UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

DISSERTAÇÃO DE MESTRADO

PREDITORES DE HETEROGENEIDADE COGNITIVA NO TRANSTORNO BIPOLAR: UMA ABORDAGEM *MACHINE-LEARNING*

Francisco Diego Rabelo da Ponte

Orientador: Prof. Dr. Maurício Kunz

Porto Alegre

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Dissertação apresentada à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento como requisito parcial para a obtenção do título de Mestre em Psiquiatria e Ciências do Comportamento.

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Porto Alegre, 02 de março de 2018

A Comissão Examinadora, abaixo assinada, aprova a Dissertação elaborada por Francisco Diego Rabelo da Ponte, como requisito parcial para a obtenção do Grau de Mestre em Psiquiatria e Ciências do Comportamento.

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Prof. Dr. Ives Cavalcante Passos

Prof. Dr. Maurício Kunz– Universidade Federal do Rio Grande do Sul – Orientador

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LISTA DE ABREVIATURAS E SIGLAS

ANOVA – Análise de variância

BDNF - *Brain-derived neurotrophic factor*

CART - *Classification and Regression Tree*

CVLT - *California Verbal Learning Test*

DFA - Análise de Função Discriminante

DSM – Manual Estatístico e Diagnóstico de Transtornos Mentais

FAS -Fluência Verbal Fonológica

HAM-D-17- Escala de Avaliação de Depressão de Hamilton

HCA - Análise de Cluster Hierárquica

HCPA - Hospital de Clínicas de Porto Alegre

HVLT-R Hopkins Verbal Learning Test – Revised

MANOVA – Análise multivariada de variância

PROTAHBI - Programa de Transtorno de Humor Bipolar

SCID-4-CV- Entrevista Clínica Estruturada para os Transtornos do DSM-4 – Versão Clínica

SNL - Sequência de Números e Letras

SWCT - Stroop Word Color Test

TB – Transtorno Bipolar

TMT-A - Trail Making Test -A

TMT-B- Trail Making Test-B

YMRS - Young Mania Rating Scale

WAIS-III - Escala de Inteligência Wechsler para Adultos – 3ª Edição

RESUMO

Objetivos: Identificar os preditores de heterogeneidade cognitiva nos sujeitos com Transtorno Bipolar (TB). *Métodos:* Foi recrutado 142 sujeitos com TB em atendimento ambulatorial e 100 voluntários sem transtornos psiquiátricos do Brasil e da Espanha para realizar avaliação neuropsicológica. Foi realizado Análise de *Cluster* Hierárquica e Análise de Função Discriminante para determinar e confirmar os subgrupos cognitivos. Por fim, foi usado o algoritmo *Classification and Regression Tree* (CART) para identificar os preditores dos subgrupos cognitivos anteriormente estabelecidos. *Resultados:* Foi observado a presença de três *clusters* cognitivos: indivíduos cognitivamente intacto (38%), seletivamente prejudicados (38%) e globalmente prejudicados (21%). Os preditores mais importantes foram anos de educação, anos de doença, número de hospitalizações, idade e idade de início. *Conclusão:* Os resultados corroboram com recentes achados sobre a heterogeneidade cognitiva nos sujeitos com TB. Além disso, os presentes achados indicam uma sobreposição entre aspectos neurodesenvolvimentais e história de doença.

Palavras-chave: Transtorno Bipolar, heterogeneidade cognitivo, análise de cluster, árvore de decisão.

ABSTRACT

Objective: We aimed to determine predictors of cognitive heterogeneity in subjects with Bipolar Disorder (BD).

Methods: We recruited 142 outpatients with Bipolar Disorder and 100 unaffected volunteers from Brazil and Spain that underwent a neuropsychological assessment. We performed Hierarchical Cluster Analysis and Discriminant Function Analysis to identify and validate cognitive subgroups, respectively. Then, we used Classification and Regression Tree (CART) algorithm to determine predictors of the cognitive clusters.

Results: We identified three cognitive clusters in BD: intact (38%), selectively impaired (38%), and globally impaired subjects (21%). The most important predictors of cognitive subgroups were years of education, years of disease, the number of hospitalizations, age, and age of onset, respectively.

Conclusion: These results corroborate with recent findings of neuropsychological heterogeneity in Bipolar Disorder. Furthermore, the present findings suggest overlapping between neurodevelopmental and morbid aspects.

Key words: Bipolar Disorder, cognitive heterogeneity, cluster analysis, decision tree.

SUMÁRIO

1. Apresentação

O Transtorno Bipolar (TB) é um transtorno psiquiátrico crônico e grave, cuja prevalência é de aproximadamente 1% da população(1). Além disso, é considerado uma das dez doenças mais incapacitantes no mundo(1). É um transtorno com altas taxas de suicídio. Aproximadamente, 7,8% dos homens e 4,9% das mulheres com TB cometem suicídio(2,3). Seus sintomas são caracterizados pela presença de episódios maníacos ou hipomaníacos e depressivos, intercalados por intervalos eutímicos(4). Os sujeitos acometidos pelo TB apresentam um marcante prejuízo funcional mesmo em períodos assintomáticos. Assim, pacientes com esse transtorno comumente possuem dificuldades no trabalho, em executar as atividades de vida diária, nos relacionamentos interpessoais e em outros domínios psicossociais (5).

Os déficits cognitivos e sintomas subsindrômicos são importantes preditores de prejuízos funcionais (6). Essa população tem 4 a 10 vezes mais disfuncionalidade que a população geral (7,8). As alterações cognitivas presentes no TB são independentes do estado do humor, persistindo mesmo em períodos eutímicos para a maioria dos pacientes. Os principais domínios cognitivos prejudicados são memória verbal, função executiva, velocidade de processamento e atenção sustentada (8).

A presente dissertação consiste em um estudo multicêntrico transversal envolvendo avaliação cognitiva de pacientes com TB e utilizando algoritmos de *machine learning* para analisar os dados. O artigo resultante dessa pesquisa foi submetido no JAMA Psychiatry com o título “Predictors of cognitive heterogeneity in a transcultural sample of individuals with Bipolar Disorder”.

2. Introdução

2.1 Neurodesenvolvimento cognitivo no Transtorno Bipolar

O desenvolvimento cognitivo dos pacientes com TB ocorre de maneira particular ao longo da vida. No período pré-mórdido, a cognição se desenvolve de maneira ascendente similar a de um indivíduo sem histórico de transtorno psiquiátrico. Em alguns casos, esses sujeitos apresentam um desenvolvimento cognitivo acima da média da população infanto-juvenil (9). Entretanto, esse cenário muda a partir do primeiro episódio de humor, modificando a trajetória do desenvolvimento cognitivo. Dessa forma, os déficits na cognição já se tornam visíveis desde esse momento (4). A cada episódio de humor aumenta a severidade do prejuízo cognitivo, tornando-se progressivo e persistente mesmo em fases eutímicas. Além disso, múltiplos episódios aumentam a vulnerabilidade a episódios subsequentes e reduzem a resposta ao tratamento (10,11). Dessa maneira, os pacientes em estágios avançados do TB apresentam severos déficits cognitivos similares aos pacientes com esquizofrenia (12).

Entretanto, um subgrupo de pacientes apresenta um atraso no desenvolvimento cognitivo antes do primeiro episódio de humor, exibindo padrão semelhante aos pacientes com esquizofrenia. Algumas teorias neurodesenvolvimentais afirmam que determinados fatores de risco podem levar a um atípico desenvolvimento cerebral e, consequentemente, uma dificuldade na aquisição de habilidades cognitivas (9). Um recente estudo aponta que possivelmente esse subgrupo de pacientes compartilha genes em comum com a esquizofrenia (13). Outro estudo tem evidenciado que o déficit cognitivo pré-mórbido no TB pode estar associado com genes responsáveis pela maturação cerebral (14). Além disso, insultos pré-natais como influenza gestacional

pode aumentar em quatro vezes o risco de desenvolver TB na vida adulta (15). Em um estudo longitudinal com crianças em idade escolar, acharam uma associação entre baixo rendimento acadêmico e o risco de desenvolver TB (16). Nessa mesma direção, crianças de mães com TB ou esquizofrenia apresentam três vezes mais chances de terem deficiência intelectual (17). Deste modo, distintos cursos neurodesenvolvimentais podem estar relacionados com a heterogeneidade cognitiva entre os pacientes com TB após início da doença.

Outros eventos durante o curso de vida podem aumentar a gravidade da doença. Dentre eles, o trauma precoce é um importante fator pré-mórbido no TB, uma vez que há altas taxas de pacientes com TB que sofreram trauma infantil (18). A exposição à estressores na infância está associado a uma idade de início precoce do transtorno, presença de comorbidade com Transtorno de Estresse Pós-Traumático, ciclagem rápida, sintomas ansiosos, maior número de tentativas de suicídio e maior quantidade de episódios de humor (19,20). O TB parece ser um transtorno sensível ao estresse com o primeiro episódio sendo, frequentemente, engatilhado por eventos estressores ambientais (21). Cognitivamente, o trauma precoce está relacionado a um pior desempenho em funções como controle inibitório, atenção, memória verbal e de trabalho (22,23).

Além do trauma precoce, outro aspecto pré-mórbido relacionado a desfechos cognitivos é a reserva cognitiva. Reserva cognitiva é a capacidade do cérebro de sustentar as atividades cognitivas e enfrentar processos patológicos cerebrais (24). Os anos de estudo são um importante *proxy* de reserva cognitiva (25). Diferentes níveis de reserva cognitiva podem levar a múltiplos desfechos após um insulto cerebral (26). Distintas características de reserva cognitiva podem influenciar o prejuízo cognitivo em vários transtornos psiquiátricos como no TB. Foi visto que pacientes com TB com alta

reserva cognitiva apresentam melhores desempenhos em testes neuropsicológicos e melhor funcionamento psicossocial (25). Dessa forma, a reserva cognitiva é um significativo preditor de funcionamento cognitivo e psicossocial em pacientes eutímicos, exercendo um papel modulador em diferentes trajetórias cognitivas no TB (24,27).

2.2 Neuroprogressão

Há evidências que os pacientes com TB apresentam um declínio nas habilidades cognitivas associado ao número de hospitalizações e ao número de episódios de humor (28). Essa deterioração ao longo do curso do TB é chamada de neuroprogressão, ou seja, com os anos de doença e o número de episódios de humor, os pacientes começam apresentar uma deterioração cognitiva e funcional, refratariedade ao tratamento, vulnerabilidade ao estresse e atrofia cerebral (29,30). Pacientes em estágios tardios da doença com mais de dez episódios maníacos e, ao menos, com uma hospitalização exibiram um pior desempenho em testes de memória verbal que pacientes em estágios iniciais e pessoas sem transtornos psiquiátricos (31,32). Uma recente metanálise apontou que o número de episódios maníacos afetava memória verbal e função executiva, enquanto o número de episódios depressivos não apresentou essa associação (33). Há outros dados evidenciando que o número de episódios, anos de doença, número de hospitalizações, idade de início da doença são marcadores de gravidade relacionados a uma piora em habilidades cognitivas como velocidade psicomotora, flexibilidade cognitiva, função executiva, memória verbal e atenção (28).

Além dos aspectos cognitivos, a progressão da doença também está associada aos desfechos clínicos mais desfavoráveis como elevadas taxas de comorbidades clínicas, pior disfuncionalidade, menor intervalo inter-episódios, aumento de risco de

suicídio e de hospitalização(34). Pacientes em estágios mais tardios do transtorno têm uma pior resposta ao lítio, à terapia cognitivo-comportamental e à psicoeducação de seus cuidadores(35–37). Outros medicamentos como olanzapina e lamotrigina só melhoraram os sintomas daqueles pacientes com poucos episódios de humor e poucas hospitalizações (38,39). Um estudo transversal mostrou que, no estágio I, era mais frequente monoterapia, no estágio II, a combinação de duas drogas e, nos estágios tardios, era necessário o uso de três ou mais medicações ou clozapina. Ademais, havia uma correlação positiva entre funcionamento psicossocial e uso de medicações psicotrópicas (40).

Ativação imune e falhas nos mecanismos compensatórios podem ser mecanismos relacionados à fisiopatologia da neuroprogressão no TB. Pacientes em estágios tardios tem menores níveis de fator neurotrófico derivado do cérebro (*Brain-derived neurotrophic factor* - BDNF), citocinas anti-inflamatórias, maiores níveis de substratos do estresse oxidativo e citocinas pró-inflamatórias que pacientes em estágios iniciais (34,41). Em estudos *post-mortem*, tem mostrado que pacientes com TB têm alterações no número, tamanho e densidade de neurônios em regiões corticais e subcorticais (42). Um estudo recente utilizando *machine-learning* identificou que os pacientes com TB tinham maiores níveis de eotaxin-1 (CCL11) e glutationa S-transferase que indivíduos sem transtornos mentais. Porém, o algoritmo não conseguiu diferenciar os pacientes com TB e esquizofrenia em relação a esses biomarcadores periféricos, sugerindo que esses transtornos compartilham de fisiopatologias semelhantes(43).

2.3 Heterogeneidade cognitiva

Os pacientes com TB não são homogêneos em relação ao prejuízo cognitivo. Apenas um terço dos pacientes apresenta disfunção cognitiva durante os períodos eutímicos (44). Essa variabilidade cognitiva pode refletir as diferentes etiologias do transtorno, a gravidade dos sintomas, os fatores de suscetibilidade genética e outros aspectos pré-mórbidos (45). Alguns autores sugerem que apenas um subgrupo de pacientes com TB apresenta um curso progressivo da doença associado aos fatores clínicos da doença(46).

Anteriormente, os pacientes eram agrupados em grupos cognitivamente prejudicados e não-prejudicados determinados por pontos de corte arbitrários. Em geral, esses pontos de corte eram baseados na amostra de sujeitos sem transtornos psiquiátricos em que um desvio-padrão abaixo de 0,5 a 1,5 era considerado prejuízo cognitivo (47). O problema desse tipo de estratificação binária é a perda de especificidades que possam existir dentro dessas sub-amostras (47). A partir disso, tem crescido o número de estudos que tem utilizado algoritmos de *machine-learning* para identificar subgrupos cognitivos. Esses métodos utilizam algoritmos (p.ex. *k-NN* ou *k-means algorithm*) para identificar automaticamente similaridades e diferenças dentro de um grupo e dividi-lo em subgrupos baseados na homogeneidade intra-grupo e/ou heterogeneidade entre-grupos (48).

Dessa maneira, várias pesquisas têm usado esses algoritmos para classificação cognitiva dos pacientes com TB. Em geral, apontam para a existência de três subgrupos (*clusters*) cognitivos: I) cognitivamente intacto; II) seletivamente prejudicado; III) globalmente prejudicado. O primeiro *cluster* apresenta um funcionamento neuropsicológico similar ao dos indivíduos sem transtornos psiquiátricos, sendo 30 a 46% dos pacientes. Já o segundo *cluster* possui um prejuízo cognitivo moderado a grave em dois ou três domínios cognitivos similar ao grupo globalmente prejudicado. Porém,

em outras funções cognitivas, possuem funcionamento semelhante ao *cluster* intacto. As funções cognitivas afetadas no *cluster* seletivamente prejudicado variam dependendo do estudo. Por fim, o grupo globalmente prejudicado apresenta um grave comprometimento cognitivo em todos os domínios com desvio-padrão bem abaixo de 1,5 (i.e. memória de trabalho, memória verbal, velocidade de processamento, controle inibitório, fluência verbal) (8,24,49).

Um recente estudo utilizando análise de classe latente identificou quatro subgrupos cognitivos: um com bom desempenho cognitivo, outro severamente prejudicado e outros dois com prejuízo moderado no controle inibitório e na resolução de problemas(45). Nessa mesma linha, outros autores acharam também quatro *clusters* cognitivos. Um subgrupo com prejuízo global, outro com funcionamento cognitivo normal e os outros dois com desempenho neuropsicológico próximo do normal. Porém, esses dois subgrupos diferiam apenas na memória verbal, pois um possuía prejuízo nesse domínio, enquanto o outro *cluster* teve um desempenho acima da média nessa função cognitiva (50).

De maneira geral, tem se replicado os achados a respeito da existência de um subgrupo com funcionamento cognitivo intacto e outro subgrupo com um funcionamento cognitivo globalmente prejudicado. No meio desses dois *clusters*, há a presença de outro subgrupo que apresenta uma performance cognitiva prejudicada em alguns domínios.

2.4 *Machine learning*

Machine learning é um campo da Inteligência Artificial que detecta automaticamente padrões em uma base de dados por meio de alguns tipos de aprendizado. É necessários seguir alguns passos para a aplicação de qualquer algoritmo

de *machine learning.* O primeiro passo é a coleta dos dados. O segundo é preparação e exploração dos dados. Nessa etapa é preciso eliminar ou corrigir qualquer dado que seja desnecessário para a performance da máquina. O terceiro passo é o treino do modelo em que será aplicado o algoritmo. Assim, a máquina irá reconhecer um padrão no banco de dados de treino e o algoritmo representará o dado em forma de modelo. O passo seguinte consiste em avaliar o modelo. Dessa maneira, será avaliado quão bem o algoritmo aprendeu a partir da sua experiência com um banco de dados(48).

O aprendizado em *machine learning* é classificado em duas categorias: aprendizado supervisionado e não supervisionado. O primeiro utiliza a experiência de um banco de treino para ganhar perícia ao analisar um banco de teste. Em outras palavras, é mostrado à máquina exemplos rotulados de *input* e *output* em um banco de treino. Dessa forma, a máquina, em um banco de teste, verificará o que aprendeu, ou seja, é um processo em que o algoritmo aprende por meio de uma instrução (48,51).

O aprendizado não supervisionado é usado em dados sem rótulos anteriores e o algoritmo deve identificar um padrão nas variáveis apresentadas. Não há distinção entre o banco de treino e teste como é no aprendizado supervisionado. Além disso, Uma tarefa clássica de aprendizado não-supervisionado é análise de *cluster*, pois agrupa objetos de acordo com a sua similaridade sem a necessidade de um treino ou de um rótulo para predizer os grupos (52).

3. Justificativa

Apesar dos avanços na compreensão dos aspectos cognitivos do TB, poucos estudos têm investigado a cognição nos subgrupos nessa população psiquiátrica e nenhum estudo investigou a relação de fatores pré-mórbidos e mórbidos relacionados a esses desfechos cognitivos. Esse tipo de pesquisa é importante para compreender a

complexidade do transtorno e entender as diferentes trajetórias da doença. Portanto, torna-se necessário investigar a heterogeneidade neuropsicológica dessa população e pesquisar os fatores associados às diferentes trajetórias no TB.

4. Objetivos

4.1 Objetivos gerais

Investigar o impacto dos fatores pré-mórbidos e mórbidos na cognição de Pacientes com TB.

4.2 Objetivos específicos

- Identificar quais são os *clusters* cognitivos existentes no TB;
- Investigar o impacto da reserva cognitiva dos pacientes com TB nos domínios cognitivos;
- Determinar quais aspectos mórbidos influenciam nos desfechos cognitivos.

5. Método

5.1 Critérios de inclusão

Os critérios de inclusão para os pacientes foram: homens e mulheres entre 18 e 65 anos, diagnóstico de Transtorno Bipolar Tipo I ou II pelo DSM-IV, pacientes eutímicos por, no mínimo, dois meses antes da avaliação com pontuação na *Young Mania Rating Scale* (YMRS) e *Hamilton Depression Rating Scale* (HAM-D-17) menor ou igual a sete, capacidade para entender e concordar com todos os aspectos do Termo de Consentimento Livre Esclarecido.

Os critérios de inclusão para os sujeitos sem transtornos psiquiátricos foram: homens e mulheres entre 18 e 65 anos, sem uso de medicação psiquiátrica e sem

história prévia de transtornos psiquiátricos, capacidade para entender e concordar com todos os aspectos do Termo de Consentimento Livre Esclarecido.

5.2 Critérios de exclusão

Os critérios de exclusão para os pacientes foram diagnóstico de deficiência intelectual, grave comorbidade médica, presença de demências, analfabetismo, eletroconvulsoterapia no último ano e abuso de substância.

Os critérios de exclusão para os sujeitos sem transtornos psiquiátricos foram histórico atual ou passado de transtorno psiquiátrico ou doença neurológica, analfabetismo, presença de familiar de primeiro grau com transtorno psiquiátrico ou doença neurológica.

5.3 Instrumentos e medidas

5.3.1 Entrevista clínica e escalas de sintomatologia e diagnóstico

- Entrevista Clínica Estruturada para os Transtornos do DSM-4 – Versão Clínica (SCID-4-CV)(53).
- Escala de Avaliação de Mania de Young (YMRS) (54).
- Escala de Avaliação de Depressão de Hamilton (HAM-D-17) (55).
- Entrevista estruturada para a coleta dos dados sócio-demográficos e características clínicas do paciente;

5.3.2 Avaliação neuropsicológica

- *Hopkins Verbal Learning Test – Revised*(56);
- *California Verbal Learning Test* (CVLT)(57);
- O subteste Sequência de Números e Letras da Escala de Inteligência Wechsler para Adultos – 3ª Edição (WAIS-III)(58);

- *Trail Making Test -A* e *Trail Making Test*-B(59);
- *Stroop Word Color Test*(60);
- Fluência Verbal Fonológica (FAS) (61).

Tabela 1. Instrumentos que serão utilizados e as funções avaliadas

Instrumentos	**Função avaliada**
Escala de Avaliação de Mania de Young (YMRS)	Sintomas Maníacos
Escala de Avaliação de Depressão de Hamilton (HAM-D-17)	Sintomas depressivos
Hopkins Verbal Learning Test – Revised *California Verbal Learning Test*	Memória verbal
Sequência de Números e Letras (WASI-III)	Memória de trabalho
Trail Making Test –A	Velocidade de processamento
Trail Making Test-B	Flexibilidade cognitiva
Stroop Word Color Test	Controle inibitório
Fluência Verbal Fonológica (FAS)	Fluência verbal

5.4 Procedimento

A amostra de pessoas sem transtornos psiquiátricos foi recrutada, por conveniência, de dois hospitais universitários do Brasil e da Espanha. A amostra foi de 242 participantes. 142 pessoas com diagnóstico de TB e 100 indivíduos sem transtornos psiquiátricos. Do Brasil, foram 59 voluntários saudáveis e 72 pacientes. Da Espanha, foam 41 indivíduos saudáveis e 70 pacientes com TB. A amostra de pacientes foi recrutada do Programa de Transtorno Bipolar dos mesmos hospitais universitários. O diagnóstico foi dado por experientes psiquiatras de acordo com Entrevista Clínica

Estruturada para os Transtornos do DSM-IV – Versão Clínica (SCID-4-CV). Os testes neuropsicológicos e as escalas psicométricas foram aplicados por experientes psicólogos. As avaliações foram realizadas individualmente, em um ambiente climatizado e sem ruídos de acordo com as diretrizes para o uso de testes da Comissão Internacional de Testes. Dados sobre variáveis sociodemográficas e clínicas foram coletadas para este protocolo.

5.5 Análise estatística

O programa estatístico utilizado foi R *software* versão 3.4.2 para *Windows* para analisar os dados (https://www.Rproject.org/). Teste qui-quadrado e ANOVA foram realizados para verificar as diferenças entre os grupos das variáveis demográficas, considerando um nível de significância $p<0,05$.

Para identificar a presença de subgrupos cognitivos em nossa amostra foi realizado alguns passos. As variáveis neuropsicológicas dos pacientes foram convertidas em *z-score* baseadas na média e desvio-padrão da amostra de controles correspondente de cada país. A conversão dos valores brutos em *z-score* foi feita para que todas as variáveis fossem comparéveis entre si. Em seguida, foi realizada uma Análise de *Cluster* Hierárquico (HCA) com o método de Ward e distância euclidiana ao quadrado com todos os domínios cognitivos avaliados para identificar os membros de cada *cluster* e o número de *clusters.*

Na próxima etapa, foi usado a Análise de Função Discriminante (DFA) para examinar a distância entre os centroides dos *clusters* e o poder preditivo da classificação da HCA. Por fim, realizaremos uma análise multivariada de variância (MANOVA) com a média dos *z-score* dos subgrupos para cada domínio cognitivo.

Após a identificação do número ideal de *cluster* e os seus membros, foi utilizado o algoritmo *Classification and Regression Tree* (CART) para realizar a árvore de

decisão. O objetivo desse tipo de análise é identificar quais são as variáveis pré-mórbidas e mórbidas que poderiam predizer cada *cluster* cognitivo. O *root node* foi os *clusters* cognitivos e, a partir disso, o algoritmo selecionou as variáveis de maior "peso" e realiza a divisão até que os *nodes* finais sejam homogêneos.

6. RESULTADOS

6.1 Artigo 1:

Carta de submisão no JAMA Psychiatry

February 20, 2018

Dear Dr Kunz:

Thank you for submitting your manuscript, "Predictors of cognitive heterogeneity in a transcultural sample of individuals with Bipolar Disorder," received on February 20, 2018, to JAMA Psychiatry. Your manuscript has been assigned the following manuscript number: PSY18-0263. Please refer to the manuscript number and corresponding author in all subsequent communications.

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Thank you for the opportunity to consider your work.

Sincerely yours,

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Predictors of cognitive heterogeneity in a transcultural sample of individuals with Bipolar Disorder: a machine-learning approach.

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KEY POINTS

Question: What are the clinical predictive factors of cognitive heterogeneity in subjects with Bipolar Disorder?

Findings: In this cross-sectional study involving 142 subjects with Bipolar Disorder and 100 unaffected subjects, there were three cognitive subgroups in individuals with Bipolar Disorder: intact (38%), selectively impaired (38%), and globally impaired individuals (21%). The most important predictors of cognitive subgroups were years of education, years of disease, the number of hospitalizations, age, and age of onset, respectively.

Meaning: Bipolar Disorder is a cognitively heterogeneous disease with an overlapping between premorbid and morbid factors, influencing multiple cognitive courses.

ABSTRACT

Importance: Bipolar Disorder (BD) is an illness with heterogeneous outcomes, with a subset of patients exhibiting a progressive cognitive decline over the course of the disease. Early detection of neuropsychological subgroups is an important challenge in BD treatment and may help the clinical decision-making.

Objective: We aimed to identify predictors of cognitive clusters in individuals with Bipolar Disorder.

Design, Setting, and Participants: This is a multicenter cross-sectional study with a convenience sample. We recruited 142 outpatients with Bipolar Disorder and 100 unaffected volunteers from Brazil and Spain that underwent a neuropsychological assessment.

Main Outcomes and Measures: Of 142 participants with BD, 92 (64.9%) were female, and the mean (SD) age was 45.30 (12.24) years. Among 100 healthy volunteers, 63

(63%) were female, and the mean (SD) age was 42 (14.72) years. Individuals with BD were older compared to unaffected subjects ($p<0.001$). Cognitive tests used were Stroop Color and Word Test (inhibitory control), Trail Making Test A (processing speed), Trail Making Test B (cognitive flexibility), Verbal Fluency Test with letters F-A-S (verbal fluency), Letter-Number Sequencing from WAIS-III (working memory), Hopkins Verbal Learning Test–Revised trials 1-3 or California Verbal Learning Test trials 1-5 (short-term verbal memory), HVLT-R delayed recall trial or CVLT delayed recall trial (long-term verbal memory). We performed Hierarchical Cluster Analysis and Discriminant Function Analysis to determine and confirm cognitive clusters, respectively. Then, we used Classification and Regression Tree algorithm to determine predictors of the previously defined cognitive clusters.

Results: We identified three cognitive clusters in subjects with Bipolar Disorder: intact (38%), selectively impaired (38%), and globally impaired individuals (21%). The most important predictors of cognitive subgroups were years of education, years of disease, the number of hospitalizations, age, and age of onset, respectively.

Conclusion and Relevance: These results corroborate with recent findings of neuropsychological heterogeneity in Bipolar Disorder. Furthermore, the present findings suggest overlapping between premorbid and morbid aspects, influencing distinct courses of the disease.

Key words: Bipolar Disorder, cognitive heterogeneity, cluster analysis, decision tree, machine learning.

1. INTRODUCTION

Bipolar Disorder (BD) is a complex disease due to its clinical and cognitive heterogeneity. Cognitive deficits in euthymic patients with BD vary between 30 to 62% (62,63). The individuals with BD show dysfunctions in a wide range of cognitive domains as processing speed, memory, and executive functions(64). Furthermore, only one-third of patients after first-episode mania recover their psychosocial functioning similar to baseline(65). Previously, patients with BD were grouped into subjects with impaired and preserved cognitive function using arbitrary cut-off scores. The issue with this dichotomous classification is a lack of specificity that could be present at the sample. For this reason, data-driven approach such as cluster analysis is a method better than the ones to classify cognitive subgroups. Recently, several reports have suggested that there are three neuropsychological subgroups: a first group of patients with cognitive functioning similar to unaffected individuals (32%-48% of BD patients); a second group of patients who exhibited cognitive impairment in some cognitive functions, such as processing speed and attention (29%-40% of BD patients); and a third group of patients with severe cognitive impairment in several domains (12%-40% of BD patients)(8,66). These clusters showed similar intensity of mood symptoms but presented different degrees of psychosocial functioning, stress and quality of life(8,67).

The cognitive profiles in BD may be due to distinct trajectories of the disease, such as the influence of premorbid factors. For example, patients with high Cognitive Reserve (CR) displayed better cognitive performance than patients with low CR(24,25). CR refers to brain capacity of maintaining cognitive functions and coping pathological processes(24). Other premorbid features like childhood trauma and family history of psychiatric disorders may have different effects on the disease development. Furthermore, morbid factors such as number of hospitalizations, number of mood

episodes, and early onset of disease are also related to worse clinical, functional and cognitive outcomes(68,69). However, although there seems to be a subset of patients that exhibit a progressive cognitive decline over the course of the disease(70). BD is a highly variable illness that not necessarily will lead to unfavorable clinical outcomes.

Moreover, little is known about the possible predictors of the different cognitive profiles in BD, which could greatly improve our comprehension about the mechanisms of the illness progression. Clinically, early detection of neuropsychological subgroups is an important challenge in BD treatment. Therefore, our aim was to identify predictive factors of cognitive clusters in BD patients using Classification and Regression Tree (CART) algorithm. CART is a flexible machine-learning method widely used for diagnosis and classification of high-risk behaviors(71–74). This technique is able to identify complex nonlinear relations with interactive models(75,76). In other words, the algorithm automatically selects relevant features and determines cut points according to characteristics of data. These cut-points may be clinically relevant, indicating distinct clinical courses and helping the clinical decision-making.

2. METHODS

2.1 Participants

The sample included 242 participants, 142 individuals with BD and 100 healthy controls (HC). Participants were 59 healthy volunteers and 72 outpatients from the Bipolar Disorder Program at Hospital de Clínicas de Porto Alegre (HCPA) - Brazil, and 41 unaffected individuals and 70 outpatients from the Barcelona Bipolar Disorder Program at Hospital Clinic - Spain. Experienced psychiatrists carried the diagnosis of Bipolar I or II Disorder confirmed by Structured Clinical Interview for DSM-IV (SCID). All patients with BD were receiving psychiatric medication. Inclusion criteria

for outpatients were: age between 18 and 65 years, and euthymia for at least one month before assessment confirmed by Hamilton Depression Rating Scale (HAM-D-17) and Young Mania Rating Scale (YMRS) ≤ 7. Exclusion criteria for outpatients were a diagnostic of intellectual disability, significant neurologic or physical disease, electroconvulsive therapy (ECT) within the past year and substance abuse or dependence. Criteria for unaffected individuals comprised age between 18 and 65 years, not in use of any psychiatric medication, having no current, past history or first-degree family history of a severe mental disorder, dementia or intellectual disability. All participants provided written informed consent. The local ethical committees from both Brazil and Spain approved all procedures.

2.2 Assessments

All patients completed a structural interview with experienced clinicians that included sociodemographic and clinical aspects. After, experienced clinical psychologists administered the neuropsychological battery. Cognitive domains assessed were inhibitory control (Stroop Color and Word Test)(60), processing speed (Trail Making Test A), cognitive flexibility (Trail Making Test B)(59), verbal fluency (Verbal Fluency Test with letters F-A-S)(61), working memory (Letter-Number Sequencing from WAIS-III)(58); short-term verbal memory (Hopkins Verbal Learning Test–Revised [HVLT-R] trials 1-3 or California Verbal Learning Test [CVLT] trials 1-5), long-term verbal memory (HVLT-R delayed recall trial or CVLT delayed recall trial)(57,77).

2.3 Statistical Analysis

We performed statistical analyses in R (https://www.Rproject.org/).

2.3.1 Data Transformation

TMT-A and B were subtracted by 300 (maximum score) to be compatible with the direction of the other cognitive tests. Cognitive variables were transformed to z-score based on the mean and standard deviation of unaffected subjects (78). We truncated extremely low z-scores (<-4.0) to z = -4.0. All cognitive tests were the same for both samples except verbal memory tests. On the Brazilian sample, we carried out the verbal memory assessment with Hopkins Verbal Learning Test–Revised (HVLT-R), while on the Spanish sample, we assessed with California Verbal Learning Test (CVLT). In order to include a memory domain in our analysis, we converted scores of HVLT-R trials 1-3 and delayed recall trial into z-score based on the mean and standard deviation of the Brazilian sample of unaffected individuals. We performed the same procedure with CVLT trials 1-5 and delayed recall trial based on the Spanish sample of unaffected subjects. After, we gathered the z-scores of HVLT-R trials 1-3 and CVLT trials 1-5 as a short-term verbal memory domain and delayed recall of HVLT-R and CVLT as a long-term verbal memory domain.

2.3.2 Cognitive Subgroups

We performed the hypothesis testing in three steps. First, we used Hierarchical Cluster Analysis (HCA) to investigate the presence of cognitive subgroups in the BD sample using Ward's method and squared Euclidean distance(79,80). We inspected visually the dendrogram generated through HCA to identify the number of clusters. We performed a Discriminant Function Analysis (DFA) to confirm the clusters retained and to investigate the predictive power of the classification.

Second, we checked the variables for outliers and normal distribution using Kolmogorov-Smirnov test. All variables in common with both groups were normally distributed. We performed Student's *t* and Chi-square tests when appropriated to compare the groups. We tested for cluster effects on neuropsychological characteristics through multivariate analysis of variance (MANOVA) with post-hoc Tukey's HSD test for multiple comparisons. Statistical significance was $p<0.05$ (two-tailed) for all tests. Z-scores less than -1 standard deviation were considered as moderate impairment. Criteria for severe cognitive impairment were established in z-score $\leq$ -2.

2.3.3 Classification and Regression Tree model

Lastly, we used the Classification and Regression Tree (CART) model to identify the predictors of cognitive clusters in BD patients. CART algorithm is a non-parametric model with high-order interactions which predicts outcomes based on the average value of observations(48,71). This algorithm uses automatic feature selection in each leaf. Then, we inserted categorical and continuous variables as predictors. Outcomes were cognitive subgroups (intact, selective or global) previously defined. Variables included in the CART analysis were: years of education, age, number of hospitalizations, years of disease, age of onset, first-episode types (depressive or manic episode), first episode psychosis (dichotomous variable: yes or not), family history of mood disorders (dichotomous variable: yes or not), and type of bipolar disorder (Type I or II). We selected these variables because they are widely described in the literature as being related to cognitive performance and greater illness severity. We used the default pruning parameter to avoid overfitting (complexity parameter = 0.01). The number of cases was set of 142 for the root node.

3. RESULTS

3.1 Cognitive subgroups

The demographic and clinical variables of the sample are presented in Table 1. The groups (BD and unaffected individuals) had similar gender distribution. Individuals with BD were older and had fewer years of education compared to unaffected subjects (Student's t-test: all $p \leq 0.049$).

The Hierarchical Cluster Analysis (HCA), through the visual inspection of the dendrogram, demonstrated the presence of three cognitive clusters (Figure 1), comprised by 38% of patients with intact cognition (n=55), 38% with selective impairments (n=56), and 21% with global impairments (n=31). The Discriminant Function Analysis (DFA) showed the presence of two discriminant functions, which explained 95.5% and 4.05% of the variance, respectively (Wilks' $\lambda = 0.15$, $\chi2= 257.09$, $p <0.001$, Wilks' $\lambda = 0.86$, $\chi2= 26.06$, $p <0.001$). The patients were correctly classified into 93% of the cases, evidencing the validity of the three cognitive clusters. Cognitive Flexibility and Verbal Fluency were domains that better classified BD patients into cognitive clusters by means of correlations between discriminating variables and discriminant functions (Function 1: r=0.68 and r=0.38. Function 2: r= -0.34 and r= -0.19, respectively). The cognitive subgroups are shown in Figure 2.

The multivariate ANOVA displayed a significant effect of group comparing the cognitive clusters across neuropsychological variables ($F(_{12, 270})= 20.954$, $p<0.001$). The post-hoc test revealed that all cognitive groups are different (Table 2). The intact cognition group had better performance than the other two cognitive clusters. The selective group had also better performance compared to the global impairment group, except for inhibitory control. This group exhibited an intermediate performance between the intact cognition and the global impairment groups. The globally impaired

group had worse performance than the other two cognitive groups. The selective group showed moderate impairment (-1≥ z-score≥ -2) in working memory, short and long-term verbal memory and severe deficit (z-score<-2) in cognitive flexibility. The global group exhibited moderate deficit in working memory, verbal fluency, and short-term verbal memory. The same group displayed severe neurocognitive impairment in processing speed, cognitive flexibility, and long-term verbal memory. The mean z-scores across domains between the three clusters of BD patients are displayed in Figure 3.

3.2 Classification and Regression Tree model

The tree-based CART prediction model is shown in Figure 4. There were seven terminal nodes, which are results of 'if-then' conditions. The split criterion is indicated in each decision node. The most important criterion was years of education, which split the root node into two branches (≥9.5 years of education and <9.5 years of education). About 78% of the sample had more years of education. Additionally, the CART showed the following predictors of cognitive clusters: years of disease (<10 and ≥10), number of hospitalizations (First split: ≥2.5 and <2.5. Second split: <5.5 and ≥5.5), age (<58 and ≥58), and age of onset (≥28 and <28) respectively. First-episode type, first episode psychosis, family history of mood disorders and type of bipolar disorder were not included in the model.

A portion of subjects with globally impaired cognition showed less years of education (<9.5) and more years of illness duration (≥10). The frequency of individuals with global impairment was 62% for this terminal node. Another fraction of the global

group (50% for this terminal node) exhibited more years of education (≥9.5), a lower number of hospitalizations (<2.5) and were older age (>58).

In relation to subjects with selectively impaired cognition, there were two sub-groups: 1) individuals with more years of education (≥9.5), lower number of hospitalizations (<2.5), younger age (<58), and early-age onset (<28) (66% for this terminal node); 2) individuals with more years of education and a higher number of hospitalizations (≥5.5) (62% for this node).

The intact cluster subdivided into three groups: 1) subjects with less years of education (<9.5) and less years of illness duration (<10) (100% for this terminal node); 2) patients with more years of education (≥ 9.5) and a lower number of hospitalizations (<5.5) (63%); 3) subjects with more years of education (≥9.5), lower number of hospitalizations (<2.5) with age less than 58 years old, and the late-age onset of BD (≥28) (50%).

4. DISCUSSION

Our study identified the presence of three cognitive subgroups of euthymic patients with BD. The cognitive clusters were patients with intact cognition (39%), selectively impaired cognition (39%), and globally impaired cognition (22%). The percentage of subjects in each cluster was similar to previous data, indicating that only a small portion of BD patients exhibited a global cognitive impairment (8,66). Some authors reported that moderate cognitive deficit might be considered when standard deviation is 1 score below the mean of an unaffected subject sample(81–83). The global group displayed neurocognitive deficits in all domains except for inhibitory control. The moderately impaired cognitive functions as working memory, verbal fluency, short-term

verbal memory were below -1 standard deviation. The severely impaired cognitive domains (z-score ≤-2) were processing speed, cognitive flexibility, and long-term verbal memory.

On the other hand, the majority of patients showed neuropsychological functioning similar to unaffected subjects (intact cluster) or displayed cognitive impairments in some domains (selective cluster). The selective group showed a mild performance between 0 and -1 standard deviation in inhibitory control, processing speed, verbal fluency consistent with previous works (8,45,66,84). However, the selective cluster had a moderate cognitive deficit in working memory, short-term and long-term verbal memory below -1 standard deviation and a severe deficit in cognitive flexibility below -2 standard deviation.

In relation to predictors of cognitive clusters, the most important criterion to predict neuropsychological subgroups was years of education, subdividing the cognitive clusters into subgroups with more years of education (Intact, Selective, and Global) and less years of education (Intact and Global). Only 22% of the sample had less years of education (<9.5 years). As we know, this variable is an important proxy of Cognitive Reserve (CR), e.g., the brain capacity of resisting to damage due to certain lifetime experiences such as the level of education. Thus, the majority of patients in the global group had fewer years of education and more years of disease. In other words, these patients showed lower CR and were more chronically ill. Previous studies indicated that low CR is associated with neuronal loss before the onset of symptoms, cognitive decline and brain atrophy(85,86). In addition, years of education are positively linked to grey matter volume in patients with dementia(86). In BD patients, CR is a predictor of neuropsychological functioning. Patients with low CR have worse cognitive

performance in several domains, suggesting that CR may play a critical function in the course of BD(25) .

However, years of disease were a factor more capable to specifically discriminate the intact and the global group. In a recent research that used cognitive cluster analysis, authors found a significant difference of years of illness between the cluster with good performance and the cluster with severe impairment. Nonetheless, the selectively impaired group was not different from the cluster with severe impairment and from the cluster with good performance in relation to years of illness(45). The present study results are in line with this early finding, which the globally impaired group had more years of disease than group with good performance. Moreover, others reports have shown that illness duration is negatively associated with processing speed, executive function, attention, and cognitive flexibility(87–92).

The number of hospitalizations was another predictor of the cognitive cluster in our study. This predictor differentiated a portion of intact, selective, and global clusters with lower number of hospitalizations (<2.5) from intact and selective clusters with higher number of hospitalizations (≥2.5). We considered this factor as the number of hospitalizations due to mood episodes. Number of hospitalizations is a harder endpoint with minimum recall bias and probably is strongly related with acute mood episodes in BD. Moreover, rates of hospitalizations are a crucial marker of illness severity associated with worse clinical outcomes(93). As showed by our data, a fraction of the intact group had a lower number of severe mood episodes (≤5.5) than the selective group (>5.5). Several findings are consistent with our data linking the number of hospitalizations and cognitive performance. Recent reports indicate patients with multiple episodes and with many hospitalizations exhibit cognitive deficits in several domains, whereas patients with few episodes had better cognitive performance(94–96).

Furthermore, there is evidence that length of hospital stay is negatively correlated with neuropsychological performance at discharge from inpatient care(97).

Years of education (≥9.5), number of hospitalizations (<2.5) and older age (≥ 58) were predictors of a sub-sample among the global group. This sub-sample had medium education level but was older. An early study concluded that older BD patients had poorer cognitive performance, despite having higher education (98). Furthermore, a few number of hospitalizations associated with an old age were predictors of cognitive global impairment in our study. Similarly, a longitudinal study found that number of hospitalizations was a predictor of cognitive deficit in elderly patients with BD(99). Some authors reported that the number of mood episodes might be a factor for dementia due to decreased CR during mood episodes(69,100,101). A growing body of scientific evidence indicates that the age-related cognitive impairment is higher in BD patients than in healthy controls (102,103). Another longitudinal study provided evidence that older BD patients exhibited severe cognitive deficit and rapid cognitive decline when compared to unaffected subjects(104).

In the other branch (age <58), the decision node split into two terminal nodes according to age of disease onset. The selective group had earlier age of onset (<28) than the intact group (≥28). A recent meta-analysis demonstrated that earlier age of onset was associated with selective cognitive deficit, specifically in verbal memory and processing speed(105).

One of the limitations of our study is its cross-sectional design. In addition, we did not measure IQ and other premorbid variables as childhood trauma, drug use, and prodromal symptoms. Another limitation was the presence of two different instruments (HVLT and CVLT) to assess verbal memory in each country. In addition, we

investigated each domain with few neuropsychological tests. Nonetheless, the strength of our work was the large sample size, transcultural study and the use of a new method analysis, not previously used in neuropsychology.

In conclusion, individuals with bipolar disorder could be slip into three cognitive profiles: similar performance to healthy controls, selective impairments in some cognitive functions and global impairments across domains. The most important predictor of these cognitive subgroups was years of education, followed by years of disease, number of hospitalizations due to a mood episode, age and age of disease onset, respectively. These results corroborate with recent findings of neuropsychological heterogeneity in bipolar disorder and suggest that an interaction between premorbid and morbid aspects influence the observed distinct courses of the disease. Future research should focus on other premorbid factors and differences in neuroimaging between cognitive clusters.

Table 1. Sociodemographic and clinical characteristics of individuals with Bipolar Disorder and unaffected subjects.

	Individuals with Bipolar Disorder	Healthy Controls	Statistics
Gender F/M [%]	64.9/35.2	63/37	$X^2(1) = 0.24$, $p = .62$
BD type I/II [%]	83.1/16.9		
Age [mean(SD)]	45.30 (12.24)	42 (14.72)	T (237.63)= 48.74, p <0.001
Years of education [mean(SD)]	12.40 (4.40)	14.8 (4.00)	T(179.24) = 34.99, p < 0.001
Age of onset [mean(SD)]	26.36 (9.98)	-	-
Years of disease [mean(SD)]	18.70 (11.87)	-	-
Number of mood episodes [mean(SD)]	11.96 (9.43)	-	-
Number of Hospitalizations [mean(SD)]	3.01 (4.32)	-	-
HAM-D [mean(SD)]	3.40 (2.35)	-	-
YMRS [mean(SD)]	1.22 (1.51)	-	-
Current psychiatric medication			
Mood stabilizers [%]	63.0	-	-
Antipsychotics [%]	48.7	-	-
Benzodiazepine [%]	18.5	-	-
Antidepressant [%]	15.9	-	-

SD: Standard deviation; HAM-D: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale

Table 2. Comparison between neurocognitive clusters of bipolar disorder and unaffected individuals across cognitive domains (Z scores).

	Clusters					
	Intact BD (n=55)	Selective BD (n=56)	Global BD (n=31)	Controls (n=100)	*F*	Interaction
Working memory	-0.02 (0.97)	-1.14 (0.92)	-1.88 (0.94)	0.03 (0.97)	42.41	Intact *v.* Selective[a] Intact *v.* Global[a] Global *v.* Selective[a]
Inhibitory control	0.19 (0.93)	-0.26 (0.73)	-0.67 (0.66)	0.00 (1.00)	12	Intact *v.* Selective[b] Intact *v.* Global[a]
Processing speed	-0.08 (1.01)	-0.84 (1.03)	-2.82 (1.37)	0.03 (0.96)	61.46	Intact *v.* Selective[a] Intact *v.* Global[a] Global *v.* Selective[a]
Cognitive flexibility	0.50 (1.38)	-2.13 (1.31)	-3.85 (0.35)	0.04(0.96)	142.7	Intact *v.* Selective[c] Intact *v.* Global[c] Global *v.* Selective[c]
Verbal Fluency	-0.03 (1.04)	-0.72(1.22)	-1.81 (0.80)	0.02 (0.98)	27.44	Intact *v.* Selective[a] Intact *v.* Global[a] Global *v.* Selective[a]
Short-term verbal memory	0.15 (0.97)	-1.16 (1.09)	-1.99 (0.83)	0.02 (0.99)	51.11	Intact *v.* Selective[a] Intact *v.* Global[a] Global *v.* Selective[a]
Long-term verbal memory	-0.14 (1.00)	-1.20 (0.96)	-2.14 (1.05)	0.00 (1.00)	42.03	Intact *v.* Selective[a] Intact *v.* Global[a] Global *v.* Selective[a]

Multivariate analysis of variance (MANOVA) with post-hoc Tukey's HSD test for multiple comparisons. Data showed as mean (standard deviation) of z-scores.

[a] $p<0.001$; [b] $p<0.01$; [c] $p<0.05$

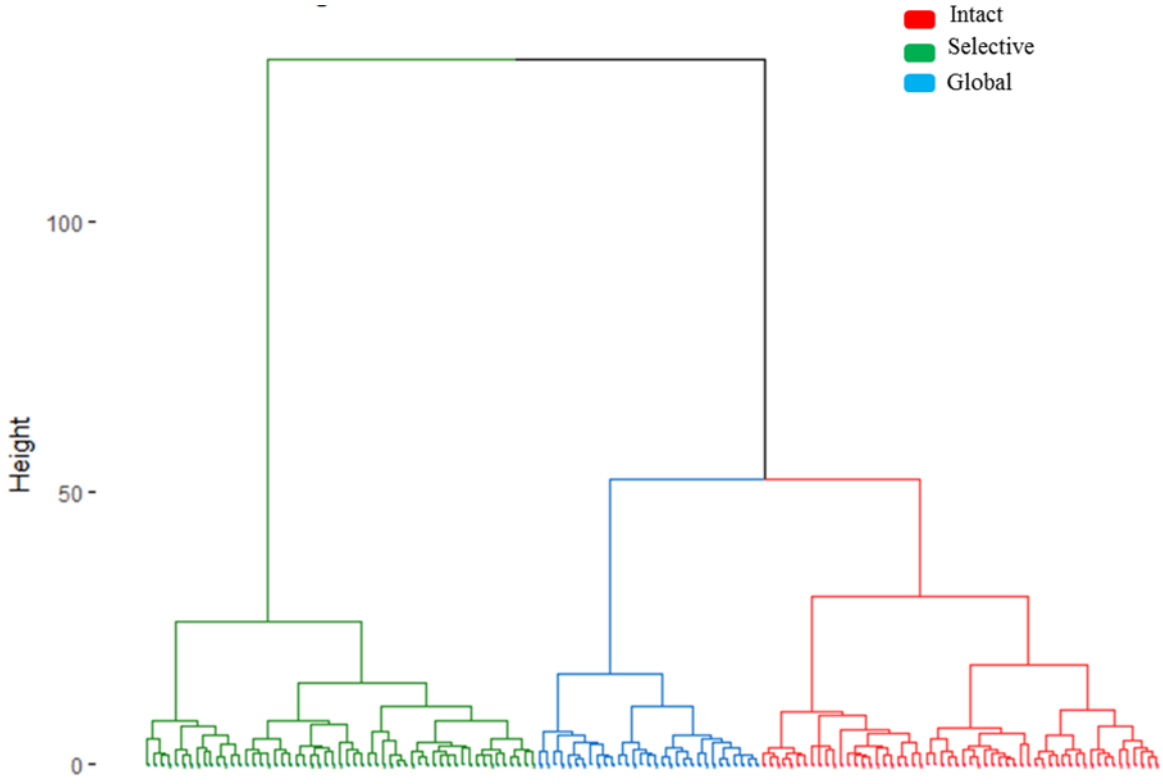

Figure 1 – Dendrogram of individuals with bipolar disorder produced by Hierarchical Cluster Analysis, illustrating the arrangement of the cognitive clusters. Abbreviations: Intact (cognitively intact cluster), Selective (selectively impaired cluster), Global (globally impaired cluster).

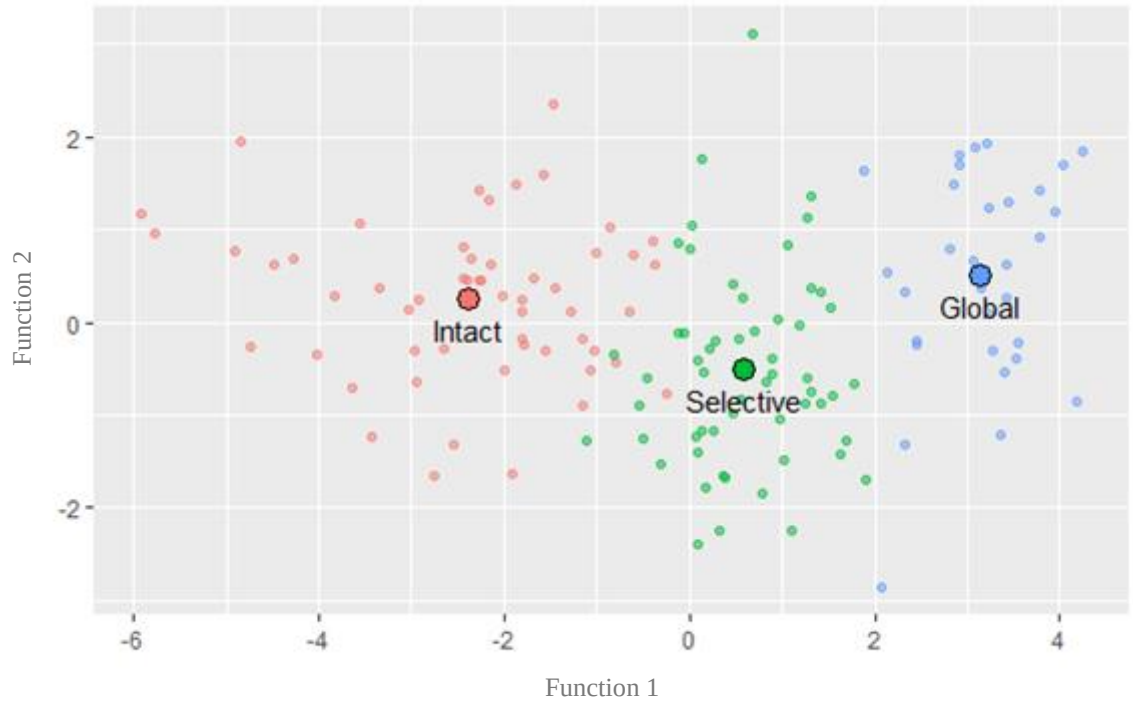

Figure 2 – Agglomeration of individuals with bipolar disorder produced by Discriminant Function Analysis (DFA) based on cognitive performance in three groups. The higher symbols are the centroids for each cluster.

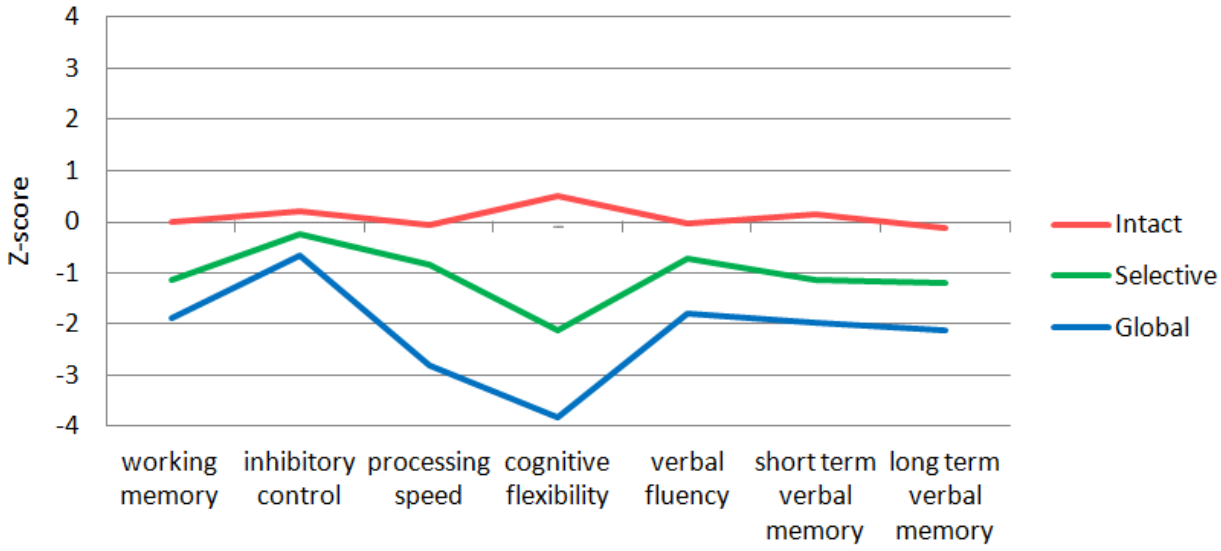

Figure 3 – Mean of neuropsychological performance between three clusters of individuals with bipolar disorder. The X-axis is the domains cognitive and Y-axis is the value of z-score based on mean and standard-deviation of unaffected subjects in cognitive tests. Statistical tests among groups are shown in Table 2.

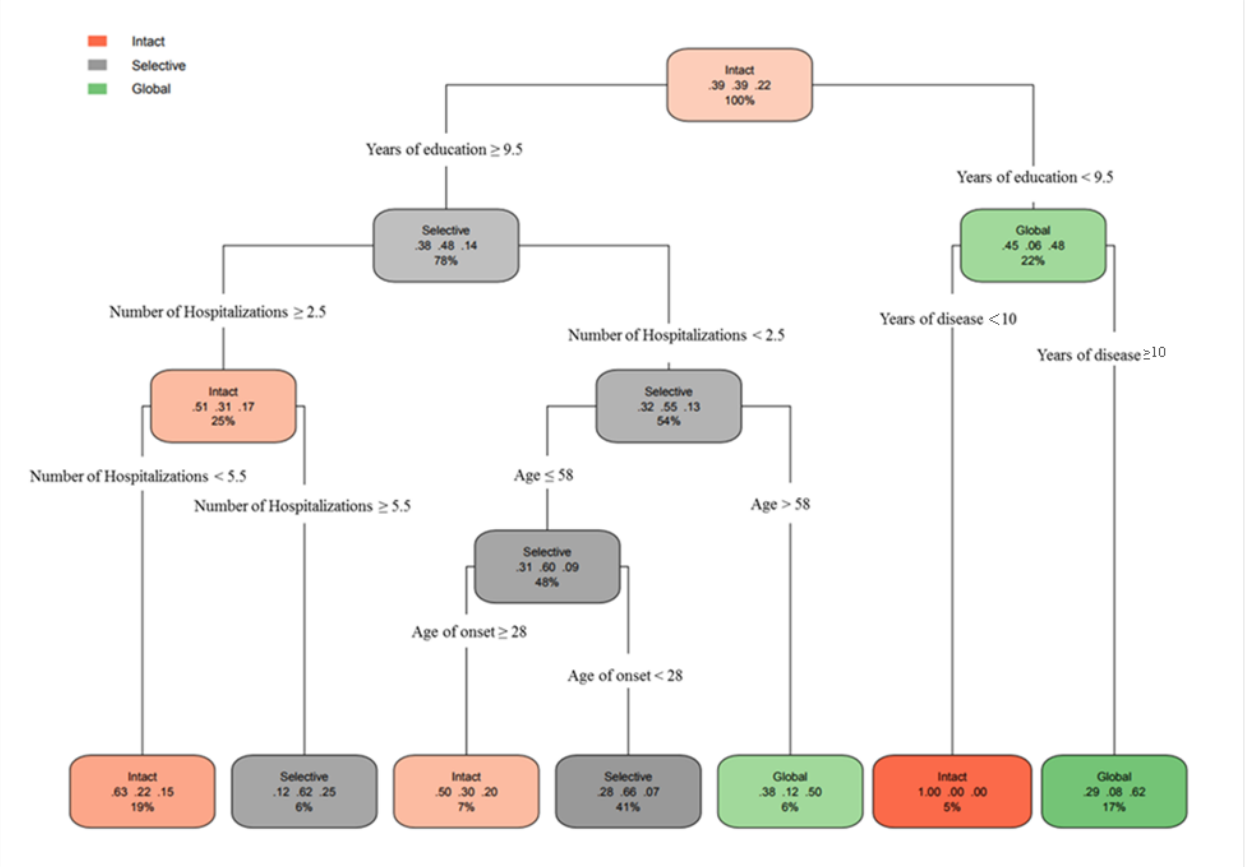

Figure 4– Classification and Regression Tree (CART) model using predictors of cognitive clusters in bipolar disorder. Each node shows the predicted class (intact cognition, selective cognitive impairment or global cognitive deficits), the predicted probability of each cluster and the percentage of observations in the node.

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7. Aspectos éticos

O estudo seguiu as condições estabelecidas pela Declaração de Helsinque e foi submetido ao comitê de ética de cada hospital. Todos os pacientes ou os seus responsáveis legais assinaram o termo de consentimento informado conforme aprovado pelo comitê de ética local, estando livres para decidir, a qualquer momento, sobre sua descontinuidade.

8. Considerações finais

A partir dos dados apresentados, o resultados indicam que há três *clusters* cognitivos no TB: indivíduos cognitivamente intacto, seletivamente prejudicado e globalmente prejudicado. A frequência dos pacientes entre os subgrupos replicam achados anteriores (19).

Os preditores de heterogeneidade cognitiva mais importantes foram anos de educação, anos de doença, número de hospitalizações, idade e idade de início. Esses resultados sugerem uma variedade de trajetórias de doença no TB, impactando de diferentes formas ao longo da doença.

Referências

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