**UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL FACULDADE DE MEDICINA**

**PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA CIÊNCIAS DO COMPORTAMENTO**

**DISSERTAÇÃO DE MESTRADO**

MATHIAS HASSE DE SOUSA

# O PAPEL DO AGRUPAMENTO SEMÂNTICO NA RELAÇÃO ENTRE MEMÓRIA VERBAL E FUNCIONALIDADE NA ESQUIZOFRENIA E TRANSTORNO BIPOLAR: UMA POSSÍVEL VIA COGNITIVA DISTINTA

PORTO ALEGRE
2022

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*Men's memories are uncertain and the past that was differs little from the past that was not.*

(Cormac McCarthy)

## LISTA DE ABREVIATURAS E SIGLAS

SZ: esquizofrenia
TB: transtorno bipolar
FAST: Functioning Assessment Short Test
HVLT – R: Hopkins Verbal Learning Test - Revised
PRODESQ: Programa de Esquizofrenia
PROTHABI: Programa de Transtorno Bipolar
SCID: Structured Clinical Interview (SCID)
HAM-D: Hamilton Depression Scale
YMRS: Young Mania Rating Scale
TCLE: Termo de Consentimento Livre e Esclarecido
ANOVA: Análise de Variância
ANCOVA: Análise de Covariância

## RESUMO

**Contexto**: A memória verbal está comumente prejudicada em esquizofrenia (SZ) e transtorno bipolar (TB), além de associada com funcionalidade. No entanto, há uma escassez de pesquisas analisando o papel de componentes da memória verbal nesses transtornos. O agrupamento semântico, particularmente, é um componente de possível relevância para tal associação, uma vez que é um processo cognitivo complexo dependente de atividade pré-frontal. **Objetivos:** Investigar componentes da memória verbal na SZ e TB e o papel do agrupamento semântico no relacionamento entre memória verbal e funcionalidade. **Método**: 495 participantes foram incluídos – 154 SZ, 172 TB, e 167 controles saudáveis (CS) – e passaram por uma avaliação clínica e neuropsicológica. A *Hopkins Verbal Learning Test – Revised* foi usada para avaliar memória verbal e a *Functioning Assessment Short Test* para funcionalidade. Conduzimos uma ANOVA para comparações clínicas e sociodemográficas, e uma ANCOVA para comparações em memória verbal, controlando para idade, sexo, e anos de estudo. Para investigar o papel do agrupamento semântico entre desempenho em memória verbal e funcionalidade, conduzimos análises de regressão linear. **Resultados**: SZ apresentou pior desempenho geral em memória verbal que TB, que por sua vez foi pior que CS. CS usaram mais agrupamento semântico que SZ e TB, porém não houve diferenças entre os dois grupos. Nos CS, o agrupamento semântico impactou o relacionamento entre desempenho em memória verbal e funcionalidade. No entanto, tal interação não ocorreu em SZ e TB. **Conclusões**: Nossos resultados indicam que SZ e BD podem utilizar uma via cognitiva alternativa na qual o relacionamento entre memória verbal e funcionalidade é independente de processos cognitivos complexos como agrupamento semântico.



Palavras-chave: esquizofrenia; transtorno bipolar; componentes da memória verbal

## ABSTRACT

**Introduction:** Verbal memory (VM) is commonly impaired in schizophrenia (SZ) and bipolar disorder (BD), as well as associated with functioning. However, there is a lack of research analyzing the role of VM components in these disorders. Semantic clustering, particularly, is an interesting component of relevance for such association, as it is a complex cognitive mechanism reliant on prefrontal activity. **Objectives:** To investigate VM components in SZ and BD and the role of semantic clustering in the relationship between VM and functioning. **Methods:** 495 participants were included - 156 SZ, 172 BD, and 167 healthy controls (HC) - and underwent a clinical and neuropsychological evaluation. The Hopkins Verbal Learning Test – Revised was used to assess VM and the Functioning Assessment Short Test for functioning. We conducted an ANOVA for clinical and sociodomographical comparison, and an ANCOVA for VM comparison, controlling for age, sex, and years of education. To investigate the role of semantic clustering in the relationship between VM performance and functioning, we conducted linear regression analyses. **Results:** SZ had overall worse VM performance than BD, which performed worse than HC. HC used more semantic clustering than SZ and BD, but there were no differences among the two groups. In HC, semantic clustering impacted the relationship between VM performance and functioning. However, no interaction occurred in SZ or BD. **Conclusions:** Our results indicate that SZ and BD may use an alternative cognitive pathway in which the relationship between VM and functioning is independent of complex cognitive processes such as semantic clustering.



**Keywords:** schizophrenia; bipolar disorder; verbal memory components

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## 1. INTRODUÇÃO

A esquizofrenia (SZ) e o transtorno bipolar (TB) são transtornos psiquiátricos graves e altamente incapacitantes (JAMES *et al.*, 2018). Embora a SZ e o TB sejam considerados entidades diagnósticas distintas (o primeiro pertencendo aos transtornos psicóticos, e o segundo aos transtornos de humor) (AMERICAN PSYCHIATRIC ASSOCIATION, 2014), debates seguem há décadas discutindo as possíveis sobreposições clínicas, funcionais, e cognitivas dos dois transtornos (BOWIE *et al.*, 2018; CHEN *et al.*, 2018; SMELAND *et al.*, 2020).

Indivíduos com SZ ou TB apresentam diversos prejuízos funcionais em suas vidas cotidianas (JIMÉNEZ-LÓPEZ *et al.*, 2018; REICHENBERG *et al.*, 2014; TOULOPOULOUAND; MURRAY, 2004), frequentemente sendo incapazes de terem uma vida autônoma e independente. Não surpreendentemente, isso acarreta em diversos prejuízos econômicos, seja com performance laboral prejudicada, anos de vida com a doença, aumento de custos do Estado, ou necessidade de aposentadoria por invalidez (CHONG *et al.*, 2016; JAMES *et al.*, 2018; VOS *et al.*, 2012). Por conta disso, esforços têm sido feitos para identificar fatores que contribuem para o prejuízo funcional nessas doenças. Variáveis clínicas já foram sugeridas, como sintomas de humor persistentes (HOWER *et al.*, 2019) ou subclínicos (JIMÉNEZ-LÓPEZ *et al.*, 2018), além de gênero masculino e maior idade (SANCHEZ-MORENO *et al.*, 2018).

No entanto, apenas variáveis clínicas não aparentam explicar integralmente o prejuízo funcional na SZ e TB. Embora o manejo farmacológico seja o padrão ouro de tratamento em ambas as doenças, pessoas com esses transtornos frequentemente apresentam prejuízos funcionais, mesmo com melhora sintomatológica (GITLIN; MIKLOWITZ, 2017; GREEN, M. F., 1996). Assim, intervenções meramente farmacológicas não são o suficiente para uma compreensão dos mecanismos responsáveis pelos prejuízos funcionais nesses transtornos. Um estudo clássico, por exemplo, encontrou prejuízos cognitivos como sendo os principais responsáveis por déficits em desfechos funcionais em pessoas com SZ, com sintomas clínicos apresentando um papel secundário (GREEN, M. F., 1996). Nesse contexto, o estudo da cognição e do funcionamento neuropsicológico mostra-se necessário para elucidar lacunas no entendimento do prejuízo funcional

em SZ e TB. Estudos recentes estabelecem a cognição como um fator essencial para o desfecho funcional na SZ e TB (AMORETTI *et al.*, 2020; JIMÉNEZ-LÓPEZ *et al.*, 2018). Isso dá-se pela clara relação entre os dois âmbitos: pessoas com déficits em atividades que envolvam domínios cognitivos podem vir a ter dificuldades em questões intrínsecas à funcionalidade geral, como organização pessoal e financeira, capacidade de trabalhar e viver de maneira independente, e o desenvolvimento de estratégias adequadas em contextos sociais (ROSA, Adriane R *et al.*, 2007; TOHEN *et al.*, 2000).

Um dos domínios cognitivos de maior importância em relação à funcionalidade na SZ e TB é a memória verbal. De fato, a associação entre prejuízos em memória verbal e prejuízos na funcionalidade já é bem estabelecido na SZ (DANION *et al.*, 2007; FU *et al.*, 2017). Similarmente, performance em memória verbal também está associada com prejuízo funcional no TB (BONNÍN *et al.*, 2010a; MARTINEZ-ARAN *et al.*, 2007), assim como em status ocupacional (TSE *et al.*, 2014) e variáveis psiquiátricas clínicas como tempo de doença e número de episódios maníacos (MARTÍNEZ-ARÁN *et al.*, 2004). Dessa forma, o estudo da memória verbal demonstra-se crucial para um melhor entendimento dos mecanismos cognitivos dessas doenças e suas relações com desfechos funcionais.

## 1.1 ESQUIZOFRENIA

A SZ é um transtorno psiquiátrico crônico e incapacitante, com início de doença geralmente desenvolvido no fim da adolescência e início da adultez, caracterizado por sintomas positivos e negativos. Os sintomas positivos consistem do surgimento de episódios psicóticos, através de alucinações e/ou pensamentos com conteúdo delirante, além de pensamento e fala desorganizados. Os sintomas negativos, por sua vez, consistem de estados de embotamento afetivo, avolia, anedonia, e/ou alogia, ou seja: há uma redução ou ausência de condições consideradas essenciais para um funcionamento normal (AMERICAN PSYCHIATRIC ASSOCIATION, 2014).

Estimativas apontam a prevalência de SZ na população geral entre 0.40% (SAHA *et al.*, 2005) e 0.48% (SIMEONE *et al.*, 2015). Em relação a origens, a SZ tem etiologia multifatorial, com um forte componente genético (SULLIVAN; DALY; O'DONOVAN,

2012). Através de estudos com gêmeos e de coorte, estima-se que a SZ possua uma herdabilidade de mais de 70% (BOOMSMA; BUSJAHN; PELTONEN, 2002; HILKER *et al.*, 2018). No entanto, fatores ambientais, como uso de cannabis na adolescência, urbanicidade, e adversidades de vida precoces, também desempenham um papel significativo no desenvolvimento da doença (VAN OS; KENIS; RUTTEN, 2010).

A SZ é um transtorno vastamente incapacitante. O custo econômico da SZ é estimado em aproximadamente US$155bi por ano apenas nos Estados Unidos (CLOUTIER *et al.*, 2016). Isso dá-se não apenas pelos gastos diretos com a doença, como internações e tratamento ambulatorial, mas também relacionados a gastos indiretos envolvendo não-produtividade, desemprego, necessidade de auxílio por invalidez, entre outros. De fato, diversos estudos evidenciam um significativo prejuízo funcional em pessoas com SZ. No período pré-mórbido, cerca de 80% dos indivíduos relataram possuir alguma ocupação ou educação formal, enquanto esse número foi reduzido para 10-20% após o primeiro episódio e diagnóstico de SZ (HARVEY *et al.*, 2012). Da mesma forma, apenas 6% de pessoas com SZ atingem múltiplas conquistas da vida concomitantemente em domínios sociais, vocacionais e residenciais (HARVEY *et al.*, 2012). Ademais, há ampla evidência de dificuldades de pessoas com SZ em viverem sozinhos e de serem financeiramente independentes (MAUSBACH *et al.*, 2007), além de dificuldades em adesão e manutenção medicamentosa (VELLIGAN *et al.*, 2009), menos amigos (HARLEY; BOARDMAN; CRAIG, 2012), e menos relacionamentos afetivos (MACCABE; KOUPIL; LEON, 2009). Por fim, pessoas com SZ frequentemente relatam passar a maior parte do seu tempo em atividades sedentárias ou pouco engajadas, como assistir a televisão ou deitar (STRASSNIG *et al.*, 2021).

No cotidiano clínico, os sintomas positivos costumam ser o foco de intervenção, uma vez que sua presença é facilmente identificável e leva a maiores disrupções na vida do indivíduo. O tratamento com antipsicóticos é considerado essencial em indivíduos com SZ, geralmente apresentando alguma melhora dos sintomas positivos (HUHN *et al.*, 2019; MCCUTCHEON *et al.*, 2021). Antipsicóticos de segunda geração, como clozapina, olanzapina e risperidona, têm preferência prescritiva, uma vez que apresentam maior tolerabilidade e menos efeitos adversos, como sintomas extrapiramidais (LEUCHT *et al.*, 2009). A clozapina, particularmente, vem sendo proposta como uma das principais intervenções farmacológicas para a SZ,

especialmente para casos refratários (SISKIND *et al.*, 2016). Sintomas negativos, no entanto, costumam ser deixados em segundo plano, uma vez que suas manifestações são mais insidiosas e não tão facilmente perceptíveis (CARBON; CORRELL, 2014). Além disso, tratamentos para sintomas negativos não possuem eficácia semelhante ao de sintomas positivos. Uma metanálise de 168 ensaios clínicos randomizados com placebo, por exemplo, não encontrou resultados de eficácia com relevância clínica para melhora de sintomas negativos em indivíduos com SZ (FUSAR-POLI *et al.*, 2015). Há, no entanto, evidências de que os tratamentos com antipsicóticos, no geral, são protetivos em relação à cognição de pessoas com transtornos psicóticos (BALDEZ *et al.*, 2021).

## 1.2 TRANSTORNO BIPOLAR

O DSM 5 caracteriza o TB como um transtorno de humor com episódios alternados de mania, hipomania e/ou depressão (AMERICAN PSYCHIATRIC ASSOCIATION, 2014). Dentro do TB, há duas categorias: o TB tipo I e o TB tipo II. O TB tipo I consiste de episódios de mania, caracterizada como um estado elevado de humor, com ideias infladas sobre si e pensamento e comportamento acelerado, com duração de pelo menos 7 dias ou até ser necessária hospitalização psiquiátrica. O TB tipo II, por sua vez, é diagnosticado após um episódio depressivo e um hipomaníaco. A hipomania é definida como uma alteração de elevação do humor, porém com uma duração de até 4 dias e sem a severidade e prejuízo funcional extremo causados pela mania (AMERICAN PSYCHIATRIC ASSOCIATION, 2014; GRANDE *et al.*, 2016).

A prevalência do TB na população em geral é estimada em pouco mais de 1%, tanto para TB tipo I quanto TB tipo II (CLEMENTE *et al.*, 2015). Apesar de multifatoriais, suas origens têm um significante fator genético. Estudos de associação genômica ampla estimam a herdabilidade do TB entre 20-40% (LEE, S. H. *et al.*, 2011; PETTERSSON *et al.*, 2019). Em estudos com gêmeos, esta herdabilidade é maior, com aproximadamente 60% (JOHANSSON *et al.*, 2019; SONG *et al.*, 2015).

Assim como a SZ, o TB também é um transtorno altamente incapacitante. Nos Estados Unidos, o custo econômico do TB é estimado entre US$195-US$202 bilhões por ano (BESSONOVA *et al.*, 2020; CLOUTIER *et al.*, 2018). Em questões

ocupacionais, o TB não é tão incapacitante como a SZ. No entanto, mesmo com 60% das pessoas com TB sendo capazes de trabalhar, uma significativa percentagem apresenta prejuízos no rendimento ou muda para um cargo menos qualificado (MARWAHA; DURRANI; SINGH, 2013). Tais prejuízos já são apresentados no início da doença, mesmo em jovens em remissão (HOWER *et al.*, 2019).

O tratamento farmacológico é considerado a principal intervenção clínica em indivíduos com TB. Para isso, diversas classes de medicações podem ser prescritas, como estabilizadores de humor, antipsicóticos e antidepressivos. A prescrição de lítio é o padrão ouro no manejo farmacológico do TB, tanto para a prevenção de recaída de sintomas (CIPRIANI *et al.*, 2013b) quanto para o manejo de risco de suicídio (CIPRIANI *et al.*, 2013a; SONG *et al.*, 2017). Antidepressivos também podem ser prescritos, embora a monoterapia apresente riscos de desencadear um episódio de mania (MELHUISH BEAUPRE *et al.*, 2020). Por conta disso, evidências sugerem que antidepressivos sejam utilizados em combinação com estabilizadores de humor (LIU *et al.*, 2017).

## 1.3 COGNIÇÃO NA ESQUIZOFRENIA E TRANSTORNO BIPOLAR

A cognição na SZ e TB vem sendo continuamente estudada nas últimas décadas, por conta de suas diversas associações com desfechos clínicos e funcionais. Já é bem estabelecido que a SZ (BARCH; CEASER, 2012; FIORAVANTI; BIANCHI; CINTI, 2012; KAHN *et al.*, 2015) e o TB (TSITSIPA; FOUNTOULAKIS, 2015) apresentam prejuízos cognitivos, embora não haja um consenso em relação à severidade destes. Evidências de metanálises indicam prejuízos cognitivos globais em todos os domínios cognitivos na SZ (BORA, Emre; PANTELIS, 2015; LI *et al.*, 2020) e TB (BOURNE *et al.*, 2013).

Apesar disso, o perfil cognitivo de ambos os transtornos não é homogêneo. Na SZ, modelos propõem que o prejuízo cognitivo origina-se durante o neurodesenvolvimento do indivíduo – ou seja, na aquisição da habilidade cognitiva, e não na sua perda (BORA, E, 2015; RECKZIEGEL *et al.*, 2021; WOODWARD, 2016). Isso dá-se através de evidências que demonstram que o prejuízo cognitivo já está presente em indivíduos na fase pré-mórbida da SZ (ANDA *et al.*, 2019; LEE, S.

J. *et al.*, 2017; MOLLON; REICHENBERG, 2018). Além disso, é estimado que o risco de desenvolver SZ aumenta em 3.8% a cada redução de 1 ponto de QI (KENDLER *et al.*, 2015; KHANDAKER *et al.*, 2011). Adicionalmente, funções cognitivas específicas também estão prejudicadas no período pré-mórbido da doença, como memória, atenção, funções executivas e velocidade de processamento (MEIER *et al.*, 2014; SHEFFIELD; KARCHER; BARCH, 2018). Mais evidências de que o prejuízo cognitivo na SZ é de origem neurodesenvolvimental apontam que o desempenho cognitivo de indivíduos com SZ com trajetória crônica é semelhante ao de indivíduos com SZ no início da doença (MCCLEERY *et al.*, 2014), mesmo com longos momentos de psicose não-tratada (SOLÍS-VIVANCO *et al.*, 2020) ou com análises longitudinais após 10 anos (RUND *et al.*, 2016). Há, no entanto, alguns estudos com resultados contrários, apontando um declínio cognitivo em indivíduos com SZ ao longo do tempo (FUJINO *et al.*, 2017). Tais resultados podem ser interpretados à luz de ampla heterogeneidade na SZ (RECKZIEGEL *et al.*, 2021; SHMUKLER *et al.*, 2015). De fato, diferentes perfis cognitivos já foram estabelecidos na SZ (BOSIA *et al.*, 2019; VAN RHEENEN, T. E. *et al.*, 2017), com análises longitudinais apresentando estabilidade (ISLAM *et al.*, 2018). O número mais consistente de *clusters* de perfis cognitivos encontrados é o de 3 grupos: intelectualmente preservado, com prejuízos específicos, ou globalmente prejudicado (GREEN, M. J. *et al.*, 2020), embora outros *clusters* também sejam propostos, como 5: severamente alterado, moderadamente alterado, suavemente alterado, normal, e alta performance (ISLAM *et al.*, 2018).

Em relação ao TB, um dos modelos vigentes para compreender o perfil cognitivo da doença é o da neuroprogressão e estadiamento. Ele propõe que o TB segue uma trajetória neuroprogressiva em que a pessoa com TB, gradativamente, desenvolve prejuízos clínicos, cognitivos e funcionais, através de disrupções inflamatórias e neuronais em decorrência da neurotoxicidade de seguidos episódios afetivos ao longo do tempo (GAMA *et al.*, 2013; KAPCZINSKI *et al.*, 2009). Dessa forma, o modelo propõe que o desempenho cognitivo de indivíduos com TB com mais tempo de doença é significativamente pior do que indivíduos durante os primeiros anos de doença. De fato, estudos evidenciam uma associação entre maior tempo de doença e pior desempenho cognitivo (CARDOSO *et al.*, 2015; GILDENGERS *et al.*, 2009) e funcionalidade mais preservada em pessoas com TB no início da doença (ROSA, A

R *et al.*, 2012). No entanto, há também resultados contrastantes de estudos que não encontraram evidências de neuroprogressão (BORA, E; ÖZERDEM, 2017), ou encontraram apenas prejuízos cognitivos específicos no *follow-up* (SANTOS *et al.*, 2014). Dessa forma, modelos de neuroprogressão também possuem seus críticos (DUFFY; MALHI; GROF, 2017; MARTINO *et al.*, 2016).

Parte da razão por tais resultados contrastantes pode ser devido, assim como na SZ, à heterogeneidade do TB. Embora prejuízos cognitivos estejam evidenciados no TB (BO *et al.*, 2017; MISKOWIAK *et al.*, 2017), recentemente estudos têm mostrado perfis cognitivos distintos, com 3 grupos comumente identificados: cognitivamente preservados, com prejuízos específicos, ou globalmente prejudicados (JENSEN *et al.*, 2016; LIMA *et al.*, 2019; VAN RHEENEN, T. E. *et al.*, 2017). Assim, não há uma única expressão da doença em aspectos cognitivos, tanto na SZ quanto no TB.

Alguns estudos sugerem que a SZ apresenta mais prejuízos cognitivos do que o TB (BORTOLATO *et al.*, 2015; CHEN *et al.*, 2018; LI *et al.*, 2020; LYNHAM *et al.*, 2018; SCHRETLEN *et al.*, 2013), embora outros apontam significativa sobreposição entre ambos os transtornos (KUSWANTO, C. *et al.*, 2016; KUSWANTO, C. N.; SUM; SIM, 2013; VASKINN *et al.*, 2020). Por conta disso, alguns autores propõem que as diferenças cognitivas entre SZ e TB são, em natureza, quantitativas e não qualitativas (SCHRETLEN *et al.*, 2013; TSITSIPA; FOUNTOULAKIS, 2015).

## 1.4 MEMÓRIA VERBAL NA ESQUIZOFRENIA E TRANSTORNO BIPOLAR

A memória episódica verbal, comumente descrita na literatura apenas como “memória verbal”, consiste de um aspecto central da cognição, sendo definida como a habilidade de codificar, consolidar e recuperar informações sobre eventos, instruções, experiências ou conversas passadas quando necessário (GAZZANIGA; HEATHERTON; HALPERN, 2017; TULVING, 2002). Ela distingue-se da memória semântica, um outro sugrupo da memória declarativa, pois ela se encarrega de informações de experiências pregressas de uma pessoa (*“durante os ataques do 11 de setembro, eu estava na escola com meus amigos”),* enquanto a memória semântica é responsável por armazenar informações concretas de fatos e eventos (*“os ataques do 11 de setembro ocorreram em 2001”).* Um prejuízo na memória

verbal, não surpreendentemente, causa prejuízos na vida do indivíduo, uma vez que ela é essencial para o funcionamento adequado da vida (GREEN, M. F. *et al.*, 2000; HARVEY; STRASSNIG; SILBERSTEIN, 2019).

A base neurológica da memória verbal é o hipocampo, estrutura do lobo temporal medial (EICHENBAUM, 2017; MOSCOVITCH *et al.*, 2016). Há um consenso geral na literatura de que o hipocampo e demais estruturas límbicas são indispensáveis para um desempenho adequado na memória (BECKER; LIM, 2003; BUCKNER, 2004; EICHENBAUM, 2017), considerando o processo integral de codificação, consolidação e recuperação da memória (GAZZANIGA; HEATHERTON; HALPERN, 2017). De fato, pessoas com lesões hipocampais apresentam prejuízos severos em memória verbal (VARGHA-KHADEM *et al.*, 1997).

Além do hipocampo, o córtex pré-frontal tem sido proposto como um elemento crucial para um desempenho adequado em memória verbal, agindo como um mediador responsável pela seleção e manutenção de processos atencionais, assim como a manipulação ativa de elementos da memória, através do controle cognitivo para a execução apropriada de uma tarefa (BARCH; CEASER, 2012; DIAMOND, 2013; FRIEDMAN; ROBBINS, 2021; GUO; RAGLAND; CARTER, 2019). Dessa forma, a memória verbal apresenta-se como um processo cognitivo dinâmico, que depende da interação de diversas áreas cerebrais para um funcionamento adequado. Assim, os prejuízos em memória verbal testemunhados na SZ e no TB podem ser interpretados, parcialmente, à luz de deficits em conectividade e atividade pré-frontais de controle cognitivo (EICHENBAUM, 2017; GUO; RAGLAND; CARTER, 2019), especialmente dadas as evidências de que estes transtornos possuem atividades pré-frontais prejudicadas (CHAI *et al.*, 2011). Além disso, estudos passados encontraram atividade pré-frontal reduzida em pessoas com SZ e TB ao realizar tarefas de memória verbal (GUO; RAGLAND; CARTER, 2019; OERTEL-KNÖCHEL *et al.*, 2013; RAGLAND *et al.*, 2009).

Na SZ, diversos estudos já identificaram prejuízos na memória verbal (BARCH; CEASER, 2012; CZEPIELEWSKI, Leticia S *et al.*, 2015; CZEPIELEWSKI, Leticia Sanguinetti *et al.*, 2018; FIORAVANTI; BIANCHI; CINTI, 2012; HARVEY *et al.*, 2004; VOHRINGER *et al.*, 2013). Evidências recentes também apontam que pessoas com esquizofrenia mais jovens apresentam pior desempenho em memória episódica que pacientes idosos com amnésia moderada (KANCHANATAWAN *et al.*, 2018).

Ademais, há também um prejuízo mais acentuado mesmo ao comparar a performance em memória verbal com a de idosos saudáveis (SILVER; BILKER, 2015). Os déficits em memória verbal apresentados na esquizofrenia estão relacionados a alterações neurológicas, como diminuição de massa cinzenta, volume cerebral total e hipoativação pré-frontal (BARCH *et al.*, 2003; CZEPIELEWSKI, Leticia Sanguinetti *et al.*, 2017, 2018; HAIJMA *et al.*, 2013; WOODWARD; HECKERS, 2015). Por outro lado, existem evidências de que a memória verbal não está relacionada com alguns biomarcadores, como TNF-α e interleucina-6 (REBOUÇAS *et al.*, 2018). Por conta desta série de achados, acredita-se que prejuízos de memória verbal na esquizofrenia não se devem a um único aspecto, mas sim à contribuição de diversos fatores clínicos, genéticos, neurológicos, e biológicos (BARCH; SHEFFIELD, 2017; RECKZIEGEL *et al.*, 2021).

No TB, a memória verbal também está comumente prejudicada (VAN RHEENEN, Tamsyn E; ROSSELL, 2014), mesmo em indivíduos no início da doença (CHAKRABARTY *et al.*, 2015; LERA-MIGUEL *et al.*, 2015). Alterações em áreas fronto-parietais estam associadas a pior desempenho em memória episódica (OERTEL-KNÖCHEL *et al.*, 2014). Há evidências também de que a memória verbal se deteriora ao longo da doença, como em um estudo longitudinal que identificou memória verbal como a única função cognitiva com deterioração após *follow-up* de 5 anos (SANTOS *et al.*, 2014). Além disso, indivíduos com TB em estágios médios e tardios apresentaram menor volume hipocampal e pior desempenho em memória verbal se comparados com indivíduos com TB no início da doença e controles saudáveis (CAO *et al.*, 2016). Semelhantemente, apenas indivíduos com TB num estágio tardio da doença apresentaram prejuízos em memória verbal em outro estudo (CZEPIELEWSKI, Leticia S *et al.*, 2015).

No entanto, não há também um consenso sobre comparações de desempenho em memória verbal entre SZ e TB. Algumas demonstram que há um maior prejuízo na SZ do que no TB (HAUT *et al.*, 2015; KUSWANTO, C. *et al.*, 2016; LI *et al.*, 2020; LYNHAM *et al.*, 2018; SÁNCHEZ-MORLA *et al.*, 2009). Um estudo apontou memória verbal preservada em indivíduos com TB no início da doença, enquanto indivíduos com TB em estágios tardios tinham performance semelhante a SZ – que, por sua vez, não apresentou diferenças entre pessoas com SZ no início da doença vs. SZ crônica (CZEPIELEWSKI, Leticia S *et al.*, 2015). No entanto, há também resultados

que não encontraram diferenças entre ambos os transtornos (ALTSHULER *et al.*, 2004). Alguns dos resultados negativos são mantidos mesmo com o acréscimo de transtorno esquizoafetivo na comparação (CHEN *et al.*, 2018) ou separação de TB com e sem sintomas psicóticos (JIMÉNEZ-LÓPEZ *et al.*, 2017). Por conta de tais resultados contrastantes, as diferenças de memória verbal na SZ e TB ainda não estão claras.

## 1.5 COMPONENTES DA MEMÓRIA VERBAL NA ESQUIZOFRENIA E NO TRANSTORNO BIPOLAR

Além disso, há uma escassez de estudos analisando os componentes subjacentes da memória verbal na SZ e no TB, com estudos normalmente relatando apenas o resultado final – geralmente o número de palavras lembradas durante a aplicação de instrumentos comumente utilizados para avaliar esse domínio. Isso, no entanto, não elucida os mecanismos cognitivos por trás de tal resultado.

Por exemplo, há diversas possíveis estratégias de organização da memória em tarefas de memória verbal, com crescentes níveis de complexidade cognitiva em suas execuções. Dentre os de mais baixa complexidade, existem os efeitos de *primazia* e *recência* (MURDOCK JR., 1962), nos quais o participante prioriza a recuperação de elementos que foram apresentados em primeiro e último lugar, respectivamente. Similarmente, há também a estratégia de *agrupamento seriado*, na qual o participante organiza os elementos da memória na ordem temporal em que eles foram apresentados (KAHANA, 1996). Por fim, exigindo um processamento cognitivo mais avançado e complexo, há a estratégia de *agrupamento semântico*, na qual o participante agrupa os elementos da memória em suas categorias implícitas (por exemplo, perceber que as palavras “gato”, “vaca”, e “coelho” pertencem à categoria “animais”) (WOODS *et al.*, 2005a). Tais estratégias ilustram os conceitos de *processamento raso* e *processamento profundo* propostos por Brébion e colegas (2000): durante o processamento raso, apenas características superficiais dos elementos são percebidas (como a ordem nas quais foram apresentadas – agrupamento seriado), enquanto o processamento profundo se encarrega de processar características mais complexas (como a afiliação a uma categoria semântica – agrupamento semântico). O uso de estratégias de processamento

profundo está associado a melhor performance em memória verbal, enquanto o oposto ocorre em estratégias de processamento raso (GSOTTSCHNEIDER *et al.*, 2011).

O agrupamento semântico, particularmente, mostra-se um construto com interessante potencial para a compreensão de mecanismos da memória verbal, estando associado a um melhor desempenho nela (BRUNET *et al.*, 2020; GOH; AN; RESNICK, 2012). Por ser um processo cognitivo complexo, diversos autores apontam o agrupamento semântico como dependente de atividade e maturação pré-frontal (GUIMOND; HAWCO; LEPAGE, 2017; HAWCO; BERLIM; LEPAGE, 2013; YU *et al.*, 2018), no qual pessoas com lesões nessas áreas apresentam prejuízos significativos (GERSHBERG; SHIMAMURA, 1995). Estudos de neuroimagem também indicam associações entre volume de substância cinzenta em áres pré-frontais e uso de agrupamento semântico, enquanto estratégias menos complexas, como o agrupamento seriado, não apresentaram tal associação (KIRCHHOFF; GORDON; HEAD, 2014). Resultados semelhantes são encontrados em estudos de ressonância magnética funcional, nos quais ativação em áreas pré-frontais são preditoras de uso de estratégias de agrupamento semântico (GUIMOND; BÉLAND; LEPAGE, 2018; GUIMOND; HAWCO; LEPAGE, 2017; LONG; ÖZTEKIN; BADRE, 2010).

Por envolver processos complexos de manipulação de elementos da memória, o agrupamento semântico pode ser considerado uma medida de funções executivas, definidas como processos cognitivos complexos e não-automatizados (DIAMOND, 2013). De fato, o agrupamento semântico já foi utilizado como medida de funções executivas em estudos de neuropsicologia (BROADWAY *et al.*, 2019). Assim, transtornos relacionados a prejuízos pré-frontais, como a SZ e o TB, podem também apresentar desempenho pior em memória verbal e agrupamento semântico. Isso é evidenciado em estudos demonstrando que indivíduos com SZ (GUO; RAGLAND; CARTER, 2019; RAGLAND *et al.*, 2009) e TB (OERTEL-KNÖCHEL *et al.*, 2013) apresentam atividade pré-frontal reduzida em tarefas de memória verbal, o que pode dificultar o processamento complexo de elementos da memória. Mais evidências apontam uma dificuldade em pessoas com SZ de auto-iniciarem estratégias de agrupamento semântico, associada ao córtex pré-frontal dorsolateral (GUIMOND; HAWCO; LEPAGE, 2017), embora essas pessoas tenham conseguido aumentar a

atividade nessa área após um treino de estratégias semânticas (GUIMOND; BÉLAND; LEPAGE, 2018), indicando que tal capacidade ainda é possível de ser utilizada com o devido treinamento.

Dentro desse contexto, o agrupamento semântico pode ser entendido como um reflexo de um controle cognitivo eficaz, que seria traduzido na vida do indivíduo em maneiras otimizadas de adquirir e recuperar elementos da memória pertinentes para seu cotidiano (como lembrar-se de quando tomar seus remédios, organizar finanças, e manter-se num emprego), contribuindo para uma funcionalidade preservada. Tal proposta é reforçada por resultados recentes que encontraram uma associação entre uso de agrupamento semântico e *status* ocupacional em uma amostra comunitária (WILLIAMS; ULRICH; WOODS, 2021).

Assim, o estudo do agrupamento semântico na memória verbal mostra-se uma área com potencial para maior entendimento dos processos cognitivos por trás da memória verbal na SZ e no TB. Em comparações com controles saudáveis, um estudo encontrou prejuízo de uso de agrupamento semântico em pessoas com TB (NITZBURG *et al.*, 2017), embora outros estudos não tenham encontrado diferenças entre os grupos (BEARDEN *et al.*, 2006b, 2006a; VAN RHEENEN, Tamsyn E; ROSSELL, 2014). Em relação à comparação entre controles saudáveis e pessoas com SZ, estudos encontraram prejuízo no uso de agrupamento semântico no último grupo (HILL *et al.*, 2004; ROOFEH *et al.*, 2006). No entanto, não há estudos na literatura comparando o uso de agrupamento semântico entre pessoas com SZ e TB.

Instrumentos de memória verbal que contenham itens pertencentes a categorias implícitas permitem o cálculo de uso de agrupamento semântico. Um deles é a *Hopkins Verbal Learning Test – Revised* (HVLT-R), pertencente à MATRICS Consensus Cognitive Battery (MCCB) (FONSECA *et al.*, 2017), que permite também a medida de diversos componentes subjacentes. Utilizando a HVLT-R, um estudo comparou os componentes de memória verbal de pessoas com TB e controles saudáveis, não encontrando diferenças (VAN RHEENEN, Tamsyn E; ROSSELL, 2014). No entanto, até o momento, não há estudos comparando os componentes da memória verbal na SZ e TB utilizando a HVLT-R. Uma vez que o uso da MCCB tem se popularizado para avaliar cognição na SZ e TB (LI *et al.*, 2020), é importante investigar seus instrumentos e respectivos componentes de maneira completa.

Dessa forma, o presente estudo tem como objetivo analisar os componentes da memória verbal em indivíduos com SZ e TB, assim como avaliar sua relação com a funcionalidade, particularmente o componente de agrupamento semântico, utilizando a HVLT-R. Hipotetizamos que controles saudáveis teriam melhor desempenho em memória verbal do que indivíduos com SZ e TB, e que o grupo de TB teria melhor performance do que SZ. Da mesma maneira, hipotetizamos que uma direção semelhante resultados semelhantes seriam encontrados em componentes da memória verbal relacionados a performance, com controles saudáveis com melhor desempenho em TB, que, por sua vez, teriam melhor desempenho que SZ. Por fim, também desenvolvemos a hipótese de que estratégias de agrupamento semântico teriam um impacto na relação entre memória verbal e funcionalidade em todos os grupos.

# 2. OBJETIVOS

## 2.1 OBJETIVO GERAL

Investigar o papel do agrupamento semântico na relação entre memória verbal e funcionalidade em indivíduos com SZ e TB comparados com controles saudáveis

## 2.2 OBJETIVOS ESPECÍFICOS

- Investigar o desempenho em memória verbal em indivíduos com SZ e TB comparados com controles saudáveis
- Avaliar o efeito de interação do agrupamento semântico na relação entre memória verbal e funcionalidade em indivíduos com SZ e TB comparados com controles saudáveis
- Comparar os componentes da memória verbal em indivíduos com SZ e TB comparados com controles saudáveis
- Avaliar a funcionalidade de indivíduos com SZ e TB comparados com controles saudáveis

# 3. MÉTODO

## 3.1 DELINEAMENTO

O presente trabalho trata-se de um estudo transversal quantitativo.

## 3.2 PARTICIPANTES

Os participantes incluídos na amostra fizeram parte de diversos estudos já existentes com coletas de avaliações clínicas e cognitivas na SZ e TB. A amostra foi selecionada por conveniência. Pacientes com SZ foram recrutados no Programa de Esquizofrenia (PRODESQ) do Hospital de Clínicas de Porto Alegre e no ambulatório do Programa de Transtornos Psicóticos do Hospital de Clínicas do Paraná. Participantes com TB foram recrutados no Programa de Transtorno Bipolar (PROTHABI) do Hospital de Clínicas de Porto Alegre. Controles saudáveis foram recrutados através de convite a doadores de sangue no hospital e em anúncios *online*. 495 participantes foram incluídos: 156 SZ, 172 TB, e 167 controles saudáveis.

Critérios de inclusão específicos para SZ foram: diagnóstico confirmado de SZ de acordo com a *Structured Clinical Interview* (SCID) do DSM 5; sem alterações farmacológicas nos últimos 3 meses; remissão de sintomas agudos por pelo menos 6 meses. Critérios específicos para TB foram: diagnóstico confirmado de SZ de acordo com a SCID do DSM 5; estado de humor eutímico confirmado por pontuações < 12 na Hamilton Depression Scale (HAM-D) (FREIRE *et al.*, 2014) e < 7 na Young Mania Rating Scale (VILELA *et al.*, 2005). Critérios específicos de inclusão para controles saudáveis foram: ausência de diagnóstico psiquiátrico pessoal prévio; ausência de diagnóstico psiquiátrico prévio na família em primeiro grau; ausência de histórico de lesões traumáticas na cabeça. Todos os participantes tinham idade entre 18 e 70 anos e assinaram um termo de consentimento livre e esclarecido. O estudo foi aprovado pelo comitê de ética local e seguiram a última declaração de Helsinki.

### 3.3 INSTRUMENTOS E MEDIDAS

Entrevista diagnóstica estruturada (*Structured Clinical Interview for DSM-5 (SCID)* traduzida para o português em 2017, como Entrevista Clínica Estruturada para os Transtornos do DSM-5 (SCID-5-CV).

Questionário de dados clínicos e sociodemógraficos: entrevista estruturada para o levantamento de informações clínicas (como medicação atual, histórico de tentativa de suicídio, número de internações, etc) e sociodemográficas (como idade, escolaridade, situação conjugal, etc).
*Hamilton Depression Rating Scale* (HAM-D) (FREIRE *et al.*, 2014) (FREIRE *et al.*, 2014): instrumento de avaliação de sintomas depressivos. Possui 21 itens avaliando diversos domínios depressivos, como humor, alterações no sono ou apetite, ou ideação suicida. Cada item é pontuado através de uma escala Likert de 0 a 4, com a pontuação máxima sendo 52. O ponto de corte para episódio depressivo foi estabelecido em 12.

*Young Mania Rating Scale* (YMRS) (VILELA *et al.*, 2005): instrumento de avaliação de sintomas de mania. Possui 11 itens avaliando diversos domínios da mania, como fala acelerada, elevação de humor, diminuição da necessidade de sono, entre outros. Cada item é pontuado através de uma escala Likert de 0 a 4 (com exceção dos itens 5, 6, e 8, com pontuação de 0 a 8, e o item 9, com pontuação de 0 a 6), com pontuação máxima de 58. O ponto de corte para episódio maníaco ou hipomaníaco foi estabelecido em 7.

*Functioning Assessment Short Test* (FAST) (ROSA, Adriane R *et al.*, 2007): escala de avaliação da funcionalidade. Consiste de 24 itens avaliando a funcionalidade em 6 domínios: autonomia, trabalho, cognição, problemas financeiros, relações interpessoais, e lazer. Cada item é pontuado numa escala Likert de 0 (sem prejuízo) a 3 (grande prejuízo). Quanto maior a pontuação, maior o prejuízo funcional do participante.

*Hopkins Verbal Learning Test – Revised* (HVLT-R) (BENEDICT *et al.*, 1998): instrumento de avaliação de memória verbal. A HVLT-R consiste de uma lista de 12 palavras pertencentes a 3 categorias distintas (como animais, joias, e utensílios de cozinha), cada uma com 4 palavras cada. As palavras são apresentadas em ordem

mista. Na primeira etapa, o participante é apresentado verbalmente à lista de palavras, e precisa lembrar em voz alta todas as palavras que lembra após a leitura da lista. A ordem das palavras são registradas pelo aplicador, assim como possíveis intrusões (lembrança incorreta de palavras que não foram lidas) ou perseverações (palavras corretas sendo lembradas mais de uma vez). Isto é repetido mais duas vezes. (*Trials* 1 – 3*).* Após isso, um intervalo de 20 – 25min é realizado, no qual o participante não realiza nenhuma tarefa que envolva memória verbal. Após o intervalo, os participantes devem lembrar quais palavras foram ditas sem uma nova leitura do aplicador (*Trial* 4). Por último, os participantes respondem a uma tarefa de reconhecimento “sim / não” de uma nova lista que contém as 12 palavras originais, 6 palavras falsas-positivas semanticamente relacionadas e 6 palavras falsas-positivas não-semanticamente relacionadas.

Os seguintes componentes da memória verbal foram considerados:

a) Recuperação livre imediata (número de palavras corretas nos *trials* 1 – 3)

b) Recuperação livre imediata total (soma das pontuações dos *trials* 1 – 3)

c) Recuperação tardia (número de palavras corretas no *trial* 4)

d) Taxa de retenção (*trial* 4 dividido pelo maior dos *trials* 2 ou 3)

e) Acertos de reconhecimento (número de palavras corretamente reconhecidas)

f) Discriminabilidade de reconhecimento (acertos de reconhecimento menos número de falsos-positivos)

g) Índice de recuperação (discriminabilidade de reconhecimento menos recuperação tardia) (WOODS *et al.*, 2005a)

h) Razão de agrupamento semântico (número de vezes em que duas ou mais palavras da mesma categoria foram lembradas consecutivamente dividido pela pontuação total) (WOODS *et al.*, 2005b)

i) Razão de agrupamento seriado (número de vezes em que duas ou mais palavras foram lembradas de maneira adjacente à ordem em que foram apresentadas dividido pela pontuação total)

j) Inclinação de aprendizado (o maior dos *trials* 2 ou 3 menos o *trial* 1)

(BENEDICT *et al.*, 1998)

k) Aprendizagem cumulativa de palavras (inclinação de aprendizado multiplicado pela recuperação livre imediata total) (FOSTER *et al.*, 2009)

l) Número de perseverações

m) Número de intrusões

## 3.4 PROCEDIMENTO DE COLETA DE DADOS

O presente estudo é uma integração de diversos projetos de pesquisa já existentes que realizaram coletas de memória verbal através da HVLT – R no Hospital de Clínicas de Porto Alegre e no Hospital de Clínicas do Paraná. O recrutamento no Hospital de Clínicas de Porto Alegre foi realizado através de convite por um membro da pesquisa no PRODESQ e no PROTHABI, onde a entrevista também foi agendada. No Hospital de Clínicas do Paraná, o recrutamento era realizado no ambulatório do Programa de Transtornos Psicóticos. Durante esse processo, todas e quaisquer dúvidas foram esclarecidas, além do processo ser explanado ao participante.

As coletas foram realizadas no Centro de Pesquisa Clínica do Hospital de Clínicas de Porto Alegre e no Hospital de Clínicas do Paraná. No início, o membro da pesquisa fornece ao participante uma via do Termo de Consentimento Livre e Esclarecido (TCLE), o qual era lido e assinado antes de dar início à coleta, ficando uma via com o participante e outra com o pesquisador. Após isso, o membro da pesquisa inicia uma entrevista estruturada, com dados clínicos e sociodemográficos, e em seguida aplica escalas clínicas. Ao final dessa etapa, um psicólogo realizou a avaliação neuropsicológica do participante, incluindo a HVLT-R. Ao todo, o processo tinha uma duração aproximada de 2 horas. Após isso, os protocolos eram digitados para o banco de dados por dois membros da pesquisa, com comparação de cada item ao final para prevenção de possíveis erros de digitação.

## 3.5 ANÁLISE DE DADOS

As análises estatísticas foram realizadas no software SPSS v.22 para Windows, R (versão 4.0) e RStudio (versão 1.3.959). Para comparação de variáveis clínicas e sociodemográficas entre grupos de SZ, TB, e controles saudáveis, realizamos uma análise de variância (ANOVA) de uma via, com correção *post-hoc* de Bonferroni. Para comparações apenas entre os grupos de SZ e TB, realizamos teste-t de amostras independentes ou qui-quadrado. Para as variáveis relacionadas à memória verbal, realizamos uma análise de covariância (ANCOVA) para comparação de componentes da memória verbal entre SZ, TB, e controles saudáveis, controlando para sexo, idade, e anos de estudo, com correção *post-hoc* de Bonferroni. Por fim, para investigar o possível impacto do agrupamento semântico na relação entre memória verbal e funcionalidade, conduzimos modelos de regressões lineares para cada grupo separadamente com pontuação na FAST como variável dependente, e a interação entre recuperação livre imediata total e razão de agrupamento semântico imediato total como variável independente, controlando para sexo, idade, e anos de estudo.

## 3.6 CONSIDERAÇÕES ÉTICAS

O presente estudo considerou todas as normas e diretrizes éticas em todo seu andamento. Os projetos de pesquisa foram aprovados pelo Comitê de Ética em Pesquisa com seres humanos do Hospital de Clínicas de Porto Alegre (nº 15-0298 e 1502-82). O presente estudo também segue as diretrizes da Resolução 466/2012 (Conselho Nacional de Saúde, 2012) e a Resolução 016/2000 (Conselho Federal de Psicologia, 2000). Todos os participantes assinaram um termo de consentimento livre e esclarecido antes da coleta ser iniciada. Em todas as etapas do estudo, a anonimidade dos participantes foi preservada, assim como nas publicações produzidas a partir do estudo.

## 4. RESULTADOS

*Artigo submetido para a revista Journal of Affective Disorders*

Title: The role of semantic clustering in the relationship between verbal memory and psychosocial functioning in schizophrenia and bipolar disorder: possible distinct cognitive pathway compared to healthy controls

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Highlights

- Semantic clustering impacted the relationship between verbal memory and functioning in HC
- However, no such impact occurred in SZ or BD patients
- SZ had the most impaired overall verbal memory, while BD had intermediate impairments

Abstract

Background: Verbal memory (VM) is commonly impaired in schizophrenia (SZ) and bipolar disorder (BD), and predicts psychosocial functioning. However, there is a lack of research exploring the role of VM component processes, including semantic clustering, in these disorders. Semantic clustering might impact this association, as effective semantic memory strategies may reflect unimpaired executive control and lead to an adequate functioning. We aimed to investigate VM components in SZ and BD, and the role of semantic clustering in the relationship between VM and functioning.

Methods: We included 495 participants (156 SZ, 172 BD, and 167 healthy controls (HC)) that underwent an assessment using the Hopkins Verbal Learning Test – Revised for VM and the Functioning Assessment Short Test for psychosocial functioning. We compared groups through ANOVAs and investigated the effect of semantic clustering in the relationship between VM total recall and functioning through linear regression models.

Results: The SZ group had worse overall VM performance compared to BD, which performed worse than HCs. HCs used more semantic clustering than patients with SZ and BD, but there were no differences between the two clinical groups. In HCs, semantic clustering impacted the relationship between VM performance and functioning, while no interaction was observed in SZ or BD.

Limitations: Cross-sectional design and no medication effects or other cognitive functions were assessed.

Conclusions: Our results indicate that SZ and BD may use an alternative cognitive pathway in which the relationship between VM and functioning is independent of complex cognitive processes such as semantic clustering.

Keywords: schizophrenia; bipolar disorder; verbal memory components

*Introduction*

Cognition is commonly impaired in schizophrenia (SZ) (BARCH; CEASER, 2012; CZEPIELEWSKI, Letícia Sanguinetti *et al.*, 2021) and bipolar disorder (BD) (TSITSIPA; FOUNTOULAKIS, 2015). Although SZ has been proposed to be more impaired than BD (CHEN *et al.*, 2018; LI *et al.*, 2020; LYNHAM *et al.*, 2018; SCHRETLEN *et al.*, 2013), cognitive performance often overlaps among the two disorders (KUSWANTO, C. *et al.*, 2016; KUSWANTO, C. N.; SUM; SIM, 2013; VASKINN *et al.*, 2020), with differences being suggested as quantitative rather than qualitative (SCHRETLEN *et al.*, 2013; TSITSIPA; FOUNTOULAKIS, 2015). This, along with some evidence of genetic (PRATA *et al.*, 2019; SMELAND *et al.*, 2020) and neurological (BIRUR *et al.*, 2017; DONG *et al.*, 2017) overlap, bring to question the Kraepelinian dichotomy between SZ and BD (VAN RHEENEN, T E *et al.*, 2017; VAN RHEENEN, Tamsyn E. *et al.*, 2016).

One element of cognition that is consistently impaired in SZ and BD is verbal memory (ALEMAN *et al.*, 1999; BEARDEN *et al.*, 2006b; NITZBURG *et al.*, 2017; VAN RHEENEN, Tamsyn E; ROSSELL, 2014), which is the ability to encode, consolidate and retrieve information regarding past events, instructions, and conversations (TULVING, 2002). Verbal memory is an essential cognitive ability required to live in an organized, well-established routine (HARVEY; STRASSNIG; SILBERSTEIN, 2019). Thus, it is not surprising that verbal memory impairment has been consistently linked to poor functioning in SZ and BD (DANION *et al.*, 2007; FU *et al.*, 2017) (BONNÍN *et al.*, 2010b; MARTINEZ-ARAN *et al.*, 2004, 2007; TSE *et al.*, 2014), although the equivalence of the impairment across the two disorders is not clear.

That is, some studies have found verbal memory performance in SZ to be more impaired than BD (HAUT *et al.*, 2015; KUSWANTO, C. *et al.*, 2016; LI *et al.*, 2020; LYNHAM *et al.*, 2018). In a previous study by our group we found that individuals with early-stage BD performed similarly to healthy controls (HC) on verbal memory tests, while late-stage BD had impairments similar to both early and chronic SZ (CZEPIELEWSKI, Leticia S *et al.*, 2015). Other studies have instead found no significant difference between the disorders (ALTSHULER *et al.*, 2004; CHEN *et al.*, 2018), even when separating individuals with BD into groups with a history of psychosis (JIMÉNEZ-LÓPEZ *et al.*, 2017). Finally, in

another study, individuals with SZ remembered fewer words than BD, but there were no group differences in memory organization processes (SÁNCHEZ-MORLA *et al.*, 2009). The differences in verbal memory performance in SZ and BD, therefore, are still unclear.

Relevantly, most studies of cognition in SZ and BD commonly analyze only the final outcome on verbal memory tests (i.e., the total amount of words recalled), and little attention has been given to the underlying component processes involved. This hampers understandings of the driving factors behind verbal memory impairment itself. The ability to group items within an implicit category, called semantic clustering, is an organizational strategy contributing to verbal memory performance (BRUNET *et al.*, 2020; GOH; AN; RESNICK, 2012). It is of relevance to our understanding of verbal memory and its effects on functioning in SZ and BD, since it is mediated by prefrontal brain activity (GERSHBERG; SHIMAMURA, 1995; HAWCO; BERLIM; LEPAGE, 2013; KRAMER *et al.*, 2005) which is altered in both of these disorders (CHAI *et al.*, 2011). Semantic clustering usage has been shown to be particularly important for verbal memory performance in SZ (GSOTTSCHNEIDER *et al.*, 2011), and individuals with SZ exhibit decreased prefrontal activity when performing memory tasks dependent on semantic encoding strategies (GUIMOND; HAWCO; LEPAGE, 2017). Within that context, semantic clustering usage may be viewed as a measure of executive functioning (BROADWAY *et al.*, 2019), in which effective semantic memory strategies reflect executive control over memory acquisition, which may lead to individuals being better able to function adequately in their routine (i.e., being able to live independently, managing finances, finding and maintaining employment). Indeed, a recent study found that semantic clustering usage was associated to employment status in a community sample (WILLIAMS; ULRICH; WOODS, 2021). Therefore, semantic clustering plays a critical role in verbal memory and may play as well as in its functional outcomes in SZ and BD.

Moreover, it is unclear if the pattern of semantic clustering usage in SZ and BD is different to what is seen in unaffected individuals. While one study found that BD patients had impaired semantic clustering usage compared to HCs (NITZBURG *et al.*, 2017), other studies found no differences among these two

groups (BEARDEN *et al.*, 2006b, 2006a; VAN RHEENEN, Tamsyn E; ROSSELL, 2014). When compared to SZ patients, HCs used more semantic clustering in previous studies (HILL *et al.*, 2004; ROOFEH *et al.*, 2006). Nonetheless, literature is scarce regarding comparisons of semantic clustering and other verbal memory components in SZ and BD patients. Among other analyses, Sánchez-Morla and colleagues used the California Verbal Learning Test to compare verbal memory components of SZ and BD, finding no differences except for the number of words recalled, in which BD had a better performance (SÁNCHEZ-MORLA *et al.*, 2009). However, to the best of our knowledge, no past study has ever compared the verbal memory components of SZ and BD using the Hopkins Verbal Learning Test – Revised (HVLT-R) (BENEDICT *et al.*, 1998) – a verbal memory task included in the MATRICS Consensus Cognitive Battery (MCCB) (FONSECA *et al.*, 2017; NUECHTERLEIN *et al.*, 2008). As the MCCB is being increasingly used to assess cognition in both SZ and BD (LI *et al.*, 2020), it is important to investigate its verbal memory assessment to its full potential, since it might lead to a better understanding of clinically relevant aspects such as everyday functioning. Van Rheenen & Rossell (2014) used the HVLT-R to compare verbal memory components in 49 BD patients and 41 HCs, finding that those with BD performed worse in immediate and delayed recall trials, but no differences in memory organizational strategies, learning slope, errors, and retention. In a follow-up study from this group using a larger sample of 114 BD patients and 105 HCs, these results were largely replicated (Gogos et al., in review). However, neither study included individuals with SZ. Apart from this, there are no studies to our knowledge investigating the role of verbal memory components and functional outcomes in SZ and BD.

Therefore, this study aimed to analyze the verbal memory components of BD, SZ, and HC, using the HVLT-R in a larger sample than the previously mentioned studies. Additionally, we aimed to investigate the relationship between verbal memory and functioning, particularly the role of semantic clustering. We hypothesized that HC would perform better in the total amount of words recalled than BD and SZ, and that individuals with BD would perform better than individuals with SZ. We further hypothesized that similar results would be found

in other verbal memory components related to overall performance, with HC outperforming BD, which in turn would outperform SZ. Finally, we hypothesized that semantic clustering memory strategies would impact the relationship between verbal memory total recall performance and functioning in all groups.

## *Methods*

### *Participants*

This study is an integration of several research projects which have collected HVLT-R data in southern Brazil. 495 total participants were included: 156 SZ, 172 BD, and 167 HCs. Individuals with SZ and BD were invited to participate at the outpatient facility in which they were receiving treatment. Specific inclusion criteria for the BD sample were: 1) confirmed DSM-5 diagnosis of BD; 2) euthymic mood state confirmed by the Hamilton Depression Rating Scale (HAM-D) (FREIRE *et al.*, 2014) score of < 12 and Young Mania Rating Scale (YMRS) (VILELA *et al.*, 2005) scores of < 7. Specific inclusion criteria for the SZ sample were: 1) confirmed DSM-5 diagnosis of SZ; 2) no alterations in medication for the past 3 months 3) symptomatic remission for the past 6 months. HC were recruited via invitation at the hospital blood bank and online community adverts. Specific criteria for the HC were: 1) no previous or current diagnosis of psychiatric disorders; 2) no first-degree family history of psychiatric disorders; 3) no history of head injuries. All participants were 18 years or older of age and signed a written consent form. The studies were approved by the local ethics committee and followed the latest declaration of Helsinki. Participants' anonymity was preserved at all times.

### *Clinical and cognitive measures*

Clinical information was collected via an interview and patient records. We assessed participants' functional outcome through the Functioning Assessment Short Test (FAST), which measures functioning through 24 items evaluating 6 functioning domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time) in a Likert scale (0 – "no impairment" to 3 – "greatly impaired") (ROSA, Adriane R *et al.*, 2007).

*HVLT-R and verbal memory components*

The HVLT-R consists of a list of 12 words from 3 distinct semantic categories (e.g., kitchen utensils, jewels, animals), each containing 4 words presented in a mixed order. Initially, the list is presented verbally, and participants are asked to immediately recall words in any order. The order of the recalled words is recorded, as well as any perseverations (correct words being recalled more than once) or intrusions (words that have not been presented being recalled by the participant). This process is repeated twice (Trials 1 – 3). After an interval of 20min - 25min, participants are asked to recall the words without a new verbal presentation (Trial 4). Finally, participants perform a “yes/no” recognition task of a list consisting of the previous 12 verbally presented words, as well as 6 semantically related words and 6 non-semantically related words that have potential to generate false-positive responses. One study (38 SZ patients, 55 BD patients, and 50 HCs) used form 2 of the HVLT-R (consisting of kitchen utensils, alcoholic beverages, and weapons categories), while the remaining studies used form 1 (dwellings, jewels, and animal categories).

The following verbal memory component scores were calculated: a) Immediate free recall (number of correct words recalled in trials 1 – 3); b) Total immediate free recall (the sum of trials 1 – 3); c) Delayed recall (number of words recalled on trial 4); d) Retention rate (trial 4 divided by the highest of trials 2 or 3); e) Recognition hits (number of words correctly recognized) and its subcomponents – semantically related and non-semantically related false-positive hits; f) Recognition discriminability (recognition hits minus false-positive hits); g) Retrieval index (recognition discriminability minus delayed recall) (WOODS *et al.*, 2005a); h) Semantic clustering ratios (raw number of times a recalled word was followed by another from the same category divided by the number of words recalled) (WOODS *et al.*, 2005b); i) Serial clustering ratios (raw number of times a recalled word was followed by its direct subsequent word divided by the number of words recalled); j) Learning slope (the highest of trial 2 or 3 minus trial 1) (BENEDICT *et al.*, 1998); k) Cumulative word learning (learning slope multiplied by total immediate free recall) (FOSTER *et al.*, 2009); l) number of perseverations; m) number of intrusions.

*Statistical analyses*

We compared clinical and demographic variables among the SZ, BD, and HC groups using one-way ANOVA with Bonferroni *post-hoc* correction. For the verbal memory variables, we conducted a series of a one-way ANCOVAs with Tukey HSD *post-hoc* correction controlling for age, sex, and years of education to compare SZ, BD, and HC groups. Then, to investigate the possible impact of semantic clustering in the relationship between verbal memory and functioning, we conducted linear regression for each group separately with the total FAST score as the dependent variable and the interaction between total immediate free recall score and total immediate free recall semantic use as independent variables, controlling for age, sex, and years of education.

*Results*

*Clinical and demographic results*

Table 1 provides a clinical and demographic description of our sample. Individuals with SZ were younger than BD and HC (SZ vs. HC: $p = .027$, SZ vs. BD: $p < .001$). HCs had more years of education than SZ and BD patients ($p < .001$ for both comparisons), but no differences were found between the clinical groups ($p = .675$). SZ patients had more repeated years in school than BD patients ($p = .001$), who in turn had more repeated years than HC ($p = .002$).

Regarding FAST scores, SZ patients had reduced overall functioning compared to BD patients and HCs ($p < .001$ for both comparisons). Functioning in the BD group was also reduced compared to HCs ($p < .001$). The same direction occurred throughout all FAST domains, with lower functioning scores in patients with SZ than BD, who were lower than HCs.

*Verbal memory group comparisons*

Table 2 shows the ANCOVA comparisons between SZ, BD, and HC groups while controlling for age, sex, and years of education. Regarding total score, HCs remembered more words than BD patients, who scored better than SZ

patients in all trials (1, 2, 3, total immediate free recall and delayed recall) ($p < .001$ for all comparisons). There was no group difference in learning slope (HC vs SZ: $p = .051$; HC vs BD: $p = .198$; SZ vs BD: $p = 1.0$), but HCs had better on cumulative word learning scores than BD patients ($p = .002$), who performed better than SZ patients ($p < .001$) (Figure 1, Table 2).

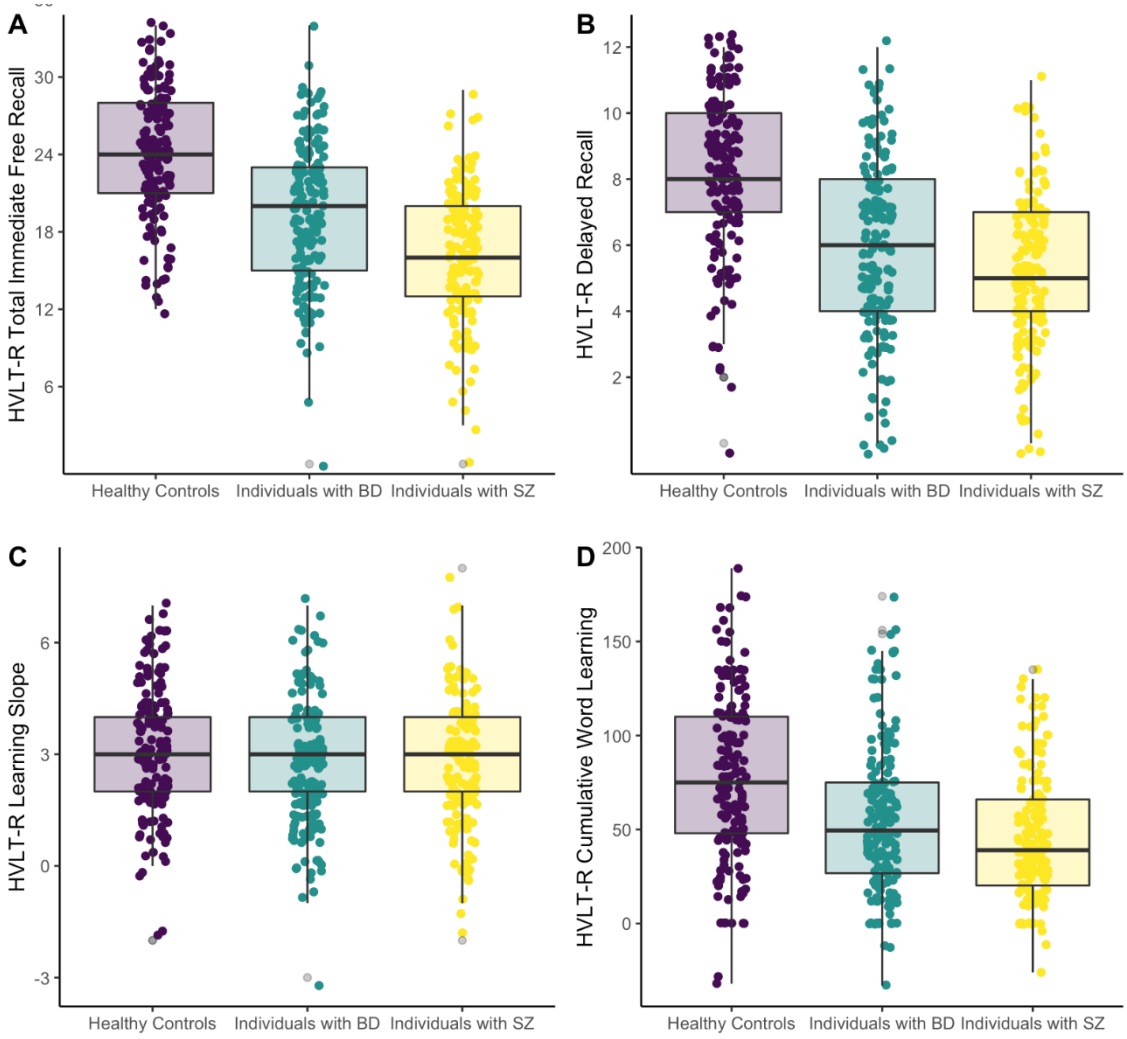


*Figure 1. Total immediate free recall (A), delayed recall (B), learning slope (C), and cumulative word learning (D) scores distribution in healthy controls, individuals with bipolar disorder (BD), and individuals with schizophrenia (SZ). HVLT-R: Hopkins Verbal Learning Test – Revised*

HCs recognized more words than SZ ($p < .001$) and BD ($p = .002$) patients on the recognition trial, with no differences in words recognized between those with SZ and BD ($p = .095$). SZ patients had more recognition errors than BD and HCs, both for semantically- related (SZ vs BD: $p = .009$; SZ vs HC: $p = .008$)

and semantically-unrelated words (SZ vs BD: p = .002; SZ vs HC: p = .002). HCs had superior recognition discriminability than BD (p = .03), who performed better than those with SZ (p < .001). However, SZ patients had fewer perseverations than BD (p = .002) and HC (p < .001) groups, while HC and BD groups had no differences (p = .263). On the other hand, SZ patients displayed more intrusions than BD patients (p = .01) and HCs (p = .042), with no differences between HCs and those with BD (p = 1.0) (Table 2).

Regarding memory organization strategies, HCs clustered more words across all trials than SZ (trial 2: p = .003; trial 3: p < .001; total immediate free recall: p < .001; trial 4: p = .002) and BD patients (trial 1: p = .007; trial 2: p = .017; trial 3: p = .002; total immediate free recall: p < .001; trial 4: p = .038), with no differences between the clinical groups themselves (trial 1: p = 1; trial 2: p = 1; trial 3: p = .485; immediate total free recall: p = 1; trial 4: p = .655). This was with the exception of trial 1, where HC and SZ groups had no differences in semantic clustering (p = .051). SZ patients used more serial clustering than HCs on trial 3 (p = .005) and total immediate free recall (p = .006), with no statistical difference compared to patients with BD (trial 1: p = .719; trial 2: p = .254; trial 3: p = .072; total immediate free recall: p = .071; trial 4: p = 1) (Table 2, Figure 2).

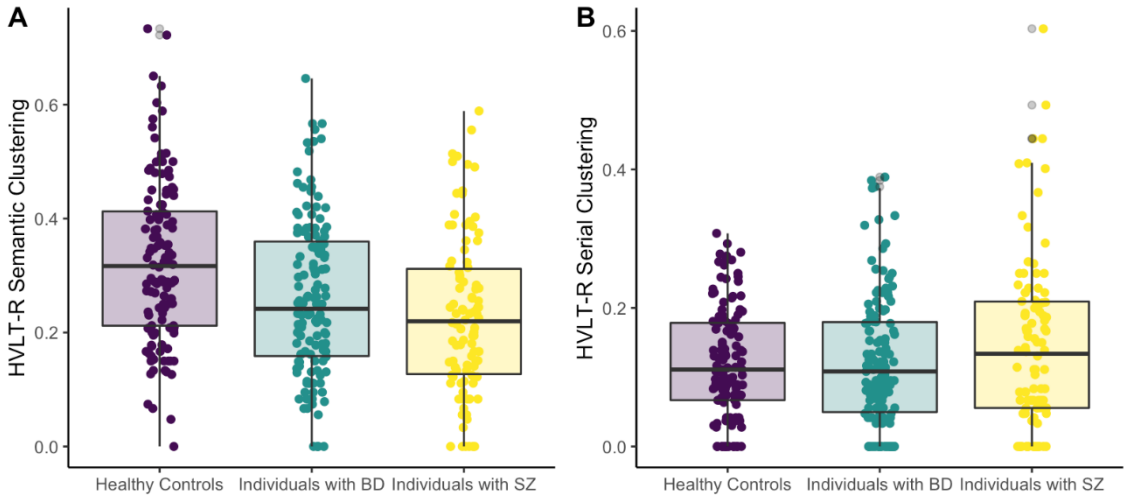


*Figure 2. Semantic clustering scores (A) and serial clustering scores (B) distribution in healthy controls, individuals with bipolar disorder (BD), and individuals with schizophrenia (SZ). HVLT-R: Hopkins Verbal Learning Test –*

*Revised*

*Exploring the role of semantic clustering in the relationship between total immediate free recall and psychosocial functioning*

To explore the role of semantic clustering, we conducted separate linear models for each group with FAST score as the dependent variable, total immediate free recall and semantic clustering as the independent variables and the interaction between them, controlling for age, sex, and years of education.

For HCs, we found an interaction between total immediate free recall and semantic clustering ($t = -2.185$, $p = .031$, $\beta = -1.43$) on the FAST total score, controlling for age, sex, and years of education ($F(6,92) = 3.348$, $p = .0049$, Adj.$R^2 = 0.13$). Here, there was a stronger positive relationship between total immediate free recall and better functioning (lower FAST scores) in those with higher semantic clustering use compared to those with lower semantic clustering (Figure 3A).

For the individuals with BD, we did not find an interaction between total immediate free recall score and semantic clustering ($t = -0.488$, $p = .63$, $\beta = -0.19$) in a model with FAST total score as the dependent variable, controlling for age, sex, and years of education ($F(6,97) = 2.054$, $p = .0658$, Adj. $R^2 = .058$). This was also the case for the SZ group ($t = 0.344$, $p = .731$, $\beta = .15$, $F(6,77) = 1.513$, $p = .185$, Adj. $R^2 = .04$). These findings indicate that there is no effect of semantic clustering in the relationship between total immediate free recall and functioning for patients with BD and SZ (Figure 3B and 3C, respectively).

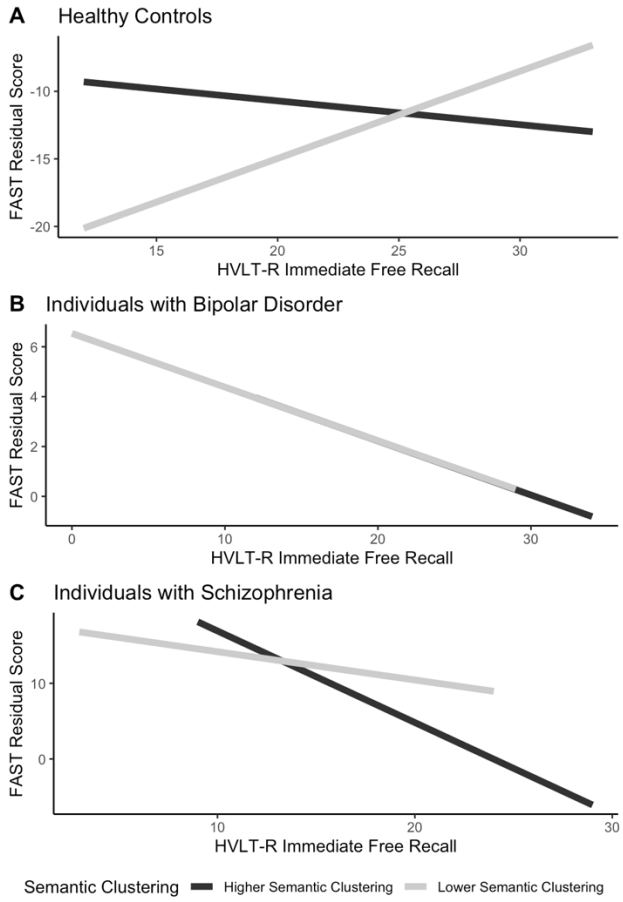


*Figure 3. Association between total immediate free recall and functioning scores by semantic clustering in healthy controls (HC) (A), individuals with bipolar disorder (BD) (B), and schizophrenia (SZ) (C). Higher or lower semantic clustering represented by individuals above or below the 50$^{th}$ percentile. HVLT-R: Hopkins Verbal Learning Test – Revised; FAST: Functioning Assessment Short Test*

*Discussion*

To our knowledge, this is the first study to compare verbal memory component processes between SZ, BD, and HC using the HVLT-R, and examine whether the relationship between verbal memory and functioning is impacted by semantic clustering use. Our main finding is that the relationship between verbal memory performance and functioning was moderated by semantic clustering usage in HC, but not in SZ and BD groups. We also found that HCs had better performance on total and delayed recall than BD patients, who in turn performed better than SZ patients. The same pattern was also found for cumulative word

learning and recognition discriminability performance. HCs outperformed both psychiatric groups in retention rate, recognition hits, and semantic clustering usage. No differences were found in semantic clustering usage between BD and SZ patients, while HCs outperformed both groups.

Regarding total and delayed recall performance, our results indicate that individuals with SZ have the most impaired verbal memory capacity, followed by BD, which is consistent with past results (HAUT *et al.*, 2015; KUSWANTO, C. *et al.*, 2016; LI *et al.*, 2020; LYNHAM *et al.*, 2018). However, other studies have also found no differences between both groups (CHEN *et al.*, 2018; JIMÉNEZ-LÓPEZ *et al.*, 2017), although it is worth noting that they had relatively small samples for each group.

We found no differences in the learning slope among all three groups, such that the ability learn new words across trials was intact in SZ and BD even though total recall scores were impaired. This is in line with previous results finding that SZ and BD could learn across trials, even if to a lesser extent (CZEPIELEWSKI, Leticia S *et al.*, 2015). However, cumulative word learning has been proposed as a more sensitive learning measurement than learning slope, as it considers the interaction between learning slope and total immediate free recall score (FOSTER *et al.*, 2009). Indeed, when observing cumulative word learning, we found that HCs outperformed BD patients, who in turn were superior to patients with SZ. Our cumulative word learning results indicate, then, that learning processes, when interacting with total immediate free recall scores, were distinct among all groups. Therefore, cumulative word learning may be a more sensitive measurement for eliciting group differences in verbal memory in future work. Our learning slope findings matched other studies which found no differences among HC and BD, although, contrary to our results, they did not find differences among cumulative word learning (Van Rheenen and Rossell, 2014; Gogos et al., under review).

We found that HCs used semantic clustering more than SZ and BD. Regarding BD x HC comparisons, our results were similar to one previous study (NITZBURG *et al.*, 2017), while other studies found no differences in semantic clustering between HC and BD groups (BEARDEN *et al.*, 2006b, 2006a; VAN RHEENEN, Tamsyn E; ROSSELL, 2014). In SZ, past studies have found

differences between semantic clustering in SZ patients and HCs (HILL *et al.*, 2004; ROOFEH *et al.*, 2006). One unexpected result was that SZ and BD did not differ in semantic clustering usage, contrary to our hypothesis, even with worse SZ performance in verbal memory.

One possible explanation for the worse performance in SZ versus BD on most measures of interest but not in semantic clustering strategies could be that cognitive impairment in SZ is compounded by neurodevelopmental factors (CZEPIELEWSKI, Leticia Sanguinetti *et al.*, 2017; RECKZIEGEL *et al.*, 2021). Indeed, individuals with SZ present with cognitive impairments before illness onset (MOLLON; REICHENBERG, 2018), but there is only limited evidence that this is the case for BD (VAN RHEENEN, T E *et al.*, 2017; VAN RHEENEN, Tamsyn E *et al.*, 2020). Similar verbal memory impairments are evident in both early and later stage SZ patients (CZEPIELEWSKI, Leticia S *et al.*, 2015; MCCLEERY *et al.*, 2014), and individuals at ultra high-risk for schizophrenia and psychosis also perform worse than HCs on verbal memory tasks (ANDA *et al.*, 2019). Therefore, the higher verbal memory impairment in SZ in our sample may have occurred due to underpinning neurodevelopmental impairments.

Interestingly, we found that in HC participants, semantic clustering usage interacted with verbal memory performance to predict psychosocial functioning. This is unsurprising, as semantic clustering relies on prefrontal activity (GUIMOND; HAWCO; LEPAGE, 2017; HAWCO; BERLIM; LEPAGE, 2013), which underlies cognitive abilities required for appropriate functioning (FRIEDMAN; ROBBINS, 2021). As previous research has shown (BROADWAY *et al.*, 2019), semantic clustering usage may be viewed as a measure of executive functioning since it is a sophisticated cognitive operation that requires active manipulation of memory elements, which is essential for an adequate functioning in one’s life (DIAMOND, 2013), contributing to functioning milestones such as employment (WILLIAMS; ULRICH; WOODS, 2021). On the other hand, we found no such interaction for individuals with SZ or BD. This indicates that individuals with SZ and BD might display a distinct cognitive pathway in which semantic clustering usage does not play a role the relationship between verbal memory performance and functioning.

This alternative cognitive avenue may occur due to impairments in activity and

connectivity in the cognitive control network, a putative network proposed to guide one's behavior by an active and complex goal representation and maintenance in order to achieve a task (BARCH; CEASER, 2012; NIENDAM *et al.*, 2012; RAY *et al.*, 2017). Cognitive control impairments may contribute to the verbal memory and semantic clustering deficits witnessed in SZ and BD (RANGANATH; MINZENBERG; RAGLAND, 2008). This has been evidenced by previous studies that found reduced prefrontal activity during memory tasks in BD (OERTEL-KNÖCHEL *et al.*, 2013) and SZ, particularly in the dorsolateral prefrontal cortex (GUO; RAGLAND; CARTER, 2019; RAGLAND *et al.*, 2009), which could hinder complex memory processing. Further studies display a failure of SZ to self-initiate semantic strategies that has been associated with the dorsolateral prefrontal cortex (GUIMOND; HAWCO; LEPAGE, 2017), although participants were also able to increase left dorsolateral prefrontal cortex activity and semantic usage after a semantic association training (GUIMOND; BÉLAND; LEPAGE, 2018), indicating that the ability to use complex encoding strategies is not unimaginable in psychiatric patients. The absence of interaction, thus, appears to portray the relationship between verbal memory and functioning in individuals with SZ and BD as independent of higher-order cognitive processes such as semantic clustering.

Our study is not without limitations. Our cross-sectional design restricts us from inferring causality, as well as any longitudinal inferences. We also did not administer other cognitive tests to assess further associated cognitive functions, such as executive functioning and processing speed, nor did we analyze possible medication effects on participants. Participants were also recruited via acceptance of the invitation, so selection bias may have occurred. Also, our HAM-D cutoff of < 12 for BD patients may have included low level symptomatic patients, although it is worth noting that only 5 participants presented a HAM-D score between 8 and 12. Strengths of the study include the large sample size, and diversity in sampling as participants were from a low and middle income countries (LMIC).

In conclusion, we found that, contrary to HC, semantic clustering use did not have an effect in the relationship between verbal memory performance and functioning in BD and SZ. This indicates that the relationship between verbal

memory and functioning in individuals with SZ and BD may operate through an alternative cognitive pathway which does not rely on higher-order processes such as semantic clustering. We also found overall impaired verbal memory in individuals with SZ and BD, with SZ generally performing worse than BD. Our results help to bring light to the importance of verbal memory in psychiatric patients, as it is essential for individuals to carry an adequate life. Therefore, verbal memory should be a central target for cognitive remediation in SZ and BD (BONNIN *et al.*, 2016; BUONOCORE *et al.*, 2017). We also propose that further research expand on our results, with additional assessments of executive functioning and other cognitive functions to investigate its relationship with verbal memory and functioning to its full potential.

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**Table 1: Clinical and socio-demographic characteristics of individuals with schizophrenia (SZ), bipolar disorder (BD), and healthy controls (HC)**

| | SZ (n = 156) | BD (n = 172) | HC (n = 167) | Group comparison | Post-hoc (Bonferroni) |
|---|---|---|---|---|---|
| Age (mean/sd) | 40.66 (12.64) | 47.98 (13.43) | 44.7 (15) | F (493) = 11.546, p < .001 | HC = BD > SZ |
| Sex (female/%) | 43 (27.74%) | 121 (70.34%) | 113 (68.07%) | $\chi2$ (2) = 74.484, p < .001 | - |
| Years of education (mean/sd) | 9.8 (3.26) | 10.4 (3.6) | 13.3 (4,45) | F (421) = 32.847, p < .001 | HC > BD = SZ |
| Marital status: Single (n/%) | 122 (83.56%) | 44 (31.42%) | 41 (29.92%) | $\chi2$ (2) = 107.032, p < .001 | - |
| Marital status: Married (n/%) | 14 (9.58%) | 64 (46.42%) | 74 (54.01%) | $\chi2$ (2) = 69.958, p < .001 | - |
| Marital status: Divorced (n/%) | 10 (6.84%) | 22 (15.71%) | 19 (13.86%) | $\chi2$ (2) = 5.924, p = .052 | - |
| Marrital status: Widowed (n/%) | 0 (0) | 9 (6.42%) | 3 (2.18%) | $\chi2$ (2) = 11.023, p = .004 | - |
| Work status: Employed (n/%) | 9 (6.2%) | 37 (26.61) | 77 (55.39%) | $\chi2$ (2) = 83.870, p < .001 | - |
| Work status: Unemployed (n/%) | 50 (34.48%) | 19 (13.66%) | 1 (0.71%) | $\chi2$ (2) = 59.825, p < .001 | - |
| Work status: Receiving government aid due to illness (n/%) | 21 (14.48%) | 15 (10.79%) | 0 (0) | $\chi2$ (2) = 20.501, p < .001 | - |
| Work status: | 57 (39.31%) | 47 (33.81%) | 1 (0.71%) | $\chi2$ (2) = 65.604, p < | - |

| | | | | | |
|---|---|---|---|---|---|
| Disability benefits (n/%) | | | | .001 | |
| Work status: Retired (n/%) | 2 (1.37%) | 9 (6.47%) | 23 (16.54%) | $\chi 2$ (2) = 22.772, p < .001 | - |
| Number of repeated years in school (mean/sd) | 1.53 (1.58) | 0.96 (1.1) | 0.46 (0.72) | F (364) = 25.702, p < .001 | SZ > BD > HC |
| FAST: Autonomy subdomain (mean/sd) | 5.04 (3.42) | 2.88 (2.75) | 0.71 (1.26) | F (428) = 95.160, p < .001 | SZ > BD > HC |
| FAST: Work subdomain (mean/sd) | 11.59 (4.86) | 9.66 (6.47) | 1.33 (2.79) | F (421) = 169.245, p < .001 | SZ > BD > HC |
| FAST: Cognition subdomain (mean/sd) | 7.58 (4.05) | 5.7 (3.69) | 2.62 (2.3) | F (426) = 74.963, p < .001 | SZ > BD > HC |
| FAST: Finances subdomain (mean/sd) | 2.79 (2.25) | 1.88 (2.2) | 0.73 (1.21) | F (428) = 39.708, p < .001 | SZ > BD > HC |
| FAST: Relationships subdomain (mean/sd) | 7.65 (4.48) | 4 (3.85) | 1.2 (1.76) | F (426) = 116.766, p < .001 | SZ > BD > HC |
| FAST: Leisure subdomain (mean/sd) | 2.64 (1.97) | 2.02 (1.66) | 0.87 (1.29) | F (428) = 40.592, p < .001 | SZ > BD > HC |

FAST: Functioning Assessment Short Test

**Table 2: ANCOVA of Hopkins Verbal Learning Test – Revised components in individuals with schizophrenia (SZ), bipolar disorder (BD), and healthy controls (HC).**

| | SZ (n = 156) | BD (n = 172) | HC (n = 167) | Group comparison | $\eta^2$ | Post-hoc (Bonferroni) |
|---|---|---|---|---|---|---|
| Trial 1 score (mean/sd) | 4.02 (1.63) | 5.22 (1.66) | 6.39 (1.58) | F(2, 412) = 47.068, p < .001 | .186 | HC > BD > SZ |
| Trial 2 score (mean/sd) | 5.7 (1.93) | 6.8 (2.23) | 8.53 (1.97) | F(2, 412) = 41.455, p < .001 | .168 | HC > BD > SZ |
| Trial 3 score (mean/sd) | 6.46 (1.98) | 7.59 (2.32) | 9.36 (1.84) | F(2, 412) = 48.619, p < .001 | .191 | HC > BD > SZ |
| Total immediate free Recall score (Trials 1 – 3) (mean/sd) | 16.07 (4.93) | 19.47 (5.81) | 24.28 (4.64) | F(2, 414) = 58.950, p < .001 | .222 | HC > BD > SZ |
| Trial 4 score (mean/sd) | 5.11 (2.25) | 5.81 (2.72) | 8.29 (2.23) | F(2, 412) = 42.414, p < .001 | .171 | HC > BD > SZ |
| Retention rate (mean/sd) | 0.74 (0.29) | 0.71 (0.28) | 0.86 (0.18) | F(2, 414) = 7.725, p = .001 | .036 | HC > BD = SZ |
| Learning slope (mean/sd) | 2.72 (1.66) | 2.64 (1.67) | 3.19 (1.6) | F(2, 414) = 3.128, p = .045 | .015 | HC = BD = SZ |
| Cumulative word learning (mean/sd) | 46.08 (33.85) | 55.33 (39.69) | 79.19 (42.38) | F(2, 414) = 18.079, p < .001 | .080 | HC > BD > SZ |
| Recognition hits (mean/sd) | 10.2 (2.1) | 10.5 (1.85) | 11.42 (1.01) | F(2, 411) = 14.493, p < .001 | .066 | HC > BD = SZ |

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|---|---|---|---|---|---|---|
| Recognition semantically related errors (mean/sd) | 1.17 (1.4) | 0.78 (0.99) | 0.55 (0.93) | F(2, 411) = 5.823, p = .003 | .028 | SZ > BD = HC |
| Recognition semantically unrelated errors (mean/sd) | 0.64 (1.26) | 0.31 (0.75) | 0.14 (0.61) | F(2, 411) = 7.705, p = .001 | .036 | SZ > BD = HC |
| Recognition - total errors (mean/sd) | 1.79 (2.44) | 1.08 (1.5) | 0.69 (1.35) | F(2, 414) = 8.299, p < .001 | .039 | SZ > BD = HC |
| Recognition discriminability (mean/sd) | 8.27 (3.22) | 9.34 (2.5) | 10.73 (1.69) | F(2, 414) = 21.810, p < .001 | .095 | HC > BD > SZ |
| Retrieval index (mean/sd) | 3.19 (3.04) | 3.57 (2.53) | 2.44 (2.02) | F(2, 414) = 6.538, p = .002 | .031 | SZ = BD > HC |
| Trial 1 semantic clustering ratio (mean/sd) | 0.22 (0.2) | 0.22 (0.18) | 0.3 (0.2) | F(2, 282) = 5.324, p = .005 | .036 | HC = SZ, HC > BD, SZ = BD |
| Trial 2 semantic clustering ratio (mean/sd) | 0.23 (0.19) | 0.26 (0.19) | 0.34 (0.17) | F(2, 283) = 6.429, p = .002 | .043 | HC > BD = SZ |
| Trial 3 semantic clustering ratio (mean/sd) | 0.23 (0.15) | 0.27 (0.18) | 0.36 (0.18) | F(2, 284) = 10.732, p < .001 | .07 | HC > BD = SZ |
| Total immediate free recall (trials 1 – 3) semantic clustering ratio (mean/sd) | 0.22 (0.14) | 0.24 (0.14) | 0.33 (0.14) | F(2, 285) = 12.272, p < .001 | .079 | HC > BD = SZ |
| Trial 4 semantic clustering ratio (mean/sd) | 0.27 (0.18) | 0.3 (0.21) | 0.4 (0.19) | F(2, 277) = 6.326, p = .002 | .044 | HC > BD = SZ |

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|---|---|---|---|---|---|---|
| Trial 1 serial clustering ratio (mean/sd) | 0.12 (0.17) | 0.1 (0.12) | 0.1 (0.12) | F(2, 282) = 1.265, p = .284 | .009 | HC = BD = SZ |
| Trial 2 serial clustering ratio (mean/sd) | 0.18 (0.18) | 0.13 (0.15) | 0.12 (0.11) | F(2, 283) = 2.377, p = .095 | .017 | HC = BD = SZ |
| Trial 3 serial clustering ratio (mean/sd) | 0.16 (0.16) | 0.12 (0.15) | 0.1 (0.15) | F(2, 284) = 5.133, p = .006 | .035 | SZ > HC, SZ = BD, HC = BD |
| Total immediate free recall (trials 1 -3) serial clustering ratio (mean/sd) | 0.15 (0.12) | 0.11 (0.09) | 0.11 (0.07) | F(2, 285) = 4.924, p = .008 | .033 | SZ > BD = HC |
| Trial 4 serial clustering ratio (mean/sd) | 0.09 (0.14) | 0.07 (0.12) | 0.06 (0.09) | F(2, 277) = .385, p = .681 | .003 | HC = BD = SZ |
| Total perseverations (mean/sd) | 0.27 (1.02) | 0.73 (1.26) | 0.87 (1.38) | F(2, 414) = 12.076, p < .001 | .055 | HC = BD > SZ |
| Total intrusions (mean/sd) | 1.3 (3.31) | 0.53 (1.08) | 0.54 (1.34) | F(2, 414) = 4.880, p = .008 | .023 | SZ > BD = HC |

## 5. CONSIDERAÇÕES FINAIS

O presente estudo teve como objetivo avaliar componentes de memória verbal em indivíduos com SZ, TB, e controles saudáveis, além de investigar o papel do agrupamento semântico na relação entre memória verbal e funcionalidade. Nosso principal achado é de que, embora o uso de agrupamento semântico tenha impactado a relação entre desempenho em memória verbal e funcionalidade em controles saudáveis, o mesmo não ocorreu em indivíduos com SZ e TB.

Os resultados auxiliam a elucidar a complexa relação entre memória verbal e funcionalidade em pacientes psiquiátricos. Tais achados indicam uma via cognitiva alternativa utilizada por pacientes psiquiátricos, na qual a relação entre memória verbal e funcionalidade é independente de processos complexos de alta ordem como uso de agrupamento semântico. Possíveis explicações para isso podem se dever a prejuízos no controle cognitivo desses indivíduos, causados por déficits na conectividade e atividade nas áreas cerebrais associadas a esta função cognitiva.

Além disso, encontramos uma piora progressiva de desempenho em memória verbal e funcionalidade entre controles saudáveis, indivíduos com TB, e indivíduos com SZ. O mesmo ocorreu com o componente de aprendizagem cumulativa de palavras, com controles saudáveis tendo uma melhor capacidade de aprendizado do que pessoas com TB, que, por sua vez, tiveram melhor habilidade de aprender novas palavras do que pessoas com SZ. Também encontramos maior uso de agrupamento semântico em controles saudáveis do que os dois grupos psiquiátricos. Um resultado inesperado, no entanto, foi que não houve diferenças entre uso de agrupamento semântico entre pessoas com SZ e TB. Tal achado vai contra nossa hipótese inicial de que um uso reduzido de agrupamento semântico acompanharia o prejuízo em memória verbal em SZ. Uma possível explicação para as diferenças em memória verbal, mas não em agrupamento semântico, em SZ e TB seria uma capacidade cognitiva geral mais prejudicada por conta de fatores neurodesenvolventais (RECKZIEGEL *et al.*, 2021).

Dessa forma, nossos resultados reforçam a importância da memória verbal e seus componentes numa compreensão panorâmica da SZ e do TB. Intervenções focadas em memória verbal, por exemplo, devem ser consideradas um dos focos de

remediação cognitiva nessas doenças. Além disso, propomos que futuros estudos expandam nossos resultados com avaliações mais aprofundadas de componentes cognitivos de interesse, como funções executivas e velocidade de processamento, para que a relação entre memória verbal e funcionalidade na SZ e TB seja cada vez mais elucidada.

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