



## Research Article

### Cognitive Impairment not only in NeuroBehcet but also for all Behcet Disease Phenotypes

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## Summary

**Background:** Cognitive impairment has been reported for Behçet's Disease (BD) patients, but studies are limited. This study is aimed to investigate neurocognitive profile of Neurobehcet Disease (NBD) patients and BD patients without neurologic involvement (BD-only) in comparison to healthy controls (HC).

**Patients and method:** Totally 49 BD patients (11 NBD, 38 BD-only) and 32 HC were included into the study. After neurological evaluation, all subjects were given a comprehensive battery of neuropsychological tests: Self report of neuropsychological condition (by visual analogue scale-VAS, 0-100), RAVLT, Stroop, PASAT, TMT, SDMT, JLOT, DST, COWAT, ACTT, FST.

**Results:** In the comparison of HC to NBD and BD-only subjects, a poorer performance was observed in both group of patients in almost all the neurocognitive tests, except for Stroop interference score. Both group of patients had lower scores on learning, immediate memory, working memory (ACTT), lexical fluency (COWAT) and attention (DST) comparing to healthy subjects ( $p \leq 0.003$ ). The differences between NBD and BD-only patients were observed on response inhibition ability (STROOP-spontaneous corrections;  $p=0.000$ , and errors;  $p=0.002$ ) and learning (RAVLT-sum of five trials;  $p=0.002$ ). NBD patients had further decrease on free recall (RAVLT), complex visual processing (JLOT), information processing speed (PASAT), attention (TMT-B) and psychomotor speed (TMT-A) ( $p \leq 0.003$ ).

**Conclusion:** Cognitive functions of not only NBD patients but also BD-only patients were worse than control group. Compared to BD-only patients, NBD patients reveal further impairment on memory and executive functions rather than complex visual perception and verbal attention.

**Key words:** Cognitive impairment, NeuroBehcet Disease, Behcet disease

### Behçet Hastalığında Kognitif Bozukluk, Sadece Nörobeçet Değil Tüm Fenotiplerde Görülür

## Özet

**Giriş ve Amaç:** Behçet Hastalığında kognitif yıkım bildirilse de çalışmalar sınırlıdır. Bu çalışma nörobeçet hastaları (NB) ve nörolojik tutulumu olmayan behçet hastalarının (BH) nörokognitif profilini sağlıklı kontrollere (SK) kıyasla araştırmayı amaçlamıştır.

**Hastalar ve metot:** Toplam 49 hasta (11 NB ve 38 BH) ve 32 SK çalışmaya dahil edildi. Nörolojik değerlendirmenin ardından tüm katılımcılara nöropsikolojik test bataryası [Vizüel

Analog Skala (VAS) ile nöropsikolojik durumu öz değerlendirme, RAVLT, Stroop, PASAT, TMT, SDMT, JLOT, DST, COWAT, ACTT, FST] uygulandı.

**Sonuçlar:** Nörobekçet ve Bekçet hastalarında, sağlıklı kontrollere kıyasla Stroop interference skoru hariç hemen hemen tüm nörokognitif testlerde daha düşük performans gözlemlendi. Her iki grup hastanın öğrenme, hızlı hafıza (ACTT), sözel akıcılık (COWAT) ve dikkat (DST) testlerinde, sağlıklı kontrollere göre daha düşük skorlar aldığı görüldü ( $p \leq 0.003$ ).

Nörobekçet ve BH hastaları arasında yanıt inhibisyon kabiliyeti (STROOP-spontan düzeltme;  $p=0.000$  ve hatalar;  $p=0.002$ ) ve öğrenme (RAVLT-5 denemenin toplamı;  $p=0.002$ ) açısından farklılıklar saptandı. Nörobekçet hastaları sağlıklı kontrollere göre serbest geri çağırma (RAVLT), kompleks vizüel işleme (JLOT), bilgi işleme hızı (PASAT), dikkat (TMT-B) VE psikomotor hız (TMT-A) açısından azalmış nörokognisyon düzeyine sahipti ( $p \leq 0.003$ ).

**Sonuç:** Sadece Nörobekçet hastaları değil diğer Bekçet hastalarının da kognitif fonksiyonları kontrol grubundan düşük bulunmuştur. Nörobekçet hastalarında diğer Bekçet hastalarıyla kıyasla kompleks vizüel değerlendirme ve verbal dikkatten ziyade hafıza ve yürütücü işlev fonksiyonları bozuk bulunmuştur.

**Anahtar Kelimeler:** Kognitif bozukluklar, Nörobekçet Hastalığı, Bekçet Hastalığı

## INTRODUCTION

Bekçet's disease (BD) is a chronic, relapsing, multisystem, vascular inflammatory disorder characterized by recurrent oral and genital aphthous ulcers, uveitis and skin lesions.<sup>(25)</sup> It is now accepted as a vasculitis that could affect all size of vessels. Central nervous system (CNS) involvement is seen in 5% to 13% of patients.<sup>(19)</sup> Neurological manifestations of BD are caused by primary neural parenchymal lesions or secondary to vascular involvement.<sup>(19)</sup> These manifestations are considered as adverse prognostic factor.<sup>(13)</sup>

Studies of cognitive functions in BD are limited.<sup>(2,6,8,11,13,14)</sup> As it is considered as a motor-mental disease, changes in mental status of the patients were investigated and reported in early Japanese studies.<sup>(8)</sup> One of the few reports suggested that the most frequent neuropsychological impairments in BD were in measures of attention, memory and executive functions.<sup>(6)</sup> The other one suggested that cognitive impairment might be seen also in BD patients without neurological involvement (BD-only).<sup>(13)</sup> The main aim of the present study is to investigate neurocognitive impairment in neuroBekçet disease (NBD) and BD-only patients and compare them

with healthy controls (HC) using a more detailed set of neuropsychological tests.

Self report of neurocognitive levels has been used in different diseases recently.<sup>(5)</sup> In the present study, subjects were asked to report their self neurocognitive levels. Relationship between self reported cognitive abilities with their neuropsychological scores was also studied.

## MATERIAL AND METHODS

This case-control study was approved by local ethics committee of Ankara Numune Education and Research Hospital. Inclusion criterias were; age  $\geq 18$  years, giving informed consent and fulfilling International Study Group for Bekçet's disease criteria<sup>(12)</sup>. Subjects with depression (assessed with Beck Depression Inventory Scale-a cut-off value  $\geq 17$ ), missing clinical data and having difficulties in cooperation to the tests were excluded from the study.

### Subjects

Totally 56 BD patients and 36 HC were evaluated. Seven of BD patients and 4 of HC were excluded from the study.

Patients with neurological findings or history of neurological involvement were classified as cases of NBD. NBD was

confirmed with Brain MRI. Patients without past/current symptoms of neurological involvement, other than tension-type headache and/or migraine, were classified as BD-only.

Eye involvement was positive in 24 (49%) of all BD patients. Seven of the patients had vascular involvement. Among 15 (30.6%) NBD patients, 11 (22.4%) patients had parenchymal involvement and 4 of them had cerebral venous thrombosis (CVT).

Two of the NBD patients had single attack and had normal neurologic examination findings at time of evaluation. Distribution of other NBD patients was as; five patients with pyramidal signs, two patients with cerebellar signs and two patients with brain stem syndrome.

Most of the patients (83.7%) were on colchicine treatment. 63.3% of patients had

ever used corticosteroids and 22 of them were still using a dose of  $12 \pm 12.8$  mg/day.

### Neurocognitive tests

A comprehensive battery of neuropsychological tests was administered to all patients and healthy comparison subjects.<sup>(3,4,7,10,16,18,20,21,22,24)</sup>

Neuropsychological tests administered and the cognitive domains tested by these tests were summarized in Table I. The tests were administered in fixed order and took around 90 minutes for each subject. Standardized procedures were employed in administration and scoring of neuropsychological tests. In self-report of neurocognitive condition (self-reported VAS), patients and controls were asked to indicate their cognitive status on a visual analogue scale (0-100 mm, 0: the worst and 100 the best).<sup>(5)</sup>

**Table I.** Neuropsychological testing

<b>Cognitive function</b>	<b>Test included in the battery</b>
Verbal memory	Rey Auditory Verbal Learning Test (RAVLT) The Auditory Consonant Trigram Test (ACTT)
Executive Functions	Stroop Test Controlled Oral Word Association Test (COWAT)
Information processing speed	Symbol Digit Modalities Test (SDMT) Paced Auditory Serial Addition Test (PASAT)
Complex visual perception	Judgment of Line Orientation Test (JLOT) The Faces Symbol Test (FST)
Attention and psychomotor speed	Trail-Making Test (TMT) A and B
Verbal attention and concentration	Digit Span Test (DST)

### Rey Auditory Verbal Learning Test (RAVLT)<sup>(21)</sup>

It includes five presentations of a 15 word list. (List A) After the fifth recall, examiner reads a further list (list B) of 15 new words, followed by the subjects' free recall (B). Finally there is a sixth recall trial of the first list and after 20 minutes seventh recall trial is administered. Total learning

scores (1-5) and the number of correctly recalled words summed over the five learning trials were analyzed.

### Paced Auditory Serial Addition Test (PASAT)<sup>(10)</sup>

PASAT is presented on compact disc. Single digits are presented auditory and the subjects add each consecutive digit to the

one immediately preceding it. Number of correct responses is used.

### **The Symbol Digit Modalities Test (SDMT)<sup>(7)</sup>**

SDMT consists of digits and symbol pairs. Under the digits, subjects write down the corresponding symbol as fast as possible. The number of correct answers within a test of 90 seconds duration is measured.

### **Faces Symbol Test (FST)<sup>(18)</sup>**

Subjects match the 67 items composed of nine faces to their nine matching symbols. The score is the mean time in seconds per correct them.

### **Judgment of Line Orientation Test (JLOT)<sup>(3)</sup>**

The JLOT examines the ability of a subject to estimate angular relationships between line segments by visually matching angled line pairs to 11 numbered radii forming a semi-circle.

### **Digit Span Test (DST)<sup>(24)</sup>**

In the digit span forwards the participants are asked to repeat the numbers in a forward order while in digit span backwards they are asked to recall the numbers in reverse order. The number of correct answers is used.

### **STROOP Test<sup>(22)</sup>**

First page of Stroop contains words, the second colored squares; third page contains colored words. Subjects read the stimuli as quickly as possible. Telling the colors of the words provides the greatest cognitive interference and sensitivity to a variety of neurological disorders.

### **Trail making Test parts A & B (TMT A&B)<sup>(16)</sup>**

In part A subjects connect series of numbered circles as quickly as possible. Part B consists of circles contain of numbers and letters. On this trial participants connect the circles alternating between the numbers and letters.

### **Auditory Consonant Trigrams Task (ACTT)<sup>(20)</sup>**

Three letter cluster followed by a number is verbally given to the participants. They are asked to count backward from the given number for a specified period. Then the participants are required to recall the three letter cluster.

### **Controlled Oral Word Association Test (COWAT)<sup>(4)</sup>**

We used letters K, A and S and recorded participants' responses. A successful performance implies normal perseverance and scanning of internal data stores.

### **Statistical Analysis**

The Kruskal-Wallis nonparametric test was used to determine intergroup difference. Values were labeled as mean  $\pm$  standard deviation and/or median (min-max). All of the neurocognitive tests were independent variables. Numeric values were compared with Student's t-test and Mann Whitney U tests. Categorical comparisons were done with Chi-square test. The Mann-Whitney U test was applied as post-hoc test for pair wise comparisons. P-value  $\leq$  0.05 was considered to be statistically significant. Bonferroni correction was applied for determination of the cut-off level for p-values for multiple comparisons. Spearman's correlation coefficient was used to assess correlations between neuropsychological tests and age, disease duration, education duration and steroid dose.

### **RESULTS**

The patient and HC groups were well matched for age, gender, and years of education (Table II,  $p > 0.05$ )

### **Neuropsychological assessment**

The mean and standard deviation values of the cognitive tests of each group were shown in Table III. Post hoc Mann-Whitney U test revealed significant differences between HC and each of NBD

and BD-only groups. There was no significant difference between the groups in self report-VAS ( $p>0.05$ ).

In the comparison of HC to NBD and BD-only subjects, a poorer performance was observed in both group of patients in almost all the neurocognitive tests, except for Stroop interference score of BD-only patients and SDMT and FST scores of NBD patients. When the cut-off limit for the p-value was adjusted using Bonferroni's correction for the comparison of 16 parameters, the cut-off limit for the p-value had to be lowered to 0.003. According to this p-value, the differences between NBD and BD-only patients were observed on response inhibition ability (STROOP-spontaneous corrections; NBD $2.9\pm 2.9$  vs. BD  $0.6\pm 0.8$ ,  $p=0.000$ , and errors; NBD $1.8\pm 1.2$  vs. BD  $0.5\pm 0.7$ ,  $p=0.002$ ) and learning (RAVLT-sum of five trials; NBD $28\pm 7.8$  vs. BD  $35.7\pm 6.6$ ,  $p=0.002$ , Table III and IV). Both group of patients had lower scores ( $p\leq 0.003$ ) on learning, immediate memory, working memory (ACTT), lexical fluency (COWAT) and attention (DST) comparing to HC (Table IV). Additionally, these

patients made more mistakes in Stroop task. NBD patients had further decrease on free recall (RAVLT), complex visual processing (JLOT), information processing speed (PASAT), attention (TMT-B) and psychomotor speed (TMT-A).

In the comparison of BD patients with CVT, neurocognitive scores were not statistically different from BD-only patients ( $p>0.05$ , data not shown).

There was no statistically significant difference between NBD and BD-only patients regarding divided attention and working memory (ACTT), verbal attention (DST), and visuo-spatial processing (JLOT) (Table III-IV). Also there was no significant differences on self report VAS scores between three groups ( $p>0.003$ ).

### Correlation analysis

In the correlation analysis, self-report VAS was not correlated with any of objective neuropsychological tests. But all of the objective scores were negatively associated with age and positively associated with duration of education. No relationship was found between the objective scores and steroid dose or disease duration.

**Table 2.** Demographic characteristics of patients and healthy controls

	Parenchymal NBD (n=11)	BD-only (n=34)	HC (n=32)	P
<b>Gender (M/F)</b>	8/3	19/15	16/16	0.566
<b>Age, years</b>	39.1± 10.4	36.8 ± 9.3	34.4 ± 9.7	0.298
<b>Education, years</b>	8.6± 3.1	7.9 ± 3.8	8.8± 3.7	0.393
<b>Disease duration, years</b>	11.5±6.5	7.5 ± 7.2	Not Administrated	NBD vs. BD, $p=0.436$

**Table III.** Neuropsychological tests of NBD patients, BD-only and healthy controls

	<b>NBD (n=11)</b>	<b>BD-only (n=34)</b>	<b>HC (n=32)</b>
<b>Self-report VAS,(0-100mm)</b>	70.7±14.7 <b>75 (40-90)</b>	76.0±13.1 <b>80 (40-100)</b>	75.3±13.9 <b>80 (40-100)</b>
<b>Auditory- verbal learning and memory</b>			
RAVLT-immediate memory	4.0±1.3 <b>4 (3-7)</b>	4.7±1.3 <b>5 (2-8)</b>	6.2±1.4 <b>6 (3-10)</b>
	28±7.8	35.7±6.6	45.3±7.1
RAVLT-learning	<b>25 (16-47)</b>	<b>35 (21-56)</b>	<b>45.5 (30-60)</b>
	4.1±2.1	6.2±2.1	7.3±2.1
RAVLT-delayed free recall	<b>4 (1-8)</b>	<b>5 (2-10)</b>	<b>8 (4-11)</b>
	2.9±2.5	3.2±2.6	6.4±2.9
ACTT	<b>3 (0-8)</b>	<b>2 (0-8)</b>	<b>6 (0-14)</b>
<b>Executive Functions</b>			
STROOP-interference (sec)	56.2±20.4 <b>62.5 (20-79)</b>	49.9±24.1 <b>46 (10.4-120)</b>	40.9±15.7 <b>40 (18-90)</b>
STROOP-spontaneous corrections	2.9±2.9 <b>2 (0-4)</b>	0.6±0.8 <b>0 (0-2)</b>	0.5±0.8 <b>0 (0-3)</b>
	1.8±1.2	0.5±0.7	0.4±0.8
STROOP-errors	<b>11 (7-15)</b>	<b>6 (1-19)</b>	<b>3 (0-9)</b>
	12.2±5.6	17.7±8.6	23.8±7.4
COWAT	<b>12 (5-23)</b>	<b>17.5 (3-42)</b>	<b>23.5 (12-42)</b>
<b>Information processing speed</b>			
SDMT	6.4±3.2 <b>5.7 (3.2-10.9)</b>	11.9±7.9 <b>11.8 (1.56-35.5)</b>	6.7±6.8 <b>4.0 (2.0-25.0)</b>
PASAT	18.5±8.7 <b>17 (10-30)</b>	34.1±12.2 <b>33 (14-59)</b>	42.4±8.2 <b>47 (26-52)</b>
<b>Complex visual perception</b>			
JLOT	14.9±3.8 <b>14 (7-20)</b>	15.7±6.3 <b>16 (4-28)</b>	19.7±3.9 <b>20.5 (12-27)</b>
FST (sec/correct item)	6.1±1.5 <b>5.9 (3.9-8.9)</b>	6.4±3.1 <b>5.7 (2.5-18)</b>	4.6±1.4 <b>4.5 (2.1-8.1)</b>
<b>Attention and psychomotor speed</b>			
TMT A (sec)	108.3±46.9 <b>103 (57.2-210)</b>	68.0±37.0 <b>60 (20-180)</b>	50.4±21.6 <b>43.2 (20-100)</b>
TMT B (sec)	179.7±46.9 <b>180 (115-270)</b>	147.0±70.5 <b>120 (48-300)</b>	104.3±43.9 <b>101 (40-240)</b>
<b>Verbal attention and concentration</b>			
DST	6.4± 2.6 <b>7 (2-11)</b>	7.5 ±2.6 <b>8 (2-13)</b>	11.0± 4.2 <b>10.5 (4-24)</b>

Values are labeled as mean±S.D., median (min-max), BD:Behçet's Disease, NBD:Neuro-Behçet's Disease, HC: Healthy Controls, S.D.:Standard Deviation, VAS:Visual Analogue Scale,RAVLT: Rey Auditory Verbal Learning Test, SDMT: Symbol Digit Modality Test, JLOT:Judgment of Line OrientationTest,TMT: Trail Making Test, DST: Digit Span Test,COWAT: Controlled Oral Word Association Test, ACTT:Auditory Consonant Trigrams Test, FST: Faces symbol test

**Table IV.** p values of the groups when compared NBD vs. HC, BD-only vs. HC, and NBD vs. BD-only

	<b>NBD</b>	<b>BD-only</b>	<b>NBD</b>
	<b>vs.</b>	<b>vs.</b>	<b>vs.</b>
	<b>HC</b>	<b>HC</b>	<b>BD-only</b>
<b>Self-report VAS,(0-100mm)</b>	ns	ns	ns
<b>Verbal Memory</b>			
RAVLT-immediate memory	<b>.000**</b>	<b>.000**</b>	ns
RAVLT-learning	<b>.000**</b>	<b>.000**</b>	<b>.002**</b>
RAVLT-delayed free recall	<b>.002**</b>	.026*	.017*
ACTT	<b>.001**</b>	<b>.000**</b>	ns
<b>Executive Functions</b>			
STROOP-interference (sec)	.037*	ns	ns
STROOP-spontaneous corrections	<b>.000**</b>	ns	<b>.000**</b>
STROOP-errors	<b>.000**</b>	<b>.000**</b>	<b>.002**</b>
COWAT	<b>.000**</b>	<b>.003**</b>	.039*
<b>Information processing speed</b>			
SDMT	ns	.007*	ns
PASAT	<b>.003**</b>	.024*	.018*
<b>Complex visual perception</b>			
JLOT	<b>.003**</b>	.004*	ns
FST (sec/correct item)	ns	.028*	ns
<b>Attention and psychomotor speed</b>			
TMT-A (sec)	<b>.000**</b>	.028*	.004*
TMT-B (sec)	<b>.000**</b>	.012*	.045*
<b>Verbal attention and concentration</b>			
DST	<b>.001**</b>	<b>.000**</b>	ns

**BD:**Behçet's Disease, **NBD:**Neuro-Behçet's Disease, **HC:** Healthy Controls, **S.D.:** Standard Deviation, **ns:** not significant, **VAS:**Visual Analogue Scale, **RAVLT:** Rey Auditory Verbal Learning Test, **SDMT:** Symbol Digit Modality Test, **JLOT:**Judgment of Line OrientationTest, **TMT:** Trail Making Test, **DST:** Digit Span Test, **COWAT:** Controlled Oral Word Association Test, **ACTT:**Auditory Consonant Trigrams Test, **FST:** Faces symbol test

**\*\* in bold:**Mann-Whitney U test significant at  $p \leq 0.003$  after Bonferroni correction

\*:  $p < 0.05$

## DISCUSSION

The present study showed both NBD and BD-only patients had impaired verbal memory, executive functions, information processing speed, complex visual perception, attention and psychomotor speed, verbal attention and concentration compared to controls. Furthermore NBD patients had worse results in verbal memory, executive functions, and information processing speed and attention

and psychomotor speed than BD-only patients.

Neurological involvement occurs in BD in two major forms- parencyhmal involvement is seen among majority of patients whereas CVT is seen among 20% of patients.<sup>(2)</sup> Previously, cognitive functions in patients with CVT were not investigated separately. Our BD patients with CVT had similar neurocognitive functions with BD-only patients. Non-

parenchymal neurologic involvement has a favorable course. In a prospective study of 25 BD patients with CVT, neurologic symptoms had improved rapidly.<sup>(23)</sup> Thus it could be expected that results of the patients CVT might not be different from BD-only patients. As we have small number of patients with CVT, further investigations are required on this concern.

Memory impairment is reported to be major and early finding among NBD patients.<sup>(14)</sup> Deficits in attentional processes and in executive functions of frontal system were other cognitive signs. Although memory impairment was not related with the lesions in brain MRI at early stages, it was correlated with enlargement of the third ventricle and atrophy of the posterior fossa structures at the late phase.<sup>(2)</sup> In parallel to the previous studies<sup>(6,8)</sup> neurocognitive results of our NBD patients reflected impairments regarding executive function, visual memory, attention and complex visual perception. Poorer performance on cognitive measures in parenchymal involvement might be a result of relapsing-remitting course of neurological destruction.<sup>(2)</sup> Concordantly, nine of our NBD patients had relapsing-remitting course.

Our results indicate that BD-only patients presented cognitive impairment including verbal attention and concentration, auditory-verbal learning and memory, verbal fluency, and response inhibition skills. The cognitive impairment observed in these patients was even more widespread without taking notice the Bonferroni correction. BD-only patients also showed decreased performance on information processing speed, complex visual perception and free recall abilities.

A few previous reports showed that BD affects cognitive abilities in the absence of overt neurological symptoms.<sup>(6,8,13)</sup> Dutra et al reported 41.0% of BD patients had impairment in executive functions, language and visuoconstructive abilities.<sup>(8)</sup>

The prevalence of cognitive impairments on tasks evaluating long term memory and visuospatial skills was 46.1%.<sup>(13)</sup> Neurocognitive decline in BD patients might be a worldwide finding proven with studies from four different geographic areas (Brazil, Portuguese, Italy, Turkey).

Possible explanations of impaired cognitive functioning in BD-only patients have been discussed previously. BD is a vasculitis and pathogenic mechanisms include vascular injury, neutrophil hyperfunction and increased cytokines which can lead to tissue injuries.<sup>(1,17)</sup> Together with T cell hyperimmunity and hypercoagulable state could have been responsible for cognitive impairments in BD.<sup>(13)</sup>

NBD patients revealed further impairment on memory and executive functions comparing to BD-only patients. This impairment was even more widespread without taking into consideration the Bonferroni correction. In this case these patients had also lower performance on attention and psychomotor speed, information processing speed, verbal fluency and delayed recall of memory tests when compared to BD-only patients. These results are in agreement with those of Cavaco et al. which showed that NBD patients had more cognitive impairment compared to BD-only patients.<sup>(6)</sup>

Visuospatial impairment was also reported in BD patients with or without neurologic involvement.<sup>(6,8,13)</sup> Our findings on memory, executive functions and visuospatial abilities are in line with previous studies showing that both groups of patients have deficits on RAVLT learning and immediate memory, verbal fluency, Stroop and JLOT tasks comparing to HC. The MRI studies reported that the main lesions in the brain structures of BD patients extent from the upper brainstem to the diencephalic regions which may lead to the memory deficits observed in these patients. The impairment on JLOT may be due to right temporo-parieto-occipital



hypoperfusion, observed in a SPECT study conducted on BD patients.<sup>(13)</sup>

Neither attention, nor executive functions, nor memory are really unitary functions: each can be decomposed into many subfunctions and none of the neuropsychological tests alone is able to assess one specific cognitive domain. For instance, TMT assesses visual scanning, number and letter sequencing, rote memory, visuomotor coordination, psychomotor speed, and ability to alternate between conceptual categories. In the present study TMT was used, to evaluate the attention and psychomotor speed as in the Italian study.<sup>(13)</sup> We observed that NBD patients had deterioration on these abilities too.

Different from previous studies, we assessed PASAT, SDMT and a newly test-FST. However, less than half of subjects could succeed in finishing PASAT and SDMT. Furthermore normal control group had low score of SDMT. Thus further studies are required in assessing PASAT and SDMT. Although frequent use in MS, PASAT and SDMT are not vulnerable for BD. Additionally, no difference was found between groups in terms of FST (NBD vs. BD-only).

There are numerous factors those potentially affect cognitive functions such as depression, disease characteristics and therapies. Depression and anxiety could affect neuropsychological results<sup>(2)</sup>, especially executive functions, memory and processing speed.<sup>(15)</sup> Higher depression and anxiety scores were reported in BD.<sup>(13)</sup> Depression is common among BD patients possibly due to corticosteroid treatment rather than organic cause.<sup>(9)</sup> Cognitive impairment was found even though excluding depressive patients in our study.

Significant associations between cognitive impairment and both disease activity and prednisolone dosage were found in BD.<sup>(13)</sup> We didn't observe any relationship between disease duration and corticosteroid dosage. This discordance

might be explained by different patient characteristics between two groups.

Neuropsychological tests are a core component of the process of conducting neuropsychological assessment along with personal, interpersonal and contextual factors. Neuropsychological batteries combine a range of tests to provide an overview of cognitive skills.<sup>(16)</sup> Most of these batteries take more than an hour to administer. It is difficult to perform in routine practice. Self-reported cognitive functioning with VAS might be a useful alternative and has been used in different diseases.<sup>(9)</sup> We performed a self-reported VAS for assessing global neurocognitive functions. However, these scores were not related to objective tests. Therefore it is not recommended using self-report VAS in BD patients.

One of the limitations of our study was not to have used more comprehensive tests in order to evaluate executive functions. For this purpose, The Clock Drawing Test and/or Wisconsin Card Sorting Test (WCST) could have been used which in a previous study was found to be impaired in BD-only and NBD patients.<sup>(8)</sup>

In conclusion, both BD patients with and without neurological involvement have impaired neurocognitive abilities. These impairments could affect quality of life in BD. Compared to BD-only patients, NBD patients reveal further impairment on memory and executive functions rather than complex visual perception and verbal attention. A further study including imaging and neuropsychological tests, may contribute to a better understanding of this concern.

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