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Evaluation of Executive Functions With Functional Near-Infrared Spectroscopy in Euthymic Bipolar and Borderline Personality Disorders

Güney Zeybek Dalyan[1], Serkan Uslu[2], Özmen Metin[3], Tunca Nüzket[2], Buket Cinemre[3], Murat Canpolat[2], Özge Doğanavşargil Baysal[3]

[1]Department of Psychiatry, Antalya Training and Research Hospital, Antalya, Turkey
[2]Department of Biophysics, Faculty of Medicine, Akdeniz University, Antalya, Turkey
[3]Department of Psychiatry, Faculty of Medicine, Akdeniz University, Antalya, Turkey

ABSTRACT

Introduction: Bipolar disorder (BD) and borderline personality disorder (BPD) are often indistinguishable, given both the key features of impulsivity and emotional dysregulation. This indicates widespread comorbidity and potential misdiagnosis in both groups. Therefore, this study aimed to differentiate BD and BPD by using alterations of brain hemodynamics under the influence of executive tests.

Methods: Twenty patients with the euthymic phase of BD and 20 patients with BPD, and 20 healthy control subjects were included in this study. The prefrontal cortex (PFC) hemodynamic responses were evaluated using functional near-infrared spectroscopy (fNIRS) during the Stroop Test and Wisconsin Card Sorting Test (WCST).

Results: Left dorsolateral prefrontal cortex (DLPFC) activation was significantly decreased in BPD during both tests. On the other hand, the BD group showed medial PFC hypoactivation during both tests, and this finding is distinct from BPD ($p<0.05$).

Conclusion: Our results indicate that brain hemodynamics during the executive test can highlight differences between BP and BPD. While medial PFC hypoactivation was more prominent in the BP group, DLPFC hypoactivation was more pronounced in the BPD group.

Keywords: Bipolar disorder, borderline personality disorder, functional neuroimaging

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INTRODUCTION

Current studies indicate that bipolar disorder (BD) is not only associated with affective symptoms but also that cognitive deficits play an essential role in BD. Moreover, neurocognitive impairment is altered even in the BD episodes (1). Sole et al. reported that 40–60% of euthymic patients present with neurocognitive disturbances (2). Reduced neurocognitive activity in BD euthymic period involves executive functions, memory, verbal learning, attention, response inhibition, and set-shifting (1,3,4). Therefore, neurocognitive tests that focus on executive functions gain importance in understanding and distinguishing BD.

However, decreased neurocognitive activity is not specific to BD and may be a symptom in many psychiatric disorders such as borderline personality disorder (BPD), which has a high misdiagnosis rate with BD (5). BPD has a poor diagnosis rate; its main symptoms are emotional dysregulation, impulsive aggression, repetitive self-harm, and suicidal tendencies (6). While its similarity with schizophrenia was previously emphasized, recent studies have indicated its similarity with mood disorders (7). Neurocognitive tests show that hypofrontality is prominent in BPD too, but neuroanatomical regions may differ from BD (8–10). It is becoming increasingly important to distinguish between these diseases using neurocognitive tests. International Society for Bipolar Disorders prepared a consensus article and recommended appropriate tests for BD (11). This consensus recommends the Stroop Test (ST) due to its capacity to evaluate verbal learning and memory and the Wisconsin Card Sorting Test (WCST) due to its capacity to evaluate set-shifting, attention, and response inhibition (11). In addition, many studies show that the dorsolateral prefrontal cortex (DLPFC) is one of the affected brain regions in BD (12) and neuroimaging studies revealed that WCST stimulates this region with decision-making and set-shifting tasks (13). Jacob et al. state that the intensity of the emotional response is one of the main factors in

Highlights

- **Bipolar disorder (BD) and borderline personality disorder (BPD) were distinguished via fNIRS under WCST for the first time.**
- **The medial PFC hypoactivation is more pronounced in the BD.**
- **The left DLPFC hypoactivation is more prominent in the BPD.**

Correspondence Address: Özmen Metin, Akdeniz Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, Dumlupınar Blv. Campus, Antalya, Turkey • **E-mail:** ozmenmetin@akdeniz.edu.tr
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high impulsivity and that the negative emotions associated with this high impulsivity are not only amplified but also longer lasting (14,15). Many studies show that inhibition is one of the fundamental mechanisms of emotion regulation, and inhibitory dysfunctions play a crucial role in BPD patients (16,17). Stroop task is a commonly used method for evaluating inhibition of interference, and many studies show that it is appropriate for investigating neural correlates of emotional stimuli and inhibitory control (15). Nevertheless, the main limitation of the neurocognitive test is that performance scores alone are not sufficient. Therefore, recent studies showed that combining neurocognitive tests with neuroimaging methods is more beneficial for diagnosis (18–20).

Functional near-infrared spectroscopy (fNIRS) is a relatively new neuroimaging method compared to other neuroimaging techniques. It provides information about hemodynamic changes depending on the interaction of light with the cortical tissue. In the fNIRS, two wavelengths of light, usually between 750 and 850 nm, are sent to the tissue (21). A fraction of the back-reflected diffuse light detected by photodiodes provides information about the hemodynamic change in the cortical tissue. The modified Beer-Lambert (MBL) law is used to measure the changes in the concentration of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) in the region of interest during the test. The advantages of fNIRS are high temporal resolution and low motion artifacts, while the disadvantages are low spatial resolution and the inability to evaluate subcortical areas (22). These characteristics make fNIRS extremely useful for monitoring the executive function of the cortical regions, particularly in psychiatric disorders such as schizophrenia, depression, and addictions (18).

Considering both diseases' main symptoms, decision regarding to use WSCT and ST as stimulation, has been taken. Regarding decision-making mechanisms altered in both disease groups, we thought that these tests, which stimulate the DLPFC and the ventrolateral prefrontal cortex (VLPFC), may provide beneficial information for the differentiation of the two diseases. We postulate that stimulating decision-making, attention, and working memory with appropriate neurocognitive tests and monitoring hemodynamic responses in the prefrontal regions can differentiate BD and BPD patients.

METHODS

Subjects

This study was conducted at the Department of Psychiatry and Biophysics, Akdeniz University, following institutional review board approval (Ethical Committee of Clinical Research, approval number: 05.04.2017/216). Written informed consent was obtained from all participants after a complete description of the study. Twenty euthymic BD patients, 20 patients with BPD, and 20 healthy control (HC) subjects were included in this study.

Patients with bipolar I disorder (according to The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria) were evaluated with the Young Mania Rating Scale (YMRS) (8) and Hamilton Depression Rating Scale (HDRS) (9) scores and were considered to be euthymic below five points in HDRS and below seven points in YMRS.

The inclusion criteria were: 1- age older than 18 years and younger than 60 years. 2- a diagnosis of BD or BPD according to DSM-5 criteria, and is stable for at least the last three months. The exclusion criteria were; left-handedness, comorbid psychiatric disorders, mental retardation, a history of head trauma with loss of consciousness, dementia, and neurological disorders. In addition, all participating patients were taking second-generation antipsychotics (BD: 20, BPD: 20), and all BD patients were taking mood stabilizers (n=10 lithium, n=10 valproic acid).

Neurocognitive Tests

WCST was first developed by Berg and its final version was designed by Heaton in 1981 (23). In the present study, the WCST was implemented with software developed in the MATLAB platform (24). The stimulus (four cards) and reaction cards (64 cards, 2 sets) specified in the test were prepared in advance and embedded in the software. Each card has a geometric figure with a different color, shape, and quantity. The geometric shapes on the cards are: i) a plus sign, ii) a circle, iii) a star, and iv) a triangle. The colors of the geometric shapes are red, green, yellow, and blue. The quantities are one, two, three, and four. The program notifies the participant whether his or her match is "correct" or "wrong" after each reaction. After ten right answers, the software switches the category without informing the participant (category order: color, shape, quantity). The second set was applied after the first set was completed. The test was complete when the participant had used 128 cards (64×2) or completed six true categories. The WCST is used as a frontal lobe test, and scores were calculated as previously reported in the literature (25).

The ST is used to evaluate impulse disorders to test selective attention and create new judgments, especially when under the influence of interference. The cards in the ST were embedded in software developed on the MATLAB platform by transferring them to digital media. The ST consists of four cards, each visualized on the computer screen sequentially with the click of the mouse. On the first screen, words denoting colors – RED, GREEN, YELLOW, and BLUE – were written in black. On the second screen, names of colors were written in colors other than those to which they referred. On the third screen, there were 24 circles colored green, blue, yellow, and red. On the fourth screen, there were neutral words in different colors. On the fifth and last screen, the second card was displayed again. At the beginning of the test, the participants were asked to read five cards loudly and as fast as possible according to the given instructions. All participants were informed that they could correct any mistake they had made. The instructions were as follows:

- For the first screen, "Read these words"
- For the second screen, "Read these words"
- For the third screen, "Utter the colors of the circles"
- For the fifth screen, "Read these neutral words"
- For the fifth screen, "Utter the color of the print, but do not name the letter"

Task Procedures and Measurement of Hemodynamic Changes fNIRS recorded PFC hemodynamic responses during the performance of both neurocognitive tests. All attendees rested for 15 minutes before starting the measurement. The room temperature was kept constant throughout the measurement in order to reduce the effect of autonomic nervous system contamination. All instructions are provided to the participants prior to the measurement, and the surveying personnel moves away from the computer to avoid distracting the participants' attention. Pre-test and post-test measurements were taken before and after the test for 60 seconds.

A custom-made fNIRS system was used. The system consists of an optical probe, an electronic control circuit, and a graphical user interface (GUI). The probe was made using a flexible printed circuit, 10 silicon photodetectors (OP101, Texas Instruments, Dallas, TX, USA), and four dual-wavelength sources composed of 770 nm and 850 nm LEDs (MTMD7885T38, Marktech Optoelectronics, Latham, NY, USA). Sequentially, the 770 nm and 850 nm LED were active for 50 ms, and four

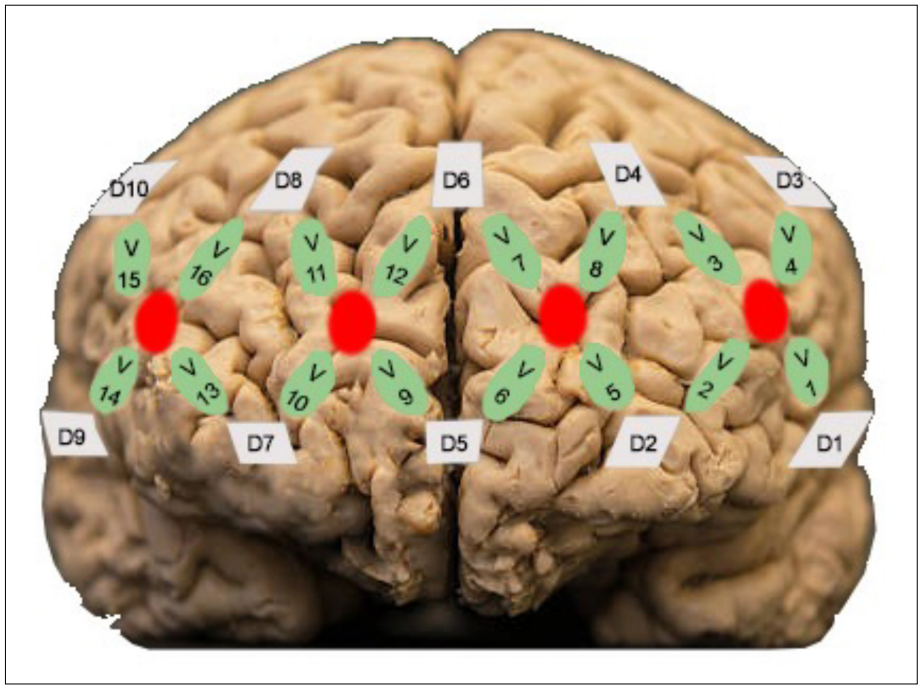

Figure 1. Schematic illustration of the channels and corresponding anatomical regions. D1-D10 represents detectors, red circles represent light sources, and V1-V16 represents scanned volumes. Optical probe placement was performed according to EEG 10–20 reference system and to locate the first channel over the left ventrolateral prefrontal cortex (VLPFC) region, the fourth channel over the dorsolateral prefrontal cortex (DLPFC) region, the 14th channel over the right VLPFC region, and the 15th channel over the right DLPFC region.

photodiodes around them detected diffuse light reflected back from the PFC. In total, 16 channel measurements were acquired.

The fNIRS probe was placed based on the EEG 10–20 system by two psychiatrists. First, the nasion (middle point of the nasofrontal area), inion (occipital protuberance), and right and left preauricular points were marked. Later, Cz (the intersection of the nasion-inion line with the right and left preauricular points; 50% of the nasion-inion and 50% of the right-left preauricular distance), Fpz (10% of the nasion-inion distance), Fp1 and Fp2 (5% of the total circumference distance to the right and left of Fpz), Fz (30% of the nasion-inion distance) were marked. The centerline of the fNIRS probe was first aligned concerning the Fz region. Thus, the horizontal axis coincides with the symmetry of the eyes and is adjusted in the vertical plane so that the lower optodes correspond to the positions of Fp1 and Fp2 (26,27). Thus, optical probe placement was performed to locate the first channel over the left VLPFC region, the fourth channel over the DLPFC region, the 14th channel over the right VLPFC region, and the 15th channel over the right DLPFC region. The optical probe and channel mapping are shown in Figure 1, where the source-detector distance was 2.5 cm. This distance was determined according to the literature (21,28–30).

The data obtained during the tests were evaluated using the modified Beer-Lambert law, and the changes in oxy-Hb and deoxy-Hb concentrations were calculated. All the acquired data were filtered with the Butterworth Band-Pass Filter (f=0.01 to 0.3 Hz) to minimize the physiological noise and movement artifacts.

Statistical Analyses

The test performance and mean oxy-Hb concentration change were compared among the three groups. One-way ANOVA and Kruskal-Wallis tests were chosen according to whether the data followed the normal distribution. The Tukey test was used to compare the two groups for the normally distributed groups, and the Mann – Whitney test was used for the groups that followed the condition of non-normality. All statistical analyses were performed in Statistical Package for Social Sciences (SPSS) version 18.0. A value of $p<0.05$ was chosen as a significant difference. Data are represented as mean ± SEM (standard error of mean) values.

RESULTS

Sociodemographic and Clinical Characteristics

There was no significant difference between healthy control and patient groups according to age, education years, occupational and marital status. Furthermore, there was no difference in disease duration or family history of psychiatric illness between the BD and BPD groups. However, the number of participants in physical and sexual abuse is higher in the BPD group compared to the BD group ($p<0.05$). Detailed sociodemographic and clinical characteristics are shown in Table 1. There were no catatonic features in any of the BD patients. A total of 10 patients were treated with lithium, and 10 patients were treated with valproic acid. All the BD and BPD patients were using antipsychotic drugs.

Neurocognitive Test Performances

Both BD and BPD groups performed worse in the ST than the healthy control group ($p<0.05$). Although there is an increasing time tendency in Stroop interference in the BPD group compared to BD, there was no significant difference ($p>0.05$).

There was no significant difference between all groups in the total number of trials and the total number of correct responses in WCST ($p>0.05$). However, the BD group has a higher number of errors than the healthy control group ($p<0.05$). Moreover, the majority of errors in the BD group are perseverative errors. The healthy control and BPD group have much fewer perseverative errors than the BD group. On the other hand, the BPD group's non-perseverative error rate is much higher than other groups. Also, the BPD group showed a significant difference in failure to maintain the set ($p<0.05$). These results indicate that the BPD group tended to shift between categories while the BD group tended to continue in the same category. All the test results are shown in Table 2.

Hemodynamic Changes during Neurocognitive Test

Although the BD group showed a very similar hemodynamic response to the healthy control group in the left hemisphere (Channel 1–4), they showed a hypoactivation pattern in the medial PFC (Channel 8), different from both groups ($p<0.05$) during the ST. Conversely, in the BPD group, the hemodynamic changes in the medial PFC and the right hemisphere were similar to the healthy control, while hypoactivation

Table 1. Sociodemographic and clinical characteristics

		HC	BD	BPD	p
Age (years) ǂ		30.6±2.00	30.2±1.24	26.95±1.26	0.34
Gender§	Female	20	20	20	
Education (years)ǂ		11.66±0.65	11.1±0.7	11.4±0.6	0.75
Occupational statusǂ	Employed	18	16	18	0.56
	Unemployed	2	4	2	
Marital statusǂ	Married	10	13	8	0.28
	Single	10	7	12	
Parent divorce§		1	1	12	**<0.05**
Family history of psychiatric illness§		-	12	9	0.52
Physical abuse§		-	1	10	**<0.05**
Sexual abuse§		1	1	8	**<0.05**
Disease duration (years) ǂ		-	7.37±1.01	6.15±0.77	0.34
Number of manic episodesǂ		-	1.25±0.1	-	-
Number of depressive episodesǂ		-	1.60±0.11	-	-
Number of total episodesǂ		-	2.85±0.08	-	-
Episode duration (days) ǂ		-	22.1±2.07	-	-
Fully recovery between episodes§		-	20	-	-
Number of psychiatric hospitalizationǂ		-	1.15±0.22	-	-
Catatonic features		-	-	-	-
Suicide attempt§		-	9	15	0.10

BD: Bipolar disorders; BPD: Borderline personality disorders; HC: Healthy control.
§n (%); ǂMean±SEM (standard error of mean).

Table 2. Neurocognitive test performances

	HC Mean ± SEM (95% CI)	BD Mean ± SEM (95% CI)	BPD Mean ± SEM (95% CI)
Stroop Test			
Stroop Card 1 (s)	9.02±0.40 (8.17–9.86)	10.44±0.38* (9.62–11.25)	11.60±0.71* (10.11–13.10)
Stroop Card 2 (s)	9.539±0.49 (8.5–10.58)	11.52±0.84 (9.75–13.29)	11.82±0.92 (9.88–13.77)
Stroop Card 3 (s)	11.64±0.38 (10.84–12.44)	15.48±1.1* (13.17–17.79)	14.60±0.94* (12.63–16.58)
Stroop Card 4 (s)	8.88±0.5 (7.82–9.94)	12.89±0.92* (10.95–14.84)	15.14±1.77* (11.42–18.87)
Stroop interference (s)	24.15±2.1 (19.75–28.55)	30.66±1.87* (26.74–34.58)	33.74±1.91* (29.74–37.74)
Wisconsin Card Sorting Test			
Total errors	44.25±5.38 (32.99–55.51)	62.15±3.87* (54.03–70.27)	57.3±4.46 (47.95–66.65)
Total corrects	73.10±3.5 (65.75–80.45)	62.7±2.63 (57.2–68.2)	68.8±3.98 (60.46–77.14)
Categories completed	3.85±0.43 (2.93–4.76)	2.4±0.37 (1.62–3.18)	2.55±0.43 (1.63–3.46)
Perseverative errors	21.10±2.35 (16.16–26.04)	34.53±2.89* (28.45–40.6)	15.30±2.88** (9.25–21.34)
Non-perseverative errors	24.55±3.10 (18.06–31.04)	27.89±2.37 (22.9–32.89)	42±3.17*,** (35.36–48.64)
Trials to complete first category	31.39±8.04 (14.41–48.36)	24.25±4.85 (14.10–34.10)	33.63±7.22 (18.23–49.02)
Failure to maintain set	0.75±0.21 (0.29–1.2)	0.95±0.25 (0.4–1.4)	2.10±0.28*, ** (1.51–2.68)

BD: Bipolar disorders; BPD: Borderline personality disorders; CI: Confidence Interval; HC: Healthy control ; SEM: standard error of mean; s: second
*p<0.05 compared to HC; **p<0.05 compared to BD.

was observed in the left hemisphere (Channel 4, p<0.05). Figure 2a depicts all channel activations with mean and SEM, while Figure 3 depicts bar graphs of statistically significant channels. Although right hemisphere DLPFC hypoactivation is more prominent, the BPD group showed hypoactivation in both right and left DLPFC during WCST (Channel 3 and Channel 15). Interestingly, while other groups showed similar reduced activation patterns in the right hemisphere DLPFC, the BD group showed hyperactivation contrary to the other groups (Channel 15, p<0.05). However, the same pattern did not observe in VLPFC. VLPFC activation of the BD group is very similar to the healthy control group (p>0.05). Although not statistically significant, VLPFC activation in the BPD group's left hemisphere (Channel 2) was increased

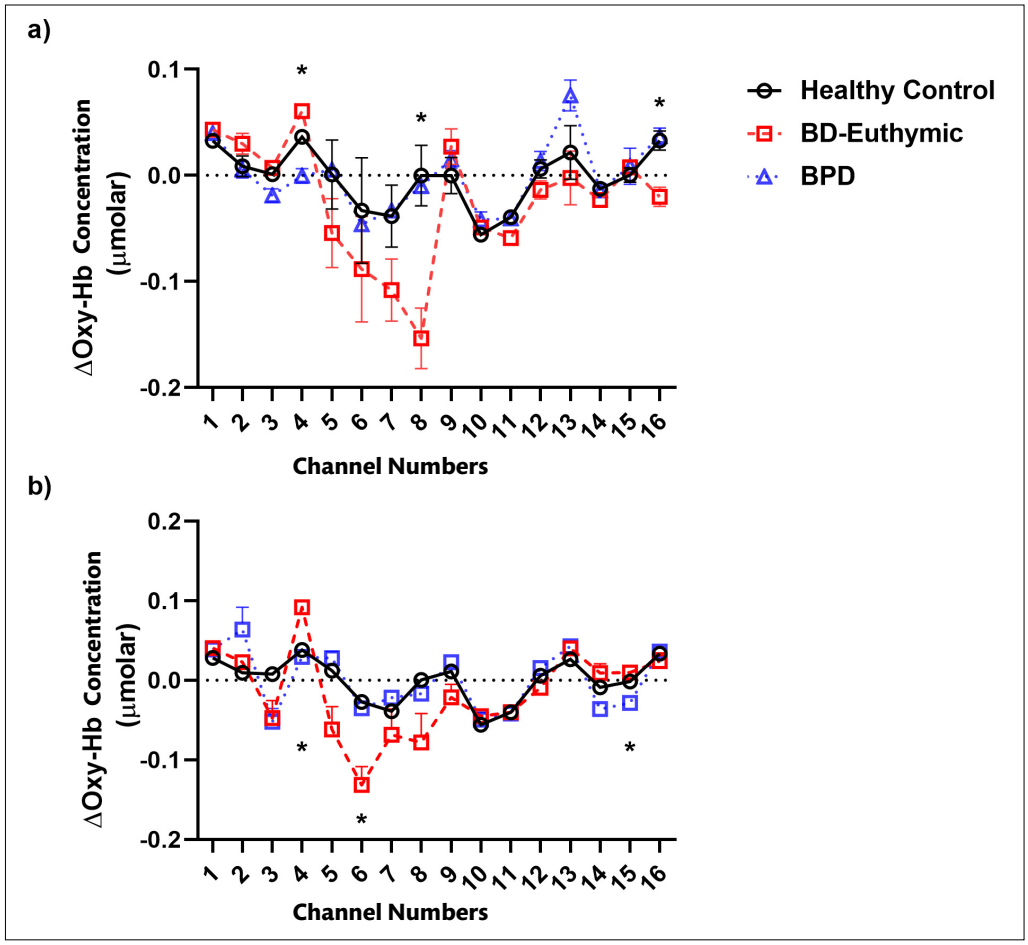

Figure 2. The mean of oxy-Hb concentrations for each group over all channels during the Stroop Test (a) and Wisconsin Card Sorting Test (WCST) (b). The black line represents the healthy control group, the blue line represents the borderline personality disorder (BPD) group, and the red line represents the bipolar disorder (BD) group.

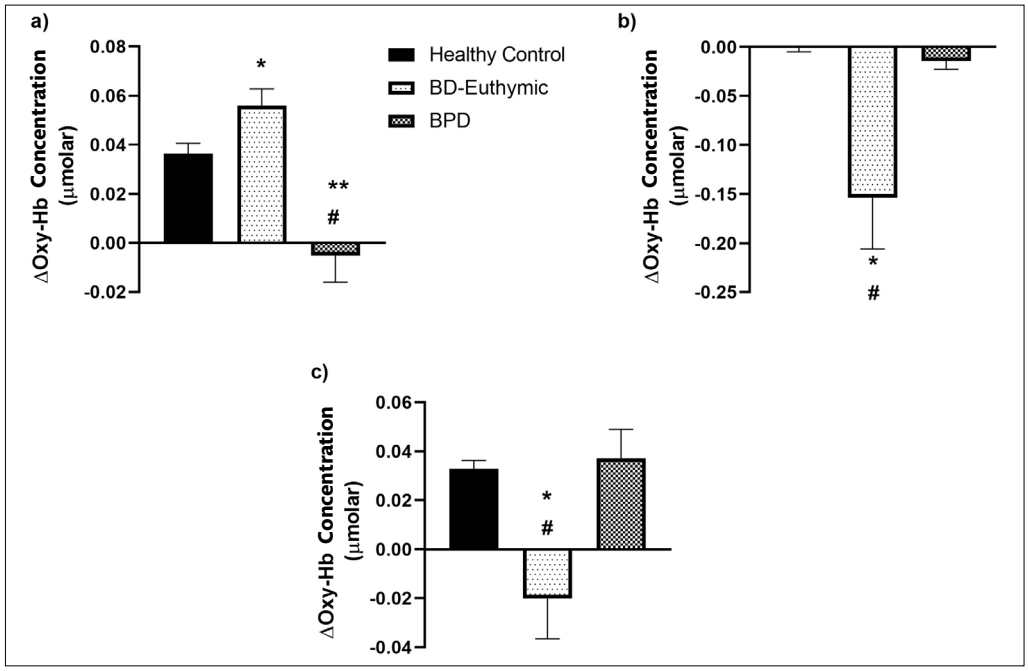

Figure 3. Bar graphs of channels with statistically significant differences observed during the Stroop Test. While the borderline personality disorder (BPD) group showed hypoactivation in the left dorsolateral prefrontal cortex (DLPFC) (a, Channel 4, p<0.05), the bipolar disorder (BD) group showed a distinct hypoactivation pattern in the medial prefrontal cortex (b, Channel 8), different from both groups (p<0.05) and in the right DLPFC (c, Channel 16) during Stroop Test.

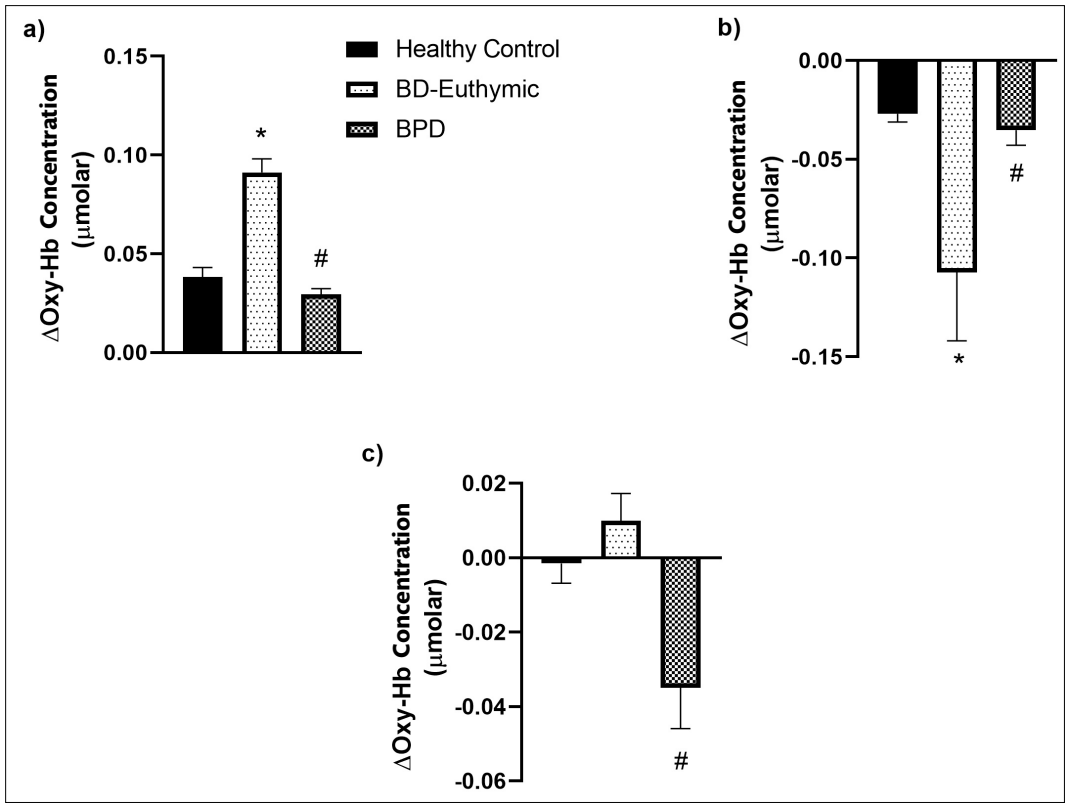

Figure 4. Bar graphs of channels with statistically significant differences observed during the Wisconsin Card Sorting Test (WCST). While the borderline personality disorder (BPD) group showed hypoactivation in the dorsolateral prefrontal cortex (DLPFC) of both hemispheres (a, Channel 4 and c, Channel 15), the bipolar disorder (BD) group showed hyperactivation ($p<0.05$). On the other hand, the BD group showed hypoactivation in medial prefrontal cortex areas (Channel 6, $p<0.05$), similar to the Stroop test.

compared to the other two groups ($p=0.07$). On the other hand, the BD group showed hypoactivation in medial PFC areas (Channel 6, $p<0.05$) similar to the ST. All channel activations with mean and SEM are represented in Figure 2b and bar graphs of statistically significant channels are represented in Figure 4.

DISCUSSION

The findings of the presented study show that hemodynamic changes during the neurocognitive test may represent a different pattern of BD and BPD. Furthermore, the medial PFC hypoactivation pattern is more prominent in the BD group (Channel 8 during the ST and Channel 6 during the WCST) while left DLPFC hypoactivation is more pronounced in the BPD group (Channel 4 during both tests). Moreover, our results indicate that both Stroop and WCST can be used as stimulation effects for hemodynamic measurements. To the best of our knowledge, the presented study is the first one that used fNIRS under the WCST and ST for the distinction of BD and BPD.

Many studies indicated the similarity of BPD with BP and showed that misdiagnosis is very common (5). Therefore, neuroimaging techniques are frequently used (18). Malhi et al. employed fMRI during emotional processing and demonstrated that DLPFC activity is lower in both groups when compared to healthy control groups, but medial PFC activation is different (31). Kronhause et al. used fMRI during the ST and showed that medial PFC activation is reduced in BP (32). Our results are consistent with the former fMRI studies for medial PFC activation. There can be several explanations for this hypoactivation pattern. Stuss et al. emphasize that the medial part of the frontal cortex can be activated under interference effects such as Stroop and hypoactivation in these regions leading to worse performance (33). Indeed, in our study, BD showed a much more prominent Stroop interference effect. Although we did not observe any latency in text reading cards, BD groups showed a higher time to read color cards compared to other groups. This result emphasizes that the worsening pattern of BD is not associated with PFC. However, the Stroop interference effect of the BPD group is higher than both BD and healthy controls. Thus, we can suggest that DLPFC has a more prominent role under the Stroop interference effect. Therefore, hemodynamic changes during Stroop interference have a better chance of identifying BPD compared to BD.

In our study, we also evaluated hemodynamic changes during WCST. BPD showed hypoactivation in DLPFC during WCST. This result is also consistent with fMRI studies. However, there is no fNIRS research against which we may compare our BPD results. On the other hand, it is generally recognized that BPD patients struggle to keep their focus when distracted (5). Thus, hemodynamic changes in DLPFC, which are responsible for decision-making, are highly acceptable. However, the critical issue here is that the WCST is almost stimulating in all parts of PFC. Therefore, hypoactivation of BD in the medial PFC is crucial. Many studies show that medial PFC is essential in reward-guided learning (34). "True-false" feedback in WSCT mimics this reward-guided learning. We observed that the perseverative errors of the BD group are higher than others. Thus, we can suggest that the BD group cannot identify this feedback consistent with the hypoactivation of medial PFC. Moreover, medial PFC is also responsible for error detection (35). Therefore, the increased number of perseverative errors and hypoactivation of medial PFC is in harmony. Furthermore, decreased activation of medial PFC did not observe in the BPD group. Thus, this result indicates a different hypoactivation pattern from BPD.

In conclusion, hemodynamic responses in the PFC of the healthy control, euthymic BD, and BPD groups were evaluated during Stroop and WCST using fNIRS. One of the limitations of the study is the drug effect. Although we paid attention to the number of BD patients is equal according to their medications (n=10 for lithium and n=10 for valproic acid) used, there was not a sufficient sample size to observe the drug effect. Secondly, most BD patient has recurrent depression episode (1.60±0.11). This could affect executive function. Therefore, the acute depression effect can be varied. Finally, the number of patients in the study is also a limitation. Concerning these limitations, it seems to be

congruent with previous reports and support that hemodynamic change monitoring with fNIRS can highlight differences between BP and BPD. To the best of our knowledge, the presented study is the first one that used fNIRS under WCST and Stroop for the distinction of BD and BPD.

In conclusion, in this study, we hypothesize that stimulating decision-making, attention, and working memory with appropriate neurocognitive tests and monitoring hemodynamic responses in the prefrontal regions can differentiate BD and BPD patients. Our results indicate that brain hemodynamics during the executive test can highlight differences between BP and BPD. While medial PFC hypoactivation was more prominent in the BP group, DLPFC hypoactivation was more pronounced in the BPD group.

Ethics Committee Approval: This study was conducted at the Department of Psychiatry and Biophysics, Akdeniz University, following institutional review board approval (Ethical Committee of Clinical Research, approval number: 05.04.2017/216).

Informed Consent: Written informed consent was obtained from all participants after a complete description of the study.

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Author Contributions: Concept- ÖM, GZY, SU, ÖDB, MC; Design- ÖM, GZY, SU, ÖDB, MC; Supervision- ÖM, ÖDB, MC; Resource- ÖM, ÖDB, MC; Materials- GZY, ÖM, BC, ÖDB; Data Collection and/or Processing- GZY, SU, TN; Analysis and/or Interpretation- ÖM, GZY, SU, ÖDB, MC; Literature Search- GZY, SU, ÖM; Writing- ÖM, GZY, SU; Critical Reviews- ÖDB, MC.

Conflict of Interest: The authors declared that there is no conflict of interest.

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