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Neurocognição na Esquizofrenia e Perturbação Bipolar

Neurocognition in Schizophrenia and Bipolar Disorder

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I. Index:

II. Abbreviations

SCZ – Schizophrenia

BPD – Bipolar Disorder

WCST – Wisconsin Card Sorting Test

MCCB – MATRICS Consensus Cognitive Battery

ICD-10 – International Classification of Diseases, 10th edition

DSM IV-TR – Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision

WAIS-III – Wechsler Adult Intelligence Scale – 3rd edition

WMS-III – Wechsler Memory Scale

LM I – Logical Memory Test I

III. *Abstract:*

Schizophrenia (SCZ) and bipolar disorder (BPD) are severe mental disorders whose distinction, namely in early phases, might be challenging to clinicians. While it is true that these conditions share some similarities and overlap in symptoms, treatment, genetic predisposition, and outcome, some dimensions of the disease have not been thoroughly studied, namely in Portuguese patients.

Neurocognition is an area worth evaluating, given its repercussions on patients' functioning and quality of life. With this study, we set out to analyze and compare neurocognitive performance in patients suffering from SCZ and BPD and compared the results with healthy controls. To achieve this, we gathered information from 210 Portuguese participants: 70 were diagnosed with BPD, 70 had SCZ, and 70 were healthy individuals. Based on available gold-standard neurocognitive tests and data derived from previous studies of our group, we decided to evaluate four major neurocognitive areas: thought velocity, memory and verbal fluency, visuospatial capacity, and executive function. Our results show a statistically significant decline in neurocognitive function when comparing clinical and control groups, though less evident when comparing BPD with SCZ.

Although comparisons can be made because there is a general decline in cognitive function in both disorders, our study has revealed significant differences between these diseases. When looking at cognitive dimensions, patients diagnosed with SCZ, showed more severe impairments in tests like Stroop – Color test, and the Wisconsin Card Sorting Test (WCST) total errors, when compared to BPD. Furthermore, some cognitive tasks had greater specificity and sensitivity in distinguishing between the clinical and control groups.

This study demonstrated that, in line with international data, there is a decline in neurocognitive function in Portuguese individuals with BPD or SCZ, with consistently worse results in people facing SCZ.

IV. *Resumo:*

A esquizofrenia (SCZ) e a perturbação bipolar (BPD) são graves transtornos mentais cuja distinção pode ser desafiadora, especialmente nos estádios iniciais. Embora seja verdade que estas patologias partilham algumas semelhanças, como sobreposição de sintomas, tratamento,

predisposição genética e “outcomes”, algumas dimensões da doença ainda não foram completamente estudadas, especialmente em doentes portugueses.

A neurocognição é uma área que vale a pena avaliar, dada as suas repercussões no funcionamento e na qualidade de vida dos doentes. Com este estudo, propusemo-nos a analisar e comparar o desempenho neurocognitivo em doentes com SCZ e BPD, comparando os resultados com controlos saudáveis. Para isso, reunimos informações de 210 participantes portugueses: 70 foram diagnosticados com BPD, 70 tinham SCZ e 70 eram indivíduos saudáveis. Com base em testes neurocognitivos “gold standard” e dados derivados de estudos anteriores do mesmo grupo, decidimos avaliar quatro áreas neurocognitivas principais: velocidade de pensamento, memória e fluência verbal, capacidade visual-espacial e função executiva. Os resultados mostram um declínio estatisticamente significativo na função neurocognitiva quando comparados os grupos clínicos com os controlos, embora menos evidente ao comparar os doentes com BPD com os que sofrem com SCZ.

Embora haja um declínio geral na função cognitiva em ambos os transtornos, o nosso estudo revelou diferenças significativas entre as patologias. Ao analisar as dimensões cognitivas, os doentes diagnosticados com SCZ apresentaram prejuízos mais graves em testes como o *“Stroop - Cores”* e o *“número total de erros do WCST”*, em comparação com o BPD. Além disso, algumas tarefas cognitivas apresentaram maior especificidade e sensibilidade na distinção entre os grupos clínicos e controlo.

Este estudo demonstrou que, em linha com os dados internacionais, há um declínio na função neurocognitiva em indivíduos portugueses com BPD ou SCZ, com resultados consistentemente piores em pessoas que sofrem de SCZ.

V. Keywords:

Schizophrenia, Bipolar disorder, Cognition Disorders

VI. Palvras-Chave:

Esquizofrenia, Transtorno Bipolar, Cognição

VII. ***Introduction:***

In Eugene Bleuler's seminal works on schizophrenia, more than a century ago, it was clear that he had a perceptive understanding of cognitive impairment as a core part of this psychotic disorder; that was consubstantiated in the definition of his fundamental symptoms—substantially cognitive in their essence yet distinguished from what was observed in organic dementias[1,2]. Cognitive dysfunction has also been implicated as a key contributor to functioning in bipolar disorder patients, and while several common genetic variants were identified that confer risk to both SCZ and BPD, with current evidence favouring a differentiation between SCZ and BPD that is more dimensional than categorical.[3,4]

Neurocognitive deterioration in SCZ and BPD was initially a disregarded subject in traditional scientific studies of both diseases; however, in recent years, this once-ignored feature has come to light due to its great impact on quality of life and functioning. In SCZ many studies have made a link between the functional disabilities of these patients and their cognitive impairment.[5] Even though many papers and studies have been published over recent years, there are still many problematic hypotheses and uncertainties about the meaning and origins of the cognitive problems associated with schizophrenia.[6]

When addressing BPD, cognitive function studies evidenced significant impairment, with moderate to large effect sizes, in all tasks of executive and attention functions.[7]We know that some neurocognitive markers such as processing speed, visual memory, and fluency are clearly altered in BPD as a whole. Furthermore, studies show that when looking at genetic susceptibility for the disease, areas like response inhibition, executive function, verbal memory and sustained attention deficits are common features for BDP patients from small to large effect groups. However, when looking at the vast majority of studies, verbal memory, executive function and attention deficits are without a doubt the most reported cognitive alterations in BDP patients.[8]

A recent focus of attention has been the comparison between SCZ and BPD in terms of biomarkers, namely cognitive performance. When looking at the available data it becomes clear that patients with SCZ have a steeper decline in their cognitive function when compared with patients with BPD. A recent study showed that when looking at performances in an array of neuropsychological tests, SCZ performed relatively worse than BPD.[9] Equally, another paper that analysed executive functioning, verbal memory, visual memory, procedural learning, visuoconstructive ability, and language functions between the two diseases, saw has expected,

a greater generalised cognitive impairment SCZ.[10] However, its sample size was too small and the tests used, where too limited, to make a clear conclusion. To overcome this limitation, we looked at a meta-analytic study that gathered data from twelve different studies and 9,518 patients, clearly showing that more pronounced cognitive impairment was found in SCZ compared to BPD, with worst performances in all 7 components - speed of processing, attention, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition - of the MATRICS Consensus Cognitive Battery (MCCB).[11]

While results have somehow varied in different comparative studies, and even though recent efforts have been made to study neurocognition in patients who suffer from SCZ and BPD, to our knowledge no study has been done in Portugal to compare neurocognitive dysfunction in these clinical populations. With this study, our hypothesis was to demonstrate that Portuguese patients that suffer from SCZ and BPD also have a decrease in their neurocognitive function and that, out of the two, schizophrenic patients had the steepest loss of function.

Based on gold-standard neurocognitive tests and available data, we decided to test four major neurocognitive areas: Thought velocity (Stroop test and Trail Making Test); Memory and verbal fluency (using the “Wechsler Adult Intelligence Scale – III” and “Wechsler Memory Scale” for memory function and “Rey’s Complex figure” to test for verbal fluency); Visual-special capacity (Rey’s complex figure); Executive function (Trail Making Test, Stroop test, and Wisconsin Card Sorting Test). We considered these four major areas and respective subsets to be well-rounded enough to include a range of cognitive evaluations, feasible in clinical routine.

This study aimed at evaluating neurocognitive dysfunction in patients that suffer from SCZ or BPD. We compared these two groups against each other and a control group, made up of healthy individuals, being our hypothesis that individuals with SCZ suffer a steeper decline in cognitive function.

VIII. Material and Methods*:*

1. *Study design and Participant Selection:*

Clinical and neuropsychological data was obtained from two research projects that contributed to a total of 70 patients suffering from SCZ, 70 from BPD and 70 healthy individuals.

A first subsample of 60 individuals (20 SCZ, 20 BPD and 20 healthy controls) originated from the research project *"Cognição Social na Doença Bipolar e na Esquizofrenia: Caracterização Fenotípica e Base Neural".* For this study, inclusion criteria were the following: (1) meeting diagnostic criteria in the International Classification of Diseases – 10th Edition (ICD-10); (2) Ages between 18 and 54 years; (3) capacity of providing informed consent; (4) right-handedness; (5) being clinically stable in the twelve weeks prior to the evaluation.[9]

Exclusion criteria were the following: (1) relevant medical or neurological comorbidity or disease; (2) Alcohol or drug dependency; (3) contraindication to doing magnetic resonance.[9]

A second subsample of 150 participants (50 SCZ, 50 BPD and 50 healthy controls) was derived from the project *"Avaliação Neuropsicológica na Perturbação bipolar: Neurocognição, cognição social, funcionamento em doentes bipolares eutímicos"*. In this research study, inclusion criteria were the following: (1) diagnosis as per the criteria for diagnosis detailed in DSM IV-TR during a euthymic state; (2) patients who suffered from bipolar disorder as per the criteria for diagnosis detailed in DSM IV-TR, being clinically stabilized in the 8 weeks prior to the evaluation.[12]

Exclusion criteria used for the participation in this study were: (1) Medically or clinically relevant disease; (2) Head trauma with loss of conscience superior to 1h; (3) History of abuse or dependency of alcohol in the past year.[12]

The control group (N=70) was made up of healthy patients without prior personal history of psychiatric disorders or a family history of mood or psychotic disorders. Groups were paired for genre, age, and literacy.

2. *Data Collection:*

We evaluated neurocognition in these patients using an array of tests that we deemed to be the best after a revision of the available literature. These tests fit into 4 major domains:

Processing velocity

- Trail Making Test A
- Stroop word and colour test

Memory and verbal fluency

- Wechsler Memory Scale
- Rey–Osterrieth complex figure
- Verbal Fluency

Visuospatial capacities

- Rey–Osterrieth complex figure (Copy)

Executive functioning

- Wisconsin Card Sorting Test
- Trail Making Test B
- Stroop Colour Word Association Test
- Vocabulary test of the Wechsler Adult Intelligence Scale

Followingly, we will revise these neurocognitive tests.

a. Trail Making Test A & B:

This test is composed by two parts, A and B. It tests attention, mental flexibility and looks for visual and motor function. Trail making test A evaluated the time needed, in seconds, to connect randomly distributed numbers, from 1 to 25 in increasing order. Trail making Test B measures, in seconds, the time needed to connect numbers and letters in alphabetical and increasing order, in an alternate manner. So, the patient must connect 1 to A, A to 2, 2 to B, B to 3 and so on. Both time (in seconds) and errors are noted.[13]

b. Stroop colour and word association test:

This test is made up of three pages, that contain each 100 elements distributed in 5 columns of 20 elements each. The first page is made up of three colours (red, green, and blue) printed in

black and ordered randomly. The second page is made up of 100 elements, in groups of 4, printed in red, green, and blue. The same print colour is not used twice in the same column and the colour sequence obeys the same order has the first page. In the third page the word on the first page is shown in the colours of the second page, given that the colour of the print is never the same has the word written. For each of the phases of the test (pages) the points given are based on the number of elements done in 45 seconds. The main scores in the Stroop Test are the following:[14]

- Stroop Word: number of words read in 45 seconds in the first page.
- Stroop Colour: number of elements correctly mentioned in the second page (in 45 seconds)
- Stroop Colour and Word: number of elements correctly mentioned in 45 seconds (third page)

Errors are not accounted for but produce a lower score given that the patient needs to repeat the failed element and so time is lost.

c. Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III):

We used the WAIS-III-digit span (forward and backward). This test is composed of two parts which should be administered independently. In the first test (forward), the patient should repeat the numbers he ears form the examiner in the same order they were presented. In the second part of the test (backward), the patient should repeat the sequence in inverse order. Each item has a score of 0,1 or 2 points, with the total being the sum of the score in the first part of the test plus the second part of the test.[12]

d. Rey–Osterrieth complex figure:

This test has the objective of measuring visual memory and perception. Rey's complex figure consists of three different parts. In the first place (copy) the patients see the figure and copy's it to a black sheet of paper. Both the visual stimulus and the paper are removed after the first phase is complete. After this first part of the test, the examiner does an unrelated verbal task with the patient for three minutes and then starts the second part of the test. The immediate recall trial requires the patient to draw the figure drawn before, from memory. 20 to 30 minutes

after the immediate recall trial, the subject does an exercise in which we test delayed recall, in which the subject draws the figure for the last time. The same scoring criteria is applied to all three trials. Each of the 18 scoring units might have a value of 0,1 or 2 depending on the accuracy of the drawing. For example, a score of 2 means that scoring unit is accurately drawn and correctly placed and a score of 0 means that the unit is inaccurately drawn and incorrectly placed or omitted.[15]

e. Verbal Fluency:

This test allows us to evaluate the patient's ability to generate words according to the letter given. For each letter there is a trial that lasts for 1 minute. For example, if the letter given is a "P" the patient has one minute to come up with the greatest number of words he can starting with the letter "P".[12]

f. Wechsler Memory Scale (WMS-III) - Logical memory test (I):

The logical memory WMS-III subtest is a reliable measure of verbal episodic memory.[16] In this test, the subject listens to two different stories read by the examiner, and immediately after it is asked to recall the stories from memory. The score is based on the precision of the recalled story and the capacity to recall the theme (thematic units).

g. Wechsler Memory Scale (WMS-III) - Logical memory test (II):

This test is made up of two parts (recall and recognition). In the recall part the subject must tell stories A and B from the logical memory test I (LM I) from memory. In the recognition part of the test fifteen yes/no recognition memory questions are then asked about each story and the recognition memory scores are recorded.[17]

h. Wisconsin Card Sorting Test (WCST-64):

This test is used to measure executive function, analysing the capacity of the patient to solve problems and is highly correlated to frontal lobe function. In this test each card measures 7x7 cm and there are various geometric shapes in different colours and numbers. The test requires

the subject to organize the set of cards in accordance with the rules and limited feedback form the examiner. The rules used for classification are changed every 10 cards. During this trial, patients tend to make errors and scores are usually based upon them. Errors can be divided into different types:[18]

- Total number of errors: the sum of the preservation and non-preservation errors
- Preservation answers
- Preservation errors: where the patient keeps applying the old rule
- Correct answers
- Total categories
- Number of trials to complete the first category
- Non-preservation errors: random errors made during the test.
- Conceptional answers
- Failures maintaining attitude

i. Wechsler Adult Intelligence Scale (WAIS-III) - Vocabulary Test:

In this test the patient should define the words read to him by the examiner while simultaneously being given words printed on a card. Sometimes it is difficult to interpret if the subject knows the definition of the word or not. In this case the examiner is allowed to ask questions like “please explain in more detail“. The answers are scored from 2 to 0, by comparing them to correction criterion and the answers on *WAIS-III manual.*[12]

3. Data Analysis:

a. Statistical Methodology:

The sample characterization was done through absolute and relative frequencies, when the variables were qualitative, and through mean (standard deviation) and median [1st and 3rd quartiles] in the case of quantitative variables. In a first approach, differences and associations were explored between sociodemographic variables and scores obtained in different dimensions of various scales applied using Fisher's exact test (qualitative variables) and the Kruskal-Wallis test, with multiple comparisons through the Mann-Whitney test adjusted with the

Bonferroni correction (quantitative variables), since their distribution had large deviations from normality, verified by the Shapiro-Wilk test.

Subsequently, all variables that presented statistical significance and had been measured simultaneously in the groups of BPD or SCZ and in the controls, were inserted into a logistic regression model in an attempt to classify and identify predictors of one of the two diagnoses relative to the controls, but also to distinguish the two diagnoses from each other. The forward stepwise method was used in the logistic regression to avoid multicollinearity, since all scale dimensions were considered. The accuracy of classification given by the logistic regression models was evaluated using the area under the ROC curve, and sensitivity, specificity, positive and negative predictive values, and Cohen's kappa coefficient of agreement were also determined.

The analysis was performed in SPSS version 27 and evaluated at a significance level of 5%.

IX. Results:

1. Characterization of the sample and comparison

The sample was made up of 210 individuals, evenly distributed between the studied groups (bipolar, schizophrenia and controls). The subjects were mainly male, both globally and individually within the groups. Each group was constituted of 39 male individuals (55.71%) and 31 females (44.29%), totalling 117 men and 93 women in the sample.

The median age was 36.24 years (DP 10.84), with half the participants with ages comprised between 18 and 34 and half years, and the rest with ages going up to 66 years old. Regarding other characteristics including social, demographic, and previous history, there doesn’t seem to be any difference or statistically significant association between literacy, duration of the disease, number of hospital admissions, and antipsychotic medication, between clinical groups.

Table I – Sample characterization and comparison between groups

		n	min - max	mean (dp)	median [Q1; Q3]	p
Age	Total	210	18 - 66	36,24 (10,84)	34,5 [27; 43,25]	0,893
	Control	70	20 - 66	36,21 (11,53)	34 [25; 44]	
	Bipolar	70	19 - 65	36,13 (11,33)	35 [27; 42,5]	
	Schizophrenia	70	18 - 58	36,37 (9,71)	35 [29; 43]	
Literacy (years)	Total	210	4 - 20	11,79 (4,32)	34,5 [27; 43,25]	0,413
	Control	70	4 - 20	12,07 (4,83)	12 [9; 17]	
	Bipolar	70	4 - 19	11,87 (4,2)	12 [9; 16]	
	Schizophrenia	70	4 - 18	11,41 (3,92)	12 [9; 15]	
Duration of disease (anos)	Total	130	1 - 37	9,67 (8,4)	12 [9; 16]	0,797
	Bipolar	69	1 - 37	9,72 (8,47)	7 [3; 14,5]	
	Schizophrenia	61	1 - 32	9,61 (8,4)	8 [2; 14]	
Hospitalizations (nº)	Total	131	0 - 11	2,06 (2,12)	7,5 [3; 14]	0,722
	Bipolar	69	0 - 11	2,04 (2,25)	1 [1; 3]	
	Schizophrenia	62	0 - 8	2,08 (1,99)	2 [1; 3]	
0 hospitalizations, n (%)	Total	27 (12,86%)				0,861
	Bipolar	14 (20,00%)				
	Schizophrenia	13 (18,57%)				
1 hospitalization, n (%)	Total	39 (18,57%)				
	Bipolar	22 (31,43%)				
	Schizophrenia	17 (24,29%)				
2 hospitalizations, n (%)	Total	28 (13,33%)				
	Bipolar	15 (21,43%)				
	Schizophrenia	13 (18,57%)				
3 or + hospitalizations, n (%)	Total	37 (17,62%)				
	Bipolar	18 (25,71%)				
	Schizophrenia	19 (27,14%)				
History of psychotic symptoms, n (%)	Total	106 (50,48%)				< 0,001
	Bipolar	46 (65,71%)				
	Schizophrenia	60 (85,71%)				
Antipsychotics, n (%)	Total	68 (32,38%)				0,277
	Bipolar	35 (50,00%)				
	Schizophrenia	33 (47,14%)				

2.Characterization of the tests in each group and comparison.

When comparing our three groups – SCZ, BPD and controls – there was a clear statistically significant difference in most tests used, a difference noticeable when comparing clinical groups with controls, but less evident when comparing SCZ and BPD groups.

Table II – Characterization of the tests in each group and their comparison

		n	min - max	mean (dp)	median [Q1; Q3]	p
TMT-A time	Control	70	11 - 54	26.1 (10.12)	23 [18.5; 33]	< 0.001
	Bipolar[C]	70	10 - 98	32.91 (16.91)	29 [20; 40]	
	Schizophrenia[C]	70	14 - 139	40.37 (24.34)	32.5 [23.75; 50]	
Stroop - Word	Control	70	62 - 130	92.36 (13.18)	94 [83; 100.5]	< 0.001
	Bipolar[C]	70	42 - 118	83.56 (15.09)	84 [76.5; 93]	
	Schizophrenia[C]	70	28 - 114	79.63 (16.08)	78.5 [69; 93.25]	
Stroop - Color	Control	70	37 - 93	68.31 (11.36)	67 [62; 75]	< 0.001
	Bipolar[C]	70	32 - 92	60.53 (12.12)	60 [53; 69.5]	
	Schizophrenia[C]	70	34 - 91	56.76 (12.46)	56.5 [47; 66]	
Digit Span - forward (WAIS-III)	Control	70	6 - 14	8.9 (2.23)	9 [6.5; 10]	0.002
	Bipolar[C]	70	3 - 12	7.77 (2.09)	8 [6; 9]	
	Schizophrenia[C]	70	5 - 12	7.63 (1.71)	8 [6; 9]	
Digit Span - backward (WAIS-III)	Control	70	2 - 13	6.93 (2.91)	6 [5; 9]	< 0.001
	Bipolar[C]	70	2 - 11	5.51 (2.35)	5 [4; 7]	
	Schizophrenia[C]	70	1 - 8	5.01 (1.61)	5 [4; 6]	
Digit Span - total (WAIS-III)	Control	70	8 - 25	15.81 (4.47)	15 [13; 19]	< 0.001
	Bipolar[C]	70	6 - 21	13.29 (4.05)	12 [10; 16.5]	
	Schizophrenia[C]	70	7 - 19	12.64 (2.85)	13 [10; 14.25]	
Phonemic Verbal Fluency	Control	70	15 - 70	36.09 (13.29)	35 [25; 43]	< 0.001
	Bipolar[C]	70	7 - 51	31.33 (10.02)	32 [23.5; 39]	
	Schizophrenia[C]	70	7 - 51	26.96 (10.28)	25 [19.5; 37]	
Logical Memory I - Recall (WMS-III)	Control	70	17 - 66	44.06 (12.19)	48 [35.5; 51.5]	< 0.001
	Bipolar[C]	70	4 - 60	34.96 (11.43)	37 [28; 43.5]	
	Schizophrenia[C]	70	7 - 60	31.14 (11.92)	31 [24; 39]	
Logical Memory I - Thematic Units (WMS-III)	Control	70	7 - 23	17.61 (3.56)	19 [15.5; 20]	< 0.001
	Bipolar[C]	70	4 - 22	15 (3.86)	16 [13; 18]	
	Schizophrenia[C]	70	4 - 22	13.66 (4.07)	14 [11; 17]	
Logical Memory I - Learning (WMS-III)-	Control	70	-2 - 10	3.84 (2.77)	5 [2; 5.5]	0.524
	Bipolar	70	-3 - 11	4.37 (2.95)	4 [2; 6.5]	
	Schizophrenia	70	-6 - 11	3.7 (3.28)	3 [1; 6]	
Logical Memory II - Recall (WMS-III)	Control[B,E]	70	10 - 44	28.5 (8.28)	30 [24.5; 34.5]	< 0.001
	Bipolar[C,E]	70	3 - 41	21.64 (8.9)	22 [17; 28]	
	Schizophrenia[C,B]	70	3 - 39	17.97 (8.48)	17 [12; 21.5]	
Logical Memory II - Thematic Units (WMS-III)	Control[B,E]	70	5 - 15	11.66 (2.39)	12 [10; 14]	< 0.001
	Bipolar[C,E]	70	1 - 15	9.74 (3.15)	10 [8; 12]	
	Schizophrenia[C,B]	70	1 - 14	8.37 (3.09)	9 [6; 10.25]	
Logical Memory II - Recognition (WMS-III)	Control	70	18 - 30	25.89 (2.66)	27 [25; 27]	< 0.001
	Bipolar[C]	70	13 - 30	24.31 (3.76)	25 [22.5; 27]	
	Schizophrenia[C]	70	15 - 30	23.63 (3.59)	23.5 [21; 26.25]	

Rey Complex Figure - Immediate Recall	Control	70	2.5 - 31.5	21.99 (6.28)	23 [18; 26.25]	< 0.001
	Bipolar	70	2 - 31	17.09 (6.64)	17.5 [12.75; 22]	
	Schizophrenia	70	0.5 - 26	14.57 (6.05)	14.75 [10; 19.63]	
Rey Complex Figure - Delayed Recall	Control	70	7.5 - 31.5	22.56 (5.68)	24 [18.75; 27]	< 0.001
	Bipolar[C]	70	0.5 - 32	16.6 (6.85)	17 [12; 21]	
	Schizophrenia[C]	70	4.5 - 27.5	14.62 (6.03)	14.25 [9.38; 19.13]	
Rey Complex Figure - Copy	Control	70	21.5 - 36	33.76 (2.63)	35 [33; 35.5]	< 0.001
	Bipolar[C]	70	16 - 36	30.92 (4.83)	32 [29.5; 34]	
	Schizophrenia[C]	70	13.5 - 36	31.42 (5.03)	33 [30; 35]	
TMT-B time	Control	70	19 - 141	54.47 (26.59)	47 [36; 70]	< 0.001
	Bipolar[C]	69	24 - 205	83.25 (39.56)	81 [46.5; 112]	
	Schizophrenia[C]	70	31 - 386	107.89 (73.58)	85 [58.75; 122.25]	
Stroop - Word-Color	Control	70	24 - 60	42.23 (9.27)	41 [37; 50.5]	< 0.001
	Bipolar[C]	70	11 - 66	36.13 (10.79)	35 [29; 43]	
	Schizophrenia[C]	70	11 - 60	32.7 (10.8)	30.5 [24; 40]	
WSCT - Total correct	Control[B,E]	70	41 - 62	53.77 (3.91)	54 [53; 56]	< 0.001
	Bipolar[C,E]	70	15 - 60	46.99 (9.77)	49 [43; 54]	
	Schizophrenia[C,B]	70	14 - 57	40.19 (12.09)	42 [31; 51]	
WCST - Total errors	Control[B,E]	70	5 - 23	10.36 (3.8)	10 [8; 11.5]	< 0.001
	Bipolar[C,E]	70	4 - 49	16.99 (9.79)	15 [10; 21]	
	Schizophrenia[C,B]	70	7 - 50	23.81 (12.09)	22 [13; 33]	
WCST - Perseverative responses	Control	69	4 - 15	6.71 (2.72)	6 [5; 8]	< 0.001
	Bipolar[C]	70	2 - 57	11.56 (9.82)	8 [5; 14.5]	
	Schizophrenia[C]	70	3 - 62	16.64 (15.2)	12.5 [6; 18.5]	
WCST - Perseverative errors	Control	70	4 - 12	6.31 (2.16)	6 [5; 8]	< 0.001
	Bipolar[C]	70	2 - 42	10.04 (7.46)	7 [5; 12]	
	Schizophrenia[C]	70	3 - 46	14.01 (11.25)	11 [6; 17.25]	
WCST - Non-perseverative errors	Control[B,E]	70	1 - 15	4.04 (2.65)	3 [2; 6]	< 0.001
	Bipolar[C,E]	70	1 - 22	6.91 (4.27)	6 [4; 8]	
	Schizophrenia[C,B]	70	2 - 32	9.8 (6.08)	9 [5; 13]	
WCST - Completed categories	Control	70	2 - 58	16.94 (20.09)	5 [5; 32.5]	< 0.001
	Bipolar[C]	70	0 - 58	16.07 (21.17)	4 [3; 40.5]	
	Schizophrenia[C]	70	0 - 54	12.89 (18.13)	3 [2; 22.25]	
WCST - Trials to complete first category	Control	70	1 - 16	9.43 (3.61)	11 [5; 11]	0.145
	Bipolar	70	2 - 65	13.71 (13.78)	11 [5; 12]	
	Schizophrenia	70	0 - 65	19.63 (21.25)	11 [5; 20.25]	
WCST - Failure to maintain set	Control	70	0 - 13	3.47 (5.01)	0 [0; 10]	0.328
	Bipolar	70	0 - 25	4.04 (5.79)	1 [0; 11]	
	Schizophrenia	70	0 - 64	4.66 (9.32)	0 [0; 10.25]	
WCST - Conceptual level responses	Control	70	0 - 57	36.79 (23.5)	50 [1; 54]	< 0.001
	Bipolar[C]	70	0 - 56	27.7 (20.75)	34 [1; 46]	
	Schizophrenia[C]	70	0 - 54	21.34 (19.2)	20 [1; 39]	
Vocabulary Test (WAIS-III)	Control	70	9 - 65	40.51 (13.64)	41 [33.5; 50.5]	0.112
	Bipolar	70	14 - 59	38.81 (11.86)	43 [32; 48]	
	Schizophrenia	70	3 - 58	36.09 (12.9)	38 [24; 46.25]	

3. Neurocognition:

After analysing results, it becomes clear that, globally, when compared to the healthy population, patients battling with SCZ have significantly worst results in various neurocognitive tests. When analysing BPD, the same can be said, given patients had lower performance when compared to healthy controls.

When comparing both diseases, our hypothesis seems to be proven true. Globally there is a steeper decline in the cognition of SCZ when compared to BPD. This difference is not significant in every test but patients suffering from SCZ have worst performance in available neurocognitive dimensions.

a. Processing velocity:

Trail Making Test A:

As can be seen in table II, when looking at the results for the *Trail Making Test A*, both SCZ and BPD show clearly statistically significant worst results when compared to the healthy population ($p<0.001$). Out of the three groups, SCZ performed the worst, having an average of 40.37 and a median of 23, which compares with an average of 32.91 and a median of 29 in BPD and 26.1 and 23 in controls. These results go hand in hand with the hypothesis that psychomotor speed suffers a deep decline in patients with SCZ.[19]

Stroop Colour and Word:

In the Stroop colour and word tests, again there were statistically significant worst results in SCZ and BDP ($p<0.001$), comparatively with controls, both in the reading words and in the naming colours part. Out of the three groups, SCZ showed a more pronounced Stroop effect, which is in accordance with our main hypothesis.

b. Memory and verbal fluency:

Wechsler Adult Intelligence Scale:

We can divide this test into two parts: digit span (forward, backwward and total) and logical memory. Regarding digit memory, we can see both disorders present a statistically significant difference ($p<0.001$), when compared to the control group, but not when compared against each

other. This difference can be seen when the total results are analysed, but also when the tests are looked at individually.

Analysing the tests used to evaluate logical memory, when looking at logical memory I – "recall" and "thematic units" both disorders present significantly ($p<0.001$) lower results when compared to controls. The same cannot be said when we analyse the results for logical memory I – "learning", in which no significant difference between patients and controls was found ($p=0.524$). Meaning, that in this test, there is no statistically relevant difference between SCZ and BPD in comparison to controls.

In logical memory II – "recall" and "thematic units" however, we find that there are significantly worst performances when comparing patients with controls ($p<0.001$), but as well as, when we compare clinical groups against each other ($p<0.001$). In the final test, logical memory II – "recognition", there is a statically relevant difference between the results obtained in the control group and the ones obtained in the two other groups, having both performed significantly worst that the control.

Verbal Fluency:

In verbal fluency tests both clinical groups scored lower than the control group. With a value ($p<0.001$), this difference was significant, with individuals with SCZ scoring lower than the other two groups.

Rey's complex figure:

Looking at recall evaluated by Rey's complex figure, we found that in immediate recall, no statistically significant difference was present between three groups. However, when we analysed delayed recall, we notice there were lower performance scores in SCZ and BPD groups when compared with healthy individuals.

c. Visuospatial capacities:

Rey's complex figure:

In Rey's complex figure - copy, which evaluates visuospacial capabilities, we see there were significantly worst results ($p<0.01$) in both disorders when compared to the control group, with the BPD group performing marginally worse than the SCZ group.

d. Executive function:

Wisconsin Card Sorting Test:

As a whole, individuals with SCZ scored significantly worse than controls and the BPD group. In the WCST – total answers, total errors and non-preservation errors, there was a significate difference between clinical groups and controls, but also when we compared them against each other, with the SCZ group scoring significantly worse. In the WCST – preserved answers, errors, complete categories and conceptional answers there was statistically significant difference found when comparing the diseased groups against the control group.

In the WCST – Number of trials to complete the first category and failure to maintain attitude, there was no significative difference found when comparing the three groups against each other, meaning that clinical groups did not score much worse than the control group.

Trail Making Test B:

Analysing the results for the Trail Making Test B, we can see that we can distinguish between the clinical groups and the control group given that their result where significantly worse ($p<0.01$) than the ones for the control group.

Stroop colour and word association tests:

Stroop colour and word test manages to differentiate between the control group and the clinical groups ($p<0.01$), but fails to differentiate between the two clinical groups. Once again, we can see that the patients with SCZ scored worst out of the three, but not significantly when compared to the BPD group.

e. Pre-morbid Intelligence:

Wechsler Adult Intelligence Scale (WAIS-III)- Vocabulary Test:

From the results presented below we can see that we can't differentiate between clinical groups and the control group ($p=0.112$), meaning intelligence was comparable between groups as per this specific test, suggesting that results obtained in previous neurocognitive tests were

significantly different because of the underlying disorders (SCZ or BPD) impact on neurocognition, and not because of their basal IQ being lower.

4. *Overall comparisons:*

After individually analysing neurocognitive tests, we decided to apply logistical regression, hoping this statistical model would allow us to identify cognitive predictors of BPD and SCZ when compared to the control group. All variables were considered but only some managed to discriminate between groups. We applied the odds ratio test to discriminative variables to demonstrate how much higher the chance of disease was relative to controls, and the chance of schizophrenia in relation to the chance of bipolar disease.

a. Results of the logistic regression models and evaluation:

In Table III, one can observe which items from which scales are predictors of either BPD or SCZ in relation to controls, and which ones allow for some accuracy in discriminating individuals with one of those two diagnoses. An individual with BPD typically shows higher values in logical memory I - learning, TMT-B time, WSCST - non-perseverative errors, and in the vocabulary test simultaneously with lower values in the complex figure of Rey - delayed recall, compared to those who do not have either of the two studied diagnoses.

An individual with SCZ is characterized, relative to controls, by lower scores on the thematic units of the logical memory I and logical memory II scales, complex figure of Rey - delayed recall, and WCST - total correct, and higher scores on the recognition of logical memory II, complex categories of the WCST scale, and in the vocabulary test (WAIS III).

Discrimination between the two diagnoses is more difficult than between each of the diagnoses and controls, but variables such as the complex figure of Rey (copy) and WSCT - total correct, seem to increase the chance of a diagnosis in a patient having SCZ, while higher scores on the thematic units of logical memory II seem to increase the chance of the diagnosis leaning towards BPD.

Table III – Results of the logistic regression models and evaluation

OR (IC95%); p	Bipolar vs Control	Schizophrenia vs Control	Schizophrenia vs Bipolar
TMT-A time			
Stroop - Word			
Stroop - Color			
Digit Span - forward (WAIS-III			
Digit Span - backward (WAIS-III)			
Digit Span - total (WAIS-III)			
Phonemic Verbal Fluency			
Logical Memory I - Recall (WMS-III)			
Logical Memory I - Thematic Units (WMS-III)		0,71 (0,51; 0,99); 0,043	
Logical Memory I - Learning (WMS-III)	1,17 (1-; 1,38); 0,053		
Logical Memory II - Recall (WMS-III)			
Logical Memory II - Thematic Units (WMS-III)		0,5 (0,31; 0,83); 0,007	0,86 (0,74; 1-); 0,043
Logical Memory II - Recognition (WMS-III)		1,67 (1,17; 2,37); 0,004	
Rey Complex Figure - Immediate Recall			
Rey Complex Figure - Delayed Recall	0,88 (0,81; 0,95); 0,002	0,75 (0,63; 0,89); 0,001	
Rey Complex Figure - Copy			1,12 (1,03; 1,22); 0,011
TMT-B time	1,03 (1,01; 1,04); 0,007		
Stroop - Word-Color			
WSCT - Total correct		0,74 (0,65; 0,85); < 0,001	
WCST - Total errors			1,06 (1,02; 1,11); 0,003
WCST - Perseverative responses			
WCST - Perseverative errors			
WCST - Non-perseverative errors	1,3 (1,11; 1,51); < 0,001		
WCST - Completed categories		1,05 (1,01; 1,09); 0,021	
WCST - Trials to complete first category			
WCST - Failure to maintain set			
WCST - Conceptual level responses			
Vocabulary Test (WAIS-III)	1,05 (1+; 1,09); 0,035	1,18 (1,08; 1,29); < 0,001	
Sensitivity	82,6% (76,3%; 88,9%); < 0,001	90,0% (85%; 95%); < 0,001	62,9% (54,9%; 70,9%); 0,002
Specificity	84,3% (78,3%; 90,3%); < 0,001	92,9% (88,6%; 97,2%); < 0,001	70% (62,4%; 77,6%); < 0,001
Positive Predictive Value (PPV)	83,8% (77,7%; 89,9%); < 0,001	92,6% (88,3%; 96,9%); < 0,001	67,7% (60%; 75,4%); < 0,001
Negative Predictive Value (NPV)	83,1% (76,9%; 89,3%); < 0,001	90,3% (85,4%; 95,2%); < 0,001	65,3% (57,4%; 73,2%); < 0,001
Concordance (kappa)	0,669 (0,591; 0,747); < 0,001	0,829 (0,767; 0,891); < 0,001	0,329 (0,251; 0,407); < 0,001
Area Under the Curve (AUC)	0,859 (0,795; 0,923); < 0,001	0,968 (0,943; 0,993); < 0,001	0,734 (0,651; 0,818); < 0,001

b. Probability of Bipolar Disorder vs Control

The risk stratification of bipolar disorder allows for a good differentiation between patients and controls with an accuracy of 85.9% (AUC = 0.859, $p < 0.001$), and an expected agreement of classification in the population ranging between 59.1% and 74.7% (k = 0.669, Table III). The sensitivity and specificity of the model are similar (Table III), as well as the predictive values but according to the Figure below, the model seems to differentiate well between cases and controls.

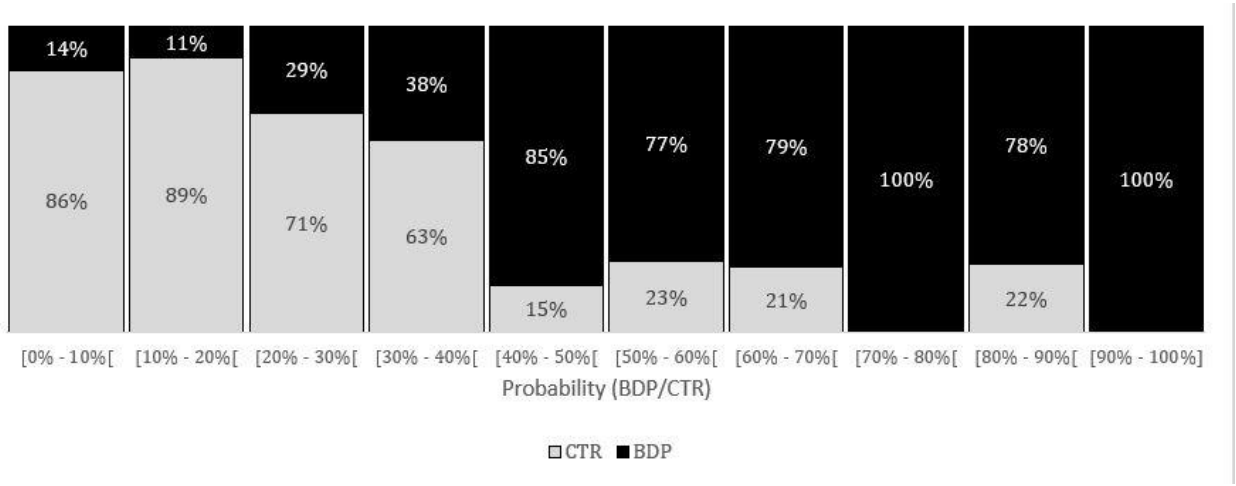

Figure I - Probability of Bipolar Disorder vs Control

c. Probability of Schizophrenia vs Control

The stratification risk of schizophrenia allows for a clear differentiation between patients and controls with an accuracy of 96.8% (AUC = 0.968, $p < 0.001$), and a classification agreement in the population expected to vary between 76.7% and 89.1% (k = 0.828, Table III). The sensitivity and specificity of the model are similar, as are the predictive values, with values above 90% observed and values above 85% expected with 95% confidence (Table III). According to the Figure below, the model appears to differentiate well between cases and controls, correctly identifying individuals with very low risks (below 30%) or very high risk (above 70%) in their entirety.

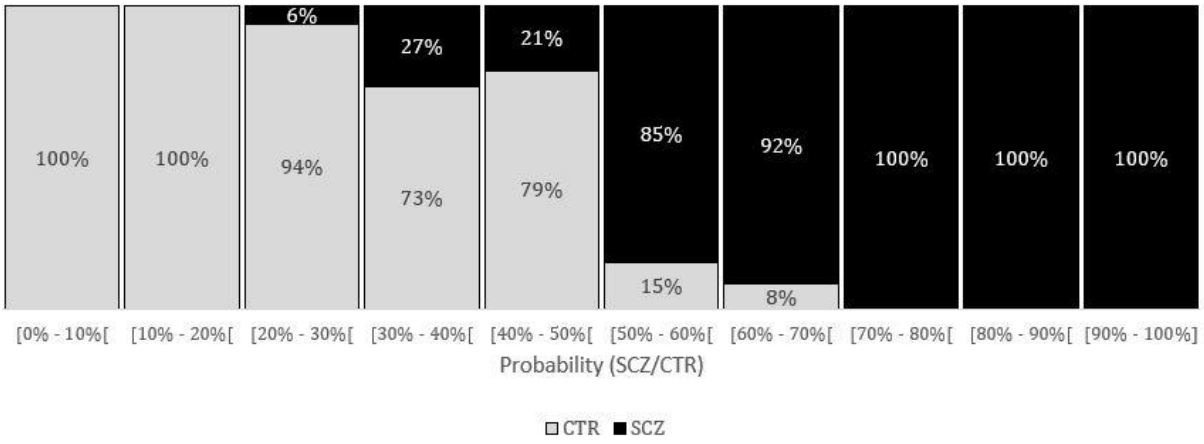

Figure II - Probability of Schizophrenia vs Control

d. Probability of Schizophrenia vs Bipolar Disorder

The discrimination of individuals with SCZ from those with BPD is less powerful than that of individuals with a diagnosis of either of those pathologies from controls (AUC = 0.734, $p < 0.001$), with sensitivity and specificity between 60% and 70%, as well as predictive values. Nevertheless, the accuracy rate observed for individuals with a risk of schizophrenia below 40% is at least 75%, and the accuracy rate for those with a risk of schizophrenia above 80% is 76% (Figure III).

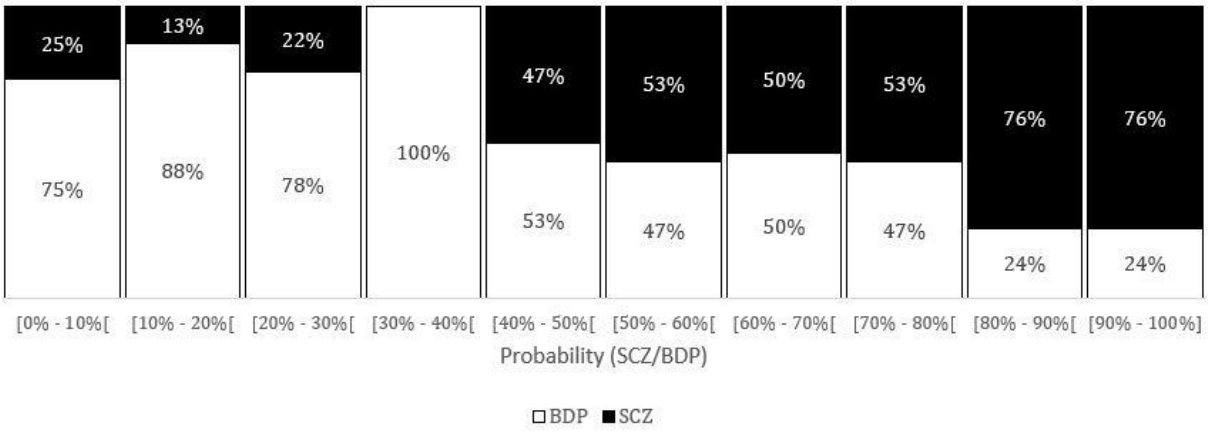

Figure III - Probability of Schizophrenia vs Bipolar Disorder

X. ***Discussion:***

Studies about the neurocognitive handicaps in BPD and SCZ individuals are very scarce in Portugal. No comprehensive study of this magnitude has been performed in Portuguese patients, and the ones that exist don't make the comparison between SCZ and BPD.

In terms of SCZ, studies in Portugal are very limited. Looking at one of the biggest, analysing neurocognition and the effect it has on quality of life, it reported that patients with SCZ had a decline in most analysed areas, with the domain of social relations being one of the most affected. Even though the results presented a medium to high correlation between neurocognitive test scores and quality of life domains, the study only had at its disposal 37 patients and no comparison to a control group was made.[20] When looking at a BPD, a study in Portugal focused on neurocognitive functioning on a larger sample of type I BPD patients. Even though this study analysed 65 patients and compared them to 50 controls, with BPD patients performing significantly worse on neurocognitive tests, especially on verbal memory and executive functions, working status did not correlate significantly with neurocognitive performance.[21]

When looking at the state of the art in the realm of cognition and performance in BPD patients, a recent study analysing 38 articles concluded that neurocognitive function is impaired across most of the domains during all clinical states, including euthymia.[22]The most affected domains are, generally, executive function, verbal and visual memory.[12] The magnitude of the impairment is severe during acute episodes of mania or depression and in a medium range during asymptomatic phases.[23]However, there is no absolute consensus regarding this topic, given some studies argue that BPD patients don't have their cognitive function severely compromised when compared to healthy controls.[9]

In our study, when comparing ***"Bipolar disease vs. Control"*** we can infer the following**:** (a) each unit increase in the test ***"Logical memory I - Learning"*** represents a chance 1.17 times higher ($p = 0.053$ - almost significant) of the patient being bipolar; (b) each unit increase in the test ***"Trail making test B"*** represents a chance 1.03 times higher ($p = 0.002$) of the patient being bipolar; (c) each unit increase in the test ***"WSC – Non-preservative errors"*** represents a chance 1.3 times higher ($p < 0.001$) of the patient being bipolar.

On the other hand, we found that some variables seem to be "protective": each unit increase in the test ***"Rey's Complex Figure – delayed recall"*** represents a 12 % decrease ($p = 0.002$) in the chance of the patient being bipolar.

Regarding SCZ we know that cognitive deficits are synonymous with this diagnosis, nowadays neurocognition decline is a major feature of this disease, with moderate to severe impact.[24] A meta-analytic study that analysed 247 papers that contributed with over 18,000 cases and looked at 5 main domains that included memory functioning, global cognitive function, language, executive function and attention, showed clear deficits across all domains studied[6] proving the standing hypothesis that individuals with SCZ suffer significative deficits in most cognitive domains studied.

Looking at our data and comparing ***"Schizophrenia vs Control",*** we found that: (a) each unit increase in the test ***"Logical memory II – Recognition"*** represents a chance 1.67 times higher ($p = 0.004$) of the individual having SCZ; (b) each unit increase in the test ***"WSC – Complete categories"*** represents a chance 1.05 times higher ($p = 0.021$) of the individual having SCZ.

As seen on the bipolar vs. control analysis we can also note that some variables were "protective": (a) each unit increase in the test "***Logical memory I – Thematic units"*** represents a 29 % decrease ($p = 0.043$) in the chance of having SCZ; (b) each unit increase in the test "***Logical memory II – Thematic units"*** represents a 50 % decrease ($p = 0.007$) in the chance of the individual having SCZ; (c) each unit increase in the test "***Reys Complex Figure – delayed recall"*** represents a 25 % decrease ($p = 0.001$) in the chance of belonging to the SCZ group; (d) each unit increase in the test "***Stroop Word- Colour"*** represents a 26 % decrease ($p < 0.001$) in the chance of having SCZ.

Studies comparing neurocognitive dysfunction in SCZ and BPD generally reported that cognitive decline in BPD patients is limited to verbal functions and, given so, less severe when compared to SCZ, where widespread decline is common on most cognitive domains.[25] Another study that compared both diseases stated that after analysing available data, both diseases carry the risk of neurocognitive regression and that SCZ show more pervasive cognitive deficits, while BPD patients present a milder and more confined impairment.[26]

Further analysing our data, we found the following when comparing ***"Schizophrenia vs Bipolar":*** (a) each unit increase in the test ***"Reys Complex Figure – Copy"*** represents a chance 1.12 times higher ($p = 0.011$ - significative) of the patient having SCZ when compared with the chance of being bipolar; (b) each unit increase in the test ***"WCST – Total Errors"*** represents a chance 1.06 times higher ($p = 0.03$ - significative) of the patient having SCZ when compared with the chance of being bipolar.

With this comparative analysis we found “protective” neurocognitive variables when addressing the chance of SCZ against BPD: (a) each unit increase in the test “***Logical memory II – thematic units”*** represents a 14 % decrease (p = 0.043) in the chance of the patient having SCZ when compared with the chance of having BPD.

Limitations:

The present study contains some limitations that must be considered in the evaluation of the results and presented data. Even though well-standardized tests were used to evaluate neurocognitive domains, it doesn’t necessarily mean that they are the most consensual tests addressing the specificities of SCZ or BPD.Given that our total sample (n=210) was obtained from two different studies - “Cognição Social na Doença Bipolar e na Esquizofrenia: Caracterização Fenotípica e Base Neuronal” (n=60) and “Avaliação Neuropsicológica na Perturbação bipolar: Neurocognição, cognição social, funcionamento em doentes bipolares eutímicos” (n=150) – with slightly different inclusion and exclusion criteria, an argument can be made that patients that participated in this study were not exactly under the same conditions and diagnostic criteria.

XI. *Conclusion:*

Cognitive research into BPD and SCZ has had a significant impact and led to remarkable insight when it comes to qualitatively discriminating two, somehow similar severe mental disorders, with a common massive impact on cognition and functioning. Recent efforts have been made to better characterise these disorders regarding cognitive dimensions, and prospective studies have shown that BPD and SCZ share a lot of similarities when it comes to neurocognitive decline.[26]

The results of our study suggest that despite several similarities, marked differences could be found. Based on available results, we can conclude that:

- patients with BPD and SCZ both show deficits in cognitive function compared to healthy controls.
- there are differences in cognitive function between the two disorders, with patients diagnosed with SCZ showing more severe impairments in some tasks (e.g., Stroop - Color, WCST - total errors).

- some cognitive tasks showed greater sensitivity and specificity in distinguishing between patient groups and healthy controls. For example, the Wisconsin Card Sorting Test and Rey's Complex Figure - delayed recall had good sensitivity and specificity in identifying patients with BPD and SCZ.

Overall, our study suggests that cognitive impairment is a feature of both BPD and SCZ, highlighting the importance of assessing cognitive function in these clinical populations.

We found support for our original hypothesis stating there is cognitive dysfunction in Portuguese patients suffering from SCZ and BPD, and that out of the two conditions, SCZ patients face a steeper decline in their cognition.

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