

By the demonstration of functionality affected more by cognitive deficits than sub-threshold symptoms and signs, there is now a new symptom domain in bipolar disorder and therefore cognitive deficits should be added to therapeutic targets. Treatments with cholinergic, dopaminergic and glutamatergic properties may be efficacious as cognitive enhancing strategies. However, when developmental and structural impairment is considered, medications used to improve cognitive deficits in bipolar disorder can be of limited value.

According to current data, verbal learning, verbal memory and working memory are the most appropriate cognitive functions to be endophenotypical indicators. In order current data to reach adequate value of evidence, there is a need for longitudinal follow-up studies with greater samples. Evaluation of stability of deficits in patients' relatives can be provided by longitudinal follow-up studies. Cognitive domains such as language, social cognition, planning and motor skills should also be investigated.

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