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# FUNCIONAMENTO COGNITIVO NO TRANSTORNO BIPOLAR

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Tese apresentada como requisito parcial para obtenção do título de Doutor em Psiquiatria e Ciências do Comportamento à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento.

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## RESUMO

Historicamente, o transtorno bipolar (TB) tem sido tipificado por seus sintomas de humor. No entanto, estudos recentes têm demonstrado que a disfunção cognitiva no TB é prevalente, persistente e heterogênea. Devido ao seu impacto negativo no funcionamento psicossocial, qualidade de vida e prognóstico da doença, a disfunção cognitiva tornou-se uma questão importante no manejo do TB. A detecção e tratamento da disfunção cognitiva pressupõe o uso de medidas cognitivas apropriadas para avaliação dos déficits cognitivos. O objetivo desta tese foi, além de estudar o funcionamento cognitivo de pacientes com transtorno bipolar eutímicos utilizando medidas cognitivas objetivas e subjetivas, identificar subgrupos cognitivos e seus correlatos demográficos, clínicos, funcionais e dificuldades cognitivas subjetivas. A Escala de disfunções cognitivas no transtorno bipolar (COBRA) foi traduzida e suas propriedades psicométricas foram examinadas e consideradas satisfatórias, portanto, a versão brasileira da COBRA pode ser utilizada para avaliação de dificuldades cognitivas subjetivas em pesquisas e na prática clínica. Para examinar a existência de subgrupos distintos foi conduzida uma análise hierárquica de clusters baseada nas medidas cognitivas objetivas. Adicionalmente, os indivíduos de cada subgrupo cognitivo foram comparados em variáveis demográficas, clínicas, funcionamento psicossocial e medidas cognitivas subjetivas. Foram encontrados três subgrupos distintos: um primeiro cluster com cognição intacta (43,5%), um segundo cluster com comprometimento cognitivo seletivo (33,3%) e um terceiro cluster com comprometimento cognitivo global (23,3%). O grupo intacto teve mais anos de escolaridade e maior QI estimado do que os subgrupos com prejuízo (global e seletivo). Além disso, o grupo intacto era mais jovem, tinha idade de diagnóstico e idade de primeira hospitalização mais precoce, e um maior número de familiares de primeiro grau com transtorno mental que os indivíduos do grupo global. Não foram encontradas diferenças significativas entre os três grupos quanto ao funcionamento psicossocial e às medidas cognitivas subjetivas. Nossos resultados corroboram os achados recentes de heterogeneidade do funcionamento cognitivo no TB, evidenciando a existência de um continuum de gravidade que varia de funcionamento cognitivo preservado a comprometimento severo. Também identificamos QI estimado e anos de educação como as variáveis que diferenciam o grupo com cognição intacta dos grupos com algum grau de comprometimento. No entanto, os três subgrupos apresentaram funcionamento psicossocial prejudicado e dificuldades cognitivas subjetivas, o que significa que mesmo os pacientes do grupo intacto vivenciam dificuldades cognitivas e psicossociais diárias. Os estudos aqui apresentados contribuem para uma melhor caracterização e compreensão da

disfunção cognitiva no TB. Uma avaliação abrangente, buscando integrar dados objetivos, subjetivos e informações clínicas, é essencial para determinar a natureza (subjetivo/objetivo) e a gravidade (intacto-seletivo-severo) da disfunção cognitiva. Esses achados fornecem apoio adicional à necessidade de desenvolver novos estudos para encontrar estratégias eficazes para prevenir e tratar o comprometimento cognitivo e funcional associado ao transtorno bipolar.

**Palavras-chave**: Transtorno Bipolar. Cognição. Avaliação Cognitiva Objetiva e Subjetiva. Análise Hierárquica de Clusters.

## ABSTRACT

Historically, bipolar disorder (BD) has been typified by mood symptoms. However, recent studies have shown that cognitive dysfunction in BD is prevalent, persistent and heterogeneous. Due to the negative impact on psychosocial functioning, quality of life and disease prognosis, cognitive dysfunction has become a relevant issue in the management of BD. The detection and treatment of cognitive dysfunction requires the use of appropriate cognitive measures for the assessment of cognitive deficits. This thesis aims to study the cognitive functioning of euthymic patients with BD using objective and subjective cognitive measures, as well as to identify cognitive subgroups and their demographic, clinical, functional and subjective cognitive difficulties correlates. In order to examine the existence of distinct subgroups, a hierarchical analysis of clusters, based on objective cognitive measures, was conducted. Also, the individuals of each subgroup were compared in demographic, clinical, psychosocial functioning and subjective cognitive measures. Three distinct subgroups were found: the first cluster with intact cognition (43.5%), the second cluster with selective cognitive impairment (33.3%) and the third cluster with global cognitive impairment (23.3%). The intact group had more years of education and higher estimated IQ than impaired subgroups. Additionally, they were younger, had an earlier age at bipolar diagnosis and first hospitalization, and a higher number of first-degree relatives with mental disorder compared to individuals with globally cognitive impairment. No significant differences were found between the three groups regarding psychosocial functioning and subjective cognitive measures. Our results corroborate the recent findings of heterogeneity in cognitive functioning in BD, evidencing the existence of a continuum of severity from preserved cognitive function to severe impairment. We also identified estimated IQ and years of education as the variables that differentiate the group with intact cognition from groups with some degree of impairment. However, the three subgroups presented impaired psychosocial functioning and subjective cognitive difficulties, which means that even the patients in the intact group experience daily cognitive and psychosocial difficulties. The studies presented in this thesis contribute to better characterization and understanding of cognitive dysfunction in BD. A comprehensive assessment, aiming to integrate clinical information, objective and subjective cognitive measures is essential to determine the nature (subjective / objective) and severity (intact-selective-severe) of cognitive dysfunction. These findings provide additional support for the need to develop new studies to find effective strategies to prevent and treat cognitive and functional impairment associated with bipolar disorder.

**Key words**: Bipolar disorder. Cognition. Objective and subjective cognitive assessment. Hierarchical cluster analysis.

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## SUMÁRIO

# 1 APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada "Funcionamento Cognitivo no Transtorno Bipolar", apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do sul, em 26 de novembro de 2018. Está organizada na ordem que segue: Introdução, Objetivos, Considerações Éticas, Artigo 1 (publicado na *Trends in Psychiatry and Psychoterapy*), Artigo 2 (submetido para publicação no *Journal of Affective Disorders*), e Considerações Finais.

Os estudos que compõem essa tese foram desenvolvidos entre os anos de 2015 e 2017 no Programa de Atendimento ao Transtorno do Humor Bipolar (PROTAHBI) e no Laboratório de Psiquiatria Molecular do Hospital de Clínicas de Porto Alegre sob orientação da Prof[a]. Dr[a]. Adriane Rosa. Na presente tese buscou-se estudar o funcionamento cognitivo no transtorno bipolar através de medidas cognitivas objetivas e subjetivas. No artigo 1 intitulado *"Validity and reliability of the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) in Brazilian bipolar patients*" realizou-se a tradução e exame das propriedades psicométricas da Escala de avaliação de disfunções cognitivas no transtorno bipolar (COBRA). No artigo 2 intitulado *"Identifying cognitive subgroups in bipolar disorder: a cluster analysis"* conduziu-se uma análise hierárquica de clusters para investigar a existência de subgrupos cognitivos em uma amostra brasileira de pacientes com TB eutímicos, bem como identificar diferenças entre os subgrupos cognitivos em relação às características demográficas, clínicas, dificuldades cognitivas subjetivas e funcionamento psicossocial. Nesses estudos realizou-se uma avaliação abrangente, utilizando um combo de medidas (objetivas e subjetivas), visando uma melhor caracterização e compreensão da disfunção cognitiva no TB.

## 2 INTRODUÇÃO

O transtorno bipolar (TB), denominado classicamente de psicose maníaco-depressiva por Emil Kraepelin (1921), é caracterizado por episódios de mania, hipomania e depressão, que se alternam com períodos de eutimia. Essa doença atinge 1% da população mundial (MERIKANGAS et al., 2011) e geralmente se manifesta entre o fim da adolescência e o início da vida adulta, afetando pessoas economicamente ativas e, portanto, gerando um alto custo para o indivíduo e a sociedade (GARDNER et al., 2006). De fato, segundo dados da OMS (Organização Mundial da Saúde), o TB é considerado uma das 10 principais causas de incapacitação no mundo (ALONSO et al., 2011).

Além dos sintomas de humor, os indivíduos acometidos pelo TB apresentam marcante prejuízo funcional e cognitivo e, consequentemente, uma redução na qualidade de vida (SOLÉ et al., 2017; VIETA et al., 2018). Esses déficits têm implicações na vida dos pacientes e das pessoas próximas a eles, pois limitam a capacidade de realizar as atividades da vida diária, tais como trabalhar, estudar, estabelecer relações interpessoais e afetivas de qualidade, desfrutar de atividades de lazer, viver de forma independente, entre outras. Adicionalmente, comorbidades psiquiátricas e clínicas são comuns no TB, entre elas, síndrome metabólica, diabetes mellitus, osteoporose, fibromialgia, transtornos endócrinos e cardiovasculares, bem como transtornos de personalidade, transtornos de ansiedade, transtornos por uso de substâncias, transtorno de déficit de atenção e hiperatividade (MERIKANGAS et al., 2017; VIETA et al., 2018).

A presença de comorbidades pode dificultar o diagnóstico e o tratamento do TB. A realização de um diagnóstico precoce, e a consequente implementação de um tratamento adequado o mais breve possível, é um grande desafio no manejo dessa doença (GRANDE et al., 2016; HENRY et al., 2011). Estudos mostram um atraso médio de 5 a 10 anos entre o início dos sintomas e o diagnóstico do TB (BERK et al., 2007a; DAGANI et al., 2017). É importante ressaltar que a duração da doença não tratada (isto é, o tempo entre o primeiro episódio e o tratamento adequado) influencia o prognóstico, sendo que um maior tempo de doença não tratada tem sido associado a uma maior morbidade e tentativas de suicídio (ALTAMURA et al., 2010).

Historicamente, o foco do tratamento do TB tem sido a estabilização dos sintomas de humor e a prevenção de recaídas. Com manejo ideal, os pacientes podem conseguir a remissão clínica completa e ter períodos sem sintomas, durante os quais o transtorno é

considerado latente (SANCHEZ-MORENO; MARTINEZ-ARAN; VIETA, 2017). Entretanto, em muitos casos, os sintomas residuais e subsindrômicos persistem de forma disseminada, dificultando a recuperação funcional, especialmente após o segundo, terceiro e subsequentes episódios (ROSA et al., 2009; VIETA et al., 2018). Estados subsindrômicos são três vezes mais comuns que episódios sindrômicos completos (JUDD et al., 2002; 2003). É por esse motivo que pesquisadores de todo mundo estão trabalhando em novos medicamentos, terapias e tecnologias para expandir as opções de tratamento para lidar com os prejuízos associados ao TB.

Sem possuir uma etiologia única definida, o TB é considerado uma doença multifatorial. Com base nos recentes avanços na elucidação da fisiopatologia do TB, alguns pesquisadores têm sugerido que essa doença segue um curso progressivo desde a forma latente até as apresentações mais graves (BERK et al., 2007b; KAPCZINSKI et al., 2008). De acordo com estes estudos a doença começaria com um período de risco (ou latente), evoluindo a partir do primeiro episódio de humor até a doença em estágios mais avançados onde pacientes tendem a ter um pior prognóstico, com mais déficits cognitivos e marcado prejuízo psicossocial, além de exigir alternativas de tratamento mais dispendiosas.

## 2.1 DISFUNÇÕES COGNITIVAS NO TRANSTORNO BIPOLAR

Nos últimos 20 anos, houve um crescimento exponencial de estudos sobre o funcionamento cognitivo no TB (Figura 1) (BURDICK et al., 2015). Os resultados desses estudos proporcionaram avanços significativos na compreensão da disfunção cognitiva associada ao TB.

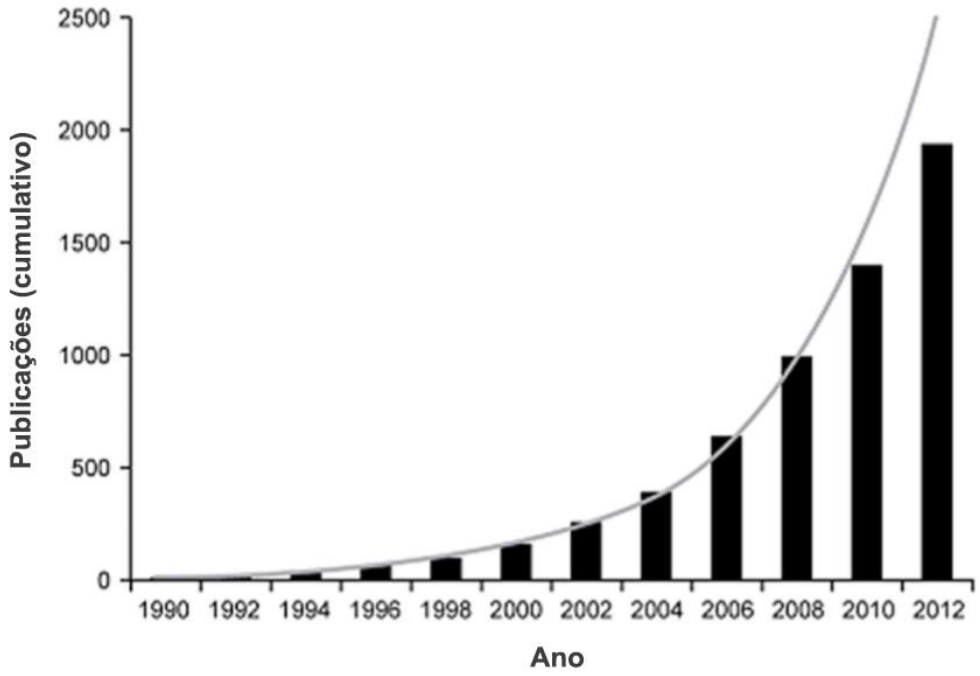


**Figura 1 - Crescimento exponencial na literatura sobre disfunção cognitiva no TB. Os dados foram obtidos a partir de buscas no PubMed entre os anos de 1990 a 2012, usando os termos "cognição" OU "cognitivo" E "bipolar" no título ou resumo.** Fonte: Traduzida e adaptada de Burdick et al., 2015.

Por muitos anos, acreditava-se que o prejuízo cognitivo no TB seria proeminente nas fases agudas da doença, e que os pacientes voltariam ao seu nível de funcionamento pré-mórbido após remissão dos sintomas de humor, apresentando intervalos livres de sintomas e alcançando uma recuperação total entre os episódios de humor (DEPP; DEV; EYLER, 2016; QURAISHI; FRANGOU, 2002). No entanto, diferentes estudos têm mostrado prejuízo cognitivo em todas as fases da doença, inclusive durante a assintomática, evidenciando que tal prejuízo é inerente ao transtorno podendo variar em maior ou menor intensidade dependendo da fase da doença (BORTOLATO et al., 2015; BOURNE et al., 2013; ROBINSON; FERRIER, 2006). O comprometimento funcional segue o mesmo padrão, com achados contemporâneos mostrando que mais da metade dos indivíduos com TB não atinge a

recuperação funcional completa apesar de assintomáticos com o tratamento recebido (HUXLEY; BALDESSARINI, 2007; ROSA et al., 2009; STREJILEVICH et al., 2013; TOHEN et al., 2000). Um estudo americano mostrou que dois anos após o primeiro episódio de mania 98% dos pacientes atingiram a remissão sintomática, enquanto apenas 38% obtiveram recuperação funcional (TOHEN et al., 2000), demonstrando que recuperação sintomática e funcional não são coincidentes.

Ao longo desses últimos anos inúmeros estudos demonstraram que o prejuízo cognitivo persistente está associado a um comprometimento funcional significativo (DEPP; MAUSBACH, 2012; ROSA et al., 2014; TORRENT et al., 2012; TSE et al., 2014). De fato, a disfunção cognitiva tem mostrado ser um forte preditor do funcionamento psicossocial em estudos transversais (DICKERSON et al., 2004; JAEGER et al., 2007; MARTINO et al., 2008) e estudos longitudinais (BONNÍN et al., 2010; MARTINO et al., 2009; TABARÉS-SEISDEDOS et al., 2008). Seguindo os achados de que a disfunção cognitiva contribuiu para a incapacidade funcional, um estudo de metanálise mostrou que habilidades cognitivas específicas influenciam negativamente a atividade profissional (DEPP; MAUSBACH, 2012; TSE et al., 2014). No estudo realizado por Bonnín (2010) o prejuízo na memória verbal, bem como os sintomas depressivos subsindrômicos foram as variáveis que melhor explicaram o comprometimento funcional. Todos esses dados encorajam o desenvolvimento de estudos para encontrar estratégias eficazes para prevenir e tratar o comprometimento cognitivo associado ao TB, uma vez que esses esforços podem levar a uma melhora no funcionamento psicossocial e na qualidade de vida desses pacientes (MISKOWIAK et al., 2018).

Entretanto, é importante ressaltar que nem todas as habilidades cognitivas estão comprometidas no TB. Estudos de metanálise, comparando a performance cognitiva de pacientes com TB eutímicos em relação a controles, revelaram que os pacientes apresentaram pior desempenho nos domínios de velocidade de processamento, atenção, memória verbal e funções executivas (BOURNE et al., 2013; KURTZ; GERRATY, 2009; ROBINSON; FERRIER, 2006).

O curso da doença tem sido um dos fatores frequentemente associado com o declínio cognitivo no TB, no sentido de que indivíduos com uma maior gravidade da doença tendem a apresentar mais disfunção cognitiva (ROSA et al., 2014). O tipo de TB também impacta a cognição, sendo que foram observados déficits cognitivos mais acentuados em pacientes com TB I versus TB II (SIMONSEN et al., 2008), embora este achado não seja

consistente (DITTMANN et al., 2008). História de sintomas psicóticos, um importante marcador de gravidade da doença, também está associada a uma maior probabilidade de comprometimento cognitivo (LÓPEZ-JARAMILLO et al., 2010; MARTINEZ-ARAN et al., 2008). Outras variáveis, como maior tempo de doença, maior número de episódios maníacos e de hospitalizações, também influenciam negativamente a cognição de pacientes com TB (CARDOSO et al., 2015; LÓPEZ-JARAMILLO et al., 2010; ROBINSON; FERRIER, 2006). Entretanto, ainda que a maior parte dos resultados aponte para uma relação positiva entre o prejuízo cognitivo e o curso da doença, alguns estudos sugerem que os déficits cognitivos são perceptíveis já no primeiro episódio e que em alguns pacientes podem ocorrer até mesmo antes do início da doença, de forma semelhante ao que acontece na esquizofrenia (BORA; PANTELIS, 2015; MARTINO et al., 2015). O atraso na aquisição de habilidades cognitivas é um fator de risco para ambos os transtornos. No entanto, ao contrário da esquizofrenia, não apenas o comprometimento cognitivo, mas também o desempenho cognitivo e escolar pré-mórbido acima da média são preditores de TB (BORA, 2015). Além disso, é possível que os achados controversos na literatura em relação à cognição devam-se a heterogeneidade etiológica do próprio TB (BORA et al., 2016b).

Enfim, como a maioria dos estudos sobre cognição no TB é transversal, e os dados sobre a trajetória longitudinal dos déficits cognitivos ao longo do curso da doença são escassos e inconsistentes, não é possível concluir se o déficit cognitivo está presente no início da doença, ou se de fato ocorre à medida que a mesma progride.

## 2.2 HETEROGENEIDADA COGNITIVA NO TRANSTORNO BIPOLAR

Uma das características marcantes do TB é sua heterogeneidade que se revela na sintomatologia, no curso da doença, na resposta ao tratamento e também no funcionamento cognitivo. Tendo isto em conta, a classificação atual dos subtipos de TB (TB I e II), baseada unicamente nos sintomas clínicos da doença, contribui modestamente para explicar a variabilidade da cognição no TB. Portanto, a estratificação de pacientes usando outros especificadores (tais como polaridade predominante, início precoce ou funcionamento cognitivo), que estão ausentes no DSM-5, poderia proporcionar a definição de subtipos mais válidos de TB e também ajudar os clínicos e pesquisadores a desenvolver estratégias de intervenção mais eficazes (VIETA; TORRENT, 2016).

Usualmente, os estudos de cognição utilizam pontos de corte arbitrariamente definidos para classificar os pacientes em grupos com ou sem disfunção cognitiva (MARTINO et al., 2008; THOMPSON et al., 2005). Estudos utilizando pontos de corte restritos (2 DP abaixo da média dos controles) encontraram 25-30% dos pacientes com déficits cognitivos (GUALTIERI; MORGAN, 2008; IVERSON et al., 2011). Foi sugerido que os estudos que relatam valores médios de funcionamento cognitivo no TB podem estar deixando de reconhecer que um subgrupo de pacientes bipolares está demonstrando a maior parte do comprometimento (MARTINO et al., 2008). O uso desse método pode mascarar os efeitos da heterogeneidade, ou seja, o fato de alguns pacientes não apresentarem déficits cognitivos, enquanto em outros eles são graves.

Por outro lado, estudos recentes têm utilizado a análise hierárquica de clusters baseada em funções cognitivas, em vez de pontos de corte arbitrários, com a intenção de categorizar os pacientes em grupos mais homogêneos de funcionamento cognitivo. Muito poucos estudos investigaram subgrupos cognitivos no TB. Um estudo pioneiro de Burdick et al. (2014) utilizou análise hierárquica de cluster para indicar que cerca de 40% dos pacientes apresentaram cognição normal, 30% apresentaram déficits seletivos na memória verbal, velocidade de processamento, atenção e cognição social, mas com funcionamento normal, e 30% eram globalmente prejudicados cognitiva e funcionalmente. Até o momento, os estudos que utilizaram a análise hierárquica de cluster para investigar a heterogeneidade no TB encontraram uma solução de 3-4 clusters: incluindo um subgrupo com desempenho cognitivo normal, outro subgrupo com comprometimento cognitivo grave e disseminado, e 1-2 conjuntos de perfis cognitivos mistos. Na sequência outros três grupos de pesquisa em TB (JENSEN et al., 2016; ROUX et al., 2017; SOLÉ et al., 2016) de diferentes países (Espanha, Dinamarca e França) conduziram estudos semelhantes com resultados na mesma linha.

Levando em consideração todos esses achados, tem-se suposto a existência de dois grupos: um grupo de pacientes bipolares que apresentam funcionamento cognitivo intacto no início da doença com notável declínio, provavelmente, influenciado pela neuroprogressão (isto é, efeitos aparentemente nocivos de repetidos episódios de humor sobre a cognição), e outro grupo de pacientes apresentando um padrão de comprometimento cognitivo comparável ao observado na esquizofrenia, caracterizado por um baixo funcionamento cognitivo pré-mórbido antes do início da doença. Este último grupo de pacientes compartilharia fatores de risco genéticos comuns com a esquizofrenia e poderia estar associado a anormalidades do desenvolvimento neurológico que poderiam resultar em

problemas na aquisição de habilidades cognitivas. No entanto, neste ponto, mais pesquisas genéticas e neurobiológicas são necessárias para confirmar essa hipótese (SOLÉ et al., 2017).

## 2.3 AVALIAÇÃO DAS DISFUNÇÕES COGNITIVAS NO TRANSTORNO BIPOLAR

O estudo do comprometimento cognitivo, suas causas e consequências, bem como o desenvolvimento de novas estratégias terapêuticas para manejar ou mesmo prevenir esses déficits, é atualmente uma das áreas mais promissoras de pesquisa em TB (MARTINEZ-ARAN; VIETA, 2015).

Apesar de sua inquestionável relevância, a avaliação e monitoramento da disfunção cognitiva no TB não é um procedimento padrão no atendimento clínico desses pacientes. Um dos motivos para essa negligência pode dever-se ao fato de que apenas recentemente um consenso de experts no assunto deixou clara a necessidade de realizar a avaliação cognitiva no TB, bem como definiu como deveria ser conduzida e quais os instrumentos deveriam ser usados (Figura 2) (MISKOWIAK et al., 2018).

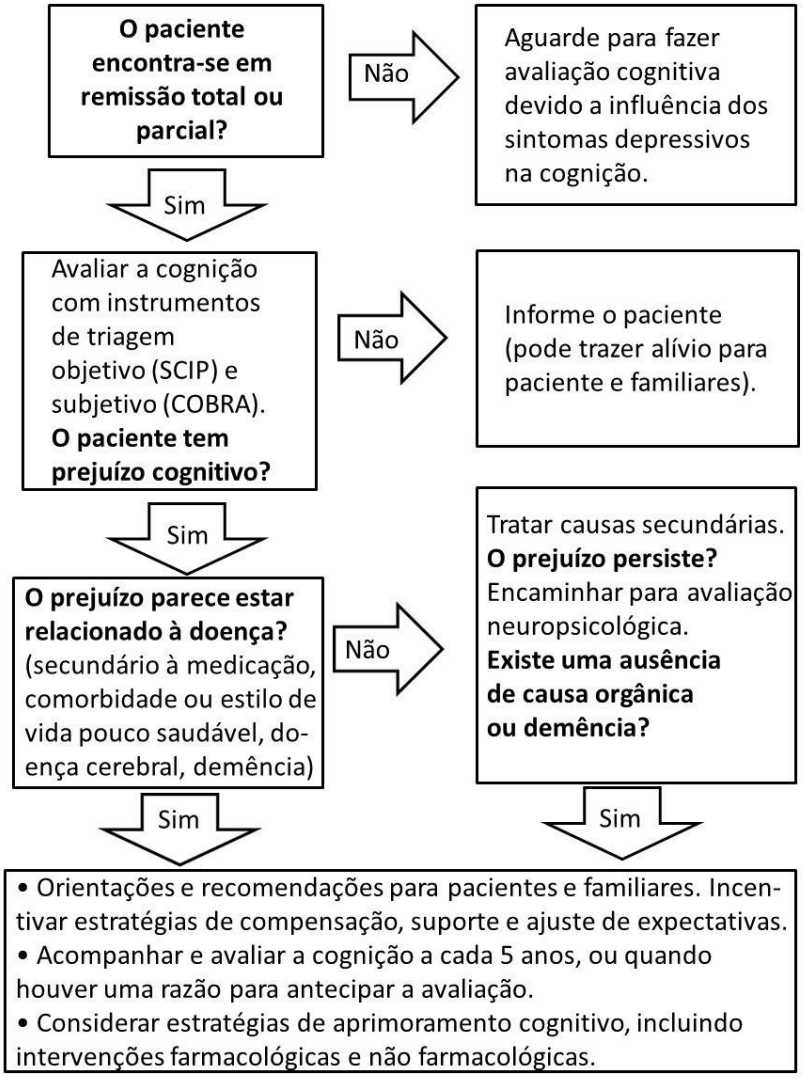


**Figura 2: Recomendações para avaliação clínica da cognição no TB.**
Fonte: Traduzida e adaptada de Miskowiak et al., 2018.

A avaliação do funcionamento cognitivo é um processo gerador de informações capaz de auxiliar os profissionais na tomada de decisão em diferentes contextos. Dito isso, é imperativo que medidas cognitivas apropriadas sejam utilizadas para uma melhor identificação e caracterizaçãodas disfunções cognitivas no TB. Das ferramentas disponíveis para esse processo de avaliação destacam-se as medidas cognitivas objetivas e subjetivas.

### 2.3.1 Medidas cognitivas objetivas

As medidas cognitivas objetivas são imprescindíveis para detectar alterações no funcionamento cognitivo. No entanto, a falta de padronização dos instrumentos utilizados dificultava a comparação dos resultados entre os estudos e a generalização dos mesmos. Por esta razão, em 2010, a Associação Internacional de Transtorno Bipolar (ISBD – *International Society for Bipolar Disorders*) propôs uma bateria de avaliação cognitiva para ser usada internacionalmente, e assim facilitar a comparação dos resultados entre diferentes grupos de pesquisa, bem como avaliar a resposta aos tratamentos que visam a melhora da função cognitiva (YATHAM et al., 2010). Considerando a sobreposição clínica e cognitiva entre esquizofrenia e TB, o comitê endossou a aplicabilidade da maioria dos subtestes da bateria MCCB [*Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) *Consensus Cognitive Battery* (MCCB)] para uso no TB, com a recomendação de incluir testes adicionais de funções executivas e memória verbal.

A bateria preliminar proposta pela ISBD, com seis domínios cognitivos derivados dos escores de dez subtestes, é apresentada no Quadro 1.

| **DOMÍNIO** | **TESTE** |
|---|---|
| Velocidade de processamento | TMT-A (*Trail Making Test* – A)<br>Codificação de símbolos (BACS)<br>Fluência verbal categórica (F A S) |
| Atenção | CPT-IP (*Continuous Performance Test Identical Pairs*) |
| Memória de trabalho | Sequência de números e letras<br>Span espacial (WMS–3) |
| Aprendizagem / memória verbal | HVLT-R (*Hopkins Verbal Learning Test Revised*)<br>CVLT (*California Verbal Learning Test*) opcional |
| Aprendizagem / memória visual | BVMT-R (*Brief Visuospatial Memory Test Revised*) |
| Função executiva | SCWT(*Stroop Color Word Test*)<br>TMT-B (*Trail Making Test* – B)<br>WCST (*Wisconsin Card Sorting Test*) opcional |

**Quadro 1: Bateria cognitiva para o TB – proposta final (ISBD-BANC – *Battery for Assessment of Neurocognition*).** Fonte: Traduzida e adaptada de Yatham et al., 2010.

Como consequência do consenso proposto pela ISBD, a partir de 2011 a bateria passou a ser adotada em diversos estudos. Em 2017 a primeira metanálise examinando o funcionamento cognitivo com a MCCB foi publicada. Essa metanálise incluiu sete estudos (TB = 487; controles = 570) e mostrou que pacientes com TB comparados aos controles apresentaram prejuízos em todos os domínios cognitivos avaliados, sendo os domínios de velocidade de processamento e memória de trabalho os mais prejudicados (BO et al., 2017).

A administração de uma bateria como a recomendada pela ISBD (ISBD-BANC) exige profissional especializado, além de ser um procedimento demorado e com alto custo, o que pode limitar seu uso, principalmente, na prática clínica. Por essa razão, em contextos clínicos, é pertinente o uso de instrumentos breves e fáceis de aplicar para uma avaliação inicial e acompanhamento de sintomas cognitivos, bem como para definir quando uma avaliação neuropsicológica deve ser solicitada. Para tal finalidade, a ISBD sugere a utilização de instrumentos como SCIP (medida cognitiva objetiva) e COBRA (medida cognitiva subjetiva – seção 2.3.2).

O SCIP (*Screen for Cognitive Impairment in Psychiatry*) é uma medida cognitiva objetiva de triagem composta por cinco testes curtos (ver Anexo I), com um tempo de administração de aproximadamente 10-15 minutos e três versões paralelas para possibilitar a repetição da medida (PURDON, 2005). Esse instrumento avalia dificuldades na memória de trabalho, memória verbal, fluência verbal e velocidade psicomotora, tendo apresentado alta sensibilidade e especificidade para detectar o comprometimento cognitivo no TB (JENSEN et al., 2015a). O SCIP está disponível em diversos idiomas: chinês, dinamarquês, inglês, francês, alemão, italiano, japonês, persa, português, russo e espanhol. As versões em dinamarquês, inglês, francês e alemão já se encontram validadas com seus respectivos dados normativos e pontos de corte, enquanto as versões em chinês, italiano, japonês, persa e português foram traduzidas, mas ainda carecem de dados normativos. Todas essas versões do SCIP podem ser obtidas gratuitamente no site da ISBD (www.isbd.org/cognitive-assessment).

### 2.3.2 Medidas cognitivas subjetivas

Os indivíduos com TB frequentemente queixam-se de dificuldades cognitivas em situações da vida diária. Problemas com atenção, concentração, memória, percepção, pensamento, linguagem, movimento e emoção (PERALTA; CUESTA, 1998) são comumente

relatados. Instrumentos confiáveis e válidos para medir as dificuldades cognitivas subjetivas no TB podem ser de grande utilidade na pesquisa e na prática clínica.

A escala de disfunções cognitivas no transtorno bipolar (COBRA) é um instrumento de autorrelato de 16 itens (ver Anexo II), desenvolvido para medir as principais dificuldades cognitivas descritas na literatura e vivenciadas pelos pacientes com TB (ROSA et al., 2013). Originalmente, a COBRA foi desenvolvida em espanhol pelo grupo de pesquisa de transtorno bipolar de Barcelona; esta versão mostrou propriedades psicométricas satisfatórias (ROSA et al., 2013). Traduções desta versão inicial foram realizadas para outros idiomas (inglês, dinamarquês, chinês, japonês e português) e recentemente validadas (JENSEN et al., 2015a; LIMA et al., 2018; TOYOSHIMA et al., 2017; XIAO et al., 2015; YOLDI-NEGRETE et al., 2018). Versões da COBRA em cinco idiomas estão disponíveis gratuitamente no site da ISBD (www.isbd.org/cognitive-assessment).

Nas pesquisas que avaliam o efeito de um tratamento, a COBRA pode ser útil como medida de resposta ao tratamento cognitivo, assim como uma medida co-primária com relevância funcional, uma vez que está relacionada ao funcionamento do dia a dia. A COBRA também pode contribuir no recrutamento e adesão ao tratamento uma vez que a presença de dificuldades cognitivas subjetivas torna a intervenção relevante para o paciente, mantendo-o motivado a participar e não abandonar o estudo.

Um dos desafios na clínica é discernir quando a presença de queixas cognitivas representam déficits cognitivos objetivos, ou quando expressam outros processos (sintomas depressivos ou ansiosos, efeitos adversos da medicação ou outros parâmetros clínicos). No entanto, alguns pacientes podem não trazer essas questões na consulta. A administração rotineira da COBRA seria, assim, uma maneira rápida e fácil do clínico abordar essa questão e esclarecer se o paciente apresenta dificuldades cognitivas subjetivas. A COBRA também pode ser usada para identificar e monitorar mudanças nas dificuldades cognitivas subjetivas de pacientes com TB, uma vez que fornece um dado basal pelo qual as avaliações subsequentes podem ser comparadas.

Ainda, medidas cognitivas subjetivas podem capturar melhor o declínio cognitivo em pacientes com funcionamento cognitivo pré-mórbido acima da média do que os testes objetivos, nos quais o desempenho é comparado com os dados normativos de indivíduos com inteligência média e, portanto, podem não mostrar déficits. A COBRA também é apropriada

para identificar as dificuldades na execução de atividades da vida diária que anteriormente eram rotineiras.

No entanto, muitos pacientes podem reportar dificuldades cognitivas subjetivas sem necessariamente apresentar déficits objetivos, e vice-versa. De fato, a percepção dos pacientes sobre suas próprias habilidades cognitivas depende de vários fatores, incluindo a capacidade de *insight* e a gravidade dos sintomas depressivos (MISKOWIAK et al., 2016a). É importante ressaltar que a correlação entre medida cognitiva objetiva e subjetiva é fraca, portanto a medida cognitiva subjetiva não deve ser utilizada em substituição à objetiva, e sim de forma complementar afim de melhor caracterizar as dificuldades cognitivas no TB.

A importância do uso de um combo de instrumentos para avaliar a disfunção cognitiva no TB pode ser ilustrada através dos resultados de um ensaio clínico (YATHAM et al., 2017), onde foi possível demonstrar que o tratamento adjuvante com lurasidona pode efetivamente melhorar a função cognitiva em pacientes com TB eutímicos. Os resultados deste estudo fornecem algumas evidências de melhora não apenas na medida cognitiva objetiva, mas também na medida cognitiva subjetiva e na qualidade de vida, sugerindo que esses achados além de estatisticamente significativos, teriam, de fato, um efeito importante também na vida dos pacientes. Adicionalmente, os achados deste estudo sugerem que o comprometimento cognitivo no TB é potencialmente tratável.

A ISBD recomenda incorporar rotineiramente o exame das disfunções cognitivas utilizando medidas cognitivas subjetivas e objetivas, dentro de avaliações clínicas iniciais no TB, visando planejar tratamentos mais específicos (sob medida) (MISKOWIAK et al., 2018). Em última análise, a adoção mais ampla de um conjunto comum de procedimentos padronizados viabilizará a comparação dos resultados entre diferentes grupos de pesquisa internacionais, e isso provavelmente proporcionará a aquisição de conhecimentos relativos ao funcionamento cognitivo no TB.

## 2.4 JUSTIFICATIVA

A partir do exposto, parece relevante estudar a disfunção cognitiva no transtorno bipolar através de uma perspectiva mais abrangente, isto é, através do uso de medida cognitiva objetiva e subjetiva. Ainda assim, a identificação de clusters cognitivos poderia

contribuir para uma melhor caracterização e compreensão da heterogeneidade cognitiva no TB, bem como ajudaria a delinear tratamentos específicos e personalizados em função das necessidades de cada paciente.

# 3 OBJETIVOS

## 3.1 OBJETIVO GERAL

1) Estudar o funcionamento cognitivo de pacientes com TB eutímicos utilizando medidas cognitivas objetivas e subjetivas.

## 3.2 OBJETIVOS ESPECÍFICOS

1) Traduzir e examinar as propriedades psicométricas da Escala de avaliação de disfunções cognitivas no transtorno bipolar (COBRA).

2) Investigar a relação entre a medida cognitiva subjetiva (COBRA), medida cognitiva objetiva (testes neuropsicológicos) e o curso da doença.

3) Examinar, através da análise hierárquica de clusters, a existência de subgrupos cognitivos em uma amostra brasileira de pacientes com TB eutímicos.

4) Identificar diferenças entre os subgrupos cognitivos em relação às características demográficas, clínicas, dificuldades cognitivas subjetivas (COBRA) e funcionamento psicossocial.

## 4 CONSIDERAÇÕES ÉTICAS

Todos os participantes deste estudo foram capazes de compreender e assinar o Termo de consentimento livre e esclarecido (TCLE).

Foi assegurada a ausência de vinculação da concordância em participar do estudo com a continuidade do atendimento no Programa de Atendimento do Transtorno de Humor Bipolar (PROTAHBI) do Hospital de Clínicas de Porto Alegre (HCPA).

Os princípios bioéticos de autonomia, beneficência, não maleficência, veracidade e confidencialidade foram seguidos. O presente estudo foi aprovado pelo Comitê de Ética em Pesquisa do HCPA.

## 5 ARTIGO 1

Publicado na *Trends in Psychiatry and Psychoterapy*

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# Validity and reliability of the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) in Brazilian bipolar patients

*Validade e fidedignidade da Escala de Disfunções Cognitivas no Transtorno Bipolar (COBRA) em pacientes bipolares brasileiros*

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## ABSTRACT

**Introduction**: In Brazil, there is no valid instrument to measure subjective cognitive dysfunction in bipolar disorder. The present study analyzed the psychometric properties of the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) in Brazilian bipolar patients. We further investigated the relationship between the COBRA, objective cognitive measures, and illness course variables. **Methods**: The total sample (N = 150) included 85 bipolar disorder patients and 65 healthy controls. The psychometric properties of the COBRA (e.g., internal consistency, concurrent validity, discriminative validity, factor analyses, ROC curve, and feasibility) were analyzed. **Results**: The COBRA showed a one-factor structure with very high internal consistency (Cronbach's alpha = 0.890). Concurrent validity was indicated by a strong correlation with the cognitive domain of the FAST ($r$ = 0.811, p<0.001). Bipolar patients experienced greater cognitive complaints (mean = 14.69; standard deviation [SD] = 10.03) than healthy controls (mean = 6.78; SD = 5.49; p<0.001), suggesting discriminative validity of the instrument. No significant correlations were found between the COBRA and objective cognitive measures. Furthermore, higher COBRA scores were associated with residual depressive ($r$ = 0.448; p<0.001) and manic ($r$ = 0.376; p<0.001) symptoms, number of depressive episodes ($r$ = 0.306; p = 0.011), number of total episodes ($r$ = 0.256; p = 0.038), and suicide attempts ($r$ = 0.356; p = 0.003). **Conclusion**: The COBRA is a valid instrument to assess cognitive complaints, and the combined use of subjective-objective cognitive measures enables the correct identification of cognitive dysfunctions in bipolar disorder.

**Keywords:** Bipolar Disorder; Cognition; Neuropsychological Tests; Cognitive Complaints.

## RESUMO

**Introdução**: No Brasil, não existem instrumentos válidos para medir a disfunção cognitiva subjetiva no transtorno bipolar. O presente estudo analisou as propriedades psicométricas da Escala de Disfunções Cognitivas no Transtorno Bipolar (COBRA) em uma amostra brasileira de pacientes bipolares. Adicionalmente, investigamos a relação entre a COBRA, medidas cognitivas objetivas e curso da doença. **Métodos:** A amostra total (n = 150) incluiu 85 pacientes com transtorno bipolar e 65 controles saudáveis. As propriedades psicométricas da COBRA (consistência interna, validade concorrente, validade discriminativa, análise fatorial, curva ROC e fidedignidade) foram analisadas. **Resultados**: A avaliação COBRA apresentou

estrutura de um fator com alta consistência interna (alfa de Cronbach = 0,890). A validade concorrente ficou demonstrada pela forte correlação com o domínio cognitivo da FAST (*r* = 0,811, p<0,001). Pacientes bipolares tiveram mais queixas cognitivas [média=14,69; desvio padrão (DP) = 10,03] que os controles (média = 6,78; DP = 5,49; p< 0,001), sugerindo a validade discriminativa do instrumento. Não houve correlação significativa entre a COBRA e medidas cognitivas objetivas. Além disso, escores mais altos na COBRA estiveram associados com sintomas residuais depressivos (*r* = 0,448; p<0,001) e maníacos (*r* = 0,376; p<0,001), número de episódios depressivos (*r* = 0,306; p = 0,011), número de episódios totais (*r*=0.256; p=0.038) e tentativas de suicídio (*r* = 0,356; p = 0,003). **Conclusão**: A COBRA é um instrumento válido para avaliar queixas cognitivas, e o uso combinado das medidas cognitivas subjetivas-objetivas possibilita a correta identificação das disfunções cognitivas no transtorno bipolar.

**Descritores:** Transtorno Bipolar; Cognição; Testes Neuropsicológicos; Queixas Cognitivas.

## INTRODUCTION

Cognitive dysfunction in bipolar disorder (BD) occurs across several domains, including attention, verbal memory and executive function.[1,2] These deficits are not only present during acute mood episodes, but persist, in some degree, into periods of remission.[3,4] In addition, cognitive dysfunction may predict functional impairment[5,6] and treatment adherence.[7,8] Thus, the correct identification and treatment of cognitive dysfunction in BD is critical and would help improve functioning and quality of life forpatients with BD.[9]

In the last two decades, cognitive function has become one of the most important construct to be evaluated in psychiatry, both clinically and in research. Indeed, emerging evidence has highlighted the relevance of assessing cognitive performance in BD.[10,11] However, the ideal methodology for assessing cognition in mental illness is still subject of debate in the literature. Whereas objective cognitive measures (e.g., neuropsychological tests) allow us to assess cognitive performance of an individual as compared to the normative population, subjective cognitive measures tend to assess the subject's cognitive function in comparison to their own premorbid levels.[10-12] Furthermore, the patient's perception of their cognitive function is an important issue and should be considered. Therefore, an adequate assessment of cognition requires not only objective neuropsychological tests but also subjective cognitive measures.[10]

Although there are several instruments evaluating subjective cognitive dysfunction in patients with mental disorders,[13-16] most of them do not specifically detect cognitive deficits experienced by patients with BD. In this context, the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) was carefully designed to assess cognitive difficulties associated with the main deficits experienced by patients with BD as reported in the literature.[11] Currently, the COBRA is available in distinct languages (such as Spanish, English, French Chinese, Danish, Japanese) and has been used in both research and clinical practice in various cultures.[11,12,17-19]

In Brazil, there is no clinically feasible screening scale to assess cognitive difficulties in BD, indicating the importance to validate instruments in this regard. The main aim of the current study was to examine the psychometric properties of the COBRA among Brazilian patients with BD. In addition, we investigated the relationship between the COBRA scale, neuropsychological tests, and the course of the illness.

## METHODS

*Participants*

Eighty-five patients with BD were recruited from the Programa de Atendimento do Transtorno de Humor Bipolar (PROTHABI), at Hospital de Clínicas de Porto Alegre, in southern Brazil, between October 2015 and July 2017. The inclusion criteria were: 1) having a diagnosis of BD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); 2) being 18 to 70 years old; 3) meeting criteria for euthymia for at least one month previous to the assessment, defined as a score ≤7 on the Hamilton Depression Rating Scale (HAM-D)[20] and the Young Mania Rating Scale (YMRS).[21] Exclusion criteria were: 1) having any medical or comorbid psychiatric condition affecting neuropsychological performance and current drug or alcohol dependence or abuse; and 2) having undergone electroconvulsive therapy within the past year.

Sixty-five healthy controls who had no current or previous history and no first-degree family history of a major psychiatric disorder, including dementia or mental retardation, assessed by the non-patient version of the Structured Clinical Interview for DSM-IV-TR (SCID), were recruited from the general population within the catchment area of Hospital de Clínicas de Porto Alegre.

This study was approved by the ethics committee of Hospital de Clínicas de Porto Alegre. Following verbal description of the study objectives and details, all participants signed a written informed consent form.

*Assessment*

Clinical and demographic features

All participants' demographic, clinical and pharmacological data were obtained through a structured interview and from medical records. The 17-item HAM-D[20] and the YMRS[21] were administered by trained raters to assess depressive and manic symptoms, respectively.

Functional status

The overall functional outcome was assessed using the Functioning Assessment Short Test (FAST), an instrument widely used in patients with BD. This scale includes 24 items that evaluate six functional domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time). The higher the score, the greater the disability.[22]

Subjective cognitive measure

The COBRA is a 16-item self-report instrument that allows to measure subjective cognitive difficulties including executive function, processing speed, working memory, verbal learning and memory, attention/concentration, and mental tracking. All items are rated using a 4-point scale: 0 = never, 1 = sometimes, 2 = often, and 3 = always (see Portuguese and English versions in Appendix 1). The total score is obtained by adding up the scores of every item. The higher the score, the higher the number of subjective complaints.[11]

The linguistic adaptation of the COBRA started with a document in Portuguese obtained by the translation/back-translation method. The items not resulting in appropriate wording equivalence with the original text were analyzed by the team of investigators and the translators until they agreed upon an appropriate expression. Subsequently, bilingual people (TAC and ARR) evaluated the degree of equivalence between the original English and the Portuguese version.

Objective cognitive measure

Based on the consensus of the International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC),[23] all participants completed a comprehensive neuropsychological battery in order to assess different cognitive domains, as follows:

- Processing speed: Phonemic Verbal Fluency (F-A-S)[24] and Trail Making Test–Part A (TMT-A)[25];
- Working memory: Letter-Number Sequencing Subtest WAIS-III (LNS)[26,27];
- Verbal learning and memory: Hopkins Verbal Learning Test – Revised (HVLT-R)[28];
- Executive functions: Stroop Color-Word Test (SCWT)[29] and Trail Making Test-Part B (TMT-B)[25];
- Attention: Continuous Performance Test – Identical Pairs (CPT-IP);
- Social cognition: Reading the Mind in the Eyes Test – Revised (RMET-R)[30];
- Estimated intelligence quotient (IQ): Wechsler Abbreviated Scale of Intelligence (WASI) – vocabulary and matrix reasoning subtests.[31,32]

*Validity and reliability assessment*

Internal consistency reliability of the COBRA was assessed using Cronbach's α coefficient. Concurrent validity was assessed in three ways: 1) to examine the relationship between COBRA results and the cognitive domain of the FAST; 2) to investigate the association between the COBRA and objective cognitive measures (neuropsychological battery); and 3) to investigate possible correlations between the COBRA and course of the illness. Validity as a discriminative measure to detect differences between patients with BD and healthy controls was analyzed using parametric independent *t*-tests. The optimal point for the COBRA was determined by means of a receiver operating characteristic (ROC) curve. An exploratory factor analysis by the principal axis factoring method (quartimax with Kaiser normalization) was performed to describe the internal structure of the COBRA. Finally, feasibility was described as the percentage of patients and controls who did respond to the questionnaire in its entirety.

*Statistical analysis*

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 18.0. Internal consistency was assessed using Cronbach's alpha. Spearman's correlation coefficients were calculated to examine the possible relationship between the COBRA, FAST, neuropsychological and clinical variables. Group comparisons (patients and controls) were made using parametric *t*-tests. The rotation was performed using the quartimax method and the ROC curve was used to detect the optimal point to discriminate between patients and controls.

## RESULTS

A total of 150 subjects (85 patients with BD and 65 healthy volunteers) were included in the study. Sixty-one (71.8%) patients and 46 (78.0%) controls were women (p = 0.240). The mean age of the patients was 49.60 (12.88) years, and that of the controls was 45.85 (15.68) years (p = 0.121). Other socio demographic and clinical characteristics of the sample are shown in Table 1.

**Table 1:** Sociodemographic characteristics of the sample and clinical characteristics of patients with BD

| | Controls (n=65) | Patients with BD (n=85) | p |
|---|---|---|---|
| Sex (female), n (%) | 46 (78.0) | 61 (71.8) | 0.240 |
| Age (years) | 45.85 (15.68) | 49.60 (12.88) | 0.121 |
| Years of education | 14.71 (4.08) | 10.67 (4.02) | <0.001 |
| Married, n (%) | 30 (46.2) | 38 (45.8) | 0.964 |
| Employed, n (%) | 30 (46.2) | 19 (22.9) | 0.003 |
| Age at onset (years) | | 33.63 (12.53) | |
| Number of hospitalizations | | 4.21 (5.17) | |
| Number of (hypo)manic episodes | | 6.25 (4.93) | |
| Number of depressive episodes | | 6.12 (5.14) | |
| Number of total episodes | | 12.48 (8.71) | |
| Duration of illness (years) | | 15.66 (9.54) | |
| Number of suicide attempts | | 1.27 (1.44) | |
| Psychotic symptoms at first episode | | 48 (61.5%) | |
| HAM-D score | | 3.52 (2.12) | |
| YMRS score | | 1.17 (1.44) | |

Data presented as mean (SD= standard deviation), unless otherwise specified. BD = bipolar disorder; HAM-D= Hamilton Depression Rating Scale; YMRS= Young Mania Rating Scale.

*Internal consistency*

The internal consistency coefficient obtained was high, with Cronbach's alpha = 0.890 for the total 16-item scale, suggesting that the items are sufficiently homogeneous.

*Associations between COBRA and FAST*

A strong correlation was found between the COBRA total score and the cognitive domain of the FAST scale, indicating the concurrent validity of the instrument ($r$ = 0.811, p<0.001; Figure 1).

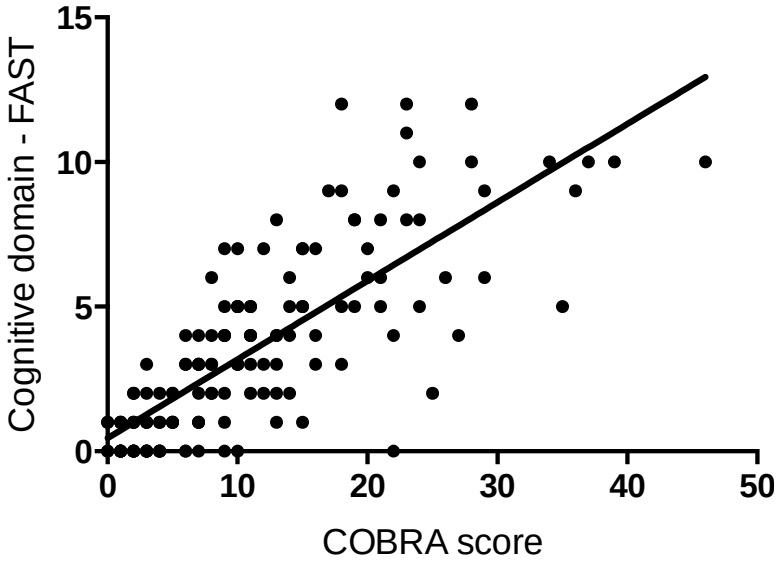


**Figure 1**: Concurrent validity of the COBRA. Spearman correlation between COBRA and the cognitive domain score of FAST scale ($r$=0.811; p<0.001). COBRA = Cognitive Complaints in Bipolar Disorder Rating Assessment; FAST = Functioning Assessment Short Test.

*Associations between subjective and objective cognitive measures*

Spearman correlations were performed to assess the relationship between subjective and objective cognitive measures in both groups. No significant correlation was found between the COBRA and neuropsychological tests among the patients (p-values > 0.107). In the control group, a negative significant correlation was found between the COBRA and HVLT-R (p = 0.006; other p-values > 0.072).

*Associations between subjective cognitive measures and course of illness*

The COBRA was positively correlated with total number of mood episodes ($r$ = 0.256; p = 0.038), number of depressive episodes ($r$ = 0.306; p = 0.011), number of suicide attempts ($r$ = 0.356; p = 0.003), residual depressive symptoms ($r$ = 0.448; p<0.001), and manic symptoms ($r$=0.376; p<0.001; Table 2).

**Table 2**: Spearman's correlation coefficients between COBRA and the course of bipolar disorder

| | **COBRA score *r* (p)** |
|---|---|
| Age | 0.052 (0.640) |
| Age at onset | 0.026 (0.821) |
| Total number of episodes | 0.256 (0.038) |
| Number of depressive episodes | 0.306 (0.011) |
| Number of manic episodes | 0.161 (0.191) |
| Number of hospitalizations | 0.005 (0.966) |
| Number of suicide attempts | 0.356 (0.003) |
| Duration of illness | 0.136 (0.233) |
| HAM-D score | 0.448 (<0.001) |
| YMRS score | 0.376 (<0.001) |

COBRA = Cognitive Complaints in Bipolar Disorder Rating Assessment; HAM-D= Hamilton Depression Rating Scale; YMRS= Young Mania Rating Scale.

*Validity as a discriminative measure to detect differences between patients with BD and healthy controls*

Patients with BD showed higher COBRA total scores (mean = 14.69; standard deviation [SD]=10.03) than healthy controls (mean = 6.78; SD = 5.49; $p<0.001$; Figure 2).

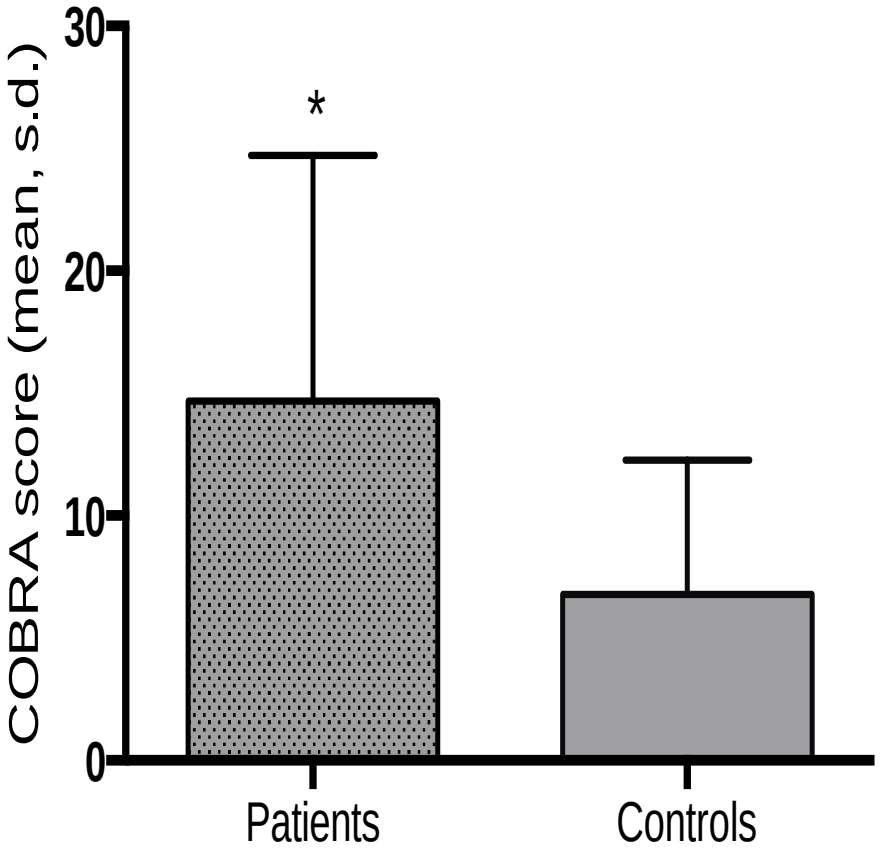


**Figure 2**: Mean and standard deviation of COBRA between patients and controls. COBRA = Cognitive Complaints in Bipolar Disorder Rating Assessment.*p<0.001.

*ROC curve*

We analyzed the scale's ability to discriminate between patients and controls by means of the diagnostic performance or ROC curve. The area under the curve was 0.752 (95% confidence interval [95% CI] 0.674-0.829), i.e., close to 1, indicating good capacity. The discriminative capacity analysis indicated that a score of 10 obtains the best balance between sensitivity (64.7%) and specificity (72.3%; Figure 3).

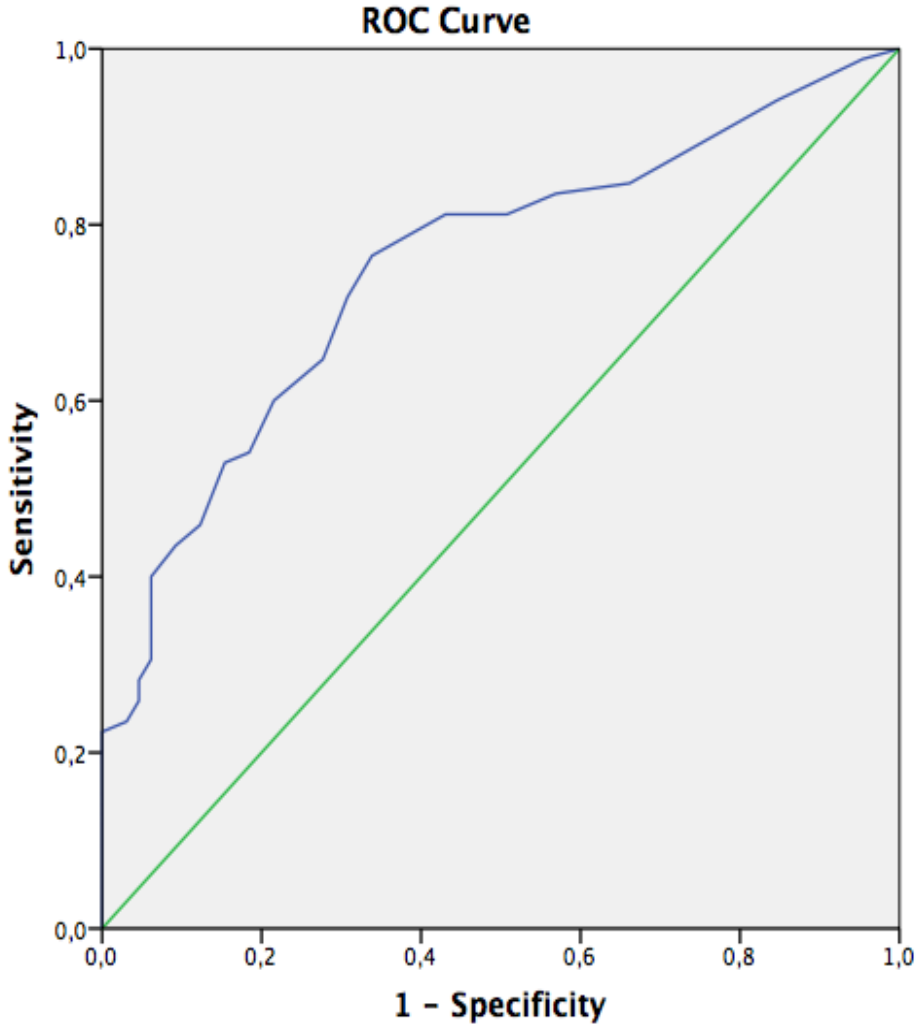


**Figure 3** -ROC curve between patients and controls. The area under the curve was 0.752 (95%CI 0.674-0.829). Cut-off point 10 indicates the best balance between sensitivity (64.7%) and specificity (72.3%). 95%CI = 95% confidence interval; ROC = receiver operating characteristic.

*Factor analysis*

The study of the internal structure of the COBRA, after rotation (using the quatrimax method), determined a three-factor structure, as shown in Table 3. However, only two items were loaded in the second factor, and one item in the third factor. As values loaded in the second factor and third factor were very close to the first load, we confirmed the original one-factor structure with 38.42% of the total variance.

**Table 3**: Factor loadings on the COBRA

| | Factor | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| Item 5 | 0.722 | | |
| Item 15 | 0.700 | | |
| Item 16 | 0.677 | | |
| Item 6 | 0.668 | | |
| Item 14 | 0.666 | | |
| Item 12 | 0.623 | | |
| Item 11 | 0.610 | | |
| Item 8 | 0.601 | | |
| Item 13 | 0.575 | | |
| Item 7 | 0.573 | | |
| Item 1 | 0.568 | | |
| Item 10 | 0.469 | | |
| Item 9 | 0.402 | | |
| Item 4 | 0.473 | 0.591 | |
| Item 3 | 0.516 | 0.534 | |
| Item 2 | 0.479 | | 0.543 |

COBRA = Cognitive Complaints in Bipolar Disorder Rating Assessment.
Extraction method: principal axis factoring (quartimax rotation with Kaiser normalization).

*Feasibility*

Finally, the results showed a high feasibility of the COBRA, since the totality of participants answered all items of the instrument.

## DISCUSSION

The results of the present study demonstrated that the COBRA is a valid method to assess cognitive complaints in Brazilian patients with BD. The instrument exhibited satisfactory psychometric properties, with very high internal consistency and convergent validity as indicated by a strong correlation with the cognitive domain of the FAST. As expected, COBRA total scores were higher in patients compared to healthy controls, suggesting the discriminative validity of the instrument. The cut-off point to discriminate subjective cognitive function between patients and controls was the same found in the Spanish validation study (>10) and similar to the Chinese study (>11). Furthermore, the COBRA presented a one-factor structure, which means that patients tend to perceive their deficits as a global cognitive dysfunction rather than to discriminate deficits in specific cognitive domains. Our finding is consistent with previous validation studies with BD in other countries.[11,12,17,19] The Portuguese version of the COBRA is now ready and available to be used as a subjective cognitive measure in clinical practice and research settings.

The weak correlation found between the COBRA and neuropsychological tests in the current study is in agreement with previous findings. For instance, the Spanish study showed significant correlations between the COBRA and some neuropsychological tests, particularly in single measures related to executive function, working memory, verbal, and visual memory.[11] A recent research in Japan observed no association between the COBRA and objective neurocognitive battery, except for COBRA and processing speed.[19] Xiao et al.[17] did not find relationships between the COBRA and the Montreal Cognitive Assessment (MoCA) total score. However, significant correlations were found between the COBRA and single measures related to executive function and verbal memory. A study conducted in Denmark[12] showed a poor association between objective cognitive measures and the COBRA. In particular, COBRA total scores correlated with working memory and executive skills on the neuropsychological tests and on the Screen for Cognitive Impairment in Psychiatry (SCIP). In contrast, we found a correlation between the COBRA and verbal memory in healthy controls. Possibly, some patients with BD have more difficulties in reporting correctly their cognitive deficits or have more difficulties in expressing their cognitive deficits. Taken together, these findings support the idea that subjective cognitive measures are not a direct expression of objective cognitive measures.[18] In particular, the COBRA is a self-report instrument expressing patients' opinion of their cognitive difficulties in daily lives, which is not always congruent with results obtained by objective neuropsychological tests that

compare patients' performance with a normative group, and therefore reflect different aspects of cognition.

In addition, as objective and subjective cognitive measures may capture somewhat different processes, some authors have suggested that simple correlational analysis between overall scores of subjective cognitive measures and neuropsychological tests may limit the understanding of this disagreement.[10] In this sense, Miskowiak et al.[10] proposed a novel methodology to quantify the degree and direction of the subjective-objective discrepancy, as well to explore predictors of discrepancy. Their findings indicated that some patients seem to have a relatively accurate sense of their cognitive abilities, whereas others may over report or underreport cognitive difficulties. In particular, patients with more mood symptoms, greater illness chronicity, BD type II, and male gender showed greater subjective than objective cognitive impairment, whereas patients with high premorbid IQ under reported objective cognitive impairment. Further studies are required to investigate concordance and discrepancy between subjective and objective cognitive measures as this understanding could guide the clinical assessment and treatment of cognitive dysfunction in BD.

Another interesting finding of the present study was that patients with more subsyndromal depressive and manic symptoms experienced greater cognitive complaints, suggesting that mood symptoms may influence self-assessment of cognitive difficulties. The impact of depressive symptoms on subjective cognitive measures has been consistently demonstrated in many studies.[11-18] For instance, using a multiple regression analysis, Ott et al.[18] identified depressive symptoms as the best predictor of subjective cognitive dysfunction in a unipolar disorder sample. Indeed, there is a trend toward increased subjective cognitive complaints alongside increased depressive symptomatology. A possible explanation for these findings is that depressive symptoms, albeit residual, lead to a negative perception of cognitive ability in these individuals, affecting their functioning. Conversely, it is possible to speculate that the patient's perception of themselves as less competent may contribute to the worsening of depressive symptoms.

Furthermore, other clinical variables such as number of depressive episodes, number of total episodes, and suicide attempts were strongly correlated with overall COBRA score. However, the relation between subjective cognitive measures and clinical course of the illness is complex. Probably, those patients with more illness chronicity represent a subgroup with poor insight, which, in turn, may affect their self-report cognitive assessment. To sum

up, these findings highlight that subclinical depressive symptoms, among other variables, may act as mediators or confounders, affecting the poor association between objective and subjective cognitive measures.

The present study has a number of limitations. First, this was a cross-sectional study, conducted in a tertiary hospital, where participants tend to present more severe symptoms, which may limit the generalization of the findings. Second, all our patients were on pharmacological treatment, which may have affected the cognitive assessment. Third, as there is not a gold standard instrument to assess subjective cognitive function in Brazil, we used the cognitive domain of the FAST to perform convergent validity analysis.

In conclusion, our findings showed that the Portuguese version of the COBRA is a valid and feasible instrument to assess cognitive complaints in BD. As objective and subjective measures assess distinct aspects of cognition, the combined use of subjective-objective instruments may greatly contribute to improve our knowledge of the nature and extent of cognitive dysfunctions in BD. Finally, the correct identification of cognitive dysfunctions would allow us to implemente specific therapeutic strategies to improve cognition and functioning in BD.

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## DISCLOSURE

Anabel Martínez-Arán has served as a speaker or advisor for Bristol-Myers Squibb, Otsuka, Lundbeck, and Pfizer.Eduard Vieta has received grants, continuing medical education-related honoraria, or consulting fees from Alexza, Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrer, the Forest Research Institute, Gedeon Richter, GlaxoSmith-Kline, Janssen, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Roche, Sanofi-Aventis, Schering-

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## Appendix 1

Portuguese and English versions of the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)

| Portuguese version | English version |
|---|---|
| **Escala de Disfunções Cognitivas no Transtorno Bipolar (COBRA)** | **Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)** |
| 1. Você tem dificuldade para se lembrar do nome das pessoas? | 1. Do you have difficulties to remember peoples' names? |
| 2. Você tem dificuldade para encontrar objetos de uso diário (chaves, óculos, relógio)? | 2. Do you have difficulties to find objects of daily use (keys, glasses, wristwatch)? |
| 3. Você tem problemas para se lembrar de acontecimentos que foram importantes na sua vida? | 3. Do you find it difficult to remember situations that were important to you? |
| 4. É difícil para você situar no tempo determinados acontecimentos? | 4. Is it hard for you to place important events in time? |
| 5. É difícil para você se concentrar na leitura de um livro, ou jornal? | 5. Do you find it hard to concentrate when reading a book or a newspaper? |
| 6. É difícil para você se lembrar do que você leu, ou do que lhe disseram, recentemente? | 6. Do you have problems recalling what you have read or have been told recently? |
| 7. Você tem a sensação de que não termina o que começou? | 7. Do you have the feeling that you do not finish what you begin? |
| 8. Você tem executado de forma mais lenta as tarefas do dia-a-dia? | 8. Does it take you longer than normal to complete your daily tasks? |
| 9. Você já se desorientou alguma vez na rua? | 9. Have you ever felt disoriented in the street? |
| 10. Quando alguém relembra uma conversa, ou comentário, que teve com você; você tem a impressão de estar ouvindo a informação pela primeira vez? | 10. When people remind you of a conversation or a comment you heard, do you get the impression that it is the first time you hear it? |
| 11. É difícil para você, em algumas ocasiões, encontrar as palavras certas para expressar as suas ideias? | 11. Is it sometimes difficult for you to find the words to express your ideas? |
| 12. Você se distrai com facilidade? | 12. Are you easily distracted? |
| 13. É complicado para você fazer cálculos simples mentalmente? | 13. Do you find it hard to do simple mental calculations? |
| 14. Você tem a impressão de perder o rumo da conversa? | 14. Do you get the impression that you cannot follow a conversation? |
| 15. Tem sido difícil para você aprender novas informações? | 15. Have you noticed that you find it difficult to learn new information? |
| 16. É difícil para você manter a concentração em uma tarefa durante muito tempo? | 16. Do you struggle to keep focused on a particular task for a long time? |
| 0. Nunca<br>1. Às vezes<br>2. Frequentemente<br>3. Sempre | 0. Never<br>1. Sometimes<br>2. Often<br>3. Always |

## 6 ARTIGO 2

Submetido ao Journal of Affective Disorders

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E-mail recebido em 07/11/2018

Dear Ms Moreira Lima,

You have been listed as a co-author of the following submission:

Submission no: JAD_2018_1361_R1
Submission title: Identifying cognitive subgroups in bipolar disorder: a cluster analysis

Corresponding author: Professor Adriane Rosa*

Listed co-author(s): Professor Eduard Vieta, Dr Maria Reinares, Miss Raissa Telesca, Ms Flavia Moreira Lima, Mr Francisco Diego Rabelo-da-Ponte, Dr Brisa Sole, Dr Letícia Czepielewski, Dr Joana Bücker, Mr Mathias Hasse-Sousa

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# IDENTIFYING COGNITIVE SUBGROUPS IN BIPOLAR DISORDER:A CLUSTER ANALYSIS

Flavia Lima, Diego Rabelo, Joana Bücker, Leticia Czepielewski, Mathias Hasse de Sousa, Raissa Telesca, Brisa Sole, Maria Reinares, Eduard Vieta, Adriane R Rosa

## ABSTRACT

**Background**: Evidence has shown heterogeneity of cognitive function among patients with bipolar disorder (BD). Our study aims to replicate recent findings of cognitive subgroups, as well as we assessed subjective cognitive difficulties and functioning in each cluster.

**Methods**: Hierarchical cluster analysis was conducted to examine whether there were distinct neurocognitive subgroups based on neurocognitive battery. Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) and Functioning Assessment Short Test (FAST) were used to assess subjective cognitive difficulties and functional impairment.

**Results**: We found three distinct subgroups: a first cluster with intact cognition (n = 30, 43.5%), a second cluster with selective cognitive impairment (n = 23, 33.3%), and a third cluster with globally cognitive impairment (n = 16, 23.3%). The intact group had more years of education ($p<0.001$) and higher estimated IQ ($p<0.001$) than globally and selectively impaired subgroups. Additionally, they were younger ($p=0.011$), had earlier age at bipolar diagnosis ($p<0.037$) and earlier age of first hospitalization ($p<0.035$) compared to individuals with globally cognitive impairment.

**Limitations:** This is a cross-sectional design with a small sample including only patients from tertiary hospital.

**Conclusion**: Our results give support to the existence of a continuum of severity from patients without impairment to those with poor cognitive functioning. Patients in the intact group seem to have higher cognitive reserve than other two groups. However, they also experienced cognitive complaints and some degree of functional impairment. These findings suggest the importance of using a combo of instruments (e.g, objective and subjective cognitive measures plus functioning instruments) for a complete assessment of patients with BD.

**Keywords**: Bipolar Disorder; Neurocognition; Cognitive Heterogeneity; Cluster Analysis; Subjective Cognitive Measure; Functional Outcome.

## HIGHLIGHTS

- Three cognitive subgroups were identified using hierarchical cluster analysis.
- Continuum of severity from intact cognition to marked impairment.
- Three cognitive clusters with a similar pattern of subjective cognitive measures.
- Importance of using a combo of instruments (e.g., neuropsychological test+COBRA+FAST).

## 1 INTRODUCTION

Historically, the main target of treatment in bipolar disorder (BD) has been the management of mood symptoms. However, research findings from the last two decades have indicated that BD is also associated with cognitive impairment, and these deficits persist beyond the resolution of acute episodesand regardless of adequate treatment (MARTINEZ-ARAN; VIETA, 2015; VIETA; TORRENT, 2016). There is a consensus in the literature that cognitive impairment has an adverse impact on psychosocial functioning in patients with BD (BONNÍN et al., 2014; SAMALIN et al., 2016; SANCHEZ-MORENO; MARTINEZ-ARAN; VIETA, 2017; SOLÉ et al., 2018), therefore, the ideal treatment of BD should focus not only on the management of mood symptoms but also on improving cognitive deficits and psychosocial functioning. Cognitively impaired BD patients displayed more functional disabilities than those who were cognitively intact (JENSEN et al., 2016). Several studies have also revealed that persistent cognitive dysfunction is a key contributor to the socio-occupational disability, independent of mood symptoms (DEPP; MAUSBACH, 2012; MARTINEZ-ARAN et al., 2007). Together with mood symptoms and illness progression, cognitive impairment is among the strongest predictors of functional disability, lower quality of life, and loss of workforce capacity in BD (BONNÍN et al., 2010; TORRENT et al., 2012).

Nevertheless, not all patients with BD suffer from cognitive dysfunction. There is evidence of heterogeneity in cognitive performance in addition to the clinical presentation. Recent studies have identified discrete neurocognitive subgroups among remitted BD patients using hierarchical cluster analyses. Generally, three subgroups have been described: a well performing “cognitively intact” subgroup with scores equivalent to the performance of healthy controls (HCs); one subgroup of “selective cognitive impairment” with modest deficits on only a subset of cognitive domains compared to HCs; and a subgroup with “global

severe impairment" across most of cognitive domains and comparable to cognitive deficits in schizophrenia (BURDICK et al., 2014; JENSEN et al., 2016; ROUX et al., 2017; SOLÉ et al., 2016). These data highlighted the variability observed in cognitive performance in BD, and the need to identify and characterize the pattern of impairment more accurately. Indeed, very little is known about why some patients with BD develop significant cognitive deficits while others remain cognitively intact.

The time is right to assess cognitive function with a more comprehensive approach, focusing on identifying distinctive neuropsychological subtypes of patients based on objective and subjective cognitive measures. A recent consensus from the International Society of Bipolar Disorders (ISBD) Targeting Cognition Task Force (MISKOWIAK et al., 2018) suggests the screening and tracking of cognitive performance in remitted patients not only by means of objective measures (e.g. neuropsychological tests) but also recommends the evaluation of patients' subjectively experienced cognitive difficulties. Indeed, cognitive function is a complex construct, and a combo of instruments that allow us to assess different aspects may greatly contribute to the knowledge about the nature and extent of cognitive dysfunctions in BD. There is evidence of a weak correlation between subjective cognitive difficulties and objective performance in individuals with BD (JENSEN et al., 2015b; ROSA et al., 2013), which means that rely purely on subjectively reported difficulties or objective cognitive impairments it is not the ideal methodology for identifying cognitive dysfunction in BD.Thus, using both objective and subjective cognitive measures could help clinicians and researchers todevelop more effective intervention strategies (e.g., cognitive rehabilitation and cognitive enhancers) targetingspecific cognitive deficits.

Therefore, the present study aims to replicate, in a Brazilian sample of remitted patients with BD, recent findings of cognitive subgroups using hierarchical cluster analysis. Additionally, we assessed subjective cognitive difficulties in each cluster as well as differences on psychosocial functioning and clinical course of the illness. As far as we know, this is the first study following the recommendation of ISBD: using the combo of a comprehensive neurocognitive battery (including social cognition) and specific instruments to measure subjective cognitive difficulties and psychosocial functioning in BD.

## 2 METHODS

### *2.1. Participants*

Seventy-three patients with BD were recruited by convenience from the Bipolar Disorders Program (PROTHABI), at the *Hospital de Clínicas de Porto Alegre*, in Southern Brazil, between October 2015 and October 2017. The inclusion criteria were: (1) diagnosis of BD according to DSM-5 (SCID), (2) age between 18 and 70 years, (3) meeting euthymia criteria for at least three months previous to the assessment defined as a score ≤7 on the Hamilton Depression Rating Scale (HAM-D) (HAMILTON, 1960) and the Young Mania Rating Scale (YMRS) (YOUNG et al., 1978). Exclusion criteria were: (1) any medical or comorbid psychiatric condition affecting neuropsychological performance, (2) estimated intelligence quotient (IQ) <70, (3) actual drug or alcohol dependence or abuse; and (4) electroconvulsive therapy within the past year. All patients received pharmacological treatment according to the Program's protocols.

Fifty seven healthy controls (HC), who had no current or previous history as well as no first-degree family history of a major psychiatric disorder, including dementia or intellectual disability assessed by the non-patient version of the Structured Clinical Interview for DSM-5 (SCID), were recruited from the general population within the catchment area of the *Hospital de Clínicas de Porto Alegre.*

This study was approved by the Ethics Committee of the *Hospital de Clínicas de Porto Alegre*. After a complete verbal description of the study, all participants provided written informed consent to enter the study.

### *2.2. Measures*

#### *2.2.1. Clinical and demographic features*

We obtained patients' sociodemographic, clinical and pharmacological data through a structured interview and from medical records. The 17-item HAM-D and the YMRS were administered by trained raters to assess depressive and manic symptoms, respectively.

#### *2.2.2. Functional status*

The overall functional outcome was assessed through the Functioning Assessment Short Test (FAST), an instrument widely used in patients with BD. This scale encompasses

24 items evaluating six functional domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time). The overall FAST score vary from 0-72 (the cut off value is 11); the higher the score, the greater the disability (ROSA et al., 2007).

*2.2.3. Subjective cognitive measure*

Cognitive difficulties in daily life situations were assessed with Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA). The COBRA is a 16-item self-report instrument, with satisfactory psychometric properties developed to assess cognitive complaints experienced by bipolar patients. The COBRA total score is obtained when the scores of each item are added up. The COBRA total score range from 0 –48 (the cut off value is 10); a higher score means a greater dysfunction (LIMA et al., 2018; ROSA et al., 2013).

*2.2.4. Objective cognitive measure*

Based on an extensive review of the literature, all participants completed a comprehensive neuropsychological battery including the following tests: Hopkins Verbal Learning Test-Revised (HVLT-R) (BENEDICT et al., 1998); Stroop Color-Word Test (SCWT) (GOLDEN, 1978); Trail Making Test–Part A (TMT-A), and Trail Making Test–Part B (TMT-B) (REITAN, 1958); Phonemic verbal fluency (F-A-S) (TOMBAUGH; KOZAK; REES, 1999); Continuous Performance Test – Identical Pairs (CPT-IP); Letter-Number sequencing subtest (LNS) from Wechsler Adult Intelligence Scale – III (WAIS-III) (WECHLER, 2001; WECHSLER, 1997); Reading the Mind in the Eyes Test-Revised (RMET-R) (SANVICENTE-VIEIRA et al., 2014). IntelligenceQuotient (IQ) was estimated with vocabulary and matrix reasoning subtests from Wechsler Abbreviated Scale of Intelligence (WASI) (WECHSLER, 1999, 2014).

*2.3. Statistical analysis*

All analyses were performed with the Statistical Package for Social Sciences version 18 (SPSS Inc., Chicago, IL, USA). Initial analyses were conducted to compare demographic and clinical characteristics and cognitive performance between patients with BD and HC using *t* student test and $\chi 2$ as appropriate.

Patients' raw scores on neuropsychological tests were standardized to z-scale scores based on the mean and standard deviation scores of the HC. Furthermore, several z-scores of different tests were summed and averaged to create cognitive domains. Following this procedure, cognitive domains were standardized against the domain scores obtained by the HC group. Six cognitive domains were designed to provide a single score in order to cover the main cognitive domains that are presumably affected in BD. The variables included in each cognitive domain were adjusted to cognitive domains proposed by the ISBD-BANC (YATHAM et al., 2010) as follows: (I) the verbal memory domain was composed of the total trials 1–3, and delayed recall scores of the HVLT-R; (II) the processing speed domain was based on the phonemic verbal fluency (F-A-S), and the TMT-A; (III) the executive functions domain was calculated based on the Stroop Interference Test, and the TMT-B; (IV) the attention domain was based on the mean of three d-prime scores on CPT-IP; (V) the working memory domain included the Letter-Number Sequencing subtest from WAIS-III; and (VI) for social cognition domain, the total score of the RMET-R was considered. The z-scores obtained from measures of TMT-A and TMT-B were reversed before constructing the corresponding composite scores, once higher scores indicate poorer performance. However, the analysis of both TMT-A and TMT-B revealed extreme scores, i.e., more than four standard deviations (SDs) below the mean, and for this reason, these scores were truncated at $z = -4.0$.

A hierarchical cluster analysis (HCA) was conducted with the cognitive domain z-scores of the BD participants to detect homogeneous neurocognitive subgroups. The similarity between cases was computed with the Euclidian distance, and Ward linkage was selected as the agglomeration procedure. The dendrogram was visually inspected to establish the appropriate number of clusters to be retained. Besides, a discriminant function analysis (DFA) was also conducted, since this analysis examines the predictive power of each participant's cognitive domain scores to the neurocognitive subgroup. The cognitive profiles of the patients in the different clusters and the HC were compared using a one-way ANOVA, with group membership (the three clusters and the HC group) as a fixed factor and the six

neurocognitive composites (verbal memory, processing speed, executive function, attention, working memory and social cognition) as dependent variables.

Further, Tukey post hoc comparisons were carried out to identify pair-wise differences between groups. Furthermore, neurocognitive composites were compared across groups utilizing amultivariate analysis of variance (MANOVA). Since multiple dependent variables were used, a prior protective MANOVA analysis was performed with age as the covariate and group membership as the main factor. Since neuropsychological tests are naturally correlated, this procedure was considered better than Bonferroni inequality correction, which would increase type II error.

Finally, comparisons (one-way ANOVA and $\chi 2$ applied as appropriate) between the different clusters were carried out to examine possible differences in demographic, clinical, functional status, subjective cognitive measure, and pharmacological treatment variables. Using an ANOVA model, the three clusters were considered as the fixed factor and the sociodemographic, clinical, functional and subjective cognitive variables as the dependent variables. Statistical significance was set at $p < 0.05$.

## 3 RESULTS

### *3.1. Clinical characteristics of the sample*

Comparisons between BD and HC samples showed no differences regarding age or gender. However, years of education, estimated IQ, actual work situation, overall functioning (FAST), and subjective cognitive dysfunction (COBRA) revealed statistically significant differences favorable to the HC group. About cognition, data analysis revealed that patients with BD, as a whole, performed significantly worse than HC on all cognitive domains and estimated IQ (all $p \leq 0.002$) (for details see Table 1).

**Table 1:** Clinical, socioemographic, and cognitive characteristics of the BD and HC subjects

| Demographicandclinicalvariables | BD (n=73) Mean (SD) | HC (n=57) Mean (SD) | Statisticalanalyses t or x² | p-value |
|---|---|---|---|---|
| Age | 49.29 (12.66) | 45.28 (15.77) | 1.278 | 0.282 |
| Sex, female*n* (%) | 53 (72.6) | 45 (78.9) | 2.327 | 0.312 |
| **Durationofeducation, years** | **11.23 (3.64)** | **15.36 (3.49)** | **28.690** | **<0.001** |
| **Estimated IQ** | **92.40 (13.51)** | **106.10 (11.89)** | **62.66** | **<0.001** |
| **Work situation, employed (%)** | **23 (31.5)** | **41 (71.9)** | **25.708** | **<0.001** |
| BD type, I *n* (%) | 65 (89%) | | | |
| Number of total episodes | 11.28 (8.23) | | | |
| Number of depressive episodes | 5.61 (4.85) | | | |
| Number of (hypo)manic episodes | 5.63 (4.62) | | | |
| Age at bipolar diagnosis | 33.44 (12.02) | | | |
| Psychotic symptoms in first episode (%) | 42 (60) | | | |
| Age at first hospitalization | 30.71 (13.23) | | | |
| Number of hospitalizations | 3.52 (3.86) | | | |
| Numberofsuicidalattempts | 1.38 (1.48) | | | |
| Family history of mental disorder (%) | 33 (45.2) | | | |
| Illnessduration, years | 15.61 (9.68) | | | |
| Numberofmedications | 2.30 (0.99) | | | |
| Lithium (%) | 19 (26) | | | |
| Anticonvulsants (%) | 52 (71.2) | | | |
| Antipsychotics (%) | 58 (79.5) | | | |
| Antidepressants (%) | 16 (21.9) | | | |
| Benzodiazepines (%) | 13 (17.8) | | | |
| HAMD | 3.66 (2.05) | | | |
| YMRS | 1.11 (1.44) | | | |
| **FAST** | **24.60 (12.60)** | **5.23 (4.97)** | **71.985** | **<0.001** |
| **COBRA** | **13.56 (9.78)** | **6.56 (5.22)** | **15.732** | **<0.001** |
| Cognitive composites: | | | | |
| **Verbal memory** | **-1.07 (1.24)** | **0.0(1.0)** | **5.285** | **<0.001** |
| **Processingspeed** | **-1.65 (1.43)** | **0.0(1.0)** | **5.3** | **<0.001** |
| **Executivefunctions** | **-1.38 (1.34)** | **0.0(1.0)** | **8.082** | **<0.001** |
| **Attention** | **-1.10 (1.05)** | **0.0(1.0)** | **6.071** | **<0.001** |
| **Workingmemory** | **-1.22 (1.15)** | **0.0(1.0)** | **6.346** | **<0.001** |
| **Social cognition** | **-0.64 (1.34)** | **0.0(1.0)** | **3.104** | **0.002** |

Measures of cognition are given as z-scores, mean (standard deviation), based on the HCs' performance. Abbreviations: SD = standard deviation; IQ = intelligence quotient; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; FAST = Functioning Assessment Short Test; COBRA = Cognitive Complaints in Bipolar Disorder Rating Assessment; Bold text in the table indicates significant values.

### *3.2. Three neurocognitive subgroups of BD patients*

Four out of 73 patients were excluded from the cluster analysis (missing cognitive measure in one test). Visual inspection of the dendrogram provided evidence for three clusters for 69 bipolar patients. The first cluster included 30 subjects (43.5%), the second cluster included 23 patients (33.3%), and the third cluster included 16 patients (23.2%). The DFA also revealed the validity of the three clusters, with the presence of one discriminant function

explaining 88.4% of the variance (Wilks' k = 0.18, x2 = 108.71, p <0.001). A total of 89.9% of subjects were correctly classified in the DFA. Processing speed and executive function composites showed the highest standardized coefficients (-0.62 and 0.54, respectively) and therefore these composites had a stronger contribution than the other composites to the assigning of patients with BD to the clusters (see Fig. 1 for graphical agglomeration of the neurocognitive subgroups).

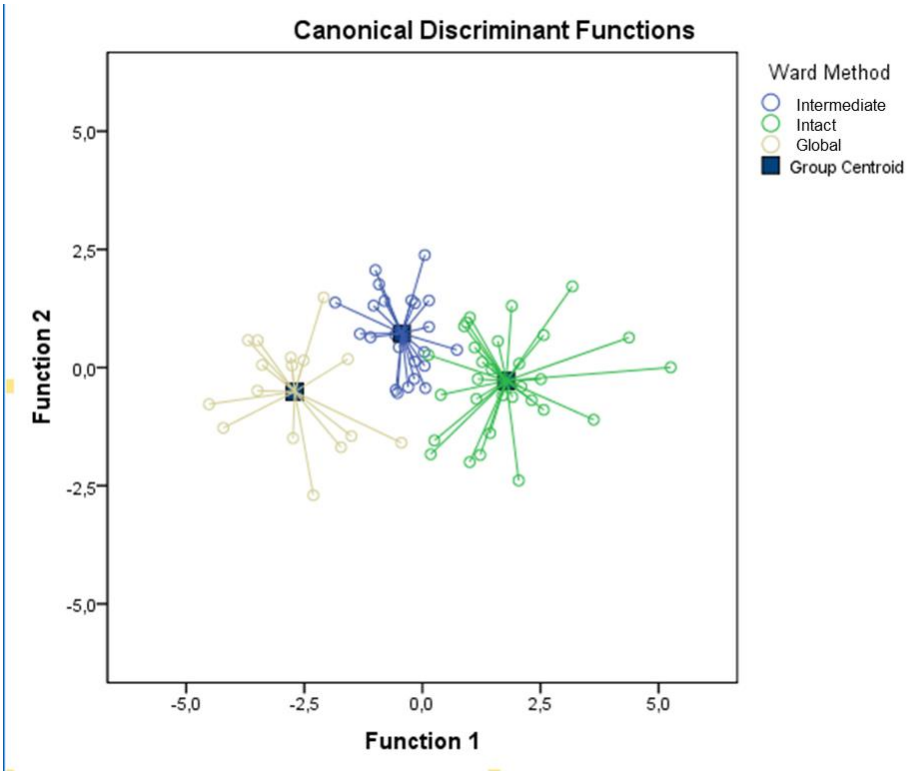



**Figure 1:** Graphical agglomeration of the neurocognitive subgroups.

Patients in the intact group were cognitively preserved when compared to the HC group, with scores of a maximum of 0.48 SDs below the mean. The second cluster (selective group) had an intermediate cognitive profile with statistically significantly poorer performance in all cognitive domains when compared to the HC, except for social cognition (p = 0.307). However, they did not differ from the intact group in attention (p = 0.113) and social cognition (p = 0.196) domains. The scores obtained by this group of patients ranged between 0.43 and 2.26 SDs below the mean, therefore showing severe deficits in processing speed and executive function and mild deficits in the other domains, except for social

cognition. Finally, patients in the third cluster (globally impaired group) were significantly impaired in all cognitive domains compared to the intact group. However, when compared with the selective group, the globally impaired group showed a statistically significantly poorer performance in verbal memory ($p = 0.023$), attention ($p = 0.001$), and social cognition ($p < 0.001$), whereas there were no significant differences in processing speed ($p = 0.772$), executive function ($p=0.163$) and working memory ($p = 0.195$). The scores obtained by the globally impaired group ranged between 2.1 and 2.5 SDs below the mean (see Fig. 2 and Table 2). MANOVA yielded Pillai's $F=9.710$, $df=2, 66$, $p=0.001$ for the main effect, indicating that there were overall differences in neurocognitive composites between the three clusters regardless of age.

**Figure 2**: Neuropsychological performance of three bipolar disorder clusters.

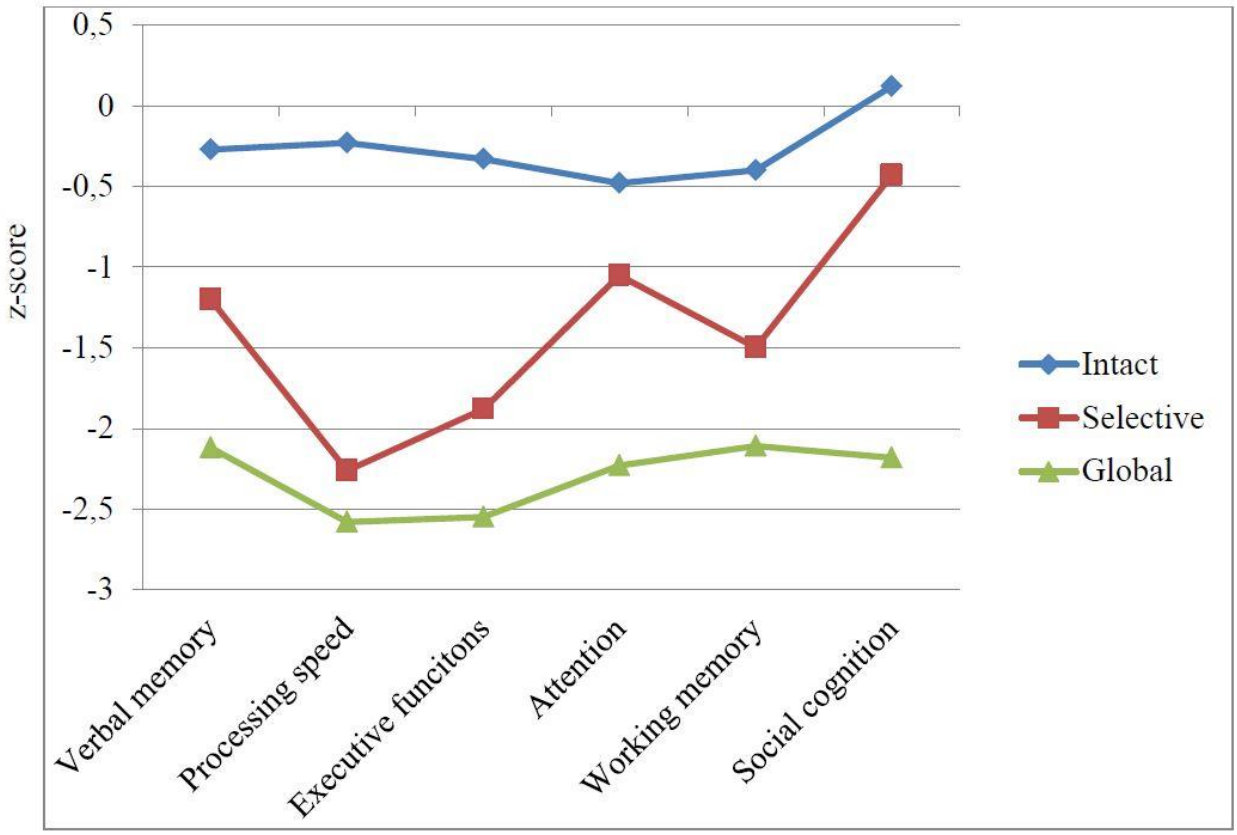


**Table 2:** Comparison between the three clusters and HCs across cognitive domains

| | Global (G) n=16, 23.2% | Selective (S) n=23, 33.3% | Intact (I) n=30, 43.5% | HC (n=57) | significance | | |
|---|---|---|---|---|---|---|---|
| | | | | | df | F | p-value |
| Verbal memory | -2.12 (0.85) | -1.20 (1.15) | -0.27 (1.08) | 0.0 (1.0) | 3 | 24.363 | **<0.001**<br>**HC *v.* G, p<.001**<br>**HC *v.* S, p<.001**<br>HC *v.* I, p=.727<br>**G *v.* S, p=.023**<br>**G *v.* I, p<.001**<br>**S *v.* I, p=.003** |
| Processing speed | -2.58 (1.13) | -2.26 (1.16) | -0.23 (0.84) | 0.0 (1.0) | 3 | 43.357 | **<0.001**<br>**HC *v.* G, p<.001**<br>**HC *v.* S, p<.001**<br>HC *v.* I, p=.160<br>G *v.* S, p=.772<br>**G *v.* I, p<.001**<br>**S *v.* I, p<.001** |
| Executive functions | -2.55 (0.75) | -1.88 (1.14) | -0.33 (0.90) | 0.0 (1.0) | 3 | 40.946 | **<0.001**<br>**HC *v.* G, p<.001**<br>**HC *v.* S, p<.001**<br>HC *v.* I, p=.455<br>G *v.* S, p=.163<br>**G *v.* I, p<.001**<br>**S *v.* I, p<.001** |
| Attention | -2.23 (0.78) | -1.05 (0.76) | -0.48 (0.88) | 0.0 (1.0) | 3 | 27.736 | **<0.001**<br>**HC *v.* G, p<.001**<br>**HC *v.* S, p<.001**<br>HC *v.* I, p=.092<br>**G *v.* S, p=.001**<br>**G *v.* I, p<.001**<br>S *v.* I, p=.113 |
| Working memory | -2.11 (0.71) | -1.50 (0.87) | -0.40 (0.96) | 0.0 (1.0) | 3 | 29.160 | **<0.001**<br>**HC *v.* G, p<.001**<br>**HC *v.* S, p<.001**<br>HC *v.* I, p=.236<br>G *v.* S, p=.195<br>**G *v.* I, p<.001**<br>**S *v.* I, p<.001** |
| Social cognition | -2.18 (0.99) | -0.43 (0.84) | 0.12 (1.09) | 0.0 (1.0) | 3 | 22.616 | **<0.001**<br>**HC *v.* G, p<.001**<br>HC *v.* S, p=.307<br>HC *v.* I, p=.949<br>**G *v.* S, p<.001**<br>**G *v.* I, p<.001**<br>S *v.* I, p=.196 |

Bold text in the table indicates significant values.

### *3.3. Comparison between BD neurocognitive subgroups on clinical course, subjective cognitive measure, and psychosocial functioning*

There were no differences among the three clusters in gender ($p = 0.452$). There were, however, significant differences among the three clusters for age ($p = 0.011$), with pair-wise comparisons indicating that patients belonging to the globally impaired group were older than the intact group, but no differences were observed between the selective and the other two groups. There were also differences on estimated IQ ($p < 0.001$) and years of education ($p < 0.001$), with pair-wise comparisons indicating that patients belonging to the intact group had higher IQ and more years of education compared to the other two groups (see Table 3). No differences were found between the selective and the globally impaired groups.

When clinical variables were considered, patients belonging to the global group had delayed diagnosis of BD ($p = 0.037$) and later first hospitalization ($p = 0.035$) than the intact group. A family history of mental disorder was higher in the intact group compared to those with globally cognitive impairment ($p = 0.042$); these differences were not observed between the selective and the other two groups.

When the influence of pharmacological treatment was evaluated, no differences were observed among the three clusters on the total number of medications or the types of medications prescribed (lithium, anticonvulsants, antipsychotics, antidepressants, or benzodiazepines). Consequently, analyses of group differences in cognitive performance were conducted with no need to control for pharmacological treatment.

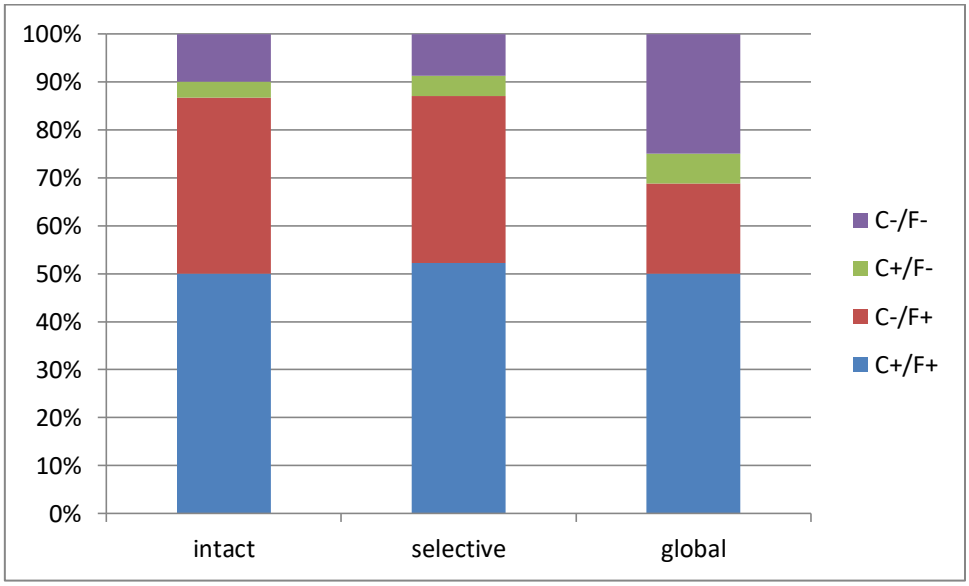
Finally, when evaluating the influence of cluster membership on subjective cognitive difficulties (COBRA) we found a similar pattern of cognitive complaints in the three subgroups. Regarding psychosocial functioning, the three groups of patients experienced a similar degree of impairment. Figure 3 shows the proportion of patients with COBRA impairment / NO impairment and FAST impairment / NO impairment in each cluster. Furthermore, we performed correlation analysis between COBRA and HAMD in each cluster showing a positive correlation between scales on selective ($r = .418$, $p = 0.047$) and intact ($r = .536$, $p = 0.002$) subgroups. No correlation was found in the global cognitive cluster.

**Table 3:** Comparisons of clinical and demographic characteristics between the three neurocognitive subgroups of BD patients

| | Global (G) n=16 (23.2%) | Selective (S) n=23 (33.3%) | Intact (I) n=30 (43.5%) | Statistical analyses *F* | p-value |
|---|---|---|---|---|---|
| **Age** | **55.56 (12.15)** | **49.65 (11.27)** | **44.17 (12.43)** | **4.835** | **0.011** |
| | | | | | G *v.* S, p=.291 |
| | | | | | **G *v.* I, p=.009** |
| | | | | | S *v.* I, p=.232 |
| Sex, female*n* (%) | 11(68.8) | 15 (65.2) | 24 (80.0) | | 0.452 |
| Work situation, employed (%) | 6 (37.5) | 7 (30.4) | 10 (33.3) | | 0.899 |
| **Durationofeducation, years** | **9.25 (3.96)** | **10.22 (2.50)** | **13.17 (3.37)** | **9.326** | **<.001** |
| | | | | | G *v.* S, p=.636 |
| | | | | | **G *v.* I, p=.001** |
| | | | | | **S *v.* I, p=.005** |
| **Estimated IQ** | **85.06 (9.56)** | **89.56 (10.83)** | **100.13 (14.03)** | **9.580** | **<.001** |
| | | | | | G *v.* S, p=.491 |
| | | | | | **G *v.* I, p<.001** |
| | | | | | **S *v.* I, p=.007** |
| BD type, I*n* (%) | 16 (100) | 21 (91.3) | 25 (83.3) | | 0.196 |
| Number of episodes | 10.18 (8.83) | 12.76 (7.86) | 11.27 (8.70) | 0.332 | 0.719 |
| **Age at bipolar diagnosis** | **39.31 (13.93)** | **32.41 (9.20)** | **29.75 (11.91)** | **3.478** | **0.037** |
| | | | | | G *v.* S, p=.176 |
| | | | | | **G *v.* I, p=.029** |
| | | | | | S *v.* I, p=.703 |
| Psychotic symptoms at first episode (%) | 8 (50.0) | 15 (65.2) | 17 (63.0) | | 0.600 |
| **Age atfirsthospitalization** | **37.86 (16.83)** | **29.89 (10.79)** | **27.15 (2.11)** | **3.549** | **0.035** |
| | | | | | G *v.* S, p=.162 |
| | | | | | **G *v.* I, p=.028** |
| | | | | | S *v.* I, p=.738 |
| Number of hospitalizations | 4.33 (6.30) | 3.786 (3.50) | 3.07 (2.43) | 0.515 | 0.600 |
| Numberof suicide attempts | 1.00 (1.35) | 1.69 (1.81) | 1.35 (1.30) | 0.735 | 0.485 |
| **Family history of mental disorder (%)** | **6 (37.5)** | **7 (30.4)** | **19 (63.3)** | | **0.042** |
| Illness duration, years | 16.25 (11.53) | 17.23 (10.09) | 13.50 (8.24) | 0.983 | 0.380 |
| No. of medication | 2.62 (1.02) | 2.22 (0.95) | 2.17 (1.05) | 1.155 | 0.321 |
| Type of medication | | | | | |
| Lithium | 3 (18.8) | 5 (21.7) | 11 (36.7) | | 0.323 |
| Anticonvulsants | 14 (87.5) | 16 (69.9) | 19 (63.3) | | 0.224 |
| Antipsychotics | 14 (87.5) | 20 (87.0) | 20 (66.7) | | 0.123 |
| Antidepressants | 4 (25.0) | 4 (17.4) | 6 (20.0) | | 0.843 |
| Benzodiazepines | 3 (18.8) | 3 (13.0) | 6 (20.0) | | 0.792 |
| HAMD | 3.250 (1.65) | 3.17 (1.95) | 4.27 (2.18) | 2.412 | 0.097 |
| YMRS | 1.00 (0.89) | 0.78 (1.54) | 1.50 (1.59) | 1.714 | 0.188 |
| FAST | 20.50 (12.71) | 24.13 (11.98) | 26.47 (13.44) | 1.136 | 0.327 |
| COBRA | 11.50 (9.63) | 13.87 (8.35) | 15.03 (11.26) | 0.652 | 0.525 |

Bold text in the table indicates significant values.

**Fig. 3.** Congruence and discrepancy between objective and subjective cognitive measures between cluster groups




C-/F- COBRA NO impairment/ FAST NO impairment

C+/F- COBRA impairment FAST NO impairment

C-/F+ COBRA NO impairment FAST impairment

C+/F+ COBRA impairment FAST impairment

## 4 DISCUSSION

In the present study, following the recommendations of ISBD consensus, patients with BD and HC were assessed using a comprehensive neuropsychological battery across six domains, as well as with measures of subjective cognitive difficulties and psychosocial functioning. The results of our hierarchical cluster analysis corroborate clinical observation and evidence of prior studies, providing three well defined clusters: (I) Intact cognition group, which does not differ from HCs, representing a 'neuropsychologically normal' cluster; (II) Selective cognitive impairment group, which represents an intermediate cluster with deficits on a subset of the domains such as verbal memory, processing speed, executive function and working memory; (III) Global cognitive impairment group, which represents a globally and significantly impaired cluster with moderate deficits across all cognitive areas.

The heterogeneous picture that emerges from these findings suggests the existence of a continuum of severity from patients without impairment to others with very low cognitive functioning. In addition, the proportion of patients allocated in each cluster is in line with recent studies from larger samples: Burdick et al. (2014) and Jensen et al. (2016) found an absence of cognitive impairment in 31-46% of patients (versus 43% of our cohort); our finding of one third of patients with selective impairment also corroborates the results of these authors (28-32%); as well as a subgroup of global impairment (23% in our study versus 21-39% in theirs). Comparing with results from Solé et al., (2016) we found higher number of patients in the globally cognitive impaired group (23% v. 11%); however, these differences may be due, not only to the distinct neuropsychological battery employed in both studies but also to the BD subtype (BD I and II vs BD II only) and cultural/educational (Brazilian vs Spanish) differences between the two samples.

According to the DFA results, the domains that best discriminated neurocognitive subgroups were processing speed and executive function, suggesting that deficits in these domains might be an important feature of cognitive impairment in BD. The degree of cognitive impairment on processing speed and executive function in the global and selective subgroups was quite similar and characterized by severe deficits in comparison to the mean of intact group and HC. These domains, together with attention and verbal memory, are recognized as the most pronounced in BD (BORA; YUCEL; PANTELIS, 2009; TORRES; BOUDREAU; YATHAM, 2007). A recent metanalysis found that a subgroup of patients has a severe and global deficit in executive function compared to HC (BORA et al., 2016a). In

other metanalysis patients with BD underperformed HC in all cognitive domains of the MCCB, however cognitive deficits in domains of processing speed and working memory were prominent (BO et al., 2017). Furthermore, processing speed has been found to be impaired in schizophrenia, leading some to suggest that processing speed represents a specific deficit in schizophrenia that contributes to the generalized deficit (DICKINSON; RAMSEY; GOLD, 2007). These findings might potentially suggest that severe deficits in this domain are associated with schizophrenia, as well as in at least in some patients with BD. Also, it might be argued that having very severe and global cognitive deficits might be associated with genetic risk factors (BORA; PANTELIS, 2015). Recent findings suggest a subset of patients with BP shares genetic risk factors with schizophrenia (CRADDOCK; OWEN, 2010; LICHTENSTEIN et al., 2009).

Furthermore, verbal memory seems to play an essential role in the distinguish between neurocognitive subgroups, since the three clusters differed significantly from one another in this domain, showing none to moderate deficits. Roux et al. (2017) found two intermediate clusters characterized by specifically enhanced or decreased verbal memory in individuals with overall average performance, suggesting that a decline in verbal memory might predict a global cognitive decline within the course of BD. Verbal memory has been correlated with functioning in everyday life especially in work performance (BONNÍN et al., 2014; TSE et al., 2014). Others studies suggest that verbal memory represents a core deficit of the BD and has been linked to functional outcome as one of the best predictors of functioning (BONNÍN et al., 2012; MARTINEZ-ARAN et al., 2007; MARTÍNEZ-ARÁN et al., 2004), including long-term functional outcome (BONNÍN et al., 2010).

We also identified that patients in the intact group experienced higher estimated IQ and had more years of education when compared to both the selectively and globally impaired subgroups. A significant difference wasalso observed in estimated IQ in FACE-BD cohort (ROUX et al., 2017), the group with the globally low cognitive performance was characterized by a lower estimated IQ than the group with high cognitive performance. Interestingly, premorbid IQ and educational level have been considered as proxy measures of cognitive reserve (FORCADA et al., 2015; STERN, 2009). Cognitive reserve appears to be protective against cognitive and functional decline (FORCADA et al., 2015; MARTINEZ-ARAN; VIETA, 2015). Additionally, patients in the intact group were younger than those in the global cluster suggesting the effect of aging on the ability to perform some cognitive tasks. In particular, aging may have adverse effects on executive functions and memory tasks

(BORA; YUCEL; PANTELIS, 2009; GOLDBERG; ROY CHENGAPPA, 2009). Finally, the intact group had an earlier age at diagnosis of BD and earlier first hospitalization than the globally cognitive impaired group. Considering these differences it is plausible to speculate that patientswith more education (intact group) have better access to healthcare or, on the other hand, patients that spend more time without treatment, have a higher chance of cognitive decline (globally impaired group).in intact cognitive group may have received early treatment as well, which would explain, in part, their better performance. Added to this, this Indeed, the literature suggests that early detection and treatment of BD may prevent a more severe and chronic course of illness (BERK et al., 2007a). However, there is a considerable delay between the onset of illness, diagnosis and appropriate treatment. Previous studies have reported that patients may wait for as long as 5-10 years from the onset of illness before the diagnosis is confirmed (DAGANI et al., 2017; GAZALLE et al., 2005). The intact group alsohad a higher proportion of relatives with a mental disorder, which could be a double-edged situation, that is, as the genetic load is associated with high risk for mental illness but may also encourage them to ask for medical assistance and earlier treatment. Having a first degree relative with a mental disorder is a well-established risk factor for BD and could lead clinicians to identify the BD sooner in these patients (GHAEMI; KO; GOODWIN, 2001).

Another interesting finding of our study is the fact that, despite patients in the selective and global clusters had an equivalent estimated IQ and educational attainment, the global cluster was significantly more impaired than selective in three domains: verbal memory, attention, and social cognition. This finding supports the idea that these deficits are not entirely explained by a shorter time spent in education, nor lower IQ. Probably, other clinical variables (e.g., mood symptoms, number of episodes, comorbidities) may have a negative impact on cognition (BURDICK et al., 2014). Also have been suggested the presence of a specific subgroup of patients with BD that is characterized by a more severe and global level of cognitive impairment which can be, at least partially, attributed to inherited risk factors (RUSSO et al., 2017). Thus, as in schizophrenia, this subgroup may have susceptibility genes that are associated with neurodevelopmental abnormalities and consequently, associated with cognitive dysfunction (BORTOLATO et al., 2015). Furthermore, it is plausible that globally impaired group is not just marked by the presence of premorbid cognitive deficits and reduced cognitive reserve (ANAYA et al., 2016; BURDICK et al., 2014), but is both premorbidly impaired and then also affected by the disease process, resulting in being vulnerable to further decline after onset.

Taking all these findings into consideration, it seems to be two groups of BD patients: a group characterized by normal neurodevelopmental and cognitive functioning, which might, or might not deteriorate over time depending on the course of illness, treatment adherence, and healthy habits (VIETA, 2014), and another group of patients presenting with a pattern of cognitive impairment comparable with that observed in schizophrenia and characterized by a low premorbid cognitive functioning before illness onsetand greater susceptibility to cognitive insults (SOLÉ et al., 2017). This latter group of patients would share common genetic risk factors with schizophrenia and might be associated with neurodevelopmental abnormalities (BORA et al., 2016a). Nonetheless, at this point, further genetic and neurobiological research is needed to confirm this hypothesis.

Finally, our study failed to detect any differences among clusters regarding subjective cognitive difficulties and psychosocial functioning. In fact, in this sample COBRA and FAST scores could not distinguish between individuals in the preserved cognitive cluster and the impaired cognitive group. In other words, subjective cognitive difficulties and psychosocial functioning could not contribute to explaining the variability in the neurocognitive performance observed in our cohort. However, all three clusters presented impaired psychosocial functioning and subjective cognitive difficulties, which means that even patients in the intact cluster struggle with daily cognitive and psychosocial difficulties. In this sense, it is possible that a person can experience cognitive complaints such as concentration problems and memory lapses during work, but still has an adequate neuropsychological performance. Another possible explanation is since not all patients with BD are conscious of their cognitive capacity as well as other factors would be mediating this discrepancy between objective and subjective cognitive measures. Actually, we found a positive correlation between subjective cognitive difficulties and residual depressive symptoms on selective and intact subgroups. This finding is in keeping with evidence that patients' insight into their own cognitive abilities relies on several factors, including metacognitive capacity and severity of mood symptoms (MISKOWIAK et al., 2016a).

Previous studies have also investigated the relationship between subjectively reported difficulties and objectively assessed neuropsychological test performance in BD showing a certain discrepancy between both assessments (JENSEN et al., 2015a; LIMA et al., 2018; MISKOWIAK et al., 2016a; ROSA et al., 2013). Such discrepancy may reflect a general problem of self-perception in patients with mood disorders in terms of a tendency for pessimism and self-deprecation (REID; MACLULLICH, 2006). On the other hand, a

neuropsychological test may lack the ecological validity necessary for tapping experiences of cognitive problems in everyday life (BEBLO; EXNER, 2010). In this sense, the test situation per se is different from one's daily life at work or at home. During a neuropsychological assessment, which is only temporary, one is usually able to muster the effort and motivation to perform the tests, while it is more difficult to concentrate when one is alone at home with several social and emotional distracters (VEEH et al., 2017).

Together with previous studies, our findings give supportto the importance of including both objective and subjective cognitive measures for a comprehensive assessment of the cognitive performance of patients with BD. This set of information would identify the nature of cognitive dysfunction, characterize the degree of impairment, and guide personalized treatments for remediating these deficits. Currently, there are no available treatments with documented direct pro-cognitive effects in BD (MISKOWIAK et al., 2016b, 2017), except for one recent positive trial that revealed cognitive benefits of intensive computerized cognitive remediation (LEWANDOWSKI et al., 2017). However, intense research effort is likely to reveal effective pharmacological, psychological and multimodal treatments in the near future (MISKOWIAK et al., 2018). Meanwhile, there are several ways to manage cognitive difficulties (e.g., cognitive rehabilitation strategies). Specifically, cognitive rehabilitation may help patients tackle and compensate for these difficulties in daily life with three different methods: (1) remediation techniques, which involve exercising cognitive skills by repetition; (2) compensatory strategies, with application of different ways to accomplish goals; (3) adaptive approaches, whereby make changes to environment to improve functioning. Also preventative and early intervention strategies, such as the implementation of good habits, including regular sleep and exercise, and to boost cognitive reserve might be suggested as important ways of reducing cognitive impairment in BD (GRANDE et al., 2016).

Some limitations of our study should be considered. In particular, due to the small sample size the negative findings reported here are very likely to be due to an underpowered sample. However, it is worth noting that our results closely replicate previous studies carried on in distinct educational and cultural patterns. All patients were on polypharmacy, and we cannot discount the influence of drugs on cognition. Finally, this is a cross-sectional design including only patients from a tertiary hospital with a more severe and chronic course. Further, longitudinal studies are required in order to answer some questions such as: how does

each member of this cognitive subgroup progress and what is the existing data on the progression of cognitive dysfunction in BD.

In summary, our findings showed three cognitive profiles in BD: intact, intermediate, and low-performance groups. It highlights the existence of a continuum of severity from patients without impairment to others with severe cognitive impairment. Additionally, we showed that even patients in the intact group experience subjective cognitive difficulties and functional impairment as those observed in the selective and global subgroups. It highlights the importance of using a combo of instruments (e.g., neuropsychological test+COBRA+FAST) for the assessment of BD patients as such strategy would help to better understand the nature and extent of cognitive/ functional impairment and finally, contribute to the treatment individualization.

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## 7 CONSIDERAÇÕES FINAIS

Nessa tese foram apresentados dois artigos que estudaram o funcionamento cognitivo no TB utilizando medidas cognitivas objetivas e subjetivas.

O primeiro artigo demonstrou que a versão brasileira da COBRA possui propriedades psicométricas satisfatórias. Por ser um instrumento de fácil e rápida aplicação, a escala COBRA pode ser utilizada para avaliação de dificuldades cognitivas subjetivas no TB, tanto no âmbito da pesquisa como na prática clínica.

Assim como estudos prévios conduzidos com este instrumento, observamos que aqueles pacientes que apresentavam mais sintomas subsindrômicos, em especial sintomas depressivos, experimentaram mais queixas cognitivas, sugerindo que os sintomas de humor podem influenciar a autoavaliação das dificuldades cognitivas. Estes resultados também apontam para a importância de tratar os sintomas depressivos residuais, uma vez que eles prejudicam o desempenho cognitivo e funcional destes indivíduos.

Em relação à correlação entre a COBRA e as medidas cognitivas objetivas, nosso estudo falhou em mostrar tal associação. Tais resultados já eram esperados, pois se acredita que as medidas cognitivas subjetivas não são uma expressão direta das medidas cognitivas objetivas, já que ambas as medidas avaliam aspectos distintos da cognição. Também é oportuno esclarecer que estas diferenças devem-se ao fato de que os testes neuropsicológicos realizados pelos pacientes com TB foram comparados com o desempenho de um grupo de indivíduos saudáveis, enquanto que a medida subjetiva (isto é, a COBRA) investigou as dificuldades cognitivas expressas pelos pacientes no momento da avaliação tendo como parâmetro de comparação o funcionamento pré-mórbido do próprio sujeito.

Em conjunto, esses achados apoiam a ideia de se utilizar um combo de medidas (objetivas e subjetivas), pois o uso de ambas as medidas contribui para a correta identificação das disfunções cognitivas, permitindo implementar estratégias terapêuticas específicas para melhorar tanto as queixas cognitivas quanto o desempenho cognitivo de pacientes com TB.

O segundo artigo identificou a presença de três perfis cognitivos no TB: intacto (43,5%), seletivo (33,3%) e global (23,3%), evidenciando a existência de um *continuum* de gravidade que varia de funcionamento cognitivo preservado a comprometimento severo. O grupo intacto teve QI estimado mais alto e mais anos de estudo do que os subgrupos global e

seletivo, sugerindo que esse grupo tem maior reserva cognitiva do que outros dois grupos. Além disso, o grupo intacto era mais jovem, tinha idade de diagnóstico de TB mais precoce e maior prevalência de história familiar para transtorno psiquiátrico que o grupo global. Muito provavelmente estes indivíduos receberam tratamento adequado mais precocemente, fato que deve ter contribuído para a prevenção de recaídas e melhor prognóstico. Entretanto, o grupo intacto também experimenta dificuldades cognitivas subjetivas e algum grau de comprometimento funcional. Esses resultados confirmam que a disfunção cognitiva no TB é heterogênea, e que há vários fatores colaborando para essa variabilidade.

Como principal limitação da presente tese convém mencionar o tamanho da amostra pequeno e possibilidade de erro tipo II, bem como o fato de todos os pacientes estarem medicados e serem oriundos de um hospital terciário. Apesar dessas limitações, nossos achados corroboram os dados de estudos anteriores, e da observação clínica, de heterogeneidade do funcionamento cognitivo no TB. Ainda assim, estudos com amostras maiores são necessários para entender por que alguns pacientes experimentam problemas cognitivos significativos, enquanto outros permanecem preservados.

Como um todo, os estudos aqui apresentados contribuem para uma melhor caracterização e compreensão da disfunção cognitiva no TB. Uma avaliação abrangente, buscando integrar dados objetivos, subjetivos e informações clínicas, é essencial para determinar a natureza (subjetivo/objetivo) e a gravidade (intacto-seletivo-severo) da disfunção cognitiva. Espera-se que esse conjunto de informações conduza ao desenvolvimento de estratégias de prevenção e tratamento do comprometimento cognitivo associado ao TB.

Por fim, os resultados corroboram que a complexidade e heterogeneidade do funcionamento cognitivo no TB parecem caber melhor num modelo dimensional (intacto-intermediário-severo) do que categórico (com disfunção X sem disfunção). Do ponto de vista da pesquisa, identificar subgrupos com comprometimento cognitivo facilitará o reconhecimento de fatores de risco específicos, bem como contribuirá para o desenvolvimento de tratamentos mais personalizados.

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## ANEXO I – SCIP

# SCIP FORMULÁRIO 1

SCREEN FOR COGNITIVE IMPAIRMENT IN PSYCHIATRY (SCIP)
Scot E. Purdon, Ph.D., Clinical Professor of Psychiatry, University of Alberta; spurdon@ualberta.ca


**1. Teste de aprendizado de lista (Leia a lista de palavras em aproximadamente 3 segundos por palavra. Teste a memória imediata. Repita mais duas vezes). Ao final do terceiro teste, diga ao participante que ele será solicitado a lembrar-se da lista depois:**

| | Tambor | Cortina | Sino | Café | Escola | Pai | Lua | Jardim | Chapéu | Fazendeiro | Σ/10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. 1 | | | | | | | | | | | | |
| T. 2 | | | | | | | | | | | | |
| T. 3 | | | | | | | | | | | | Σ/30 = |

**2. Teste de repetição de consoante: Leia cada grupo de três letras. Peça à pessoa para contar de trás para frente começando do número na coluna início, durante os segundos indicados na coluna intervalo para cada item e, então, peça para dizer as letras (a ordem não importa):**

| Estímulo | Início # | Intervalo | Resposta | | Estímulo | Início # | Intervalo | Resposta | |
|---|---|---|---|---|---|---|---|---|---|
| Q-L-X | | | | | F-X-B | 53 | 3 | | |
| H-J-T | | | | | J-C-N | 46 | 9 | | |
| X-C-P | 94 | 18 | | | B-G-Q | 117 | 18 | | |
| N-D-J | 109 | 9 | | | K-M-C | 48 | 3 | | Σ/24 = |

**3. Teste de fluência verbal. Dê 30 segundos para gerar palavras que comecem com cada letra.**

| Estímulo | Resposta | |
|---|---|---|
| C | | |
| L | | Σ = |

**4. Aprendizado de lista tardio: Peça à pessoa para lembrar as palavras do item 1; não repita a lista.**

| | Tambor | Cortina | Sino | Café | Escola | Pai | Lua | Jardim | Chapéu | Fazendeiro | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. 4 | | | | | | | | | | | Σ/.10 | t4/t3 * 100 |

----------DOBRE AQUI----------

**5. Teste de rastreamento visual-motor: Após os itens para prática, dê 30 segundos para completar da esquerda para a direita e de cima para baixo.**

| A | V | C | U | G | Y |
|---|---|---|---|---|---|
| . – | . . . – | – . – . | . . – | – – . | – . – – |

| Prática | | | | | | Teste | | | |
|---|---|---|---|---|---|---|---|---|---|
| G | U | C | Y | A | V | C | A | G | |
| V | Y | U | G | U | A | Y | C | V | |
| A | C | Y | G | U | V | C | Y | V | |
| U | G | A | V | C | G | A | V | Y | Σ/30 |

**SINTESE DA PONTUAÇÃO: Para cada subteste, divida a diferença entre a pontuação observada e a pontuação prevista pelo desvio padrão. (n=185, amostra de alunos do 1° de faculdade, QI aprox. 110): Z-Scores=((Score-Média)/DP). M±DP para TAV_I=23.59±2.87, TMT=20.66±2.45, TFV=17.44±4.74, TAP_T=7.65±1.90, TVP=14.26±2.25.**

**Nome (primeiro, último):**_____**Gênero:**_____**Examinador:**_____
**Data nascimento (d/m/a):**_____ **Data teste (d/m/a):**_____ **Hora teste:**_____
**QI estimado (indicar PPVT, NART, WAIS):**_____**Escolaridade:**_____**Lateralidade:**____

**ANEXO II – COBRA**

## Escala de Disfunções Cognitivas no Transtorno Bipolar

Nome: _____ N° prontuário: _____
Data da avaliação: ____/___/___ Avaliador:_____

Utilize: 0) nunca; 1) algumas vezes; 2) frequentemente; 3) sempre.

| Escala de Disfunções Cognitivas no Transtorno Bipolar | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| 1. Você tem dificuldade para se lembrar do nome das pessoas? | | | | |
| 2. Você tem dificuldade para encontrar objetos de uso diário (chaves, óculos, relógio)? | | | | |
| 3. Você tem problemas para se lembrar de acontecimentos que foram importantes na sua vida? | | | | |
| 4. É difícil para você situar no tempo determinados acontecimentos? | | | | |
| 5. É difícil para você se concentrar na leitura de um livro, ou jornal? | | | | |
| 6. É difícil para você se lembrar do que você leu, ou do que lhe disseram, recentemente? | | | | |
| 7. Você tem a sensação de que não termina o que começou? | | | | |
| 8. Você tem executado de forma mais lenta as tarefas do dia-a-dia? | | | | |
| 9. Você já se desorientou alguma vez na rua? | | | | |
| 10. Quando alguém relembra uma conversa, ou comentário, que teve com você; você tem a impressão de estar ouvindo a informação pela primeira vez? | | | | |
| 11. É difícil para você, em algumas ocasiões, encontrar as palavras certas para expressar as suas ideias? | | | | |
| 12. Você se distrai com facilidade? | | | | |
| 13. É complicado para você fazer cálculos simples mentalmente? | | | | |
| 14. Você tem a impressão de perder o rumo da conversa? | | | | |
| 15. Tem sido difícil para você aprender novas informações? | | | | |
| 16. É difícil para você manter a concentração em uma tarefa durante muito tempo? | | | | |
| | Total: | | | |