International Journal of Advanced Engineering Research and Science (IJAERS)
Peer-Reviewed Journal
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-8, Issue-6; Jun, 2021
Journal Home Page Available: https://ijaers.com/
Article DOI: https://dx.doi.org/10.22161/ijaers.86.50

Assessment of different domain impairments in Cognitive Functions and Functionalities found in Euthymic Patients with Bipolar Disorder I / II - during the early and late phases of the disease, using the FAB and FAST tests.

Luiz Arthur Rangel Cyrino[1,3,4], Claudia Regina Calegari[5], Maria Cecília Tomasi[3], Felipe Luis Schmoller Stammerjohann[3], Daniela Delwing-de Lima[1,2]

[1]Programa de Pós-Graduação em Saúde e Meio Ambiente;
[2]Department of Medicine - University of Joinville - UNIVILLE - Joinville, Santa Catarina, Brazil
[3]Department of Psychology - University of Joinville - UNIVILLE - Joinville, Santa Catarina, Brazil
[4] Department of Pharmacy - University of Joinville Region - UNIVILLE - Joinville, Santa Catarina, Brazil
[5] Specialist in Neuropsychology, Clinical and Institutional Psychopedagogy and Cognitive-Behavioral Psychotherapy.

Received: 14 May 2021;
Received in revised form:
03 Jun 2021;
Accepted: 19 Jun 2021;
Available online: 30 Jun 2021

Keywords *— **Bipolar Disorder, Euthymia, Executive Function, Frontal Assessment Battery – FAB, Functioning Assessment Short Test – FAST, Neuropsychological Assessment.***

Abstract *— Objective: In this study, we focus on assessing two key predictors and outcomes in Bipolar Disorder (BD), which are: cognition and functionality performance, dividing them into two subgroups, and then researching for a correlation between them. Methods; Fifty patients with BD in a euthymic phase were divided into two subgroups (≤ 3 years (n=25) and ≥ 10 years (n=25) of the disease) and were then compared with healthy controls (n=25). Psychosocial functioning was assessed using the Short Functionality Assessment Test (FAST), and the Frontal Assessment Battery (FAB) test to assess frontal cognitive functions. Clinical and sociodemographic characteristics were analyzed using unilateral variance analysis, or the chi-square test. In order to verify the correlation between the FAB and FAST tests, Spearman's correlation coefficient test was used Results: Both subgroups of euthymic patients had higher FAST total scores than the healthy control group (9.80 ± 5.94). The groups with ≤ 3 years (20.63 ± 8.21), and ≥ 10 years (27.80 ± 12.50) of the disease presented($p<0.001$). Associated with these results, bipolar patients had higher FAST scores in all domains, predominantly with moderate impairment (score 21-40), and lower scores in the following four FAB test domains: conceptualization, sensitivity to interference, inhibitory control, and motor series ($p<0.05$). The correlation between the FAB and FAST tests showed moderate intensity (r^2 = -0.539). Conclusion: This study reinforced the impact of BD on functionality and frontal cognitive functions, demonstrating changes in several domains, and impairment in social, occupational, and cognitive functions in patients with different times of disease onset. Understanding all factors is essential for these patients, which increases the possibility of rehabilitation and response to treatment.*

I. INTRODUCTION

Bipolar Disorder (BD) is characterized as being a chronic disease with severe morbidity, mortality, and high suicide rates **[1].** It is a progressive disease with episodes becoming successively shorter, and frequent over time. Multiple alterations occur in the brain such as changes in neuroplasticity, neurotransmission, failures in apoptosis, activation in the immune-inflammatory process, changes in the calcium signaling pathway; and more recently, on oxidative stress. These events involve a pathological reorganization in the brain and therefore are associated with morphological changes such as a reduction in the volume of the prefrontal cortex, hippocampus, and an enlarged amygdala **[2];[3].** These structural and biochemical changes are highly recurrent and disabling, developing a process known as neuroprogression, with a difference between the initial and final stages of BD. These secondary alterations are possibly caused by multiple episodes of mania and depression during the disease, raising the hypothesis that bipolar patients may have had changes in their neurocognitive performance, with an impact on their daily functionality and psychosocial aspects **[4];[5];[6];[7];[8];[9].** These modifications are usually measurable and characterized by reductions mainly in Executive Functions (EF). The EF is a generic term to describe cognitive processes that allow a person to develop a flexible and independent goal-directed behavior **[10];[11]**. The EF present particularly three main domains (working memory, inhibition, and cognitive flexibility), and they are considered as the basis for other more complex EF, such as; planning, problem-solving, abstract reasoning, among others **[12];[13];[14];[15].** For this reason, many different neuropsychological tests can be used like the recent FAB test **[16].** An impairment of EF is present in several neurological conditions, such as neurodegenerative disorders, traumatic brain injuries, strokes, and more recently in various psychiatric disorders like substance-use disorders **[17];[18],** and schizophrenia **[19].** Although the significance of EF`deficits is not yet fully understood, many studies have shown that patients with BD, even in the euthymic phase, have cognitive dysfunctions, in several domains, such as; verbal memory, EF, impulsivity control, attention, among others. Furthermore, it has also been observed that important functional difficulties, at an occupational, social, and autonomy level, persist in a significant number of patients, even after symptomatic remission **[20];[21];[22];[23].** The presence of this neurocognitive dysfunction in different dimensions during the euthymic state may be one of the determining factors for functional incapacity, as it occurs in patients with other mental pathologies **[24];[25];[26];[27];[28];[29];[30].** Thus, remission in BD (euthymia) is not synonymous with patients` recovery and functionality **[31].** Gitlin et al. **[32],**have already described that despite the treatment, 73% of the patients relapsed with depression and mania many times over a period of five years. Even for those who did not relapse, changes in their psychosocial functioning were observed, especially in the occupational area, generating a poor prognosis for the disease. The hypothesis related to this phenomenon is the cognitive deficits deriving from chronicity of the clinical course, and the persistent subsyndromal symptoms **[21];[31].** Also, research with patients after the first manic episode, showed that functional impairments were present in up to 70% of patients **[33].** Furthermore, occupational impairment was not significantly different in patients during their first episode, than in those with multiple episodes. Even in a prospective observational study including 3681 patients with episodes of acute or mixed mania for two years (2004 to 2006), Goetz et al. **[34],** found that functional and occupational impairment were already present in the year before their first mania episode. This low functional performance seems to be the norm in patients with BD. However, studies are lacking to establish which clinical variables are associated with cognitive impairment, and what are the impacts of these impairments in BD **[35];[36];[37].** Thus,there are still few studies that compare the profile of the neurocognitive and functional performance of patients with BD in an euthymic phase, with less than 3 years of the disease onset (early), and with more than 10 years of the disease (late), in the above-mentioned category. Therefore, the objectives of this study are to determine a) whether there is any impairment of functionality and frontal neurocognitive functions between two different groups of 25 patients with BD I/II, in an euthymic state (≤ 3 years since the diagnosis of BD since their first manic episode, and ≥10 years since the diagnosis of BD since their first manic episode) compared to healthy controls using FAST and FAB tests, respectively b) what is the nature and magnitude of this cognitive and functional impairment in euthymic bipolar patients at different stages of the disease onset c) whether there are differences in demographic, clinical, and pharmacological characteristics between the euthymic groups (≤ 3 and ≥ 10 years of the disease) and the healthy control group d) if there is any cognitive deficit, which deficits are the most frequent in patients with (≤ 3 and ≥ 10 years of the disease) during euthymia e) if the cognitive and functional deficits in euthymic patients (≤ 3 and ≥ 10 years of the disease) are correlated with younger and older patients f) if cognitive and functional deficits in euthymic patients (≤ 3 and ≥ 10 years of the disease) are correlated with study time g) research which category of cutoff scores prevails in the FAST and FAB tests between

euthymic patients (≤ 3 and ≥ 10 years of the disease) h) to correlate the variables in the FAB and FAST tests, and to assess whether the scores in the FAB test had an influence on the scores of the FAST test in both patient groups (≤ 3 years, and ≥ 10 years) which were diagnosed with BD since their first manic episode.

II. METHOD

2.1 Ethics

This study was approved by the Research Ethics Committee of Universidade da Região de Joinville - UNIVILLE (protocol number 655.037) and followed the ethical rules of the Helsinki Declaration of 1975. All participants provided written informed consent before entering the study. Each patient underwent a clinical and psychiatric evaluation, where demographic, anthropometric, pharmacological data and clinical variables (age at onset, disease duration, number of episodes, number of hospitalizations, time since last relapse and hospitalization, history of suicide attempts, history of psychosis symptoms, rapid cycling history, and family psychiatric history), were collected.

2.2 Participants

The study evaluated 50 outpatients, with BD types I/II, in their euthymic state, who were recruited from the Porto Seguro Psychiatric Hospital, located in the city of Curitiba, Brazil. The participants were divided into three distinct groups, each one with 25 individuals: 25 euthymic BD patients in the early stage of disease (≤ 3 years since the diagnosis of BD from the first manic episode); 25 euthymic BD patients in the late stage of disease (≥ 10 years since the diagnosis of BD from the first manic episode), and 25 healthy controls. The groups were matched by age, gender, profession, marital status, and educational level. Most bipolar patients (84%) of this study participated in a psychoeducation program, which was implemented over the last four years. During sessions, patients are trained in strategies to be applied in their daily routines, as well as coping with stressful situations that present themselves as triggers for new crises.The treatment of these patients includes pharmacotherapy combined with psychoeducation, and some of them have psychological interventions **[38];[39];[40].** The psychiatric diagnosis of BD patients for types I/II was defined in the Manual Diagnosis and Statistics of Mental Disorders (DSM-V), and confirmed by Semi-Structured Clinical Interview, according to DSM-V (SCID-5-CV). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) **[41],** and the 17 items version of the Hamilton Depression Rating Scale (HAMD-17) **[42],** respectively. With HAM-17 scale, were evaluated depressive symptoms that had occurred within the last week, and in YMRS, manic symptoms that had presented themselves within the last 48h. The cutoff scores used in the study were: YMRS > 7 as indicative of mania and, HAMD-17 > 7 as indicative of depression. This selection was made to minimize the bias of symptomatology on psychosocial functioning, which has been widely proven in the literature.

2.3 Criteria

The inclusion criteria of bipolar patients in the euthymic stage were: (a) the patients had been in euthymic phase at least six months (b) active age (18 - 60 years); (c) none of the patients had a history of addiction or substance abuse in last year; (d) no history of neurodegenerative diseases, cancer, morbid obesity or trauma (e) patients had no significant comorbid medical conditions, and did not receive medication in addition to those prescribed for their psychiatric condition; these should have been used for at least four weeks; (f) non-smokers (g) not pregnant or breastfeeding (h) patients were able to understand the procedures and protocol and provided written informed consent, and did not present cognitive impairment with disability or dementia, physical disabilities, e.g., visual or hearing impairing.

Healthy controls were selected among hospital staff, and the subjects were matched for demographic parameters of age, gender, education, and marital status. The inclusion criteria of healthy control patients were: (a) active age (18 – 60 years); (b) no diagnosis of BD confirmed by semi-structured clinical interview (SCID-5-CV) (c) no family history of severe mental illness such as schizophrenia, psychotic disorder, major depressive disorder, and BD in first-degree relatives (d) none of the patients had a history of addiction or substance abuse in the last year; (e) patients had no significant comorbid medical conditions and had not received medication for at least four weeks; (f) no history of neurodegenerative diseases, cancer, morbid obesity or trauma (g) non-smokers (h) not pregnant or breastfeeding (i) patients were able to understand the procedures and protocol and provided written informed consent, and did not present cognitive impairment with disability or dementia, physical disabilities, e.g., visual or hearing impairing.

2.4 Demographic, Clinical, and Pharmacological Data

All this data was systematically obtained and included in the study. Demographic variables were age, gender, marital status, education level, employment situation, and years of education.Clinical variables were age at onset, illness duration (years), hospitalization and the duration of hospitalizations, suicide attempts, relatives' antecedents of mental diseases, and participation in a psychoeducation group.Also, some psychometric tests were included to

observe the following: to assess the manic symptoms we used the Young Mania Rating Scale (YMRS), and to evaluate the depressive symptoms we assessed the 17 items version of the Hamilton Depression Rating Scale (HAMD-17). To obtain information about functional impairment, we used the Functioning Assessment Short Test (FAST, and to assess frontal lobe functions we used Frontal Assessment Battery (FAB).

2.5. Neuropsychological Assessment

2.5.1. Functioning Assessment Short Test (FAST) and Frontal Assessment Battery (FAB)

In recent years, there has been an essential advancement in clinical measurements that analyze the deterioration of superior functions and in the functional impairment. However, these measurements are elaborated, specialized, exhaustive, and expensive. Thus, more straightforward tests like FAB and FAST help to measure cognitive performance and serve as a screen for further evaluation. In this research, we tried to establish the degree of functional impairment through FAST, and the EF through FAB, analyzing a group of BD I/II patients in their euthymic phase, compared with a healthy control group.

2.5.2. Functioning Assessment Short Test (FAST)

FAST is a tool developed to evaluate functional impairment and has been validated in different populations **[43];[44];[36];[45]; [46];[47],** and ages **[48];[49]** in BD patients. An analysis of the FAST psychometric properties showed optimal values of inter-observer reliability between two independent evaluations, differing one week from each other (mean K =0.73). The internal consistency obtained was remarkably high, and Cronbach's alpha was 0.955. There was also a highly significant negative correlation with the Global Assessment of Functioning (GAF) (r = -0.9; $p < 0.001$), pointing to a reasonable degree of concurrent validity **[50].**

The FAST scores are evaluated through six functional domains: **Autonomy** (the capacity to make decisions and do things by oneself); **Occupational Functioning** (the capacity to maintain a paid job, the efficiency of performing tasks at work, working in the field in which the patient was educated and earning according to the level of the employment position); **Cognitive Functioning** (the ability to concentrate, perform simple mental calculations, solve problems, and learn and recall new information); **Financial Issues** (the capacity to manage one's finances); **Interpersonal Relationships** (relations with friends and family, involvement in social activities, sexual relationships and the ability to defend one's interests), and **Leisure Time** (the capacity to engage in sports or physical activities and to enjoy hobbies). Four categories were established in the FAST scale of functional impairment cut-offs. No impairment: from 0 to 11 in the FAST total score. Mild impairment: from 12 to 20 in the FAST total score. Moderate impairment: from 21 to 40 in the FAST total score, Severe impairment: scores above 40 in the FAST total score.**)**. However, patients are not static in a category after an intervention, either pharmacological or psychological, patients can interchange through categories **[44];[51].**

2.5.3. The Frontal Assessment Battery (FAB)

The Frontal Assessment Battery (FAB) is a brief (10-min) test of EF, consisting of six cognitive tasks that were developed specifically to assess the frontal lobe functions. An analysis of the FAB psychometric properties showed optimal values of inter-observer reliability (k = 0.87; $p < 0.001$), an acceptable internal consistency (Cronbach's alpha = 0.78), and an ability to distinguish between patients and controls of 89% **[52];[53]**. In our research, we used the Brazilian version of FAB.This battery consists of six subtests which are**: Similarities** (explores the domain of abstract reasoning/conceptualization) i.e., to identify the link between two objects from the same semantic category (an apple and a banana are both fruits). **Lexical Fluency** (letters) (explores the domains of self-organized strategy and shifting i.e. mental flexibility) where patients produce as many words as they can, beginning with the letter "S" in one minute. **Motor Series** (explores the domain of motor programming/planning). The "fist-edge-palm" series must be performed six times consecutively and spontaneously with their dominant hand. **Conflicting Instruction** (explores the domain of sensitivity to interference). It provides an opposite response to the examiner's alternating signal, e.g. tapping once when the examiner taps twice and vice versa, the single and double tappings are intermixed in a fixed order. Verbal commands conflict with sensory information and subjects should obey initial verbal commands and refrain from following what they see. **Go-No Go Task** (explores the domain of inhibitory control and assesses the ability to withhold a response, inappropriately induced by both previous learning and concomitant sensory information). The same alternating signals used in the previous subtests are again given, but the subjects must now provide different responses, e.g., not tapping when the examiner taps twice and copying the examiner when he taps once. **Prehension Behaviour** (explores the domain of environmental independence). The examiner touches both palms, without saying anything or looking at the subject. If the subject spontaneously takes the hands, it means that sensory stimuli and environmental cues can activate patterns of responses that are normally inhibited **[54]**. The maximum score for each subtest is three points (with higher scores indicating better performance), and the total score of the test is calculated

by adding the scores of the six subtests (maximum score =18). Any performance score of 18 to 15 indicates a frontal lobe without disabilities. A performance of 14 to 11 is considered a moderate impairment and below 10 is considered a severe impairment. These score cutoffs were validated to a Portuguese population **[54].**

The FAB test can provide an easier, more reliable, and quicker measure of EF, useful in initial assessments, or when available time and resources are limited. We know that there is variability in the different tests concerning the specificity for some of the different EF measured, in different pathologies **[55].** Nevertheless, this specificity is still low and has been pointed out as a limitation. Another issue is the relative usefulness of these executive screening tools in the different stages of neurodegenerative diseases since the progression generally occurs towards generalized deficits **[56].** Thus, the tests above can be useful for the differential diagnosis in the early stages of the disease (when combined with other measures), while their contribution in later stages may be more related to the description of the neurocognitive phenotype.

Although FAB was initially validated in patients with neurodegenerative diseases and was later extended to other pathologies such as extrapyramidal disorders, vascular damage such as a stroke, dementia such as Alzheimer's disease, and frontotemporal dementia **[52];[57];[58];[54];[59];** more recently, different authors have started to research the use of the FAB test for psychiatric diseases **[60]; [61]; [62]; [63]; [64].** Regarding psychiatric illnesses, the FAB test can evaluate the cognitive tasks and be associated with specific areas of the frontal lobes (that is, able to measure, i.e., conceptualization with the dorsolateral areas, word generation with the medial areas, and inhibitory control with the orbital or medial areas. The FAB test was able to exhibit a degree of sensitivity to focal lesions near the anterior insula in the middle right lower frontal gyrus, and in the lower right frontal gyrus), **[65];[66]**, but it will be discussed forward.

2.6. Statistical analysis

Demographic and clinical variables were analyzed using descriptive statistics, including (mean), and (standard deviation) for quantitative variables and absolute frequency (n), and relatives (%), for qualitative variables with a confidence interval of 95% in both cases. For the qualitative nominal and ordinal data, we used the Chi-square test ($\chi 2$) of Pearson and for two or more groups, we used Fisher's exact test. Parametric and nonparametric tests were used for the analysis of qualitative variables. The assumption of normality and homoscedasticity of each variable was analyzed with the Kolmogorov-Smirnov normality test and Levene's test, respectively. For comparisons of parametric variables between two groups, the Student *t*-test was used, and for more than two groups the Tukey's test of analysis of variance (ANOVA) was used. To compare non-parametric variables between two and three independent samples, the Mann-Whitney tests and the Kruskal-Wallis tests were used, respectively. Dunn's post hoc test was performed to peer comparisons in case the main effects were significant. For association analyses, Pearson correlation was used to test quantitative variables and Spearman correlation for non-quantitative variables. In addition, we stratified our sample into five groups according to the level of graduation: illiterate, up to primary school, up to high school, graduate, and postgraduate. The total scores of each test; FAST and FAB, were correlated with age and educational level. It is important to note that this battery of evaluation represents only the beginning of cognitive functions, and only specialists who are trained can give a diagnosis if there are any executive dysfunctions. The most recent version of the SPSS software program (SPSS Inc., Chicago, USA) was used. To calculate the statistical power analyses we used the program - G*Power 3.1. Statistical significance was set at $p < 0.05$for all tests or adopting a level of significance of 5% to reject the null hypotheses.

III. RESULTS

3.1. Demographic, Clinical and Pharmacological Characteristics

The demographic and clinical characteristics of the different groups studied were evaluated. The sample included 25 healthy controls, and 50 patients with BD divided in two groups of euthymic patients (≤ 3 and ≥ 10 years of the disease). Initially, it was calculated the sample size - difference between two independent means (two tails). The analyses showed an effect size d = 0.853; α = 0.05; power (1-β err prob) = 0.80; noncentrality parameter δ =2.89; critical t = 2.01; Df = 44; sample size group 1 = 23; sample size group 2 = 23; total sample size = 46; actual power = 0.808.

Thirty-six euthymic patients (72%) were female. The healthy control group had a mean age of (36.1 ± 9.87) and the euthymic patients analyzed had a mean age of (34.9 ± 10.04years in the group of ≤ 3 years of the disease), and (47.4 ± 8.21 years in the group of ≥ 10 years of the disease). Utilizing theone-way ANOVA followed by Dunn's post hoc test, the means of healthy controls and euthymic patients differ between ages (***p* < 0.01**). Utilizing the Chi-square test, there was no difference between groups in gender, occupational status, and marital status **(*p* > 0.05)**. Also, it was observed after performing the Chi-

square test followed by Fisher's exact test, that the groups significantly no differed in terms of their educational level **($p > 0.05$).** The mean years of education were (14.7 ± 2.18) years in the healthy control group, and the euthymic patients analyzed had a mean of (13.8 ± 2.70years in the group of ≤ 3 years of the disease), and (12.4 ± 2.77 years in the group of ≥ 10 years of the disease). After performing the Kruskal-Wallis test, the groups significantly differed in terms of years of education (**$p < 0.01$**) as seen in **Table 1.**

Table 1: Sociodemographic Characteristics of the Sample

	Healthy Controls n = 25	Bipolar Patients ≤ 3 years of disease n = 25	Bipolar Patients ≥ 10 years of disease n = 25	p - Value
Age, years [b]	36.1 (9.87)	34.9 (10.04)	47.4 (8.21)	P < 0.01 c
Gender, n				P = 0,77 a
Male	9	7	7	
Female	16	18	18	
Marital status n (%)				P = 0,08 a
Married	12 (48.0)	9 (36.0)	15 (64)	
Divorced	1 (4.0)	2 (8.0)	5 (20)	
Widowed	1 (4.0)	0 (0.0)	1 (4)	
Single	11 (44.0)	14 (56.0)	4 (12)	
Education n (%)				P = 0 ,13 d
Illiterate	-	-	-	
Up to primary school	0 (0.0)	3 (12.0)	4 (16.0)	
Up to high school	10 (40.0)	10 (40.0)	12 (48.0)	
Graduate	12 (48.0)	12 (48.0)	9 (36.0)	
Postgraduate	3 (12.0)	0 (0.0)	0 (0.0)	
Years of education [b]	14.7 (2.18)	13.8 (2.70)	12.4 (2.77)	p < 0,01 e
Work situation n (%)				P = 0,17 a
Employed	23 (92.0)	18 (72.0)	13 (52%)	
Unemployed	2 (8.0)	6 (24.0)	10 (40.0)	
Medical benefits	0 (0.0)	1 (4.0)	0 (0.0)	
Invalidity	0 (0.0)	0 (0.0)	2 (8.0)	

[a] χ^2 [b] Mean (SD) [c] One-way ANOVA followed Dunn´s post hoc [d] Fisher's exact test [e] Kruskal-Wallis

The bipolar patients had a mean of disease duration of ≤ 3 years (2.52 ± 0.65), and ≥ 10 years (15.64 ± 6.81), and the mean age at onset of the disease was ≤ 3 years (22.1 ± 7.01), and ≥ 10 years (25.1 ± 6.17). Twenty patients (40%) had previously been hospitalized. Among these patients, the mean duration of hospitalization was (13.2 days ± 0.967), and patients with ≤ 3 years of the disease, attempted suicide 18 times, whereas the patients with ≥ 10 years of the disease attempted suicide 40 times. The family history of BD was positive in 23 patients. Regarding pharmacologic treatment, our results showed that 10 (20%) of the patients were on monotherapy. Among the patients on polypharmacy, 18 (36%), 16 (32%), and 6 (12%) of the patients received 2, 3, and 4 psychotropic medications, respectively. The percentages of mood stabilizers, antipsychotics, antidepressants, and benzodiazepines used in patients according to their clinical symptoms, are presented in **Table 2.**To evaluate the absence of depression or mania in the samples, the HAM-D and YMRS tests were used in the healthy control group, and the euthymic patients' group respectively. The observed results had a mean HAM-D score of (4.32 ± 2.49) for the healthy control group, and (4.10 ± 2.02) for euthymic patients with ≤ 3 years of the disease, and (3.71 ± 1.46) for euthymic patients with ≥ 10 years of the disease. After performing the ANOVA one-way test, the groups did not differ (**$p > 0.05$**). Regarding the YMRS score, the mean was (0.64 ± 0.90) to the healthy control group, and (0.88 ± 1.01) to euthymic patients with ≤ 3 years of the disease, and (1.28 ± 1.13) for euthymic patients with ≥ 10 years of the disease. After performing the Kruskal-Wallis test the groups did not differ (**$p > 0.05$**) as seen in **Table 2.**

Table 2: Clinical and Pharmacological Characteristics of the Sample

	Healthy Controls n = 25	Bipolar Patients ≤ 3 years of disease n = 25	Bipolar Patients ≥ 10 years of disease n = 25	*p - Value*
Illness duration (years) [a]	N/A	2.52 (0.65)	15.64 (6.81)	*p < 0.001 d*
Age of onset (years) [a]	N/A	22.1 (7.01)	25.1 (6.17)	*p = 0.62 d*
HAM-D total score [a]	4.32 (2.49)	4.10 (2.02)	3.71 (1.46)	*p = 0.53 b*
YMRS total score [a]	0.64 (0.90)	0.88 (1.01)	1.28 (1.13)	*p = 0.08 c*
FAST score, median (IQR)	9 (7)	22 (10)	23 (20)	*p < 0.001 c*
FAB score, median (IQR)	16 (3)	14 (4.5)	14 (3.5)	*p < 0.001 b*
Hospitalizations n (%)	N/A	12 (48)	8 (32)	
Duration hospitalizations (day) [a]	N/A	13.4 (24.3)	13.0 (36.6)	*p = 0.90 d*
Suicide attempts n (%)	N/A	18	40	
Family history of affective disorders n (%)	N/A	10 (40)	13 (52)	
Psychoeducation Yes, n (%)	N/A	21 (84)	20 (80)	
Treatment n (%)				
Lithium	N/A	13 (52)	15 (60)	
Other mood stabilizers	N/A	11 (44)	13 (52)	
Atypical antipsychotics	N/A	8 (32)	12 (48)	
Typical antipsychotics	N/A	2 (8)	0 (0)	
Antidepressants	N/A	7 (28)	7 (28)	
Benzodiazepines	N/A	2 (8)	7 (28)	

HAM-D 17 = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; FAST = Functioning Assessment Short Test FAB = Functioning Assessment Short Test IQR = interquartile range N/A = not available [a] Mean (SD) [b] Anova one-way [c] Kruskal-Wallis [d] Mann-Whitney test

3.2. Functional Status and Neurocognitive Performance.

3.2.1. Healthy Controls versus Euthymic Patients

Initially, the means of the 25 healthy control group patients were compared with the 50 euthymic patients. The results of the general functional and cognitive assessments were measured by performing the FAST and FAB tests (mean ± SD), respectively. The means of the FAST test were (9.80 ± 5.94) and (24.6 ± 11.15), respectively; and it was observed after performing the *t*-test followed by the Mann Whitney test (t = 6.195; U= 126; $\mathbf{p < 0.001}$). The means of the FAB test were (15.72 ± 1.64) and (13.68 ± 2.61), respectively and the results were observed after performing the *t*-test followed by the Mann Whitney test (t = 3.567; U= 310; $\mathbf{p < 0.001}$). Through the FAST and FAB tests, we concluded that the patients with BD had greater functional and cognitive impairment than healthy controls, as seen in **Table 3** and **Figs. 1-2.** Our results are compatible with other research performed **[44];[50];[45];[67].**

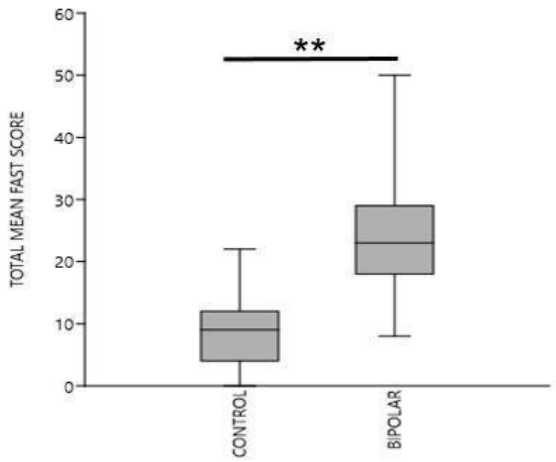

*Fig.1. Box-plot of total means (±SD) Functioning Assessment Short Test (FAST) score in Total BD patients (n=50) and their matched controls (n=25). Median levels are indicated by horizontal lines (Mann-Whitney: control vs. bipolar patients, ** p < 0.001)*

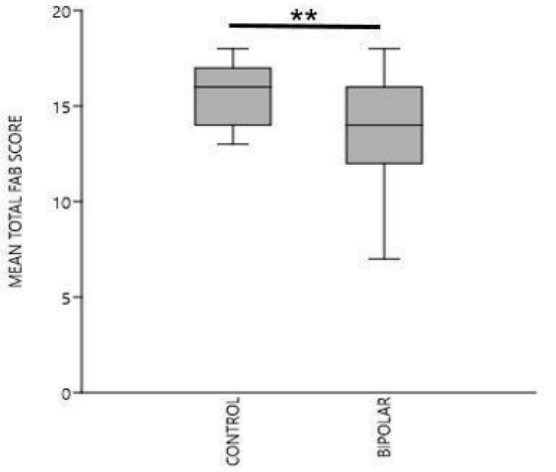

*Fig.2. Box-plot of total means (±SD) Frontal Assessment Battery (FAB) score in Total BD patients (n=50) and their matched controls (n=25). Median levels are indicated by horizontal lines (Mann-Whitney: control vs. bipolar patients, ** p < 0.001)*

Table 3: Mean Total of FAST and FAB Score in Health Controls and Euthymic Patients with ≤ 3 years and ≥ 10 years of disease

	Healthy Control n= 25	Euthymic Patients n= 50	*t*	U	*p*	*d*
FAST total score Means (± SD)	9.80 (±5.94)	24.60 (±11.09)	6.34	3.24	< 0.001**	-1.663
FAB total score Means (± SD)	15.84 (±1.64)	13.56 (±2.81)	3.56	2.50	< 0.001**	0.938

Note. Means ± standard deviation (SD). FAB = Frontal Assessment Battery FAST = Functioning Assessment Short Test. [*] indicate FAB and FAST scores significantly different between groups by t-test (*t*) and followed by Mann–Whitney test (*U*) for independent samples, *d* = Cohen's effect size. **p < 0.001

After this comparison, we divided the euthymic group (n= 50) into two groups (≤ 3 years (n= 25) and ≥ 10 years (n= 25) of the disease). The results of the general functional and cognitive assessments were measured by performing the FAST and FAB tests (mean ± SD), respectively. The total means of the FAST test score to the healthy control group was (9.80 ± 5.94) and the group with ≤ 3 years and ≥ 10 years of the disease were (20.6 ± 8.21 and 27.8 ± 12.50), respectively; and it was observed after performing the Kruskal-Wallis followed by de Dunn's post hoc test**(*p*<0.001).** Thetotal means of the FAB test score for the healthy control group was (15.84 ± 1.55), and the group with ≤ 3 years and ≥ 10 years of the disease were (14.6 ± 2.48 and 12.4 ± 2.78), respectively. The same results were observed after performing the Kruskal-Wallis followed by the Dunn's post hoc test(***p* < 0.001**)as seen in **Table 4** and **Figs. 3-4.** Our results showed a significant difference between the groups which will be discussed later.

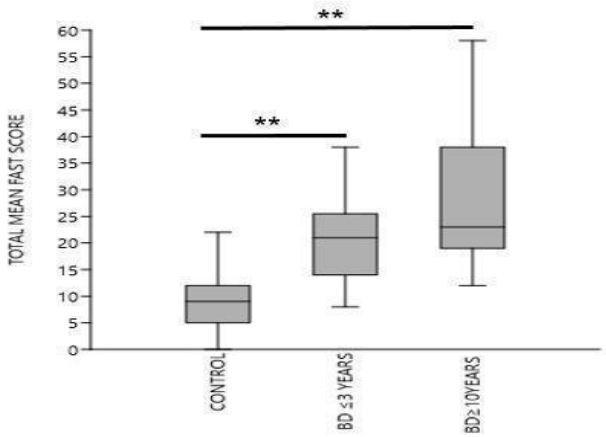

*Fig.3. Box-plot of total means (±SD) Functioning Assessment Short Test (FAST) score between Healthy Control and Patients with ≤ 3 years of disease and ≥ 10 years of disease. Means levels are indicated by horizontal lines (Kruskal-Wallis followed by Dunn´s post hoc ** p < 0.001).*

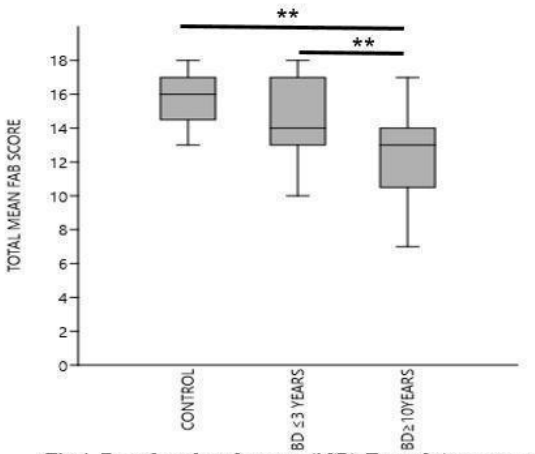

*Fig.4. Box-plot of total means (±SD) Frontal Assessment Battery (FAB) score between Healthy Control and Patients with ≤ 3 years of disease and ≥ 10 years of disease. Means levels are indicated by horizontal lines (One-way ANOVA followed by Dunn´s post hoc ** p < 0.001).*

Table 4: Mean Total of FAST and FAB Score in Health Controls and Euthymic Patients with ≤ 3 years and ≥ 10 years of disease

	Healthy Control n=25	Euthymic Patients ≤ 3 YEARS OF DISEASE n= 25	Euthymic Patients ≥ 10 YEARS OF DISEASE n= 25	*p*	f_2
FAST Means (± SD) [a]	9.80 (± 5.94)	20.63 (± 8.21)	27.80 (± 12.50)	< 0.001 **	0.7960
FAB Means (± SD) [b]	15.84 (± 1.55)	14.64 (± 2.48)	12.44 (± 2.78)	< 0.001 **	0.6042

Note. Means ± standard deviation (SD). FAB = Frontal Assessment Battery FAST = Functioning Assessment Short Test. [*] indicate FAB and FAST scores significantly different between groups. [a] Kruskal-Wallis followed by Dunn´s post hoc to FAST test ** $p < 0.001$ [b] One-way ANOVA followed by Dunn´s post hoc to FAB test ** $p < 0.001$. f_2 =the overall Cohen's effect size

3.2.2. FAST and FAB score and age

Two variables presented a significant statistical difference between the groups; age and years of education, which will be discussed below. Based on previous results, our group decided to divide the euthymic group into two groups by age. For this purpose, we used the median age of the total euthymic patients (median = 41 years). Twenty-five patients were < 41 years old, and 25 patients were ≥ 41 years old, and the following results were observed. The results of the FAST and FAB tests were performed and were demonstrated for each euthymic patient group (< 41and ≥ 41 years old), respectively. The FAST scores between the group with < 41 years old, were (24.9 ± 11.72), and the group with ≥ 41 years old were (23.3 ± 10.60), and the FAB scores between the group with < 41 years old, were (13.6 ± 3.46), and the group with ≥ 41 years old were (13.7 ± 2.09) respectively. After performing the*t*-test, the FAST and FAB scores did not differ with the age groups between (< 41 and ≥ 41 years old). Thus this study showed that to be younger or older (age < 41 years and ≥ 41 years), did not differ in the total scores of the FAST and FAB tests. However, different authors observed that age could influence the results ***p*> 0.05)** as seen in **Table 5** and **Fig. 5-6.** Thus, this study showed that to be younger or older (age < 41 years and ≥ 41 years), did not differ in the total scores of the FAST and FAB tests. However, different authors observed that age could influence the results **[63];[77],** and it will be discussed later.

Table 5: Mean Total of FAST and FAB Scores in Health Controls and Euthymic Patients with median < 41 and ≥ 41 years old

	Euthymic Patients median < 41 YEARS n= 25	Euthymic Patients median ≥ 41 YEARS n= 25	*t*	F	*p* - Value	*d*
FAST Means (± SD)	24.9 (± 11.72)	23.3 (± 10.60)	0.50	2.73	$p > 0.05$ [a]	0.143
FAB Means (± SD)	13.6 (± 3.46)	13.7 (± 2.09)	0.44	2.73	$p > 0.05$ [a]	-0.034

Note. Means ± standard deviation (SD). FAB = Frontal Assessment Battery. FAST = Functioning Assessment Short Test. After performing the *t*-test (*t*), the groups did not differ in age for independent samples. $p > 0.05$ *d* = Cohen's effect size

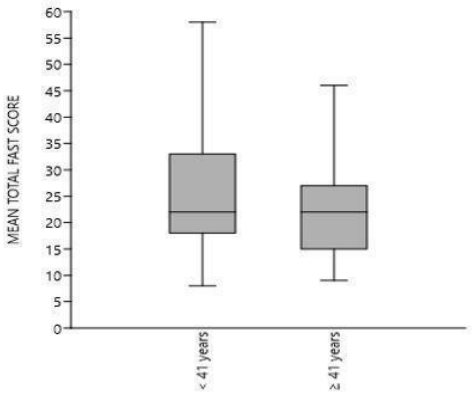

Fig.5. Mean Total of FAST Score in Euthymic Patients with Median < 41 and ≥ 41 years old

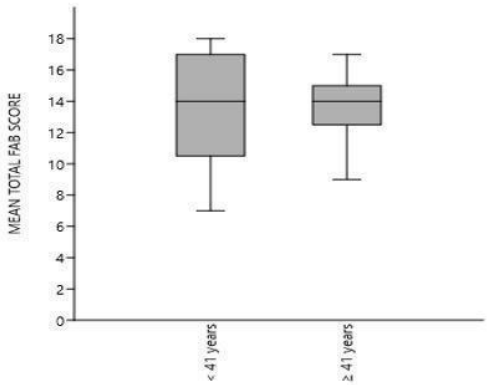

Fig.6. Mean Total of FAB Score in Euthymic Patients with Median < 41 and ≥ 41 years old

3.2.3. FAST and FAB score and years of study

In addition to age, another point that was assessed by our study and which may interfere in the FAST and FAB results, is the number of years spent studying. Various authors observed that the study time could influence the test results **[70];[68];[69].**

Our samples (healthy control patients and euthymic patients with ≤ 3 years and ≥ 10 years of the disease), presented a study time variation between (8 to 18 years). The mean total of years of study in the healthy control group, and in the groups with ≤ 3 years and ≥ 10 years of the disease, were (14.7 ± 2.18), (13.8 ± 2.70), and (12.4 ± 2.77) respectively. After performing the Kruskal-Wallis test the groups differed statistically**($p < 0.001$)** as seen in **Table 1** and **Fig. 7.** The (means ± SD) of the FAST scores between the patientsgroup with ≤ 3 years and ≥ 10 years of the disease), were (20.5 ± 8.21) and (27.7 ± 12.50) respectively. After performing the *t*-test the groups differed in study time (t = 2.40; F = 2.41; **$p < 0.04$).** The (means ± SD) ofFAB scores between the patients group with (≤ 3 years and ≥ 10 years of the disease) were (14.6 ± 2.48), and (12.36 ± 2.76) respectively. After performing the *t*-test the groups differed in study time (t = 2.49; F = 1.25; **$p < 0.01$)**, see **Table 6** and **Fig. 7.**

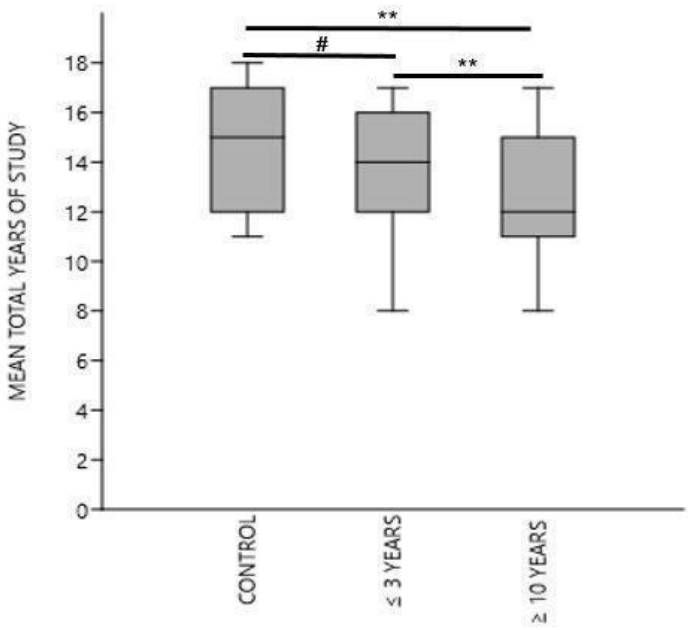

*Fig.7. Mean Total of years of study between control group and Euthymic Patients with ≤ 3 years and ≥ 10 years. ** p < 0.001 # p > 0.05*

Table 6: Mean Total of FAST and FAB Scores between Euthymic Patients with ≤ 3 years and ≥ 10 years of disease with the mean of years of study

	Euthymic Patients BD ≤ 3 YEARS n= 25 YEARS OF STUDY 13.84 (± 2.70)	Euthymic Patients BD ≥ 10 YEARS n= 25 YEARS OF STUDY 12.4 (± 2.78)	*t*	F	U	*p* - Value	*d*
FAST Means (± SD) [a]	20.5 (± 8.21)	27.7 (± 12.50)	2.40	2.31	209	$p < 0.04$ *	0.340
FAB Means (± SD) [a]	14.6 (± 2.48)	12.36 (± 2.76)	2.49	1.25	177	$p < 0.01$ **	0.417

Note. Means ± standard deviation (SD). FAB = Frontal Assessment Battery. FAST = Functioning Assessment Short Test. [*] indicate FAB and FAST scores significantly different between groups. [a] t-test (*t*) followed by Mann–Whitney test (*U*) for independent samples, *$p < 0.05$ **$p < 0.01$ *f2* =the overall Cohen's effect size

Thus, this study demonstrated that the mean total of the FAST and FAB tests scores, differed significantly between the groups with (≤ 3 years and ≥ 10 years of the disease), related to the amount of years spent on education, as seen in **Table 6.**

3.2.4. Categories Scores of FAST and FAB tests in Healthy Controls and Euthymic patients

As mentioned above, FAST and FAB tests have different scoring categories. These different categories demonstrate a greater or lesser severity in the patient´s functionality in their daily life using the (FAST) test, and impairment or non- impairment in the frontal cognitive activity, using the (FAB) test. **Tables 7-8** show the cut-off lines for the categories concerning functionality (FAST), and cognitive (FAB) impairments. **Table 7,**demonstrates that the majority of the euthymic patients (58%; n=29) presented a moderate level of impairment in the FAST test scores, both with ≤ 3 years (60%; n=15) and with ≥ 10 years (56%; n=14) of the disease, when compared to the healthy control group where the majority were in the non-impairment group (76%; n=18). The same phenomenon was observed in **Table 8**; which also showed a moderate level of impairment in the FAB test scores, and an important number of euthymic patients (54%; n=27), as well as in the group with ≤ 3 years (52%; n=13) and the group with ≥ 10 years (56%; n=14) of the disease when compared to the healthy control group, where the majority were in the non impairment group (76%; n=18)***(p*<0.01).** However,when we compared only the groups of euthymic patients with (≤ 3 years and ≥ 10 years of the disease) using the chi-square ($\chi 2$) test analysis, we observed that there was a significant

difference in the FAST test scores between the groups, but we did not observe the same concerning the FAB test.

Table 7: FAST total scale and the categories of functional impairment cut-offs

	Healthy Control N = 25	Euthymic Patients BD ≤ 3 YEARS n= 25	Euthymic Patients BD ≥ 10 YEARS n= 25	*p* - Value
FAST score				$p < 0.0001$ [a]
0 - 11 No impairment	18	5	0	
12 - 20 Mild impairment	5	5	7	
21 - 40 Moderate impairment	2	15	14	
41 - 60 Severe impairment	0	0	4	

(FAST) Functioning Assessment Short Test [a] χ^2 test

χ^2 Test $p < 0.02$

Table 8: FAB total scale and the categories of cognitive impairment cut-offs

	Healthy Control N = 25	Euthymic Patients BD ≤ 3 YEARS n= 25	Euthymic Patients BD ≥ 10 YEARS n= 25	*p* - Value
FAB score				$p < 0.01$ [a]
18 - 15 No impairment	18	8	5	
14 - 11 Moderate impairment	7	13	14	
10 - 0 Severe impairment	0	4	6	

(FAB) Frontal Assessment Battery Test [a] χ^2 test

χ^2 Test $p > 0.05$

3.2.5. Categories Scores of FAST test in Healthy Controls and Euthymic patients

Significant differences were found in all distinct domains of the FAST test between total euthymic patients (n = 50) and healthy controls (n = 25), showing the influence of BD over the functionalities**.** Specifically, patients showed a decrease in occupational, autonomy, cognitive and interpersonal domains, and also had the most significant statistical differences ***(p*< 0.001),** suggesting that these domains may be the most impaired. All effect sizes (*d*) were in the same direction, suggesting worse performance in the patient group than in the healthy control group, see **Table 9.**

Table 9: Functionalities Assessed by the FAST Subtest in Total Euthymic Patients

FAST subtests	Healthy Control n = 25	Euthymic Patients n= 50	*t*	F	*p* - Value	*d*
1. Autonomy	1.20 (±1.76)	3.32 (± 2.54)	3.52	2.20	$p < 0.001$ ** [a]	-0.916
2. Occupational Functioning	0.96 (±1.10)	5.48 (± 4.02)	5.03	14.93	$p < 0.001$ ** [a]	-1.407
3. Cognitive Functioning	4.00 (±2.25)	7.92 (± 3.36)	4.37	2.63	$p < 0.001$ ** [a]	-1.152
4. Financial Issues	1.32 (±1.49)	2.96 (± 2.20)	2.19	1.82	$p < 0.04$ ** [a]	-0.565
5. Interpersonal Relationship	1.24 (±1.56)	5.44 (± 4.47)	4.55	6.90	$p < 0.001$ ** [a]	-1.250
6. Leisure Time	1.20 (±1.22)	2.62 (± 2.39)	2.96	3.31	$p < 0.01$ ** [a]	-0.790
FAST total score	9.80 (± 5.94)	20.63 (± 8.21)	6.34	3.24	$P < 0.001$ **	-1.663

Note. Means ± Standard Deviation (SD). FAST = Functioning Assessment Short Test. Analysis of FAST subtests scores by t-test (*t*) (F) for independent samples, *d* = Cohen's effect size. * p < 0.01 and ** p < 0.001.

Using the data obtained from the evaluation of the subtests in all euthymic patients, the patients were divided into two groups (≤ 3 and ≥ 10 years of the disease) and were statistically evaluated. The analysis showed that there is no significant difference between the (≤ 3 and ≥ 10 years of the disease) groups, but there is a significant difference between the two groups comparing them with the healthy control group ***(p< 0.001).*** As previously discussed, it was observed that the duration of the disease did not influence the results among euthymic patients; as seen in **Table 10.**

Table 10: Functionalities Assessed by the FAST Subtest in Euthymic Patients with ≤ 3 years and ≥ 10 years of disease

FAST subtests	Healthy Control n = 25 (a)	Euthymic Patients BD ≤ 3 YEARS n= 25 (b)	Euthymic Patients BD ≥ 10 YEARS n= 25 (c)	*p* - Value	Post-hoc analysis	*f2*
1. Autonomy	1.20 (±1.76)	3.32 (± 2.54)	3.16 (± 2.71)	$p < 0.001$ ** [a]	a < b a < c b ≈ c	0.405
2. Occupational Functioning	0.96 (±1.10)	5.48 (± 4.02)	5.16 (± 4.53)	$p < 0.001$ ** [a]	a < b a < c b ≈ c	0.579
3. Cognitive Functioning	4.00 (±2.25)	7.92 (± 3.36)	7.08 (± 3.95)	$p < 0.001$ ** [a]	a < b a < c b ≈ c	0.515
4. Financial Issues	1.32 (±1.49)	2.96 (± 2.20)	2.48 (± 2.00)	$p < 0.01$ ** [a]	a < b a < c b ≈ c	0.357
5. Interpersonal Relationship	1.24 (±1.56)	5.44 (± 4.47)	4.8 (± 3.76)	$p < 0.001$ ** [a]	a < b a < c b ≈ c	0.529
6. Leisure Time	1.20 (±1.22)	2.62 (± 2.39)	2.80 (± 2.19)	$p < 0.04$ * [a]	a < b a < c b ≈ c	0.354
FAST total score	9.80 (± 5.94)	20.63 (± 8.21)	27.80 (± 12.50)	$P < 0.001$ ** [a]	a < b a < c b ≈ c	0.796

Note. Means ± standard deviation (SD). FAST = Functionality Assessment Short Test. n.s. = no significant [a] Kruskal-Wallis followed by Dunn´s post hoc to FAB test. [*] indicate FAST scores significantly different between groups. * $p < 0.05$ ** $p < 0.001$. *f2* =the overall Cohen's effect size

3.2.6. Categories Scores of FAB test in Healthy Controls and Euthymic patients

Our results demonstrated that significant differences were found in three distinct domains analyzing the FAB test scores between the total euthymic patients (n=50), and the healthy control patients (n= 25**).** Specifically, patients showed a decrease in Conceptualization, Inhibitory Control, and Sensitivity to Interference domains ***(p*< 0.05),** suggesting that these domains may be the most impaired. All effect sizes (*d*) were in the same direction, suggesting worse performance in the patient group than in the healthy control group. Thus, in this study, we observed that the impact of BD, even in patients during a euthymic phase, was present in their cognition functions **[71],** as seen in **Table 11.**

Table 11: Neurocognitive Functions Assessed by the FAB Subtest in Total Euthymic Patients

FAB subtests	Healthy Control n = 25	Euthymic Patients n= 50	*t*	F	*p* - Value	*d*
1. Similarities (Conceptualization)	1.84 (± 0.85)	1.34 (± 1.08)	2.01	1.61	$p < 0.04$ * [a]	0.514
2. Lexical Fluency (Mental flexibility)	2.72 (± 0.46)	2.50 (± 0.61)	1.58	1.79	$p > 0.05$ [a]	0.407
3. Motor Series (Motor programming)	2.92 (± 0.28)	2.64 (± 0.72)	1.86	6.79	$p > 0.05$ [a]	0.512
4. Conflicting Instruction (Sensitivity to interference)	2.92 (± 0.54)	2.56 (± 0.77)	2.53	7.58	$p < 0.01$ * [a]	0.606
5. Go-No Go Task (Inhibitory control)	2.32 (± 1.14)	1.52 (± 1.50)	2.45	1.62	$p < 0.02$ * [a]	0.626
6. Prehension Behaviour (Environmental autonomy)	2.96 (± 0.20)	2.80 (± 0.60)	1.28	9.18	$p > 0.05$ [a]	0.202
FAB total score	15.84 (± 1.55)	14.64 (± 2.48)	3.56	2.50	$p < 0.001$ ** [a]	0.938

Note. Means ± Standard Deviation (SD). FAB = Frontal Assessment Battery. Analysis of FAB subtests scores by t-test (*t*) (F) for independent samples, *d* = Cohen's effect size. * $p < 0.05$ ** $p < 0.001$.

Using the data obtained from the evaluation of the subtests in all euthymic patients, we divided the patients into two groups (≤ 3 and ≥ 10 years of the disease) and were statistically evaluated. The analysis showed that there is no significant difference between the ≤ 3 and ≥ 10 years of the disease groups, but there is a significant difference between the group with ≥ 10 years of the disease and the healthy control group**(*p*< 0.05).** As previously discussed, it was observed that the duration of the disease did not influence the results among euthymic patients, as seen in **Table 12**.

Table 12: Neurocognitive Functions Assessed by the FAB Subtest in Euthymic Patients with ≤ 3 years and ≥ 10 years of disease

FAB subtests	Healthy Control n = 25 (a)	Euthymic Patients BD ≤ 3 YEARS n= 25 (b)	Euthymic Patients BD ≥ 10 YEARS n= 25 (c)	*p* - Value	Post-hoc analysis	f_2
1. Similarities (Conceptualization)	1.88 (± 0.88)	1.52 (± 1.15)	1.28 (± 1.02)	$p < 0.03$ * [a]	a ≈ b b ≈ c a > c	0.240
2. Lexical Fluency (Mental flexibility)	2.68 (± 0.47)	2.48 (± 0.58)	2.56 (± 0.65)	$p > 0.05$ [a]	n.s.	0.143
3. Motor Series (Motor programming)	2.92 (± 0.27)	2.84 (± 0.47)	2.48 (± 0.87)	$p < 0.02$ * [a]	a ≈ b b ≈ c a > c	0.323
4. Conflicting Instruction (Sensitivity to interference)	2.92 (± 0.27)	2.56 (± 0.77)	2.36 (± 0.95)	$p < 0.02$ * [a]	a ≈ b b ≈ c a > c	0.331
5. Go-No Go Task (Inhibitory control)	2.32 (± 1.14)	1.52 (± 1.50)	1.60 (± 1.41)	$p < 0.05$ * [a]	a ≈ b b ≈ c a > c	0.299
6. Prehension Behaviour (Environmental autonomy)	2.96 (± 0.20)	2.84 (± 0.47)	2.76 (± 0.72)	$p > 0.05$ [a]	n.s.	0.274
FAB total score	15.84 (± 1.55)	14.64 (± 2.48)	12.44 (± 2.78)	$p < 0.001$ ** [a]	a ≈ b b > c a > c	0.6042

Note. Means ± standard deviation (SD). FAB = Frontal Assessment Battery. n.s. = no significant [a] Kruskal-Wallis followed by Dunn´s post hoc to FAB test.
* $p < 0.05$ ** $p < 0.001$. f_2 =the overall Cohen's effect size

3.3. Correlation between FAST and FAB tests scores in euthymic patients

Fig. 8 displays the impact of cognitive function (FAB test) of euthymic patients on functionality (FAST test). The correlation between frontal cognition and functionality was analyzed through the scores of the FAB and the FAST tests in euthymic and healthy control patients, using the Spearman Correlation Coefficient. Although only a small number of samples of euthymic patients were used (n=50) and healthy control (n=25), it was possible to observe a negative Spearman Correlation Coefficient, after assessing normality using the Shapiro-Wilk test. The correlation presented a moderate intensity **(r^2= -0.539)** to euthymic patients and a very weak correlation in healthy control **(r^2= -0.106).** This correlation between the variables FAB and FAST, demonstrated that euthymic patients who have lower scores on the FAB (decreased frontal activities and EF), had higher scores on the FAST (with greater loss of functionality). Since **r^2= -0.539**, it represents a moderate correlation, the FAB variable alone is not able to explain the total FAST variability. However, the sample results provide significant statistical evidence between FAB and FAST **(p< 0.0001).**Regarding the healthy control group, we did not find a significant correlation, **(p > 0.05).** Furthermore, it is important to remember that the correlation coefficient (r^2) is only an estimate of the population correlation coefficient (p), and we should not forget that the value of r is calculated based on some data pairs constituting random samples. Often the points in the sample may show a correlation, even though the population does not, in this case, we are facing an inference problem, since $r \neq 0$ is not a guarantee that $p \neq 0$.

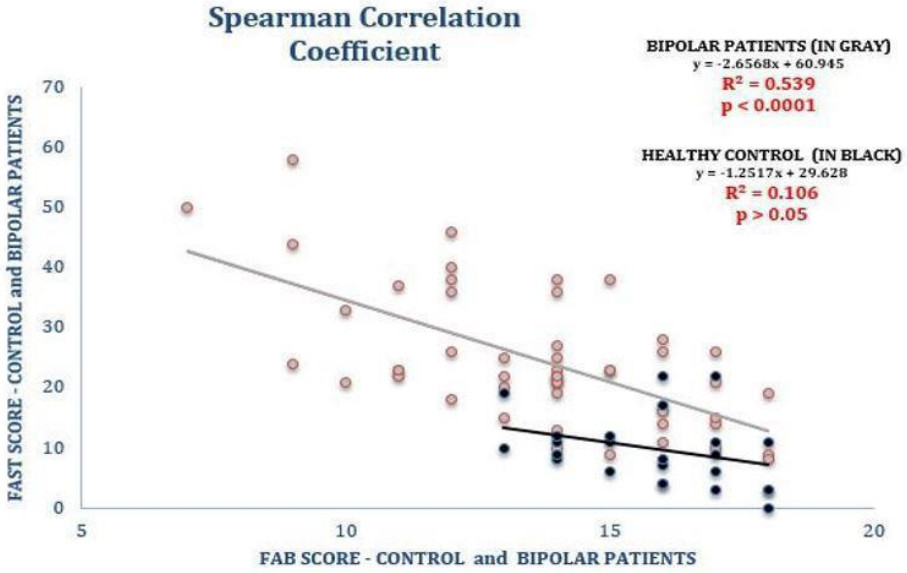

Fig. 8. **Correlation between FAST and FAB test scores in healthy control (n= 25) (in black) and euthymic patients (n=50) (in gray), using the Spearman Correlation Coefficient.**

The total group of euthymic patients was separated into two groups (≤ 3 years and ≥ 10 years of the disease), and later performed the Spearman correlation, where it was observed that the same negative correlation trend remained present, with **(r^2=0.226;*p*< 0.001)**in patients with ≤ 3 years of thedisease and **(r^2= 0.352**; ***p*<0.001)** in patients with ≥ 10 years of the disease.These results reinforce previous results whichthe correlation between the variables FAB and FAST, demonstrated that euthymic patients who have lower scores on the FAB test (decreased frontal activities and EF), had higher scores on the FAST (with greater loss of functionality), how as seen in**Fig. 9**.

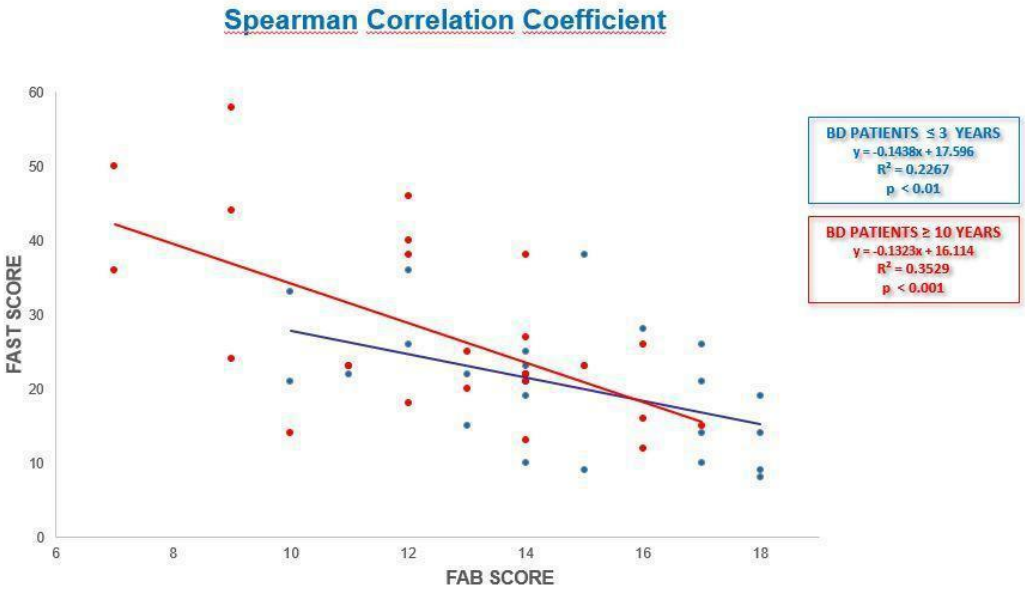

Fig.9. **Correlation between FAST and FAB test scores between BD patients ≤ 3 years (in red) and ≥ 10 years of disease (in blue), using the Spearman Correlation Coefficient.**

IV. DISCUSSION

Recently, our research group published an article on the assessment of impairment of functionality and executive functions in different domains, in 50 euthymic patients with BD I / II, using the FAST and FAB tests **[75].**In the present article, we evaluated 50 euthymic patients, but with different times of disease onset. A group (n =25) with ≤ 3 years of the disease and a group (n=25) with ≥ 10

years of the disease were evaluated. The current results found in this study were compared and discussed referring to previous research, and the results found were interesting, and produced a rich discussion. Initially, in this research, we have tried to apply standardized strict criteria for euthymic and the control group. We wanted to reduce the biases related to this research, as much as possible. The safety measurements, criteria, and diagnosis of the disease, as well as the sample of bipolar patients who had been in the euthymic phase for at least six months, resulted in more accurate data. The rigor in the application of all the tests used by our highly trained staff eliminated any dubious interpretation or results of FAST and FAB. In a meta-analysis, Rocca and Lafer **[72],** showed that many previous studies had not expressed this concern with standardization, producing a considerable variability in the results found **[73].** Despite the meticulous application of the tests by the staff; some biases were still present, e.g., the small number of patients in each group, the heterogeneity of the population, their educational level, as well as the diversity of medications used by patients, which may produce different effects on cognition. Another relevant point that was considered when analyzing the bipolar patients' cognitive abilities, was their age. Numerous age-related changes in cognitive abilities are significant to the everyday activities of the patients. According to Petersen **[74],** studies of the neurophysiological processes on cognitive performance have shown that cognitive skills reach their maximum point at the age of 30 and remain stable until they start to decline between 50 and 60 years old. Many studies demonstrated lower cognitive levels during aging **[76];[77];[78];[79].** This physiological decline in senescence is due to neuro-anatomical changes that cause a degradation of the brain structure. However, this decline in cognitive functions is not uniform. Functions such as the ability to communicate through language, the use, and definition of words; evocation and knowledge of general culture; practical or social reasoning; remain stable during their lives. However, they have difficulties in understanding long and complicated phrases, quickly forgetting specific names or terms, sometimes generating a more repetitive speech; difficulty in understanding organized and logical analysis of unfamiliar or abstract material. Performance in the planning, execution, and evaluation of complex scales of behavior and performance of new and fast perceptual-motor tasks, is also impaired **[74];[80];[75];[81];[82**]. For this reason, we only included patients with a maximum age of 60 years old, trying to reduce any bias related to the cognitive test results, both in the natural and pathological aging process.

By utilizing these strict criteria adopted for the inclusion of bipolar patients in our study, we observed significant statistical results after the application of the FAST and FAB tests. The results obtained in all euthymic patients (n=50), **see Figs. 1-2** and **Table 3,** showsome similarities in the subgroups (early (n=25) and late-onset (n=25) with ≤ 3 years and more than ≥ 10 years of the disease as shown in **Figs. 3-4** and **Table 4.** The same was observed for the different domains of the tests applied as shown in **Tables 9-10-11-12**. In the FAST test, we observed a significant decrease in the functional capacity of bipolar patients in all domains, which made us realize the impact of the disease and the patients' daily lives. These results are related to previous studies in the literature, where several authors also observed the same results **[24];[83];[84];[85];[67].** Furthermore, Bonnín et al. **[25],**evaluated a total of 32 clinically and neuropsychologically euthymic bipolar patients at baseline. After a median follow-up of 4 years, they were interviewed with the FAST test to assess functional outcomes. They observed that depressive symptoms together with neurocognitive impairments were related to verbal memory and that EF were variables that functioned as predictors for long-term functional outcomes in BD. Our study observed a result that remained present in all subtests of the FAST test when we compared the two groups of bipolar patients with different durations (≤ 3 and ≥ 10 years of the disease) and with the healthy control group. The two groups of euthymic patients showed a very significant difference from the control group in all subtests, but there were no changes in the groups with different disease durations. This data allowed us to raise the hypothesis that changes in functionality already occur since the onset of the disease, and continue over the subsequent years. Our results also corroborate with the present literature, where the subtests (autonomy, occupational functioning, cognitive functioning, and interpersonal relationship), seem to present the greatest impacts. In a recent categorical meta-analysis that included 11 other studies, with a total sample of 1083 patients, the prevalence of global functional impairment was 58.6%.Regarding specific domains, the meta-analysis showed a prevalence of impairment in the following domains: 65.6% in occupational, 49.2% in cognitive, 42.6% in autonomy, 42.1% in interpersonal relationships, 29.2% in leisure, and 28.8% in the field of financial issues - all of them statistically significant **[86].** Regarding the FAB test, and confirming one of our initial hypotheses, we observed a similar phenomenon. The FAB test performance in our study presented significantly worse scores in the following domains: similarities (conceptualization), conflicting instructions (sensitive to interference), and go/no-go (inhibitory control), which

demonstrated a significant executive dysfunction in all (50) bipolar patients as shown in **Table 11.**However, when we divide these patients into two distinct groups with ≤ 3 years and ≥ 10 years after the onset of the disease, we can observe that a phenomenon is repeated in the analyzed data. The analyzed group with less than ≤ 3 years of disease, despite presenting lower mean values of scores in all domains compared to the control group, were not significant. However, when we compared the mean scores of the domains in patients with more than ≥ 10 years since the onset of the disease with the control group, we found a decrease in the FAST test scores in all domains, however, it was statistically significant in the following domains: similarities (conceptualization), conflicting instructions (sensitive to interference), go/no-go (inhibitory control) and motor series (motor programming) as shown in**Table 12**. These data reinforce the idea that the cognitive loss occurs gradually through the years, raising the hypothesis that the impact of the disease already is observed at the beginning of the disease, with probable neuroanatomical and possibly biochemical alterations due to the process of neuroinflammation and neuroprogression of the disease. Thus, our results as shown in **Table 11-12**, reinforce the idea that EF alterations have a significant impact on the daily functionality of these patients. Since few studies up to date used the FAB test for patients with BD, we found it difficult to correlate our results with previous studies. For this purpose, we compared the results found in other studies, researching different psychiatric pathologies with altered EF, which also observed similar results **[17];[18];[19].** However, our results differed from other studies that also evaluated the components of EF in euthymic patients with BD, and who performed poorly in mental flexibility, unlike our study **[88];[89];[90].** Furthermore, other domains such as inhibitory control **[91],** and conceptualization **[29];[90],** remained preserved in these studies, nevertheless were different from our results. Even so, our results are in line with previous studies demonstrating a substantial proportion of bipolar patients who experienced unfavorable general functioning, and present a significant degree of morbidity and dysfunction associated with BD, even during euthymic periods **[37];[92].** In another study on the relationship between cognitive and occupational function in euthymic patients, it was reported that, over six months, cognitive measures at the time of symptomatic recovery, particularly in the domains of working memory/attention and processing speed, were strongly associated with concurrent occupational recovery **[87].** These findings suggest that a decline in cognitive function over time may be accompanied by a functional decline in occupation despite the euthymic state of the patients. Data from two meta-analyses demonstrated that cognitive changes persist during euthymia; even though there is a variation in the results concerning the domains involved, and the effect size produced **[93];[16]**. There are many discrepancies between authors regarding the performance in many different neuropsychological tests related to EF by bipolar patients. For example, patients in the manic phase may have difficulty adapting to conceptual changes, as can be seen in the Trail Making Test, as well as, during the depressive phases, demonstrating that bipolar patients have a poorer performance especially in verbal fluency tests when compared with unipolar patients. Also, in the euthymic phase, changes in EF were observed with several persevering errors in the Wisconsin Card Sorting Test. Thus, using different tests, to assess the EF, it was observed that the degree of commitment and the size of the effect can be quite diverse between the various domains.In summary, different EF were not equally impaired in euthymic BD patients **[94];[95];[96].** It became significant in our research because we tried to evaluate the possible confounding variables that could interfere with the result found in the correlation between the FAB and FAST tests. A characteristic of the confounding variable is that it influences both the dependent and the independent variables, which can cause a spurious association. In our study, clinical variables such as (gender, age, length of illness), showed little effect on executive performance, except the study time, which showed some correlation with the FAB test as seen in **Fig. 10**, which will be discussed next.

As previously described, this research showed that there are significant differences in years of study between healthy control patients and euthymic patients as seen in **Table 1**. The average years of studies showed that the more the disease progresses, the shorter the study time. This data seems to reflect the impact of the disease on the cognitive functions of patients as seen in **Fig.3-4-7,** and consequently the functionalityof the patients. When comparing the two groups (≤ 3 years and ≥ 10 years of the disease) we can observe the permanence of statistical differences between them, as seenin**Table 4**, reinforcing the hypothesis that the disease has a strong impact on the patient's life, since the beginning. However, our study did not take into account some significant variables, as described by Shoeyen et al. **[97],**whoobserved that the main clinical variables that were significantly associated with lower levels of education in euthymic patients, were associated with: the age of the patient during his/her first episode, the number of rapid cycling, and who had more than four depressive episodes. To resolve this issue, our group is starting a new study where these variables reported above will be included and evaluated. Another

point that was observed was the level of education between the groups. While the control group had the majority of subjects (60%) with graduate and postgraduate education, the euthymic patients with ≤ 3 years of the disease, presented a level of education up to high school and graduated (84%), and euthymic patients with ≥ 10 years of the disease, presented a level of education up to high school and primary school (66%).Ourfindings are similar, compared to a nationwide Danish register study **[98]**, reporting lower educational levels in BD compared to the general population. In a survey that compared bipolar patients to a healthy control group, where IQ levels were similar, it was observed that patients with BD completed fewer years of education than controls. Although more than 60% of both groups entered college, only 16% of bipolar patients received a university degree. In contrast, 47% of control patients completed college. Although the educational level did not differ between patients who started the disease earlier or later, nor due to substance abuse **[99].** Another research demonstrated that more education and shorter illness duration remained significantly associated with functional recovery. One more year of education was associated with a 1.45 times higher chance of functional recovery, and being ill one year longer was associated with a lower chance of functional recovery **[100].** More recently, Baune and Malhi, **[101],** observed a slightly different result, where patients with BD had the same level of education, however, had a significantly lower social and occupational function than the general population. Curiously, in our research, we also observed a shorter time concerning the years of education in the bipolar patients, which produced a greater impact on occupational activities; as seen in **Table 1**. Thus, the level of education is interrupted due to crises during BD, and the reduction in the level of education may contribute to the later functional disability in this disease. Thus, many studies showed that there is an inverse correlation between the degree of education with the social, occupational function, and risk of disability **[102];[103];[104].** Also, other studies had shown that bipolar patients' household income was below 10%, and many of them were on disability pension in comparison with the general population, **[98];[105];[106].** Thus, our results are according to literature reinforcing the previous studies.

Another variable related to cognitive functions and functionality is age. It was interesting to note that our study did not observe an association between the loss of functionality (FAST), and cognitive functions (FAB), comparing the age of the patients, as can be seen in **Table 1-5; Figs. 5-4.** Although there was a difference in the mean age between the groups of euthymic patients (≤ 3 years and ≥ 10 years of the disease) which can be observed in **Table 1.** When we adopted a median (< 41 and ≥ 41 years old) by comparing the younger euthymic patients with the older ones, we did not observe any important differences, which supports our hypothesis that it might not be the age of the subjects studied that will determine the effect on the FAB or FAST tests, but most likely the time of having the disease. We know that many of the younger patients (< 41 years old) in our euthymic group have had the pathology for more than 10 to 15 years, while many older patients (≥ 41 years old) had recently been diagnosed with the disease; less than two or three years ago. Again we need to better clarify the issue of the impact of the number of crises of depression and mania on the evolution of the disease, by collecting more data, although it was not our initial intention. Thus, our partial results are supported by many authors in the literature that showed cognitive deficits, including EF, memory, and attention, and do not seem to be strictly a later effect caused by the years of the disease. Furthermore, it showed that young people who had a recent manifestation of BD, had cognitive deficits that resemble that of older patients, and these deficits can be observed even during euthymia **[107];[78];[108];[109].** Recently, in important research, Martino et al. **[110],**evaluated a sample of 51 euthymic bipolar patients, who were followed up for a mean period of 73 months. They suggested that the longitudinal trajectory of cognitive deficits in BD is relatively independent of the number of episodes or time spent ill, and there were no differences between these patient groups in any clinical or neurocognitive variables at baseline. Also, Pavuluri et al. **[111],** followed pediatric patients with BD for 3 years. They observed that all neuropsychological profiles remained impaired, especially EF and verbal memory even though the patients were treated and in remission. In a meta-analysis of pediatric patients with BD, it was concluded that the effect sizes of the tests in the different domains indicated greater deficits among the BD group, compared to the healthy controls, although they varied greatly in the effect size. i.e. verbal learning and memory (Z = 4.65, nine studies); EF (Z = 4.07, nine studies); and attention (Z = 3.81, eight studies) **[112].** However, our results differ from other researchers showing controversies in the literature about the cognitive impairment associated with BD. In a meta-analysis, Samamé et al. **[113],** described that bipolar patients' performance in 14 cognitive measures remained stable after a mean follow-up period of 4.62 years. When the meta-analysis was restricted to controlled studies, no patient-control differences were found regarding longitudinal cognitive outcomes. Also, Cacilhas et al. **[114],** found a significant correlation between age and

functionality through the FAST test in BD patients. They demonstrated that BD was an important effect modifier on the natural age effects in general functioning, further characterizing BD as a chronic and impairing disease.

We must remember that this study was conducted with a clinical sample (or prevalence sample), which might tend to overestimate the morbidity, cognitive deficits, and functionality of patients with BD. We included in our sample patients with less than two years and more than ten years of length of illness and with very different numbers of previous affective episodes. We must also point out that, in our work, we use BD I / II patients in the same group. However, meta-analyses indicate that people with BD II also have cognitive deficits in the same way, but slightly less severe than those seen in BD I **[115];[116].** Possibly, the results of our tests would have been different if we had categorized our population into two subgroups (type I and type II). Concern to the patients with BD I may reflect greater severity of the disease symptoms, and therefore the effects of drugs such as mood stabilizers and antipsychotics, which are more commonly prescribed for BD I than II, and in larger doses, would produce iatrogenic effects in their EF, as noted by Balanzá-Martínez et al. **[117],** and with greater impacts on verbal memory and processing speed as well. However, whether these discrepancies are partly related to the long-term treatment of these patients or not, is not yet fully understood. A study demonstrated that patients treated with antipsychotics had worse results in the Trail Making Test **[118].** However, in another study with a sample of 44 bipolar patients on monotherapy with lithium, it was found that changes in EF, especially in domains that required inhibitory control, were independently related to the severity of symptoms and the medication used **[119].** Also, another longitudinal research with a sample of 15 euthymic patients treated with lithium monotherapy, were assessed for cognitive impairment twice over a 2-year follow-up. Repeated measures showed that the euthymic group was cognitively impaired in EF, which was the main long-term neuropsychological deficit of BD, though it did not worsen over 2 years. Furthermore, the results showed that the persistence of these cognitive deficits did not appear to be influenced by any clinical or pharmacological variable, remaining stable over time **[102].** A possible alternative hypothesis of our findings is that the common cause of cognitive deficits and adverse clinical course is determined by some pathophysiological alteration (i.e. neurodevelopmental abnormalities) underlying different subgroups of patients with BD. This hypothesis is supported by the involvement of the prefrontal cortex and prefrontal–subcortical pathways, which regulate both mood state and cognitive functioning, and might predispose to a greater magnitude of cognitive deficits and frequency of episodes **[120];[121].** In contrast, another subgroup of patients without such factors might have relatively preserved cognitive functioning and a lower number of affective episodes. **[122];[123];[124];[125].** To better relate the meanings of these clinical and cognitive changes reflected in the FAB test, we needed to initially discuss and relate the neuroanatomical and pathophysiological changes with the results found. Several studies are linking the impact of different psychiatric illnesses on brain functioning, and its architecture **[126];[127];[128].** Research has shown that BD presents a cyclical and recurrent course. More recently, pathophysiological changes in the brain have been observed, raising the hypothesis that this is a progressive, chronic and disabling disease. The concept of neuroprogression appears to explain this phenomenon, but this concept is still surrounded by controversy **[128];[129];[8];[9].** However, if there is an increase in the allostatic load, it produces a cumulative physiological dysregulation related to the dysfunction of the hypothalamic-pituitary-adrenal axis, altering immunity, thereby activating pro-inflammatory mechanisms with subsequent activation of oxidative stress states **[130].** With this sequence of phenomena, an inflammatory environment is created, inducing a significant risk of cognitive decline **[131];[132];[133];[134].** As previously reported, all these events involve a pathological reorganization in the brain, and therefore, are associated with morphological modifications, such as the volume reduction in the cortex and white matter of the prefrontal cortex **[135];[136];[137];[138];[139].** These prefrontal cortex alterations are possibly secondary to multiple episodes of mania and depression during their lives. In addition to these multiple episodes, the number of hospitalizations and disease duration in bipolar patients might cause changes in their neurocognitive performance, with an impact on their daily functionality and psychosocial aspects **[4];[5];[6];[140].** These structural alterations in the prefrontal cortex, produce cognitive deficits associated with an inferior functional state, similar to what occurs to some neurological patients, indicating that some of the functional impairments frequently reported by BD patients, may be due to cognitive impairment, which may be a vulnerability factor for BD, and can present itself before the onset of the disease and worsen with the progression of the same **[141].** The prefrontal cortex is a heterogeneous region that comprises several specialized sub-regions, in which EF represents only one functional category within the lobes **[142].** This is a region that communicates with the entire brain, receiving and sending projections of all types. It integrates with the

limbic system, reticular system, hypothalamus, and neurotransmitter systems **[143]**, involving the amygdala, the dorsolateral prefrontal cortex, insula, and anterior cingulate
areas **[144];[145];[146];[147];[128];[139].** Through neuroimaging, had been possible the comprehension of the neural structure and function underlying cognitive processes and it was possible to differentiate the areas of the prefrontal cortex responsible for the different components of EF, with three main regions: the orbitofrontal, the ventromedial, and the dorsolateral region. The orbitofrontal region projects into the caudate nucleus and is responsible for the inhibition capacity. An injury is characterized by personality change, including behavioral disinhibition and emotional lability. The ventromedial region begins in the anterior cingulate cortex and projects to the nucleus accumbens, mediating motivational behavior. An injury is associated with a decrease in motivation, causing apathy, indifference to pain, lack of motor and psychic initiative. The dorsolateral region projects into the caudate nucleus. Usually, this region is associated with components of EF, namely verbal fluency, cognitive flexibility, planning, decision making, inhibitory control, working memory, reasoning, problem-solving and abstract thinking. An injury in this area, leads to the inability to maintain attention, persevering thoughts, impaired reasoning as well as deficits in mental flexibility **[148];[149];[150];[151].** The same authors observed that the neuropsychiatric manifestations are related to neurocircuitry defects. Impaired EF, impulsivity, and apathy, are characteristics of frontal-subcortical circuit dysfunctions, and neuropsychiatric disorders, such as attention- deficit/hyperactivity disorder, obsessive-compulsive disorder, schizophrenia, and also BD might result from compromised integrity and functioning of these areas and projections. Recently, several researchers have sought to relate the six domains present in the FAB test, with different neural networks, demonstrated in **Table 13, [54];[152];[153];[154];[155];[156];[157].** In this study, the anatomical lesions were correlated with all the FAB subtests. Executive dysfunctions and impairment in working memory are related to lesions in the prefrontal dorsolateral cortex. Abulia and apathy are related to lesions of the ventromedial cortex, and disinhibition and mood disorders are related to the orbitofrontal cortex. When applied to the FAB subtest, the conceptualization was more related to the dorsolateral region. The results of the conflicting instructions, and go-no-go subtests, were related to the ventromedial and orbitofrontal cortex respectively. These results found in our work are fascinating because each different region of the prefrontal cortex showed an altered subtest as seen in **Table 13**. Also, a large number of these symptoms described above are observed daily during the care of bipolar patients, mainly during manic and depressive phases. However, the bipolar patients in our study were more than six months in euthymia. Even so, the results showed us significant losses in all functionality domains, as well as in some cognitive domains found mainly in EF as seen in **Table 10-12.** Some cognitive impairments persist even after remission of the symptoms, and many studies have shown that they are neuropsychologically related, at least in part, to the psychosocial difficulties of these patients **[91];[88];[158].** On the contrary, there is little data in the literature about the use of the FAB test in bipolar patients, and it is difficult to correlate this data with the anatomical lesions analyzed. Therefore, further studies using the FAB test are necessary, to better comprehend these results. It is important to note that changes in the connections between the involved structures are critical in the emotional dysregulation and cognitive functions in BD. Researchers observed that some abnormalities in some components of these neural systems are more apparent in adolescence, while other prefrontal regions appear to progress more in young adulthood, suggesting a neurological development model for this disorder **[159];[160];[37];[138];[109].**

Table 13: Prefrontal cortex regions, projections, behavioral mediation and injury, correlate to different domains assessed by the FAB test in Bipolar Patients and their respective level of significance.

PREFRONTAL CORTEX REGIONS	PROJECTIONS	BEHAVIORAL MEDIATION	FAB TEST CORRELATION	*p* – value of FAB subtests	INJURY
Orbitofrontal	Caudate Nucleus	Inhibition Capacity	Go-No Go Task (Inhibitory control) Prehension Behaviour (Environmental autonomy)	$p < 0.05$ * $p > 0.05$	Behavioral Disinhibition and Emotional Lability
Ventromedial	Accumbens Nucleus	Motivational Behaviour	Conflicting Instruction (Sensitivity to interference)	$p < 0.02$ *	Apathy Abulia
Dorsolateral	Caudate Nucleus Basal Ganglia	Executive Functions	Similarities (Conceptualization) Lexical Fluency (Mental flexibility) Motor Series (Motor programming)	$p < 0.03$ * $p > 0.05$ $p < 0.02$ *	Verbal Fluency Cognitive Flexibility Planning Decision Making Inhibitory Control Problem-Solving Abstract Thinking
Dorsolateral	Hippocampus	Memory	not valued	–	Working Memory

Although BD is related to cognitive deficits, these deficits do not appear to be universal. It is estimated that about 30% of BD patients in remission will have levels of cognitive performance within the normal range **[161];[162].** Also, longitudinal studies have shown that fluctuations in mood states do not seem to explain many of the cognitive deficits during euthymia **[163];[164].** Thus, it becomes imperative to define whether the cognitive impairment presented during euthymia, precedes the onset of the disease, that leads to the hypothesis of alterations in the neurological development, or whether it results from the negative impact of BD on cognition that corroborates the theory of neurodegenerative process (neuroprogression). Some researchers believe in the coexistence of the two hypotheses. From a neuropsychological point of view, longitudinal studies that last more than one year, are practically non-existent, which makes it challenging to confirm the cognitive impairment and determine whether it is stable or progressive **[165];[166];[35];[167];[8];[9].** One of the longer longitudinal studies with bipolar patients was performed by Santos et al. **[83]** which assessed the performance of 80 euthymic outpatients, using a group of neuropsychological tests and demonstrated that cognitive deficits in BD were stable during a follow-up after five years, except in verbal memory, showing that the clinical course during a second follow-up period (longer than 5 years), did not influence the course of cognitive dysfunction. Our research confirmed this same hypothesis raised by the authors above. The changes that occurred both in the functional and cognitive functions showed slight differences in the means of the FAB and FAST tests between the groups of ≤ 3 years and ≥ 10 years of the disease. However, there was a significant difference between control patients and the group that developed the disease more recently. This phenomenon reinforces the idea that the clinical course of the disease did not influence the course in the functionality and cognitive dysfunctions. Another important study conducted by Mora et al. **[104],** which followed up a group of euthymic bipolar patients by 6 years, and evaluated the functionality through the FAST test, observed that among the clinical factors, longer illness durations were significantly related to slow processing, whereas strong relationships were observed between impoverished cognition and poorer psychosocial functioning over time. Although cognitive deficits remained stable on average throughout the follow-up, they had enduring negative effects on the psychosocial adaptation of the patients. Thus, we can hypothesize that patients with greater cognitive impairment are less able to maintain the treatment of their disease, stopping the use of medications, the clinical and psychotherapeutic follow-up frequently, and as a result, they suffer a worse course of the disease. However, the presence of subtle deficits in cognitive functions provides an indication that cognitive impairment may represent a trace of vulnerability factors in the development of BD that is present before the onset of the disease, but worsens as the disease progresses. Thus, BD is characterized by remarkable heterogeneity regarding cognitive outcomes and probably different potential clinical predictors may be related to such outcomes, i.e., previous mixed episodes, current subclinical depressive

symptoms, previous hospitalizations, and old age, and should be the focus of treatment **[88];[35];[168];[169];167];[170];[171];[172].** Also, many other studies have shown that euthymic patients continue to have difficulties at work and in their studies, showing low performance or difficulty in maintaining them, although it is less evident, as shown also by our research **[173];[115];[127];[174].**

Finally, one of the main objectives of this article was to correlate whether the data on cognitive deficits observed in euthymic patients can help explain functional deficits. Therefore, we attempt to evaluate the clinical capability of the FAB test in bipolar patients. Studies have shown that the FAB test may have a good capability to discriminate several conditions in different clinical populations, although the evidence is still incipient and scarce in psychiatric disorders, and the results should be interpreted with caution. After performing the Spearman Correlation Coefficient Test, by comparing the FAST and FAB test scores in euthymic patients, our group was able to observe a moderate negative correlation, $\mathbf{r^2= -0.53;\ p<0.001}$. This result represents that 53% of the variation of the FAST test (functionality) is linearly related to the FAB test (cognition and EF), and the remaining 47% of the variation are resulting from other factors that were not considered in this study, like (duration of illness, time of hospitalization, number of manic or depressive episodes, among others). These results are following the literature we studied. When the total group of euthymic patients (n=50) was divided into patients with ≤ 3 years and ≥ 10 years of disease, we observed that the same negative correlation trend was present. However, the values of the Spearman's correlation in both subgroups were lower, seen in the euthymic group with ≤ 3 years **($\mathbf{r^2= 0.226;\ p<0.01}$),** and the euthymic group with ≥ 10 years of disease **($\mathbf{r^2= 0.352}$; $\mathbf{p< 0.001}$**) demonstrated in **Fig. 9.** Thus, we can infer two important aspects of this correlation; 1) the disease begins to show cognitive and functional changes from the onset of the first clinical symptoms of patients, even in euthymia for more than 6 months, and 2) the impact of the disease in the early stage is a little less than in patients with ≥ 10 years of the disease, demonstrating that the disease progresses over time, and therefore reinforcing the hypothesis of its neuroprogression. These results are very significant and they are in accordance with other studies.

In a systematic review of 52 studies, cognitive deficits were strongly associated with poor functioning in BD, both in cross-sectional and longitudinal studies **[175].** In a meta-analysis, Depp et al., **[127]** also observed the same correlation between cognitive deficits and functional impairment. The effects did not appear to be modified either by the clinical status, or the age or design of the study. As already reported above, these cognitive deficits tend to become stable over time **[113];[83]**. However, a small subset of patients showed a decline over time in cognitive functions as demonstrated by Mora et al. **[104]**, after following a group of patients for 6 years. Furthermore, the strength of the correlation between cognition and the functional outcome depends on the tests used. Baune et al. **[175],** noticed minor effects when using the Global Functioning Assessment (GAF) Test. In a meta-analysis, Depp et al. **[127],** observed an overall mean correlation of $r^2= 0.27$, $p<0.001$**,** and all of these previous studies corroborate our results.

As stated previously, studies on BD patients have shown that the predictors of cognitive impairment functioning, assessed by FAST, were subclinical depressive symptoms, and previous mixed episodes were strongly associated. These results support the evidence that the significant morbidity and severe clinical course of BD lead to greater cognitive impairments with long-term consequences. Several researchers have demonstrated an apparent linear relationship between the increase in depressive symptoms and functional impairments, even during subsyndromal depressive conditions, which would increase the likelihood of depressive relapses. This is due to a stabilization meantime for bipolar depression, which is 24 weeks, while patients with mania need 11 weeks, and patients with mixed cycling episodes need 40 weeks **[176];[177];[178];[179];[167];[170];[172]**. Rosa et al. **[24]** concluded the same results, indicating that depressive symptoms are associated with a greater negative impact on psychosocial functioning than manic (hypo) symptoms. Other deficits in functioning seem to persist even during remission. These results showed the importance of treating depression and mania early, and the need to develop psychosocial interventions to improve functional results. The use of traditional psychopharmacology associated with psychoeducation has allowed the remission of the clinical symptoms to remain stable for more extended periods, which is an achievable goal for many BD patients. However, it is no longer just about improving the patients or their remitting symptoms; but mostly to improve their recovery. Unfortunately, studies showed that psychoeducation did not alter neurocognitive functioning on a neuropsychological battery test when compared with treatment as usual or cognitive behavioral therapy in altering dysfunctional negative beliefs **[180];[181];[182];[183];[67]**. Although our patients were participating in a psychoeducation group for more than two years, we observed similar results in our study, with many significant alterations in the cognitive and functional domains. Thus, mood stability must come with the improvement of the processing speed, of the memory, and

the EF, in addition to better psychosocial, interpersonal, and occupational functioning. These are fundamental objectives to be achieved.

V. CONCLUSION

Studying the relationship between neurocognition and functionality, it was possible to extract a set of significant findings. On the one hand, the results obtained from the multidimensional tests of neurocognition, and functionality used from a hetero assessment (FAST and FAB) tests, suggest that the distinction between the different domains of these tests can be useful in euthymic bipolar patients. Also, the results allow us to consider that executive performance plays a central role, not only as a predictor of functional performance, but also as a mediator of the relationship between clinical factors, such as chronicity, and functioning. The possibility of using neuropsychological measures of neurocognitive tasks and functionality, and to assess possible subgroups of bipolar patients, as we did in this research using patients with ≤ 3 years and ≥ 10 years of the disease, we can now better understand the relationships between performance which can contribute so that patients can benefit from psychoeducation programs, and functional rehabilitation, ultimately producing the creation of intervention plans that support the recovery of people with BD.

As far as we know, this is one of the first studies that used the FAB test to assess the influence of various demographic and clinical variables, related to executive dysfunctions in BD. Although we adopted relatively strict inclusion criteria in our study, we recognize that our results should be evaluated with caution due to several limitations, which mainly derived from the administered neuropsychological tests, the sample size, and the cross-sectional design of the study. However, the limitations of the FAB and FAST tests, as well as the sample size, were partially resolved through the inclusion of a healthy control group, and the statistical evaluation regarding the sample sizes. Besides the above mentioned, there is also the clinical heterogeneity of the sample, which included patients with short- and long-term illnesses, who had different levels of education and age, which interfered in the analyzes. Another limitation was our cross-sectional design, where the data did not allow the analysis of the cause-and-effect relationship, and also studying many variables and their different areas of functioning. Regarding the FAST test, we did not control factors that could affect functional outcomes such as psychosocial interventions, familiar support, housing, and financial resources. The last weakness of our work is the lack of a deeper analysis regarding the impact of the treatments and medications used. As these patients have a chronic disease, they have had several previous treatments that may be related to current cognitive and functional deficits. This will be evaluated in future research that is already being planned. Thus, a larger sample can improve the performance of the FAB test, in addition to a better division into more clinically defined subgroups and a better control of some variables. Furthermore, our group started a new study with bipolar patients who had early and late-onset of the disease, and we are trying to assess the functionality and cognitive impairment of these patient groups, continuing to includeandcontrol more variables.

However, the so-called euthymia in the BD does not mean full recovery of the patient, and this was very clear in our group during this study. Most of our bipolar patients participated in a psychoeducation program for more than 2 years, and all were outpatients with more than 6 months of euthymia. Therefore, we expected a better response to the FAST and FAB test scores compared to what was observed in other studies. However, the present study revealed that the data of our euthymic patients showed similar deficits in specific cognitive components, and these were associated with all domains of the FAST test, showing similar results with the literature.

Despite the clinical interest, there is a gap in terms of studies of the FAB test in bipolar patients, impairing the assessment as reliability and as validity that can correspond clinically. Although the FAB test shows some limitations, there is some evidence to suggest that several FAB test domains may have good predictions. In terms of clinical practice, early and differential diagnoses are crucial elements in determining the appropriate treatments and therapies. In this sense, the FAB subscores can offer useful information to increase the accuracy of the diagnosis, which can also be of considerable importance during advanced stages in which the progression of the disease intensifies executive dysfunctions. The total performance of the FAB test can be used as a marker of severe disease, rather than a single screening test. Furthermore, we can evaluate the effectiveness of neuropsychological rehabilitation programs in future studies, measuring the results and the qualitative analysis of their performance, and also associate the impairments observed in cognitive functioning with possible brain dysfunctions. Following these strategies, it is necessary to promote functional recovery, which in many cases is not achieved through the available treatments today, which focus mainly on stabilizing mood episodes and preventing possible relapses. So far, there is no specific therapy or approaches to prevent the onset of this disorder or to treat it at the beginning of the disease. Many techniques have been developed to improve cognition in neuropsychiatric

diseases. However, more recently, new approaches, such as functional remediation and dialectical behavior therapy (DBT), have been used. These techniques cover psychosocial aspects and regulations of emotions **[184];[185];[186]**. Functional remediation seeks to improve aspects related to work, functional and interpersonal skills, increasing autonomy, and reducing financial dependence. On the other hand, the core of DBT is to help people build four essential skills: mindfulness, distress tolerance, interpersonal effectiveness, and emotional regulation. Recently these new approaches have been used to treat patients with BD **[187];[188];[189].** Thus, through this research, our group aims to select patients for a future study about DBT, allowing them to develop new behaviors and skills. Thus, we aim to prevent and minimize the impact of any deficits found in their daily lives through cognitive training, and thus, promote their future reintegration into the community, improving their quality of life and reducing health expenses through the prevention of relapses.

REFERENCES

[1] Plana-Ripoll, O., Pedersen, C. B., Agerbo, E., Holtz, Y., Erlangsen, A., Canudas-Romo, V., ... & Laursen, T. M. (2019). A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. *The Lancet*, *394*(10211), 1827-1835. https://doi.org/10.1016/s0140-6736

[2] Clemente, A. S., Diniz, B. S., Nicolato, R., Kapczinski, F. P., Soares, J. C., Firmo, J. O., & Castro-Costa, É. (2015). Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. *Brazilian Journal of Psychiatry*, *37*(2), 155-161. https://doi:10.1590/1516-4446-2012-1693

[3] Sigitova, E., Fišar, Z., Hroudová, J., Cikánková, T., & Raboch, J. (2017). Biological hypotheses and biomarkers of bipolar disorder. *Psychiatry and clinical neurosciences*, *71*(2), 77-103. https://doi.org/10.1111/pcn.12476

[4] McEwen, B. S., & Gianaros, P. J. (2011). Stress-and allostasis-induced brain plasticity. *Annual review of medicine*, *62*, 431-445.https://doi:10.1146/annurev-med-052209-100430

[5] Grande, I., Magalhães, P. V., Kunz, M., Vieta, E., & Kapczinski, F. (2012). Mediators of allostasis and systemic toxicity in bipolar disorder. *Physiology & behavior*, *106*(1), 46-50. http://doi:10.1016/j.physbeh.2011.10.029

[6] Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M. C., ... & Rossi, A. (2013). Prevalence, chronicity, burden and borders of bipolar disorder. *Journal of affective disorders*, *148*(2-3), 161-169. https://doi:10.1016/j.jad.2013.02.001.

[7] Passos, I. C., Mwangi, B., Vieta, E., Berk, M., & Kapczinski, F. (2016). Areas of controversy in neuroprogression in bipolar disorder. *Acta Psychiatrica Scandinavica*, *134*(2), 91-103. https://doi.org/10.1111/acps.12581

[8] Post, R. M. (2020). How to prevent the malignant progression of bipolar disorder. *Brazilian Journal of Psychiatry*, 42(5), 552-557. https://doi.org/10.1590/1516-4446-2020-0874

[9] Serafini, G., Pardini, M., Monacelli, F., Orso, B., Girtler, N., Brugnolo, A., ... & Nobili, F. (2021). Neuroprogression as an Illness Trajectory in Bipolar Disorder: A Selective Review of the Current Literature. *Brain Sciences*, 11(2), 276. https://doi.org/10.3390/brainsci11020276

[10] Blair, C., Zelazo, P. D., & Greenberg, M. T. (2005). The measurement of executive function in early childhood. *Developmental neuropsychology*, *28*(2), 561-571. https://dx.doi.org/10.1207/s1532942dn2802_1

[11] Goldstein, S., Naglieri, J. A., Princiotta, D., & Otero, T. M. (2014). A history of executive functioning as a theoretical and clinical construct. *Handbook of Executive Functioning. New York: Springer New York.* https://doi.org/10.1007/978-1-4614-8106-5_1

[12] Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive psychology*, *41*(1), 49-100. https://doi.org/10.1006/cogp.1999.0734

[13] Thompson, J. M., Gallagher, P., Hughes, J. H., Watson, S., Gray, J. M., Ferrier, I. N., & Young, A. H. (2005). Neurocognitive impairment in euthymic patients with bipolar affective disorder. *The British Journal of Psychiatry*, *186*(1), 32-40. https://doi:10.1192/bjp.186.1.32

[14] Bora, E., Vahip, S., Akdeniz, F., İlerisoy, H., Aldemir, E., & Alkan, M. (2008). Executive and verbal working memory dysfunction in first-degree relatives of patients with bipolar disorder. *Psychiatry Research*, *161*(3), 318-324.https://doi:10.1016 / j.psychres.2007.09.002

[15] Diamond, A. (2013). Executive functions. *Annual review of psychology*, *64*, 135-168. https://doi.org/10.1146/annurev-psych-113011-143750

[16] Bourne, C., Aydemir, Ö., Balanzá-Martínez, V., Bora, E., Brissos, S., Cavanagh, J. T. O., ... & Goodwin, G. M. (2013). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatrica Scandinavica*, *128*(3), 149-162. https://doi.org/10.1111/acps.12133

[17] Cunha, P. J., Nicastri, S., de Andrade, A. G., & Bolla, K. I. (2010). The frontal assessment battery (FAB) reveals neurocognitive dysfunction in substance-dependent individuals in distinct executive domains: Abstract reasoning, motor programming, and cognitive flexibility. *Addictive behaviors*, *35*(10), 875-881. https://doi.org/10. 1016/j.addbeh.2010.05.005

[18] Fontes, M. A., Bolla, K. I., Cunha, P. J., Almeida, P. P., Jungerman, F., Laranjeira, R. R., ... & Lacerda, A. L. (2011). Frontal Assessment Battery (FAB) is a simple tool for detecting executive deficits in chronic cannabis users. *Journal of clinical and experimental neuropsychology*, *33*(5), 523-531. https://doi.org/10.1080/13803395.2010.535505

[19] Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. Frontiers in Psychiatry, 4, 35.https://doi.org/10.3389/fpsyt.2013.00035

[20] Martínez-Arán, A., Vieta, E., Colom, F., Reinares, M., Benabarre, A., Torrent, C., ... & Salamero, M. (2002a). Neuropsychological performance in depressed and euthymic bipolar patients. *Neuropsychobiology*, *46* (Suppl. 1), 16-21. https://doi.org/10.1159/000068016

[21] Martínez-Arán, A., Vieta, E., Torrent, C., Sanchez-Moreno, J., Goikolea, J. M., Salamero, M., ... & Ayuso-Mateos, J. L. (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar disorders*, *9*(1-2), 103-113. https://doi:10.1111/j.1399-5618.2007.00327.x.

[22] Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., ... & Vieta, E. (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of affective disorders*, *109*(3), 286-299.https://doi.org/10.1016/j.jad.2007.12.234.

[23] Martino, D. J., Marengo, E., Igoa, A., Scápola, M., Ais, E. D., Perinot, L., & Strejilevich, S. A. (2009). Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *Journal of affective disorders*, *116*(1-2), 37-42. https://doi:10.1016/j.jad.2008.10.023

[24] Rosa, A. R., Reinares, M., Michalak, E. E., Bonnin, C. M., Sole, B., Franco, C., ... & Vieta, E. (2010). Functional impairment and disability across mood states in bipolar disorder. *Value in health*, *13*(8), 984-988.https://doi.org/10. 1111/j.1524-4733.2010.00768.x.

[25] Bonnín, C. M., Martínez-Arán, A., Torrent, C., Pacchiarotti, I., Rosa, A. R., Franco, C., ... & Vieta, E. (2010). Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. *Journal of affective disorders*, *121*(1-2), 156-160. https://doi:10.1016/j.jad.2009.05.014.

[26] Gitlin, M. J., Mintz, J., Sokolski, K., Hammen, C., & Altshuler, L. L. (2011). Subsyndromal depressive symptoms after symptomatic recovery from mania are associated with delayed functional recovery. *The Journal of clinical psychiatry*, *72*(5), 692-697. https://doi.org/10.4088/JCP.09m05291gre

[27] Bonnín, C. M., Sanchez-Moreno, J., Martinez-Aran, A., Sole, B., Reinares, M., Rosa, A. R., ... & Torrent, C. (2012). Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. *Journal of affective disorders*, *136*(3), 650-659. https://doi.org/10.1016/j.jad. 2011.10.012

[28] Lewandowski, K. E., Cohen, B. M., Keshavan, M. S., Sperry, S. H., & Öngür, D. (2013). Neuropsychological functioning predicts community outcomes in affective and non-affective psychoses: a 6-month follow-up. *Schizophrenia research*, *148*(1-3), 34-37. https://doi.org/10.1016 / j.schres.2013.05.012

[29] Savitz, J., Solms, M., & Ramesar, R. (2005). Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. *Bipolar disorders*, *7*(3), 216-235. https://doi.org/10.1111/j.1399-5618.2005.00203.x

[30] Robinson, L. J., & Nicol Ferrier, I. (2006). Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar disorders*, *8*(2), 103-116. https://doi:10.1111/j.1399-5618.2006.00277.x.

[31] Mur, M., Portella, M. J., Martinez-Aran, A., Pifarre, J., & Vieta, E. (2009). Influence of clinical and neuropsychological variables on the psychosocial and occupational outcome of remitted bipolar patients. *Psychopathology*, *42*(3), 148-156. https://doi.org/10.1159/000207456

[32] Gitlin, M. J., Swendsen, J., Heller, T. L., & Hammen, C. (1995). Relapse and impairment in bipolar disorder. *The American journal of psychiatry*. https://doi.org/10.1176/ajp.152.11.1635

[33] Tohen, M., Zarate Jr, C. A., Hennen, J., Khalsa, H. M. K., Strakowski, S. M., Gebre-Medhin, P., ... & Baldessarini, R. J. (2003). The McLean-Harvard first-episode mania study: prediction of recovery and first recurrence. *American Journal of Psychiatry*, *160*(12), 2099-2107. https://doi:10.1176/appi.ajp.160.12.2099.

[34] Goetz, I., Tohen, M., Reed, C., Lorenzo, M., Vieta, E., & EMBLEM Advisory Board. (2007). Functional impairment in patients with mania: baseline results of the EMBLEM study. *Bipolar disorders*, *9* (1-2), 45-52. https://doi:10.1111/j.1399-5618.2007.00325.x

[35] Rosa, A. R., Reinares, M., Franco, C., Comes, M., Torrent, C., Sánchez-Moreno, J., ... & Vieta, E. (2009). Clinical predictors of functional outcome of bipolar patients in remission. *Bipolar Disorders*, *11*(4), 401-409. https://doi.org/10.1111/j.1399-5618.2009.00698.x

[36] Cacilhas, A. A., da Silva Magalhães, P. V., Ceresér, K. M., Walz, J. C., Weyne, F., Rosa, A. R., ... & Kapczinski, F. (2009a). Validity of a short functioning test (FAST) in Brazilian outpatients with bipolar disorder. *Value in health*, *12*(4), 624-627. https://doi.org/10.1111/j.1524-4733.2008.00481.x

[37] Lee, J. H., Byun, M. S., Sohn, B. K., Choe, Y. M., Yi, D., Han, J. Y., ... & Lee, D. Y. (2015). Functional neuroanatomical correlates of the frontal assessment battery performance in Alzheimer disease: a FDG-PET study. *Journal of geriatric psychiatry and neurology*, *28*(3), 184-192. https://doi.org/10.1177/0891988715573533

[38] APA - American Psychiatric Association. (2002). *Practice guideline for the treatment of patients with bipolar disorder (revision)*. American Psychiatric Pub. PMID: 11958165

[39] Miklowitz, D. J., & Scott, J. (2009). Psychosocial treatments for bipolar disorder: Cost-effectiveness, mediating mechanisms, and future directions. *Bipolar disorders*, *11*, 110-122. https://doi.org/ 10.1111/j.1399-5618.2009.00715.x

[40] Fountoulakis, K. N., Kasper, S., Andreassen, O., Blier, P., Okasha, A., Severus, E., ... & Vieta, E. (2012). Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. *European archives of psychiatry and clinical neuroscience*, *262*(1), 1-48. https://doi:10.1007 / s00406-012-0323-x

[41] Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British journal of psychiatry*, *133*(5), 429-435. https://doi:10.1192/bjp.133.5.429.

[42] Hamilton, M. (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*, *23*(1), 56. https://doi.org/10.1136 / jnnp.23.1.56.

[43] Cunha, P. J., & Novaes, M. A. (2004). Neurocognitive assessment in alcohol abuse and dependence: implications for treatment. *Brazilian Journal of Psychiatry*, *26*, 23-27. https://doi.org/10.1590/S1516-44462004000500007

[44] Rosa, A. R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., ... & Vieta, E. (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health*, *3*(1), 1-8. https://doi:10.1186/1745-0179-3-5

[45] Barbato, A., Bossini, L., Calugi, S., D'Avanzo, B., Fagiolini, A., Koukouna, D., ... & Vallarino, M. (2013). Validation of the Italian version of the Functioning Assessment Short Test (FAST) for bipolar disorder. *Epidemiology and psychiatric sciences*, *22*(2), 187-194. https://dx.doi.org/10.1017/S2045796012000522.

[46] Suominen, K., Salminen, E., Lähteenmäki, S., Tupala, T., & Isometsä, E. (2015). Validity and reliability of the Finnish version of the Functioning Assessment Short Test (FAST) in bipolar disorder. *International journal of bipolar disorders*, *3*(1), 1-5. https://doi.org/10.1186/s40345-015-0025-1

[47] Zhang, Y., Long, X., Ma, X., He, Q., Luo, X., Bian, Y., ... & Xiang, Y. T. (2018). Psychometric properties of the Chinese version of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Journal of affective disorders*, *238*, 156-160. https://doi:10.1016/j.jad.2018.05.019

[48] Ilhan, R. S., & Sentürk Cankorur, V. (2015). Clinical and Cognitive Predictors of Psychosocial Functioning During the Euthymic Period in Bipolar Disorder Type II. *Turk Psikiyatri Dergisi*, *26*(1). https://doi.org/10.5080/u7695

[49] Orhan, M., Korten, N., Kupka, R., van Oppen, P., Stek, M., Vieta, E., ... & Dols, A. (2020). Reliability and validity of the functioning assessment short test for older adults with bipolar disorder (FAST-O). *International Journal of Bipolar Disorders*, *8*(1), 1-7. https://doi.org/10.1186/s40345-020-00193-2

[50] Moro, M. F., Colom, F., Floris, F., Pintus, E., Pintus, M., Contini, F., & Carta, M. G. (2012). Validity and reliability of the Italian version of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical practice and epidemiology in mental health: CP & EMH*, *8*, 67. https://doi.org/10.2174/1745017901208010067

[51] Bonnín, C. M., Martínez-Arán, A., Reinares, M., Valentí, M., Solé, B., Jiménez, E., ... & Rosa, A. R. (2018). Thresholds for severity, remission and recovery using the functioning assessment short test (FAST) in bipolar disorder. *Journal of affective disorders*, *240*, 57-62. https://doi:10.1016 / j.jad.2018.07.045

[52] Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. F. A. B. (2000). The FAB: a frontal assessment battery at bedside. *Neurology*, *55*(11), 1621-1626. https://doi.org/10.1212 / wnl.55.11.1621

[53] Álamo, A.R., Catalán-Alonso, M. J., & Carrasco-Marín, L. (2003). FAB: a preliminar Spanish application of the frontal assessment battery to 11 groups of patients. *Rev Neurol*, *36*(7), 605-608. https://doi.org/10.33588/rn.3607.2002363

[54] Lima, C. F., Meireles, L. P., Fonseca, R., Castro, S. L., & Garrett, C. (2008). The Frontal Assessment Battery (FAB) in Parkinson's disease and correlations with formal measures of executive functioning. *Journal of neurology*, *255*(11), 1756-1761.https://doi.org/10.1007 / s00415-008-0024-6

[55] Moreira, H. S., Costa, A. S., Castro, S. L., Lima, C. F., & Vicente, S. G. (2017). Assessing executive dysfunction in neurodegenerative disorders: a critical review of brief neuropsychological tools. *Frontiers in aging neuroscience*, *9*, 369. https://doi.org/10.3389/fnagi.2017.00369

[56] Horton, A. M., and Wedding, D. (eds) (2008). The Neuropsychology, *3rd Edn*. New York, NY: Springer Publishing Company.https://psycnet.apa.org/record/2007-16755-000

[57] Paviour, D. C., Winterburn, D., Simmonds, S., Burgess, G., Wilkinson, L., Fox, N. C., ... & Jahanshahi, M. (2005). Can the frontal assessment battery (FAB) differentiate bradykinetic rigid syndromes? Relation of the FAB to formal neuropsychological testing. *Neurocase*, *11*(4), 274-282. https://doi.org/10.1080 / 13554790590962933

[58] Wong, A., Mok, V. C., Kwong Tang, W., Lam, W. W., & Sing Wong, K. (2007). Comparing Mattis Dementia Rating Scale–initiation/perseveration subset and frontal assessment battery in stroke associated with small vessel disease. *Journal of clinical and experimental neuropsychology*, *29*(2), 160-169. https://doi:10.1080/13803390600582453.

[59] Boban, M., Malojčić, B., Mimica, N., Vuković, S., & Zrilić, I. (2012). The frontal assessment battery in the differential diagnosis of dementia. *Journal of geriatric*

psychiatry and neurology, *25*(4), 201-207. https://doi.org/10.1177/0891988712464821

[60] Reichenberg, A., Harvey, P. D., Bowie, C. R., Mojtabai, R., Rabinowitz, J., Heaton, R. K., & Bromet, E. (2009). Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia bulletin*, *35*(5), 1022-1029.https://doi.org/10.1093 / schbul / sbn044

[61] Fiorentino, N., Gleichgerrcht, E., Roca, M., Cetkovich, M., Manes, F., & Torralva, T. (2013). The INECO Frontal Screening tool differentiates behavioral variant-frontotemporal dementia (bv-FTD) from major depression. *Dementia & neuropsychologia*, *7*(1), 33-39. https://doi.org/10.1590 / S1980-57642013DN70100006

[62] Baez, S., Ibanez, A., Gleichgerrcht, E., Perez, A., Roca, M., Manes, F., & Torralva, T. (2014). The utility of IFS (INECO Frontal Screening) for the detection of executive dysfunction in adults with bipolar disorder and ADHD. *Psychiatry research*, *216*(2), 269-276. https://doi.org/10.1016/j.psychres.2014.01.020

[63] Caixeta, L., Soares, V. L., Vieira, R. T., Soares, C. D., Caixeta, V., Ferreira, S. B., & Aversi-Ferreira, T. A. (2017). Executive function is selectively impaired in old age bipolar depression. *Frontiers in psychology*, *8*, 194. https://doi.org/10.3389/fpsyg.2017.00194

[64] Gowda, S. N., Chandak, S., Sawant, V., & Kulkarni, A. (2017). Comparison of neurocognitive deficits among euthymic bipolar I disorder patients, their first degree relatives and healthy controls. *Int J Adv Med*, *4*(3), 656-660. http://dx.doi.org/10.18203/2349-3933.ijam20171513

[65] Oshima, E., Terada, S., Sato, S., Ikeda, C., Nagao, S., Takeda, N., ... & Uchitomi, Y. (2012). Frontal assessment battery and brain perfusion imaging in Alzheimer's disease. *International psychogeriatrics*, *24*(6), 994. https://doi.org/10.1017/S1041610211002481

[66] Kopp, B., Rösser, N., Tabeling, S., Stürenburg, H. J., de Haan, B., Karnath, H. O., & Wessel, K. (2013). Performance on the Frontal Assessment Battery is sensitive to frontal lobe damage in stroke patients. *BMC neurology*, *13*(1), 1-10. https://doi.org/10.1186 / 1471-2377-13-179

[67] Lomastro, M. J., Valerio, M. P., Szmulewicz, A. G., & Martino, D. J. (2021). Manic morbidity and executive function impairment as determinants of long-term psychosocial dysfunction in bipolar disorder. *Acta Psychiatrica Scandinavica*.https://doi.org/10.1111/acps.13303

[68] Yoshida, H., Terada, S., Sato, S., Kishimoto, Y., Ata, T., Ohshima, E., ... & Kuroda, S. (2009). Frontal assessment battery and brain perfusion imaging in early dementia. *Dementia and geriatric cognitive disorders*, *27*(2), 133-138. https://doi.org/10.1159/000198687

[69] Chong, M. S., Lim, W. S., Chan, S. P., Feng, L., Niti, M., Yap, P., ... & Ng, T. P. (2010). Diagnostic performance of the Chinese Frontal Assessment Battery in early cognitive impairment in an Asian population. *Dementia and geriatric cognitive disorders*, *30*(6), 525-532. https://doi.org/10.1159/000321665

[70] Lam, L. C., Tam, C. W., Lui, V. W., Chan, W. C., Chan, S. S., Chiu, H. F., ... & Chan, W. M. (2008). Screening of mild cognitive impairment in Chinese older adults–a multistage validation of the Chinese abbreviated mild cognitive impairment test. *Neuroepidemiology*, *30*(1), 6-12.https://doi.org/10.1159/000113300

[71] Wang, T. L., Hung, Y. H., & Yang, C. C. (2016). Psychometric properties of the Taiwanese (traditional Chinese) version of the Frontal Assessment Battery: A preliminary study. *Applied Neuropsychology: Adult*, *23*(1), 11-20. https://doi:org/10.1080/23279095.2014.995792

[72] Rocca, C. C., & Lafer, B. (2006). Neuropsychological disturbances in bipolar disorder. *Brazilian Journal of Psychiatry*, *28*(3), 226-237. https://dx.doi.org/10.1590/S1516-44462006000300016

[73] Paradiso, S., Lamberty, G. J., Garvey, M. J., & Robinson, R. G. (1997). Cognitive impairment in the euthymic phase of chronic unipolar depression. *The Journal of nervous and mental disease*, *185*(12), 748-754.https://doi.org/10.1097 / 00005053-199712000-00005

[74] Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine*, *256*(3), 183-194.https://doi.org/10.1111 / j.1365-2796.2004.01388.x

[75] Cyrino, L. A. R., Calegari, C. R., Tomasi, M. C., Stammerjohann, F. L. S.,& Lima, D.D. (2021) Assessment of the Impairment in Domain functionalities and Executive Functions in Euthymic Patients, with Bipolar Disorder I/II - Utilizing the FAST and FAB tests. *International Journal of Advanced Engineering Research and Science (IJAERS)*, 8(5), 81-112.https://dx.doi.org/10.22161/ijaers.85.10

[76] Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual review of psychology*, *60*, 173-196. https://doi.org/10.1146/annurev.psych.59.103006.093656

[77] Salthouse, T. A. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychological bulletin*, *137*(5), 753. https://doi.org/10.1037/a0023262

[78] Strejilevich, S., & Martino, D. J. (2017). Cognition and Bipolar Disorder in Older Adults (Including Question of "Neuroprogression").http://dx.doi.org/10.1007/978-981-10-2414-6_12

[79] Schouws, S. N., Korten, N., Beekman, A. T., Stek, M. L., & Dols, A. (2020). Does cognitive function in older bipolar patients depend on recurrent or current mood symptoms? *International Journal of Geriatric Psychiatry*, 35(10), 1163-1170. https://doi.org/10.1002/gps.5352

[80] Papilla, D. E., Olds, S. W., & Feldman, R. D. (2006). Desenvolvimentao Humano . Porto Alegre: Artmed.

[81] Teixeira, I. N. D., & Guariento, M. E. (2010). Biology of aging: theories, mechanisms, and perspectives. *Ciência &*

Saúde Coletiva, *15*, 2845-2857. https://doi.org/10.1590/S1413-81232010000600022

[82] Zepada, M., 2010. Deterioro cognitivo. Envejecimiento humano: Uma visión transdisciplinaria. 221-228. ISBN 978-607-460-175-6

[83] Santos, J. L., Aparicio, A., Bagney, A., Sánchez-Morla, E. M., Rodríguez-Jiménez, R., Mateo, J., & Jiménez-Arriero, M. Á. (2014). A five-year follow-up study of neurocognitive functioning in bipolar disorder. *Bipolar disorders*, *16*(7), 722-731. https://doi.org/10.1111/bdi.12215

[84] Vasconcelos-Moreno, M. P., Bücker, J., Bürke, K. P., Czepielewski, L., Santos, B. T., Fijtman, A., ... & Kauer-Sant'Anna, M. (2016). Cognitive performance and psychosocial functioning in patients with bipolar disorder, unaffected siblings, and healthy controls. *Brazilian Journal of Psychiatry*, *38*(4), 275-280. http://dx.doi.org/10.1590/1516-4446-2015-1868

[85] Solé, B., Bonnin, C. M., Jiménez, E., Torrent, C., Torres, I., Varo, C., ... & Reinares, M. (2018). Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. *Acta Psychiatrica Scandinavica*, *137*(6), 516-527. https://doi.org/10.1111/acps.12871

[86] Léda-Rêgo, G., Bezerra-Filho, S., & Miranda-Scippa, Â. (2020). Functioning in euthymic patients with bipolar disorder: A systematic review and meta-analysis using the Functioning Assessment Short Test. *Bipolar disorders*, *22*(6), 569-581. https://doi.org/10.1111/bdi.12904

[87] Bearden, C. E., Shih, V. H., Green, M. F., Gitlin, M., Sokolski, K. N., Levander, E., ... & Altshuler, L. L. (2011). The impact of neurocognitive impairment on occupational recovery of clinically stable patients with bipolar disorder: a prospective study. *Bipolar disorders*, *13*(4), 323-333. https://doi.org/10.1111/j.1399-5618.2011.00928.x

[88] Martínez-Arán, A., Vieta, E., Colom, F., Torrent, C., Sánchez-Moreno, J., Reinares, M., ... & Salamero, M. (2004b). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar disorders*, *6*(3), 224-232. https://doi.org/10.1111/j.1399-5618.2004.00111.x

[89] Osuji, I. J., & Cullum, C. M. (2005). Cognition in bipolar disorder. *Psychiatric Clinics*, *28*(2), 427-441.https://doi.org/10.1186/s12991-015-0080-0

[90] Goswami, U., Sharma, A., Khastigir, U., Ferrier, I. N., Young, A. H., Gallagher, P., ... & Moore, P. B. (2006). Neuropsychological dysfunction, soft neurological signs and social disability in euthymic patients with bipolar disorder. *The British Journal of Psychiatry*, *188*(4), 366-373. https://doi.org/10.1192/bjp.188.4.366

[91] Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., ... & Salamero, M. (2004a). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *American Journal of Psychiatry*, *161*(2), 262-270. https://doi.org/10.1176/appi.ajp.161.2.262

[92] Stamelou, M., Diehl-Schmid, J., Hapfelmeier, A., Kontaxopoulou, D., Stefanis, L., Oertel, W. H., ... & Höglinger, G. U. (2015). The frontal assessment battery is not useful to discriminate progressive supranuclear palsy from frontotemporal dementias. *Parkinsonism & related disorders*, *21*(10), 1264-1268. https://doi.org/10.1016 / j.parkreldis.2015.08.006

[93] Kurtz, M. M., & Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology*, *23*(5), 551. https://doi.org/10.1037/a0016277

[94] Borkowska A., Rybakowski, J. K. (2001) Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. *Bipolar Disord*. 3(2), 88-94. https://doi.org/10.1034/j.1399-5618.2001.030207.x. PMID: 11333068.

[95] [95] Besnier, N., Kaladjian, A., Mazzola-Pomietto, P., Adida, M., Fakra, E., Jeanningros, R., & Azorin, J. M. (2008). Selecting material to develop an emotional Stroop test adapted to schizophrenia and bipolar disorders. *Canadian journal of psychiatry. Revue canadienne de psychiatrie*, *53*(3), 177-188. https://doi.org/10.1177 / 070674370805300308

[96] Tsitsipa, E., & Fountoulakis, K. N. (2015). The neurocognitive functioning in bipolar disorder: a systematic review of data. *Annals of general psychiatry*, *14*, 42. https://doi.org/10.1186/s12991-015-0081-z

[97] Schoeyen, H. K., Birkenaes, A. B., Vaaler, A. E., Auestad, B. H., Malt, U. F., Andreassen, O. A., & Morken, G. (2011). Bipolar disorder patients have similar levels of education but lower socio-economic status than the general population. *Journal of affective disorders*, *129*(1-3), 68-74. https://doi.org/10.1016/j.jad.2010.08.012

[98] Tsuchiya, K. J., Agerbo, E., Byrne, M., & Mortensen, P. B. (2004). Higher socio-economic status of parents may increase risk for bipolar disorder in the offspring. *Psychological Medicine*, *34*(5), 787. https://doi.org/10.1017/S0033291703001491

[99] Glahn, D. C., Bearden, C. E., Bowden, C. L., & Soares, J. C. (2006). Reduced educational attainment in bipolar disorder. *Journal of Affective Disorders*, *92*(2-3), 309-312. https://doi.org/10.1016/j.jad.2006.01.025

[100] Wingo, A. P., Baldessarini, R. J., Holtzheimer, P. E., & Harvey, P. D. (2010). Factors associated with functional recovery in bipolar disorder patients. *Bipolar disorders*, *12*(3), 319-326. https://doi.org/10.1111/j.1399-5618.2010.00808.x

[101] Baune, B. T., & Malhi, G. S. (2015). A review on the impact of cognitive dysfunction on social, occupational, and general functional outcomes in bipolar disorder. *Bipolar disorders*, *17*, 41-55.https://doi.org/10.1111/bdi.12341

[102] Mur, M., Portella, M. J., Martínez-Arán, A., Pifarré, J., & Vieta, E. (2008). Neuropsychological profile in bipolar

disorder: a preliminary study of monotherapy lithium-treated euthymic bipolar patients evaluated at a 2-year interval. *Acta Psychiatrica Scandinavica*, *118*(5), 373-381. https://doi.org/10.1111/j.1600-0447.2008.01245.x

[103] Braw, Y., Erez, G., Sela, T., Gvirts, H. Z., Hare, E. V., Bloch, Y., & Levkovitz, Y. (2013). A longitudinal study of cognition in asymptomatic and mildly symptomatic bipolar disorder patients. *Psychiatry research*, *210*(3), 842-849.https://doi.org/10.1016/j.psychres.2013.01.003

[104] Mora, E., Portella, M. J., Forcada, I., Vieta, E., & Mur, M. (2013). Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychological medicine*, *43*(6), 1187. https://doi.org/10.1017/S0033291712001948

[105] Kogan, J. N., Otto, M. W., Bauer, M. S., Dennehy, E. B., Miklowitz, D. J., Zhang, H. W., ... & STEP-BD Investigators. (2004). Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Bipolar Disorders*, *6*(6), 460-469. https://doi.org/10.1111/j.1399-5618.2004.00158.x

[106] Mitchell, P. B., Johnston, A. K., Corry, J., Ball, J. R., & Malhi, G. S. (2009). Characteristics of bipolar disorder in an Australian specialist outpatient clinic: comparison across large datasets. *Australian & New Zealand Journal of Psychiatry*, *43*(2), 109-117. https://doi.org/10.1080/00048670802607220

[107] Lera-Miguel, S., Andrés-Perpiñá, S., Fatjó-Vilas, M., Fañanás, L., & Lázaro, L. (2015). Two-year follow-up of treated adolescents with early-onset bipolar disorder: Changes in neurocognition. *Journal of Affective Disorders*, *172*, 48-54. https://doi.org/10.1016/j.jad.2014.09.041

[108] Lima, I. M., Peckham, A. D., & Johnson, S. L. (2018). Cognitive deficits in bipolar disorders: Implications for emotion. *Clinical psychology review*, *59*, 126-136. https://doi.org/10.1016/j.cpr.2017.11.006

[109] Vaughn-Coaxum, R. A., Merranko, J., Birmaher, B., Dickstein, D. P., Hafeman, D., Levenson, J. C., ... & Goldstein, T. R. (2021). Longitudinal course of depressive symptom severity among youths with bipolar disorders: Moderating influences of sustained attention and history of child maltreatment. *Journal of Affective Disorders*, *282*, 261-271.https://doi.org/10.1016/j.jad.2020.12.078

[110] Martino, D. J., Igoa, A., Marengo, E., Scápola, M., & Strejilevich, S. A. (2018). Longitudinal relationship between clinical course and neurocognitive impairments in bipolar disorder. *Journal of affective disorders*, *225*, 250-255.https://doi.org/10.1016/j.jad.2017.08.011

[111] Pavuluri, M. N., West, A., Hill, S. K., Jindal, K., & Sweeney, J. A. (2009). Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(3), 299-307.https://doi.org/10.1097/CHI.0b013e318196b907

[112] Nieto, R. G., & Castellanos, F. X. (2011). A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. *Journal of Clinical Child & Adolescent Psychology*, *40*(2), 266-280.https://doi.org/10.1080/15374416.2011.546049

[113] Samamé, C., Martino, D. J., & Strejilevich, S. A. (2014). Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. *Journal of affective disorders*, *164*, 130-138. https://doi.org/10.1016/j.jad.2014.04.028

[114] Cacilhas, A. A., Magalhães, P. V. D. S., Ceresér, K. M., Walz, J. C., Weyne, F., Rosa, A. R., ... & Kapczinski, F. (2009b). Bipolar disorder and age-related functional impairment. *Brazilian Journal of Psychiatry*, *31*(4), 354-357. https://doi.org/10.1590/S1516-44462009000400012

[115] Bora, E., Yücel, M., & Pantelis, C. (2010b). Cognitive impairment in affective psychoses: a meta-analysis. *Schizophrenia bulletin*, *36*(1), 112-125.https://doi.org/10.1093/schbul/sbp093

[116] Torres, I. J., Qian, H., Basivireddy, J., Chakrabarty, T., Wong, H., Lam, R. W., & Yatham, L. N. (2020). Three-year longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. *Acta Psychiatrica Scandinavica*, *141*(2), 98-109. https://doi.org/10.1111/acps.13141

[117] Balanzá-Martínez, V., Selva, G., Martínez-Arán, A., Prickaerts, J., Salazar, J., González-Pinto, A., ... & Tabarés-Seisdedos, R. (2010). Neurocognition in bipolar disorders—a closer look at comorbidities and medications. *European Journal of Pharmacology*, *626*(1), 87-96. https://doi.org/10.1016/j.ejphar.2009.10.018

[118] Laere, E., Tee, SF, & Tang, PY (2018). Assessment of cognition in schizophrenia using the trail test: a meta-analysis. *Investigation in psychiatry15*(10), 945–955.https://doi.org/10.30773/pi.2018.07.22

[119] Sanches, M., Bauer, I. E., Galvez, J. F., Zunta-Soares, G. B., & Soares, J. C. (2015). The management of cognitive impairment in bipolar disorder: current status and perspectives. *American journal of therapeutics*, *22*(6), 477–486. https://doi.org/10.1097/MJT.0000000000000120

[120] Strakowski, S. M., Adler, C. M., Almeida, J., Altshuler, L. L., Blumberg, H. P., Chang, K. D., ... & Townsend, J. D. (2012). The functional neuroanatomy of bipolar disorder: a consensus model. *Bipolar disorders*, *14*(4), 313-325.https://doi.org/10.1111/j.1399-5618.2012.01022.x

[121] Scaini, G., Valvassori, S. S., Diaz, A. P., Lima, C. N., Benevenuto, D., Fries, G. R., & Quevedo, J. (2020). Neurobiology of bipolar disorders: a review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings. *Brazilian Journal of Psychiatry*, (AHEAD). https://doi.org/10.1590/1516-4446-2019-0732

[122] MacCabe, D. P., Roediger III, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology*, *24*(2), 222. https://doi:10.1037/a0017619

[123] Gale, C. R., Batty, G. D., McIntosh, A. M., Porteous, D. J., Deary, I. J., & Rasmussen, F. (2013). Is bipolar disorder more common in highly intelligent people? A cohort study of a million men. *Molecular psychiatry*, *18*(2), 190-194.https://doi.org/10.1038/mp.2012.26

[124] Arango, C., Fraguas, D., & Parellada, M. (2014). Differential neurodevelopmental trajectories in patients with early-onset bipolar and schizophrenia disorders. *Schizophrenia bulletin*, *40 Suppl 2*(Suppl 2), S138–S146. https://doi.org/10.1093/schbul/sbt198

[125] Lima, F., Rabelo-da-Ponte, F. D., Bücker, J., Czepielewski, L., Hasse-Sousa, M., Telesca, R., ... & Rosa, A. R. (2019). Identifying cognitive subgroups in bipolar disorder: A cluster analysis. *Journal of affective disorders*, *246*, 252-261.https://doi.org/10.1016/j.jad.2018.12.044

[126] Ellison-Wright, I., & Bullmore, E. (2010). Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophrenia research*, *117*(1), 1-12. https://doi.org/10.1016/j.schres.2009.12.022

[127] Depp, C. A., Mausbach, B. T., Harmell, A. L., Savla, G. N., Bowie, C. R., Harvey, P. D., & Patterson, T. L. (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar disorders*, *14*(3), 217-226. https://doi.org/10.1111/j.1399-5618.2012.01011.x

[128] Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., ... & Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA psychiatry*, *72*(4), 305-315. https://doi.org/10.1001/jamapsychiatry.2014.2206

[129] Martino, D. J., Samamé, C., Marengo, E., Igoa, A., & Strejilevich, S. A. (2016a). A critical overview of the clinical evidence supporting the concept of neuroprogression in bipolar disorder. *Psychiatry Res*, *235*, 1-6. http://dx.doi.org/10.1016/j.psychres.2015.12.012

[130] Vieta, E., Popovic, D., Rosa, A. R., Solé, B., Grande, I., Frey, B. N., ... &, F. (2013). The clinical implications of cognitive impairment and allostatic load in bipolar disorder. *European Psychiatry*, *28*(1), 21-29.https://doi.org/10.1016/j.eurpsy.2011.11.007

[131] Kupfer, D. J. (2005). The increasing medical burden in bipolar disorder. *Jama*, *293*(20), 2528-2530. https://doi.org/10.1001/jama.293.20.2528

[132] Daban, C., Vieta, E., Mackin, P., & Young, A. H. (2005). Hypothalamic-pituitary-adrenal axis and bipolar disorder. *Psychiatric Clinics*, *28*(2), 469-480. https://doi.org/10.1016/j.psc.2005.01.005

[133] Kapczinski, F., Frey, B. N., Andreazza, A. C., Kauer-Sant'Anna, M., Cunha, Â., & Post, R. M. (2008). Increased oxidative stress as a mechanism for decreased BDNF levels in acute manic episodes. *Brazilian Journal of Psychiatry*, *30*(3), 243-245. https://doi.org/10.1590/S1516-44462008000300011

[134] Kauer-Sant'Anna, M., Kapczinski, F., Andreazza, A. C., Bond, D. J., Lam, R. W., Young, L. T., & Yatham, L. N. (2009). Brain-derived neurotrophic factor and inflammatory markers in patients with early-vs. late-stage bipolar disorder. *International Journal of Neuropsychopharmacology*, *12*(4), 447-458. https://doi.org/10.1017/S1461145708009310

[135] Szmulewicz, A., Valerio, M., & Martino, D. J. (2020a). Cognitive decline and neuroprogression in bipolar disorder: A case for Hitchens' razor. *Bipolar Disorders*, *22*(5), 536-536. https://doi.org/10.1111/bdi.12953

[136] [135] Drevets, W. C., Price, J. L., Simpson, J. R., Todd, R. D., Reich, T., Vannier, M., & Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*, *386*(6627), 824-827. https://doi.org/10.1038/386824a0

[137] Adler, C. M., Holland, S. K., Schmithorst, V., Wilke, M., Weiss, K. L., Pan, H., & Strakowski, S. M. (2004). Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. *Bipolar disorders*, *6*(3), 197-203. https://doi.org/10.1111/j.1399-5618.2004.00108.x

[138] Beyer, J. L., Taylor, W. D., MacFall, J. R., Kuchibhatla, M., Payne, M. E., Provenzale, J. M., ... & Krishnan, K. R. R. (2005). Cortical white matter microstructural abnormalities in bipolar disorder. *Neuropsychopharmacology*, *30*(12), 2225-2229. https://doi.org/10.1038/sj.npp.1300802

[139] Abé, C., Ekman, C. J., Sellgren, C., Petrovic, P., Ingvar, M., & Landén, M. (2015). Manic episodes are related to changes in frontal cortex: a longitudinal neuroimaging study of bipolar disorder 1. *Brain*, *138*(11), 3440-3448.https://doi.org/10.1093/brain/awv266

[140] Mwangi, B., Wu, MJ, Cao, B., Passos, IC, Lavagnino, L., Keser, Z., ... & Soares, JC (2016). Individualized prediction and clinical staging of bipolar disorders using neuroanatomical biomarkers. *Biological psychiatry: cognitive neuroscience and neuroimaging*, *1* (2), 186-194. https://doi.org/10.1016/j.bpsc.2016.01.001

[141] Scussel, F., Salvador, L. C., Brandão, L. S., & Feier, G. (2016). Clinical profile of patients with bipolar disorder treated at a specialized clinic in southern Santa Catarina.. *Arquivos Catarinenses de Medicina*, *45*(4), 3-10.http://www.acm.org.br/acm/seer/index.php/arquivos/article/view/133

[142] Szmulewicz, A., Valerio, M. P., & Martino, D. J. (2020b). Longitudinal analysis of cognitive performances in recent-onset and late-life Bipolar Disorder: A systematic review and meta-analysis. *Bipolar disorders*, *22*(1), 28-37. https://doi.org/10.1111/bdi.12841

[143] Stuss, D. T. (2011). Functions of the frontal lobes: relation to executive functions. *Journal of the*

International Neuropsychological Society: JINS, *17*(5), 759.https://doi.org/10.1017/S1355617711000695

[144] Miller, B. L., & Cummings, J. L. (Eds.). (2017). The human frontal lobes: Functions and disorders. Guilford Publications. ISBN 9781462531837

[145] López-Larson, M. P., DelBello, M. P., Zimmerman, M. E., Schwiers, M. L., & Strakowski, S. M. (2002). Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biological psychiatry*, *52*(2), 93-100. https://doi.org/10.1016/S0006-3223(02)01350-1

[146] Frangou, S., Raymont, V., & Bettany, D. (2002). The Maudsley bipolar disorder project. A survey of psychotropic prescribing patterns in bipolar I disorder. *Bipolar disorders*, *4*(6), 378-385. https://doi.org/10.1034/j.1399-5618.2002.01223.x

[147] Bora, E., Fornito, A., Yücel, M., & Pantelis, C. (2010a). Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Biological psychiatry*, *67*(11), 1097-1105. https://doi.org/10.1016/j.biopsych.2010.01.020

[148] Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., ... & Petersen, S. E. (2011). Functional network organization of the human brain. Neuron, 72(4), 665-678.https://doi.org/10.1016/j.neuron.2011.09.006

[149] Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in clinical neuroscience*, *9*(2), 141. https://www.ncbi.nlm.nih.gov/pubmed/17726913

[150] Arnsten, A. F., & Rubia, K. (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(4), 356-367. https://doi.org/10.1016/j.jaac.2012.01.008

[151] Yang, T., Zhao, G., Mao, R., Huang, J., Xu, X., Su, Y., ... & Fang, Y. (2018). The association of duration and severity of disease with executive function: differences between drug-naïve patients with bipolar and unipolar depression. *Journal of affective disorders*, *238*, 412-417. https://doi.org/10.1016/j.jad.2018.05.051

[152] Yang, T., Lam, R. W., Huang, J., Su, Y., Liu, J., Yang, X., ... & Fang, Y. (2021). Exploring the Effects of Temperament on Gray Matter Volume of Frontal Cortex in Patients with Mood Disorders. *Neuropsychiatric Disease and Treatment*, *17*, 183. https://doi.org/10.2147/NDT.S287351

[153] Nagata, T., Shinagawa, S., Ochiai, Y., Aoki, R., Kasahara, H., Nukariya, K., & Nakayama, K. (2011). Association between executive dysfunction and hippocampal volume in Alzheimer's disease. *International Psychogeriatrics*, *23*(5), 764. https://doi.org/10.1017 / S1041610210002164

[154] Hoffmann, M. (2013). The human frontal lobes and frontal network systems: an evolutionary, clinical, and treatment perspective. *International Scholarly Research Notices*, *2013*. https://doi.org/10.1155/2013/892459

[155] Pellecchia, M. T., Picillo, M., Santangelo, G., Longo, K., Moccia, M., Erro, R., ... & Pappata, S. (2015). Cognitive performances and DAT imaging in early Parkinson's disease with mild cognitive impairment: a preliminary study. *Acta Neurologica Scandinavica*, *131*(5), 275-281. https://doi.org/10.1111/ane.12365

[156] Brugger, F., Abela, E., Hägele-Link, S., Bohlhalter, S., Galovic, M., & Kägi, G. (2015). Do executive dysfunction and freezing of gait in Parkinson's disease share the same neuroanatomical correlates?. *Journal of the neurological sciences*, *356*(1-2), 184-187. https://doi.org/10.1016/j.jns.2015.06.046

[157] Hurtado-Pomares, M., Carmen Terol-Cantero, M., Sánchez-Pérez, A., Peral-Gómez, P., Valera-Gran, D., & Navarrete-Muñoz, E. M. (2018). The frontal assessment battery in clinical practice: a systematic review. *International journal of geriatric psychiatry*, *33*(2), 237-251. https://doi.org/10.1002/gps.4751

[158] Han, M., Kim, D. Y., Leigh, J. H., & Kim, M. W. (2020). Value of the Frontal Assessment Battery Tool for Assessing the Frontal Lobe Function in Stroke Patients. *Annals of rehabilitation medicine*, *44*(4), 261–272.https://doi.org/10.5535/arm.19111

[159] Cao, B., Passos, I.C., Mwangi, B., Bauer, I.E., ZuntaSoares, G.B., Kapczinski, F., et al., (2016). Hippocampal volume and verbal memory performance in late-stage bipolar disorder. J Psychiatr Res. 73, 102-107.https://doi.org/10.1016 / j.jpsychires.2015.12.012

[160] Blond, B. N., Fredericks, C. A., & Blumberg, H. P. (2012). Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala–anterior paralimbic neural system. *Bipolar disorders*, *14*(4), 340-355. https://doi.org/10.1111/j.1399-5618.2012.01015.x

[161] Nakamura-Palacios, E. M., Souza, R. S., Zago-Gomes, M. P., de Melo, A. M., Braga, F. S., Kubo, T. T., & Gasparetto, E. L. (2014). Gray matter volume in left rostral middle frontal and left cerebellar cortices predicts frontal executive performance in alcoholic subjects. *Alcoholism: Clinical and Experimental Research*, *38*(4), 1126-1133. https://doi.org/10.1111/acer.12308

[162] Martino, D. J., Strejilevich, S. A., Marengo, E., Ibañez, A., Scápola, M., & Igoa, A. (2014). Toward the identification of neurocognitive subtypes in euthymic patients with bipolar disorder. *Journal of affective disorders*, *167*, 118-124. https://doi:10.1016 / j.jad.2014.05.059

[163] Pan, M. M., Pousa, E., Cobo, J., & Duño, R. (2014). Cognitive executive performance infl uences functional outcome in euthymic type I bipolar disorder outpatients. *Psicothema*, *26*(2), 166-173. https://doi.org/10.7334/psicothema2013.111

[164] Chaves, O. C., Lombardo, L. E., Bearden, C. E., Woolsey, M. D., Martinez, D. M., Barrett, J. A., ... & Glahn, D. C. (2011). Association of clinical symptoms and neurocognitive performance in bipolar disorder: a

longitudinal study. *Bipolar disorders*, *13*(1), 118-123. https://doi.org/10.1111/j.1399-5618.2011.00888.x

[165] Szmulewicz, A. G., Samamé, C., Martino, D. J., & Strejilevich, S. A. (2015). An updated review on the neuropsychological profile of subjects with bipolar disorder. *Archives of Clinical Psychiatry (São Paulo)*, *42*(5), 139-146. https://doi.org/10.1590/0101-60830000000064

[166] Martínez-Arán, A., Vieta, E., Colom, F., Reinares, M., Benabarre, A., Gastó, C., & Salamero, M. (2000). Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. *Psychotherapy and psychosomatics*, *69*(1), 2-18. https://doi.org/10.1159/000012361

[167] Sanchez-Moreno, J., Martinez-Aran, A., Tabarés-Seisdedos, R., Torrent, C., Vieta, E., & Ayuso-Mateos, J. L. (2009). Functioning and disability in bipolar disorder: an extensive review. *Psychotherapy and psychosomatics*, *78*(5), 285-297.https://doi.org/10.1159/000228249

[168] artino, D. J., Marengo, E., Igoa, A., Scápola, M., Urtueta-Baamonde, M., & Strejilevich, S. A. (2016b). Accuracy of the number of previous episodes reported by patients with bipolar disorder. *Comprehensive psychiatry*, *65*, 122-127.https://doi.org/10.1016/j.comppsych.2015.11.005

[169] Latalova, K., Prasko, J., Diveky, T., Kamaradova, D., & Velartova, H. (2011). Quality of life in patients with bipolar disorder–a comparison with schizophrenic patients and healthy controls. *Psychiatria Danubina*, *23*(1.), 21-26. PMID: 21448093

[170] Rosa, A. R., González-Ortega, I., González-Pinto, A., Echeburúa, E., Comes, M., Martínez-Àran, A., ... & Vieta, E. (2012). One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. *Acta Psychiatrica Scandinavica*, *125*(4), 335-341.https://doi.org/10.1111/j.1600-0447.2011.01830.x

[171] Valerio, M. P., Lomastro, J., & Martino, D. J. (2020). Neurocognitive predictors of long-term clinical course in bipolar disorder. *Australian & New Zealand Journal of Psychiatry*, *54*(11), 1101–1106. https://doi.org/10.1177/0004867420946844

[172] Chen, W. Y., Huang, M. C., Lee, Y. C., Chang, C. E., Lin, S. K., Chiu, C. C., ... & Kuo, P. H. (2020). Dissect the Heterogeneity of Longitudinal Cognitive Declines with Risk Factors and Functional Outcomes in Bipolar Disorder. https://doi.org/10.21203/rs.3.rs-97680/v1

[173] Sachs, G., Berg, A., Jagsch, R., Lenz, G., & Erfurth, A. (2020). Predictors of Functional Outcome in Patients with Bipolar Disorder: Effects of Cognitive Psychoeducational Group Therapy After 12 Months. *Frontiers in Psychiatry*, *11*, 1312.https://doi.org/10.3389/fpsyt.2020.530026

[174] Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of affective disorders*, *113*(1-2), 1-20. https://doi.org/10.1016/j.jad.2008.06.009

[175] Etkin, A., Gyurak, A., & O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues in clinical neuroscience*, *15*(4), 419–429. https://doi.org/10.31887/DCNS.2013.15.4/aetkin

[176] Baune, B. T., Li, X., & Beblo, T. (2013). Short-and long-term relationships between neurocognitive performance and general function in bipolar disorder. Journal of Clinical and Experimental Neuropsychology, 35(7), 759–774. https://doi.org/10.1080/13803395.2013.824071

[177] Martínez-Aran, A., Penades, R., Vieta, E., Colom, F., Reinares, M., Benabarre, A., ... & Gasto, C. (2002b). Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. *Psychotherapy and psychosomatics*, *71*(1), 39-46.https://doi.org/10.1159/000049342

[178] Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Leon, A. C., Solomon, D. A., ... & Keller, M. B. (2005). Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Archives of general psychiatry*, *62*(12), 1322-1330.https://doi.org/10.1001 / archpsyc.62.12.1322

[179] Tohen, M., Bowden, C. L., Calabrese, J. R., Lin, D., Forrester, T. D., Sachs, G. S., ... & Grunze, H. (2006). Influence of sub-syndromal symptoms after remission from manic or mixed episodes. *The British Journal of Psychiatry*, *189*(6), 515-519. https://doi:10.1192 / bjp.bp.105.020321

[180] Frye, M. A., Yatham, L. N., Calabrese, J. R., Bowden, C. L., Ketter, T. A., Suppes, T., ... & Thompson, T. R. (2006). Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. *Journal of Clinical Psychiatry*, *67*(11), 1721-1728. https://doi.org/10.4088 / jcp.v67n1108

[181] Zaretsky, A., Lancee, W., Miller, C., Harris, A., & Parikh, S. V. (2008). Is cognitive-behavioural therapy more effective than psychoeducation in bipolar disorder?. *The Canadian journal of psychiatry*, *53*(7), 441-448. https://doi.org/10.1177/070674370805300709

[182] Torrent, C., Bonnin, C. D. M., Martínez-Arán, A., Valle, J., Amann, B. L., González-Pinto, A., ... & Vieta, E. (2013). Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *American Journal of Psychiatry*, *170*(8), 852-859. https://doi.org/10.1176/appi.ajp.2012.12070971

[183] Solé, B., Jiménez, E., Martinez-Aran, A., & Vieta, E. (2015). Cognition as a target in major depression: new developments. *European Neuropsychopharmacology*, *25*(2), 231-247. https://doi.org/10.1016/j.euroneuro.2014.12.004

[184] Szmulewicz, A. G., Valerio, M. P., Lomastro, J., Smith, J. M., Chiappe, V., Martino, D. J., & Igoa, A. (2018). Neurocognitive functioning in first-episode Bipolar Disorder: Relationship with functional status. *Journal of*

affective disorders, *228*, 97-100. https://doi.org/10.1016/j.jad.2017.12.015

[185] Martínez-Arán, A., Torrent, C., Solé, B., Bonnín, C. M., Rosa, A. R., Sánchez-Moreno, J., & Vieta, E. (2011). Functional remediation for bipolar disorder. *Clinical practice and epidemiology in mental health: CP & EMH*, *7*, 112. https://doi.org/10.2174/1745017901107010112

[186] Bonnín, C. D. M., Torrent, C., Arango, C., Amann, B. L., Sole, B., Gonzalez-Pinto, A., ... & Martinez-Aran, A. (2016). Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *The British Journal of Psychiatry*, *208*(1), 87-93. https://doi:10.1192/bjp.bp.114.162123

[187] Eisner, L., Eddie, D., Harley, R., Jacobo, M., Nierenberg, A. A., & Deckersbach, T. (2017). Dialectical behavior therapy group skills training for bipolar disorder. *Behavior therapy*, *48*(4), 557-566. https://doi.org/10.1016/j.beth.2016.12.006

[188] Van Dijk, S., Jeffrey, J., & Katz, M. R. (2013). A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. *Journal of affective disorders*, *145*(3), 386-393. https://doi:10.1016/j.jad.2012.05.054

[189] Goldstein, T. R., Fersch-Podrat, R. K., Rivera, M., Axelson, D. A., Merranko, J., Yu, H., ... & Birmaher, B. (2015). Dialectical behavior therapy for adolescents with bipolar disorder: results from a pilot randomized trial. *Journal of child and adolescent psychopharmacology*, *25*(2), 140-149.https://doi.org/10.1089/cap.2013.0145

[190] Leichsenring, F., Steinert, C., & Ioannidis, J. P. (2019). Toward a paradigm shift in treatment and research of mental disorders. *Psychological medicine*, *49*(13), 2111-2117. https://doi.org/10.1017/S0033291719002265