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INSTITUTO DE CIÊNCIAS BÁSICAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS: BIOQUÍMICA

ESTUDO DO DESEMPENHO DE MEMÓRIA COM E SEM CONTEÚDO AFETIVO EM PACIENTES COM TRANSTORNO DO HUMOR

VERA BEATRIZ DELGADO DOS SANTOS

Orientadora Profa. Dra. Márcia Lorena Fagundes Chaves

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Tese apresentada ao Programa de Pós-Graduação em Ciências Biológicas: Bioquímica, da Universidade Federal do Rio Grande do Sul, como requisito parcial à obtenção do grau de Doutor em Ciência Biológicas – Bioquímica

Porto Alegre
2012

Dedico esta tese aos meus pais, Elder e Iara,
que me ensinaram termos como respeito e
honestidade.

O valor das coisas não está no tempo em que elas duram,
mas na intensidade com que acontecem.
Por isso existem momentos inesquecíveis,
coisas inexplicáveis e pessoas incomparáveis.
Fernando Pessoa

AGRADECIMENTOS

Aos pacientes, que carinhosamente concordaram em participar da pesquisa.

À minha orientadora Dra. Márcia Chaves, que afetivamente estava sempre disponível e que, muitas vezes, nos momentos difíceis da minha vida, foi mais amiga do que orientadora. Obrigada pelos ensinamentos e pela oportunidade de crescimento.

À equipe de enfermagem do Centro de Atenção Psicossocial do Hospital de Clínicas de Porto Alegre: agradeço pelo incentivo, carinho e compreensão.

À enfermeira Celina e, em seu nome, agradeço também a todas as enfermeiras e técnicos de enfermagem da internação psiquiátrica do Hospital de Clínicas de Porto Alegre, pela disponibilidade e preocupação com a coleta de dados.

À enfermeira Miriam pelo interesse, apoio e amizade.

Às minhas amigas, Agnes e Christine, quantos momentos de incertezas e dúvidas e vocês não apoiaram meus pensamentos malucos.

À minha irmã Kátia, e meu sobrinho Rafael, agradeço ao suporte técnico e em seus nomes agradeço a meus familiares pela amizade, amor e incentivo.

Agradeço aos professores do Programa de Pós-Graduação em Bioquímica da UFRGS pela compreensão e paciência que tiveram comigo.

SUMÁRIO

RESUMO

Objetivo geral: O objetivo geral desta tese foi comparar o desempenho de memória em tarefas com e sem conteúdo afetivo de pacientes internados com depressão maior, transtorno bipolar do tipo I na fase maníaca e indivíduos saudáveis. Além disso, também foi avaliado o efeito da presença de sintomas psicóticos no desempenho de memória nos dois grupos de pacientes.

Métodos: Pacientes com diagnóstico de transtorno do humor de acordo com o DSM VI-TR foram selecionados durante a primeira semana após a internação em uma unidade de internação psiquiátrica de um hospital universitário. Os indivíduos saudáveis foram selecionados aleatoriamente da mesma comunidade onde se localiza o hospital universitário. Para esta tese métodos e resultados são apresentados em dois estudos. O primeiro estudo foi constituído de 78 participantes (24 pacientes com transtorno bipolar do tipo I, 29 com depressão maior e 25 controles saudáveis). O segundo estudo foi composto de 31 pacientes com transtorno bipolar do tipo I (19 com sintomas psicóticos e 12 sem sintomas psicóticos) e 27 indivíduos saudáveis. Nos dois estudos, o desenho foi transversal controlado, e foram selecionados testes de memória para avaliar o desempenho com e sem valência afetiva dos participantes. Os sintomas psiquiátricos também foram avaliados com as escalas: Young, para mania, e de Hamilton, para a depressão. A presença de sintomas psicóticos foi definida pelos critérios do DSM IV-TR. O número de episódios afetivos e o tempo de doença foram controlados nas análises.

Resultados: No primeiro estudo, os pacientes com depressão maior apresentaram pior desempenho no MEEM, no teste de memória lógica (imediata e tardia) e no de span de reconhecimento visual do que os indivíduos saudáveis. No teste de span de dígitos, os pacientes com depressão maior apresentaram desempenho mais baixo do que os pacientes com transtorno bipolar e do que os controles. Os pacientes com transtorno bipolar apresentaram escores mais elevados no span de palavras com tom positivo do que os pacientes com depressão maior e controles saudáveis. Efeito significativo do número de episódios afetivos foi observado para este teste ($B = -0.13$; $p = 0,035$). Nenhuma outra diferença foi observada para os testes com tom afetivo. No segundo estudo, observou-se uma diferença significativa nos escores do span de palavras com conteúdo afetivo entre os três grupos, controlando para número de episódios de mania ($p = 0,042$). Pacientes com transtorno bipolar não psicóticos apresentaram escores mais elevados. Houve uma tendência de os pacientes com transtorno bipolar com e sem sintomas psicóticos desempenharem-se de forma mais pobre do que os controles no teste memória lógica de evocação tardia ($p = 0,069$).

Conclusão: Observou-se um efeito de congruência do humor para o span de palavras positivas entre os pacientes com transtorno bipolar, mas não encontramos efeito similar entre os pacientes com depressão maior para os itens negativos. Pacientes com depressão maior apresentaram mais comprometimentos de memória do que os

pacientes com transtorno bipolar, enquanto que os pacientes com transtorno bipolar também mostraram comprometimento de memória em relação aos participantes saudáveis. De fato, pacientes com transtorno bipolar não se assemelham aos pacientes deprimidos nos desempenhos em diferentes tarefas de memória, mas dificuldades cognitivas em pacientes com transtorno bipolar podem auxiliar a explicar comprometimentos na função de vida diária. Pacientes com transtorno bipolar com sintomas psicóticos e sem sintomas durante fase maníaca apresentaram fenômeno de congruência do humor em uma tarefa de memória verbal com conteúdo afetivo positivo em relação a indivíduos saudáveis. Evidência nítida de congruência do humor foi observada no grupo de pacientes não psicóticos, sugerindo manifestação mais pura da doença. No entanto, mais estudos são necessários para analisar a natureza diferencial de marcadores específicos do transtorno bipolar nestas duas manifestações.

Palavras-chave: humor, transtorno bipolar, depressão maior, memória.

ABSTRACT

Objectives: The objective of this study was to compare memory performance in tasks with and without affective content in patients with Major Depressive Disorder, type I Bipolar Disorder (during manic episodes) and healthy individuals. We also evaluated the effect of psychotic symptoms in memory performance on both groups.

Methods: Patients with diagnosed mood disorders according to the DSM IV-TR were selected during the first week after admission at the psychiatric ward of a hospital. The healthy individuals were randomly selected from the same community were the hospital is located. Methods and results are divided into two studies. The first study encompassed 78 participants (24 patients with type I Bipolar Disorder, 29 patients with Major Depressive Disorder, and 25 healthy controls). The second study was composed of 31 patients with type I Bipolar Disorder (19 with psychotic symptoms and 12 without) and 27 healthy controls. Both studies were transversal controlled, and we selected memory tests to evaluate performance with and without emotional valence on all patients. The psychiatric symptoms were evaluated using the following scales: Young for mania and Hamilton for depression. The presence of psychotic symptoms was defined by DSM IV-TR criteria. The number of affective episodes and disease length were controlled during the analysis.

Results: In the first study, the patients with Major Depressive Disorder presented the worse performance at the MMSE, logic memory test and visual recognition span test than normal control subjects. In the digit span test, patients with Major Depressive Disorder did worse than patients with Bipolar Disorder and healthy controls. Patients with Bipolar Disorder scored higher on the word spam test with positive tone than patients with Major Depressive Disorder and healthy controls. A significant effect related to the number of affective episodes was observed for this test (B = -0.13; p = 0,035). No other difference was observed on tests with affective tone. On the second study, we observed a significant difference on the word span scores with affective content among the three groups, controlled for the number of manic episodes (p = 0,042). Non-psychotic patients with Bipolar Disorder presented higher scores. Bipolar patients with and without psychotic symptoms tended to perform worse than controls on late evocation memory test (p = 0,069).

Conclusion: we observed an effect of humor congruence for the positive word span on bipolar patients, but we did not find the same association on patients with Major Depressive Disorder and negative items. Patients with Major Depressive Disorder presented more memory impairment than patients with Bipolar Disorder, while patients with Bipolar Disorder also showed impairment compared to healthy controls. In fact, patients with Bipolar Disorder are not similar depressed patients when it comes to performance on memory tests, but the cognitive deficit presented by bipolar patients could help explain some daily life difficulties. Bipolar patients with and without psychotic symptoms during the manic episodes a congruent humor phenomenon on a verbal memory task with positive affective content compared to healthy individuals. Clear

evidence of humor congruence was observed in the non-psychotic group, suggesting a pure manifestation of the disease. However, more studies are necessary to analyze the differential nature of the specific markers of the Bipolar Disorder in these two manifestations.

Keywords: Humor, Bipolar Disorder, Major Depression Disorder, memory.

LISTA DE ABREVIATURAS

5-HT2A – do inglês, serotonin 2A receptor

BD – do inglês, Bipolar Disorder (Transtorno Bipolar)

BDNF – do inglês, Brain Derived Neutrophic Factor (Fator Neurotrófico Derivado do Cérebro)

CID 10 – do inglês, International Statistical Classification of Diseases and Related Health Problems (Classificação Internacional de Doenças e Problemas Relacionados à Saúde)

DSM-IV – do inglês, Diagnostic and Statistical Manual of Mental Disorders (Manual de Diagnóstico e Estatístico dos Transtornos Mentais)

GABA – do inglês, γ-aminobutyric acid (ácido aminobutírico)

MDD – do inglês, Major Depressive Disorder (Transtorno Depressivo Maior)

MMSE – do inglês, Mini Mental State Examination (Miniexame do Estado Mental)

SD – do inglês, Descreptive Disorder

SPSS – Statistical Package for the Social Sciences

TB – Transtorno Bipolar

TDM – Transtorno Depressivo Maior

APRESENTAÇÃO

Esta tese apresenta os resultados sob a forma de artigo aceito para publicação: capítulo 1 e 2.

O item “Discussão” apresenta interpretação e comentários gerais dos resultados obtidos nos dois artigos.

As referências bibliográficas referem-se somente às citações que são apresentadas nos itens “Introdução” e “Discussão”.

PARTE I

1. INTRODUÇÃO

1.1. Características do Transtorno do Humor

O transtorno bipolar (TB) afeta aproximadamente em torno de 1% a 3% da população mundial. É uma doença crônica que atinge as relações afetivas e familiares, cuja característica principal é a mudança de humor da euforia à depressão (DSM-IV).

É uma doença recorrente, geralmente inicia-se aproximadamente aos 20 anos e pode aparecer de forma diferente em número e tipo de episódios de acordo com idade e sexo. Os sintomas são reduzidos nos períodos eutímicos, mas algumas dificuldades persistem como; déficit cognitivo, instabilidade do humor (Benazzi, 2004) e poder conviver com as consequências da doença (Hirschfeld *et al*., 2003).

O TB é caracterizado por episódios de mania, depressão e episódios mistos. Estudos longitudinais mostraram que pacientes com diagnóstico de depressão passam a maior parte do tempo sintomáticos, superando a mania e a hipomania, numa proporção de 3:1 (Paykel *et al*., 2006).

O diagnóstico do transtorno bipolar não é difícil, mas o diagnóstico de transtorno bipolar em pacientes depressivos não é facil porque geralmente o paciente procura ajuda no episódio depressivo (Ghaemi *et al*., 2000; Ghaemi *et al*., 1999), e os critérios para diagnóstico na fase depressiva do transtorno bipolar e para depressão unipolar são idênticos conforme o DSM-IV. Embora o TB é mais frequentemente diagnosticado

como depressão unipolar, uma série de recursos pode ajudar no diagnóstico do transtorno bipolar em pacientes com sintomas depressivos. Incluem início antes dos 25 anos, história familiar de TB, perturbações do humor e sintomas atípicos, tais como hiperfagia, ganho de peso, hipersonia. O uso do antidepressivo pode induzir para amania ou hipomania falta de resposta aos antidepressivos e a sazonalidade dos episódios ajudam a diferenciar o transtorno bipolar da depressão unipolar (Manning *et al.*, 2002).

Foi observado que TB tem um efeito negativo nas relações interpessoais e profissionais, decorrentes do aumento nos custos familiares pela perda da produtividade (Laxman *et al.*, 2008). A causa é incerta, mas a família e os estudos de gêmeos sugerem uma base genética (Murray *et al.*, 1997).

Os pacientes psicóticos apresentam delírios ou alucinações que podem ser incongruentes com o humor que não são compreensíveis no contexto do estado de humor predominante como ilusões, delírios de referência e persecutório, os congruente com humor contrastam com o estado do humor predominante, por exemplo, delírios de grandeza na mania ou delírio niilista durante depressão (DSM-IV e CID-10).

Autores têm relatado que sintomas individuais como suicídio (Thakur *et al.*,1999), distúrbios psicomotores (Charney *et al.*, 1981), insônia (Lykouras *et al.*, 1986), culpa (Parker *et al.*, 1991) e comprometimento cognitivo (Schatzberg *et al.*, 2000) em pacientes com depressão psicótica são mais frequentes ou graves quando comparados com os da depressão melancólica (Parker *et al.*, 1991).

Muitos indivíduos com TB respondem bem a tratamentos para reduzir sintomas psicóticos e afetivos, mas a capacidade de alcançar a recuperação funcional, de estudar, trabalhar, viver de forma independente e envolver-se afetivamente pode estar dificultada. Portanto, a recuperação de episódios de humor e/ou sintomas residuais não se traduz necessariamente em recuperação funcional (Carrie *et al*., 2010).

Existem pesquisas procurando identificar características clínicas para o TB, tais como história familiar, hipomania induzida por antidepressivos, personalidade hipertímica, início da doença precose, doença recorrente, história de episódios depressivos breves, sintomas atípicos e psicose (Berk *et al*., 2006; Ghaemi *et al*., 2001).

Na mania, o humor está eufórico ou elevado e frequentemente nos contagia. Os pacientes sentem-se felizes, sem problemas e não se preocupam com os sentimentos dos outros, mas, quando têm uma frustração, o humor com facilidade pode ser irritável. Apresentam aumento de energia, hiperatividade, envolvem-se com muitas atividades, pressão para falar e diminuição do sono, a autoestima encontra-se inflada e apresentam ideias de grandiosidade (CID-10).

O indivíduo que sofre de depressão apresenta alteração do humor ou afeto, angústia ou agitação, perda da autoestima ou sentimentos de inutilidade ou culpa, diminuição do apetite e das atividades, ideias ou atos de suicídio e perturbação do sono (CID-10). O transtorno depressivo maior apresenta uma prevalência durante a vida de cerca de 15% a 25% nas mulheres (Sadock *et al*., 2008). As prevalências dos transtornos unipolares têm sido consideradas duas vezes mais elevadas no sexo feminino, sendo uma observação universal, cujas razões podem incluir estresse, partos, modelos comportamental de aprendizado de impotência e efeitos hormonais, entre

outros. A faixa etária média para início do transtorno depressivo maior é dos 40 anos (Sadock *et al*., 2008). Não se observa diferença entre as raças e, em geral, ocorre em pessoas que não apresentam relações íntimas, divorciados ou separados (Sadock *et al.*, 2008).

Diversas formas psicopatológicas do transtorno depressivo maior (TDM) estão associadas com etiologias biológicas, psicológicas e comportamentais correlatos e potencialmente distintos (Fountoulakis *et al*., 2004; Leventhal *et al.*, 2005).

No tratamento do TB, é importante fornecer conhecimento sobre a doença e dar apoio aos pacientes e familiares para melhorar a qualidade de vida e evitar crises. O tratamento farmacológico mais frequente para TB são estabilizadores do humor que podem ser aplicados a várias classes de drogas, como anticonvulsivantes, antipsicóticos de segunda geração ou atípicos e o carbonato de lítio, que atuam como agentes profiláticos capazes de prevenir recidivas da doença como no tratamento dos sintomas da mania aguda (Pini *et al*., 2005), nos sintomas depressivos agudos, (Merikangas *et al*., 2007), na prevenção de sintomas maníacos (Rajagopalan *et al*., 2006) e na prevenção de sintomas depressivos (Bauer *et al*., 2004), parece que o lítio é mais eficaz do que os demais (Bauer *et al*., 2004). Para a depressão, são usados os antidepressivos como os tricíclicos, inibidor da recaptação da serotonina, inibidor da recaptação da serotonina e noradrenalina e inibidores da monoamina oxidade. Essas intervenções farmacológicas ajudam no desempenho da dopamina, os estabilizadores do humor como carbonato de lítio e valproato antagonizam a atividade dopaminérgica e os antidepressivos aumentam a ação (Cousins *et al*., 2009).

1.2. Neuroquímica e Fisiopatologia

Estudos sobre o TB têm confirmado que existem anomalias nos sistemas neurais relativos a neurotransmissores, incluindo a noradrenalina, dopamina, serotonina, acetilcolina, glutamato e GABA (Bymaster *et al*., 2002; Cannon *et al*., 2006; Kalia, 2005).

Foi evidenciado que a depressão e o TB apresentam atrofia neural, diminuição da neuroplasticidade, disfunção neuropsicológica que geralmente persiste após a remissão dos sintomas (Clark *et al.*, 2004). No período de mania, existe restauração da plasticidade sináptica com diminuição da ação da serotonina e aumento da dopamina e na depressão ambos estão diminuídas (Jacobs *et al.*, 1986). Há evidência de que o receptor da serotonina 2A (5-HT2A) afeta os sintomas psicóticos em transtornos psiquiátricos. No entanto, a relação entre o receptor 5-HT2A e os transtornos do humor com características psicóticas não foi investigada (Glenthoj *et al*., 2006).

O BDNF é altamente expresso no córtex cerebral, hipocampo e na área do cérebro que regula as funções da memória e emoção (Patterson *et al*., 2001). Estudos sugerem que as anormalidades no sistema de sinalização BDNF poderiam estar implicadas no declínio cognitivo de alguns transtornos neuropsiquiátricos, como o TB (Shaltiel *et al*., 2007) e a depressão (Schmidt *et al.*, 2008). No TB, os níveis séricos de BDNF são reduzidos durante os episódios maníacos e depressivos, mas parece que normaliza com a estabilização dos sintomas (Fernandes *et al.*, 2009), ainda existem poucos estudos longitudinais com humanos e os que existem são realizados com modelos animais ou sangue periférico humano.

1.3. Aspectos da Neuroimagem

Os pacientes com TB apresentam alargamento lateral do ventrículo esquerdo e aumento das taxas da hiperintensidade de substância branca (Kempton *et al.*, 2008) e redução de área ou volume do corpo caloso (Arnone *et al.*, 2008). Existe alteração do volume dos lobos frontais (Drevets *et al.*, 1997), lobo temporal e amígdala (Brambilla *et al.*, 2003), hipocampo (Sax *et al*.,1999) e gânglios da base (Brambilla *et al.*, 2001).

Investigações por ressonância magnética em pacientes TB indicaram a presença de alterações de “concentração” (ou densidade) de substância cinzenta, bem como anomalias da substância branca em várias áreas neocorticais e do corpo caloso (Le Bihan *et al.*, 2001). Estudos neuropsicológicos sugerem a presença de anomalias no córtex frontal de indivíduos com TB. A diminuição no volume de substância cinzenta e densidade das células da glia e da densidade de células não piramidais da camada II no córtex frontal também estavam presentes (Strakowski *et al.*, 1993).

Estudos com ressonância magnética no hipocampo de pacientes com TB têm sido inconsistentes. Algumas possíveis causas para alterações de volume do hipocampo incluem a vulnerabilidade genética, processo de neurodesenvolvimento aberrante, número de episódios ou duração da doença (Bearden *et al.*, 2001).

1.4. Função Cognitiva e Memória

A atenção é a capacidade de selecionar um estímulo especial. Essa habilidade é fundamental para a cognição, permitindo que o cérebro de maneira flexível selecione determinados pontos de interesse em detrimento de outros. Permite que o cérebro selecione informações pertinentes e relevantes para o comportamento corrente, ignorando distrações irrelevantes (Timothy *et al.*, 2010).

Foi observado déficit de atenção, memória de trabalho (Liberty *et al.*, 2009), aprendizagem verbal e não verbal e funções executivas no TB (Bora *et al*., 2009; Dittmann *et al*., 2008). Esse déficit é mais acentuado nas crises, mas permanece mesmo com a redução dos sintomas psiquiátricos (Altshuler *et al.*, 2008; Martinez-Aran *et al.*, 2004a).

Existem alguns fatores clínicos que podem influenciar o funcionamento cognitivo dos pacientes bipolares, como número de episódios, tipo da crise maníaca, cronicidade e duração da doença (Van Gorp *et al*., 1998), sintomas subclínicos, especialmente de depressão e de desempenho cognitivo (Martinez-Aran *et al.*, 2000).

Apesar de não estar comprovado que pacientes com TB apresentam disfunção cognitiva generalizada durante episódios agudos de mania e depressão, a descoberta de que esses déficits persistem durante a remissão dos sintomas aumenta a possibilidade de que o prejuízo cognitivo pode representar um traço em vez de uma variável de estado (Carrie *et al*., 2010). No estudo de Martinez-Arán (2004b) que comparou pacientes com TB na fase de eutimia, mostrou-se que pacientes apresentavam pior desempenho na memória verbal e na memória de trabalho

comparados com os controles. Portanto, a recuperação de episódios de humor e/ou sintomas residuais não se traduz necessariamente em recuperação funcional.

Em outro estudo realizado por Marieke *et al*. (2010), em uma análise *post hoc*, foram avaliados os pacientes bipolares comparados com controles saudáveis através de uma extensa bateria cognitiva, os resultados do estudo confirmam um significativo comprometimento do funcionamento cognitivo no TB.

O déficit cognitivo persistente nos períodos de eutimia tem um impacto profundo nas vidas de pacientes com TB, apresenta influência sobre o curso da doença e do funcionamento psicossocial (Tabares-Seisdedos *et al*., 2008). Diversos fatores podem influenciar no funcionamento cognitivo, tais como: sintomas psicóticos, abuso de drogas, cronicidade, distúrbios do sono, fatores hormonais e medicamentos (Martinez-Aran *et al*., 2004a).

Um recente estudo avaliou as funções cognitivas de um grupo de pacientes bipolares eutímicos após o primeiro episódio, comparados com um grupo de controle. Observou-se que os pacientes apresentaram comprometimento da atenção na função executiva, comparados com os controles. A presença de déficits cognitivos em pacientes bipolares, logo no primeiro episódio, persistindo mesmo em remissão, indica que esses déficits podem ser marcadores de traço para a doença (Elshahawi *et al.*, 2010).

Fleck *et al.* (2003) estudou 14 pacientes eutímicos e 14 pacientes bipolar I na fase maníaca. Os resultados mostraram deficiências na memória de reconhecimento

verbal durante a mania que não foram evidentes durante a eutimia, e os dois grupos apresentaram déficits de memória verbal.

De qualquer maneira, já foi salientado que a doença bipolar está associada com desempenho funcional pobre (Tohen et al., 2000).

Não devemos esquecer a importância do humor ou afeto sobre os fenômenos da memória (Chaves *et al*., 1993). O desempenho em testes de memória pode ser influenciado pelo tipo de informação a ser processada ou pelo estado afetivo do indivíduo no momento do teste (Jorm *et al*., 1992). Nos indivíduos com depressão, os desempenhos de memória em diferentes tarefas podem ser influenciados pelos seus estados afetivos, apresentando melhores aquisições e/ou evocações de informações negativas em relação aos indivíduos normais (Teasdale *et al*., 1979; Teasdale *et al*., 1983). As evidências sobre o viés negativo da depressão estão nos estudos com experiências pessoais durante episódio depressivo (Blaney, 1986; Teasdale *et al*., 1980; Teasdale *et al.*, 1983).

Na dependência de estado, o processamento de informação é influenciado pelo humor durante o aprendizado, e o desempenho de evocação será melhor se nesse momento o estado de humor for o mesmo. Na congruência do humor, a informação é mais facilmente armazenada se o conteúdo afetivo da tarefa corresponder ao estado afetivo do indivíduo (Jorm *et al*., 1992). No estudo de Serra *et al.* (2006), destaca que pacientes deprimidos apresentam menos sensibilidade a expressões faciais positivas e mais sensibilidade a expressões negativas.

No estudo realizado por Schneider *et al.* (2008), com uma amostra brasileira de pacientes eutímicos e deprimidos, concluiu-se um menor desempenho na área verbal e

não verbal do funcionamento cognitivo, comparados com os controles, sugerindo estabilidade ou cronicidade dos déficits cognitivos.

A memória de trabalho é um aspecto importante na capacidade cognitiva, o que influencia a atenção, função executiva, raciocínio e o controle cognitivo (Engle *et al.*, 2003).

O déficit cognitivo no TB é uma das principais preocupações dos pesquisadores devido a sua associação com comprometimento funcional. A melhor compreensão da função cognitiva em TB pode vir a contribuir para o desenvolvimento de estratégias para melhorar o funcionamento geral (Schneider *et al*., 2008).

O estudo de Marieke *et al.* (2010) confirmou déficit cognitivo em pacientes com TB e é mais grave em pacientes com sintomas depressivos, principalmente em relação aos domínios de velocidade e atenção.

Dois terços dos pacientes apresentam algum nível de comprometimento funcional, e a metade está desempregada (Altshuler *et al.*, 2007); apesar de muitos indivíduos com TB responderem bem aos tratamentos destinados a reduzir os sintomas, a capacidade de recuperação funcional para estudar, trabalhar, viver de forma independente está prejudicada (Harvey et al., 2010).

Muitos indivíduos com transtorno bipolar têm algum grau de déficit neurocognitivo. Embora essa deficiência possa estar influenciada pela evolução clínica, a gravidade da doença, o uso de medicação psicotrópica, bem como a herança genética sugerem que os déficits neurocognitivos sejam um aspecto importante no transtorno bipolar.

Em função do exposto acima, é de grande importância investigar a cognição no transtorno bipolar durante a fase aguda de sintomas maníacos com ou sem sintomas psicóticos. Dos instrumentos que podem ser aplicados para avaliar diferentes domínios cognitivos com ou sem conteúdo afetivo, a seguir estão descritos alguns deles.

a)* Span *(extensão) de palavras positivas, neutro e negativo (Ceitlin *et al*., 1995)

Este teste verifica a capacidade de aprendizagem e retenção de uma lista de palavras, amplitude da memória verbal, suscetibilidade à interferência. Apresenta-se verbalmente uma lista de dez palavras pausadamente (uma palavra por segundo). O sujeito deve repetir as palavras em qualquer ordem, após a apresentação da lista.

b)* Span *de reconhecimento visual (Rebok *et al.*, 1990)

Avalia atenção e memória visual consistem no assunto, indicando a posição do último círculo branco consecutivamente colocado em um quadro-negro fora da vista do examinando.

c) Teste de memória lógica (pequena história) (Wechsler, 1997)

Avalia retenção e evocação de memória. Conta-se uma história, e o sujeito deverá repetir imediatamente e dez minutos após.

d)* Span *de dígitos (Wechsler, 1997)

Avalia atenção e memória imediata, pede-se ao sujeito que repita séries crescentes de dígitos na mesma ordem em que foram ditas pelo examinador (ordem

direta).

e) Miniexame do Estado Mental (Folstein *et al*., 1975)

É um exame do estado mental abreviado, no qual as áreas avaliadas incluem orientação, memória, atenção e cálculo, linguagem e praxia construtiva (escore máximo 30).

2. OBJETIVOS

O objetivo geral desta tese foi comparar o desempenho de memória em tarefas com e sem conteúdo afetivo em pacientes internados com depressão maior, transtorno bipolar do tipo I na fase maníaca, e indivíduos saudáveis. Além disso, também foi avaliado o efeito da presença de sintomas psicóticos no desempenho de memória nos dois grupos de pacientes.

Os objetivos específicos foram:

a) Analisar o perfil de memória (aquisição e evocação) de pacientes deprimidos, maníacos e dos sujeitos de controle (intra e intergrupos);
b) Correlacionar a intensidade de sintomas afetivos com o desempenho cognitivo destes pacientes;
c) Comparar os desempenhos entre as tarefas com e sem conteúdo afetivo em cada grupo e entre grupos;
d) Comparar a congruência do humor nos pacientes maníacos com e sem sintomas psicóticos e nos pacientes deprimidos;
e) Verificar a influência do número de episódios afetivos e da duração da doença nos desempenhos cognitivos.

PARTE II

3. ARTIGOS CIENTÍFICOS

Capítulo I

Artigo publicado no "Brazilian Journal of Medical and Biological Research"

Memory mood congruency phenomenon in bipolar I disorder and major depression disorder patients

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Abstract

The objective of the present study was to evaluate memory performance in tasks with and without affective content (to confirm the mood congruency phenomenon) in acutely admitted patients with bipolar I disorder (BD) and major depression disorder (MDD) and in healthy participants. Seventy-eight participants (24 BD, 29 MDD, and 25 healthy controls) were evaluated. Three word lists were used as the memory task with affective content (positive, negative and indifferent). Psychiatric symptoms were also evaluated

with rating scales (Young Mania Rating Scale for mania and Hamilton Depression Rating Scale for depression). Patients were selected during the first week of hospitalization. BD patients showed higher scores in the word span with positive tone than MDD patients and healthy controls ($p = 0.002$). No other difference was observed for tests with affective tone. MDD patients presented significantly lower scores in the Mini-Mental State Exam, logical memory test, visual recognition span, and digit span, while BD patients presented lower scores in the visual recognition test and digit span. Mood congruency effect was found for word span with positive tone among BD patients but no similar effect was observed among MDD patients for negative items. MDD patients presented more memory impairment than BD patients, but BD patients also showed memory impairment.

Key words: Memory; Bipolar disorder; Depression; Affect

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Received . Accepted . Available online

Authors: V.B. Delgado et al.

Running title: Memory mood congruency phenomenon in bipolar I disorder

Introduction

Bipolar disorder (BD) is characterized by disturbances in mood ranging from extreme elation (mania) to severe depression often accompanied by psychotic features and cognitive changes (1). There are two types of diagnosis: bipolar I disorder and bipolar II disorder. Bipolar I disorder is characterized by recurrent episodes of mania and depression, while bipolar II disorder is defined as recurrent episodes of depression and hypomania (2). Bipolar I disorder is equally prevalent in men and women, whereas many studies have shown that there are more women than men with bipolar II disorder (3). Prevalence rates have been estimated at 0.4-1.6% for bipolar I disorder and at 0.5-1.9% for bipolar II disorder (2). However, when the spectrum of bipolarity is extended to bipolar disorder in general, the affected population is about 5% (4). BD is a genetically and neurochemically based complex, recurrent, and potentially progressive neuropsychiatric disorder involving multiple brain systems at the level of neurochemistry, physiology, and structure (5). The precise cause of BD is not known. Historically, dopaminergic models of BD have been dichotomous and global, with mania considered to be a hyperdopaminergic state throughout the brain and depression the reverse of this state (6).

Major depressive disorder (MDD) is a heterogeneous, highly prevalent, and moderately heritable disorder. According to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edn. *(DSM-IV), the diagnosis of MDD* requires a minimum of five symptoms (at least one being mood or anhedonia) for a minimum of 2 weeks. The lifetime prevalence of unipolar MDD is at least 10%, with the risk among women being

twice the risk for men (7). There are no race differences, and in general the occurrence is higher among those without close relations, divorced or separated (8). Recurrence and early age at onset characterize cases with the greatest familial risk. Most genetic studies have focused on functional polymorphisms (DNA sequence variations that alter the expression and/or functioning of the gene product) in the loci encoding the serotonin transporter (SLC6A4), serotonin 2A receptor (5HTR2A), tyrosine hydroxylase (TH) (the limiting enzyme for dopamine synthesis), tryptophan hydroxylase 1 (TPH1) (serotonin synthesis), and catechol-o-methyltransferase (COMT) (dopamine catabolism) (9). A recent etiological hypothesis is that neurotoxic effects (possibly related to excessive corticotrophin activity and/or to the inflammatory effects of cytokines) on hippocampal cells, mediate many depressive symptoms, with deficient function of neuroprotective peptides (9). Brain-derived neurotrophic factor (BDNF) is a neuroprotective protein. Initial reports have shown reduced serum BDNF in MDD (10) and association between polymorphisms in BDNF and BD (10). However, subsequent studies have not corroborated such findings uniformly for both disorders (11).

Bipolar disorder patients clearly exhibit extensive neurocognitive dysfunction during acute episodes of mania or depression; however, the demonstration that these deficits endure during remission has raised the possibility that cognitive impairment may represent a trait rather than a state (12). Euthymic bipolar patients showed limitations in a number of cognitive domains, especially executive function, declarative memory, and sustained attention (13). MDD is associated with cognitive dysfunction, in particular episodic memory impairment (14). The observed memory deficits may be explained by

the association with functional and structural changes in brain structures, including the hippocampus and prefrontal cortex that are critical for episodic memory (15).

Mood is a relatively long-lasting emotional state. Affect is the emotional experience immediately raised by an experience. During a manic episode, the mood is elevated. Patients feel happy, without problems and are not sympathetic to somebody else's feelings, but when they are submitted to frustration they can be short-tempered. Patients show high energy, hyperactivity, distractibility, may be involved in many activities, loss of ideas, pressure to talk and reduction of sleep. The self-esteem is increased and there are ideas of grandiosity (2). During a depressive episode, a patient presents mood or affect change, can feel depressed, sad and hopeless, report anxiety and agitation, loss of self-esteem or feelings of guilt or depreciation, and reduction of appetite and activities, suicidal ideas or attempts, and sleep disorders (2).

The importance of mood or affect for memory is significant because performance in memory tests may be influenced by the type of information to be processed or by the affective state of the individual at the time of the test (4). The memory performance of depressed patients in different tasks may be influenced by the affective state, with these patients presenting better acquisition and/or evocation of negative information compared to normal individuals (16). The main evidence of the negative bias of depression was derived from studies with recollection of personal experiences during a depressive episode or studies with the same type of recall during mood induction (4-17).

In state dependency, processing of information is influenced by mood during acquisition, and recall is highest if the mood state is the same. In mood congruency, information is better stored if the affective content corresponds to the subject's affective

state (5). In a study that evaluated the acute effect of diazepam on explicit memory with and without affective content in patients with major depression, no anterograde amnesia was observed following diazepam (18). The authors hypothesized that a dysfunction of limbic prefrontal cortical structures that impair the modulation of the amygdala in major depression could explain these results. No equivalent information is available for altered states of mood during mania episodes in BD (state dependency or mood congruency).

The hypothesis raised in the present study is that the mood congruence phenomenon would be present towards elation in BD patients and towards depression in MDD patients. We also intended to demonstrate that acutely manic BD patients would present impaired memory/attention performance compared to healthy participants, but not compared to acutely depressed MDD patients. Therefore, the objective of the present study was to evaluate memory performance in tasks with and without affective content (to verify the mood congruence phenomenon) in acutely admitted patients with bipolar I disorder and major depression disorder, and in a group of healthy participants.

Material and Methods

Subjects and inclusion/exclusion criteria

A cross-sectional study was carried out to evaluate inpatients with type I bipolar disorder during a mania episode, and patients with major depression disorder. The sample was composed of 78 participants (24 BD, 29 MDD, and 25 healthy controls). The inclusion of patients followed the DSM-IV criteria for BD and MDD. Exclusion criteria

were severe cognitive deficit (Mini Mental State Examination <10), legal or illegal substance abuse (alcohol and drugs), illiteracy, and age <20 and >60 years.

Patients were admitted to the Psychiatric Unit of a general university hospital, Hospital de Clínicas de Porto Alegre (Porto Alegre, RS, Brazil) for treatment during an acute exacerbation of illness. The average number of episodes among MD patients was 3.19, while duration of disease was 6.74 years. Among BD patients, the number of episodes was 5.19 and duration of disease was 8.99 years. Use of medication is presented in Table 1. Healthy controls were recruited randomly from the community where the hospital is located.

A battery of cognitive tests was administered to assess attention and memory. Testing began with a visual recognition memory task. Assessment of each participant lasted about 1 h. The same instructions were given to all subjects to prevent subtle differences of interaction with the experimenter.

Cognitive testing and symptom rating scales

A set of attention/memory tests with affective content (positive, negative, and indifferent) and without affective content was selected to evaluate the attention/memory performance of the participants. The selected tests have been previously adapted and validated for the Brazilian population (19-24):

1) Word span: word lists with emotional content, with 10 items each, presented at a rate of one word/sec starting with the positive span and presented consecutively. Higher scores represent better performance. The task evaluates verbal episodic memory (19-20).

2) Wechsler's logical memory test (immediate and delayed recall): a short story with 10 items is presented auditorily to evaluate attention and verbal episodic memory (21-22). Higher scores represent better performance.

3) Digit span: the test starts with two consecutive commands of 3 digits, which are progressively increased up to 2 commands of 10 digits. The test is interrupted when a participant fails to correctly repeat two consecutive commands. Higher scores represent better attention/memory processing. The test evaluates attentional processing, sustained attention and working memory (21-23).

4) Visuospatial recognition span: white round tokens are displayed on a black board, starting from 1 and increasing up to 20 tokens. Each time a token is added to the board, the board is covered. The examinee has to identify the last added token (places are marked and the sequence is fixed). Higher scores mean better performance. This is a task developed to evaluate sustained visual attention and visual memory (24).

Symptoms were rated in each group with the Hamilton Depression Rating Scale (HDRS) (25) and with the Young Mania Rating Scale (YMRS) for mania (26). The 17-item version was used for the HDRS scale and the Portuguese adapted version was used for the YMRS (27). The Mini Mental State Examination (MMSE) was also applied to the 3 groups to exclude cognitive impairment (28).

The study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre and all participants gave written informed consent.

Statistical analysis

Descriptive statistics (mean ± SD, and relative frequency) were calculated for demographic data, MMSE, and memory tests. Spearman's correlation coefficients were calculated for correlations between the Hamilton and Young scales, number of affective episodes, duration of illness, and memory tests. A univariate general linear model (two-way ANOVA with the Bonferroni *post hoc* test) was designed for the evaluation of the effects of group (depression, mania, controls), number of affective episodes and memory test scores (ANCOVA with the Bonferroni *post hoc* test). The statistical analysis was carried out using the Statistical Package for the Social Sciences for Windows (SPSS 14).

Results

Demographic data

To evaluate the severity of BD and of MDD symptoms we applied the Young Mania rating scale and the Hamilton scale for depression. The scores on the Hamilton scale were 27.9 for the MDD group, and the scores on the Young scale were 29.3 for the BD group (Table 1).

Depressed patients were significantly older and less educated than BD patients and healthy controls (Table 1). Females were more prevalent in all groups studied. The MMSE scores were significantly lower among MDD patients (mean ± SD, 25.56 ± 2.94) than among BD patients (27.40 ± 1.67) and healthy controls (28.23 ± 1.82).

Memory tests with affective content

In the word span with positive tone, the BD group showed higher scores than the MDD and healthy control groups (Table 2). A significant effect of the number of affective episodes was observed in this test (ANCOVA, negative correlation; B = -0.13; P = 0.035). The word lists with indifferent and negative tones did not show significant differences among groups.

Memory tests without affective content

MDD patients presented significantly lower scores in the Digit span than BD and healthy controls (Table 2). A significant effect of number of affective episodes was also observed on Digit span (ANCOVA, negative correlation; B = -0.21; P = 0.043). MDD and BD patients presented significantly lower scores than healthy controls in the visuospatial recognition span (P = 0.002; Table 2). No effect of number of affective episodes was observed.

In the Logical Memory test, immediate recall, the MDD group presented lower scores than healthy controls, but did not differ from the BD group (Table 2). In the delayed recall, both groups of patients (MDD and BD) presented a significantly worse performance than the healthy control group. No effect of number of affective episodes was observed.

Correlations

Age correlated significantly with word span positive content (rho = -0.25; P = 0.030), digit span (rho = -0.28; P = 0.015), and visuospatial span (rho = -0.26; P =

0.020). Education correlated with logical memory immediate recall (rho = 0.26; P = 0.024), word span negative content (rho = 0.38; P = 0.001), and digit span (rho = 0.27; P = 0.016). Duration of disease correlated with Word span positive content among BD patients (rho = -0.48; P = 0.022).

Discussion

This study was carried out to analyze performance in memory tasks with and without affective content in acutely manic BD patients, acutely depressed MDD patients, and in a group of healthy controls.

Type I BD patients presented higher scores in the word span with positive content than MDD patients and healthy controls. This finding suggests the hypothesis of the memory mood congruency among BD patients. Mood and affect are important for memory because they may influence performance according to the type of information to be processed or according to the affective state of the individual at the time of the test (4-17-29). Therefore, in mood congruency the information is better stored if the affective content corresponds to the subject's affective state (4), as observed in the present study. No similar information was previously available for altered states of mood and memory processing during manic episodes in BD (state dependency or mood congruency). The performance in the word span with positive content was affected by the number of affective episodes (as demonstrated by ANCOVA) and by the duration of disease (as shown by the Spearman correlation). Thus, we may assume that the task was influenced by the severity of the bipolar disorder (the more severe the disorder the lower

the scores in the test). In BD, and depending on the severity of the disease (number of episodes and duration of disease), the positive biased memory processing and the symptoms of the disease (i.e., mania) may be interconnected - one reinforcing the other.

The memory performance of depressed patients has been shown to be influenced by the affective state, with better acquisition and/or evocation of negative information (16-30). In our study, no mood congruency effect for negative items was found for MDD patients. No influence of number of episodes or duration of disease was observed in this group. The negative bias of depression was derived from studies with recollection of personal experiences during a depressive episode or studies with the same type of recall during mood induction. (4-16-17-29).

MDD patients presented poorer memory performance than healthy participants in the following tests: logical memory immediate and delayed recall, digit span, and visuospatial recognition span. These patients also showed worse performance than BD patients in the digit span and word span with positive tone. In addition to memory tests, MDD patients also presented lower scores in the MMSE, corroborating previous data on cognitive impairment in depressed patients (14-31). Because depression is a frequent and disabling disorder often characterized by a recurrent and chronic course (32), it is well established that depressive disorders are associated with cognitive dysfunction, especially episodic memory impairment (33-34). Among the explanations for these cognitive impairments in depression, the possible association with functional and structural changes in brain structures (i.e., hippocampus and prefrontal cortex - critical for episodic memory) is central (15-35).

We also found other memory impairments among BD patients. The performance in the logical memory delayed recall and in the visuospatial recognition span was lower compared to that of the healthy participants. There is now much evidence that patients with BD show cognitive impairment during the acute phases of the illness, which persists during inter-episode periods, even when mood is euthymic (36-37). Attentional processing, executive function, and verbal memory are the cognitive functions usually impaired in bipolar disorder (38). Impairment in some domains (visual and working memory, and risk-taking behavior) did not show remission during periods of euthymia, while it did show remission in others (selective attention, attentional shifting, verbal memory, verbal planning, processing speed, and the elements of executive function such as inhibitory control, response inhibition, or strategic thought) (39).

The large proportion of women among depressed patients is one of the limitations of the study; however this was evaluated in the statistical analysis. On the other hand, this investigation presents several strengths such as the evaluation of acutely hospitalized patients, the determination of disease severity with worldwide rating scales, and the use of a healthy group from the same community as that of the patients.

We detected the mood congruency effect for the word span with positive content among BD patients but no similar effect among MDD patients for negative items. MDD patients presented more memory impairments than BD patients, while BD patients also showed memory impairments compared to the healthy participants. Indeed, bipolar patients did not resemble depressed patient in the performance of different memory tasks, but cognitive difficulties in bipolar patients may help explain impairment of daily functioning.

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Table 1. Demographic and clinical data of the subjects studied.

Variables	MDD (N = 29)	BD (N = 24)	Healthy controls (N = 25)
Age (years)	45.03 ± 9.00[a]	36.83 ± 12.74[b]	39.32 ± 12.22
Education (years)	8.14 ± 2.98[c]	10.46 ± 3.60[d]	9.80 ± 3.21
Gender - Female	28 (96.6%)	15 (62.5%)	19 (76.0%)
Duration of illness (months)	80.91 ± 118.35	107.91 ± 80.70	-
Mini Mental State Examination	25.56 ± 2.94[e]	27.40 ± 1.67[f]	28.23 ± 1.82[g]
HDRS	27.90 ± 4.43	-	-
YMRS	-	29.33 ± 3.30	-
Medication			
SSRI and antipsychotic	9 31(%)	-	-
Tricyclic, benzodiazepine and antipsychotic	6 (21%)	-	-
Lithium carbonate	-	5 (21%)	-
Lithium carbonate, benzodiazepine and SSRI	4 (14%)	-	-
Lithium carbonate and antipsychotic	-	9 (37.5%)	-
Benzodiazepine, antipsychotic, SSRI and anticonvulsant	4 (14%)	-	-
SSRI	4 (14%)	-	-
IMAO and/or antipsychotic and anticonvulsant	2 (7%)	-	-
Antipsychotic and anticonvulsant	-	5 (21%)	-

Data are reported as means ± SD or number with percent in parentheses. a ≠ b (P = 0.029, Bonferroni *post hoc* test). c ≠ d (P = 0.031, Bonferroni *post hoc* test). e ≠ f; e ≠ g (P < 0.002, Bonferroni *post hoc* test). MDD = major depression disorder; BD = bipolar I disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; SSRI = selective serotonin reuptake inhibitors; IMAO = monoamine oxidase inhibitors.

Table 2. Comparison of the scores (mean ± SEM) of memory tests among the groups studied (number of affective episodes controlled)**.**

Tests	MDD (N = 29)	BD (N = 24)	Healthy controls (N = 25)
Logical memory			
Immediate recall	6.0 ± 2.34[a]	6.6 ± 1.40	7.5 ± 1.56[b]
Delayed recall	5.5 ± 2.49[c]	6.0 ± 1.53[d]	7.2 ± 1.50[e]
Word span			
Positive tone	4.4 ± 1.42[f]	5.6 ± 1.21[g]	4.9 ± 1.24[h]
Negative tone	5.1 ± 1.72	5.6 ± 1.43	5.4 ± 1.08
Indifferent tone	4.9 ± 1.32	5.3 ± 1.56	5.8 ± 1.16
Digit span	3.7 ± 2.19[i]	5.7 ± 2.24[j]	5.8 ± 2.01[l]
Visuospatial recognition span	7.1 ± 3.50[c]	6.6 ± 2.42[d]	9.8 ± 3.13[e]

The number of episodes was analyzed as a covariant. a≠b; c,d≠e; g≠f,h; i≠j,l ($P < 0.042$, $P < 0.017$, $P < 0.002$, $P < 0.001$; ANCOVA with Bonferroni *post hoc* test). MDD = major depression disorder; BD = bipolar I disorder.

Capítulo II

Artigo aceito no “Cognitive Neuropsychiatry”

Mood Congruence Phenomenon in Acutely Symptomatic Mania Bipolar I Disorder Patients With and Without Psychotic Symptoms

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Running Head: BD and Memory Performance

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Abstract

Introduction: Bipolar disorder causes substantial morbidity including cognitive impairment. The objective of the study was to evaluate memory performance of acutely mania bipolar disorder patients with and without psychosis. We also aimed to assess the mood congruence phenomenon upon memory.

Methods: A cross-sectional study was developed with mania patients (19 with, and 12 without psychotic symptoms), and 27 age and education paired healthy controls. Memory tests were selected to evaluate memory/attention performance. A verbal episodic memory task with affective content (word span) was also applied.

Results: A significant difference was observed in the scores of the word span with positive tone among the three groups, controlling for number of mania episodes ($p = .042$). Non psychotic BD patients presented higher scores. There was a statistical tendency for BD patients with and without psychotic symptoms to perform poorer than healthy controls in the delayed recall of the logical memory test ($p = .069$).

Conclusion: Psychotic and non-psychotic mania BD patients showed mood congruence phenomenon in a verbal memory task with positive tone in relation to the healthy group. Evidence of mood congruence was found in the non psychotic group suggesting a purer manifestation of the disease.

Descriptors: Bipolar disorder, mania, psychosis, memory, mood congruence

INTRODUCTION

Bipolar disorder (BD) causes substantial psychosocial morbidity, as it frequently affects independent living, vocational, and social activities (Murray & Lopez, 1996). Bipolar disorder represents 1-3% of the population and is a genetically and neurochemically based complex, recurrent, and potentially progressive neuropsychiatric disorder involving multiple brain systems at the level of neurochemistry, physiology, and structure (Merikangas, Hagop, Akiskal, Angst, Greenberg, Hirschfeld, Petukhova, & Kessler, 2007). The disorder has a long-term outcome much less favorable than previously thought, with incomplete recovery between the episodes, cognitive impairment, and functional decline (Dias, Brissos, Frey, Andreazza, Cardoso, & Kapczinski, 2009).

Great effort has been made to understand the cognitive impairment associated with BD, and there is now enough evidence that patients with BD show cognitive impairment during acute phases of illness, which persists during inter-episode periods, even when mood is euthymic (Robinson, Thompson, Gallagher, Goswami, Young, & Ferrier, 2006 Martinez-Aran, Vieta, Reinares, Colom, Torrent, Sánchez-Moreno, Benabarre, Goikolea, Comes, & Salamero, 2004; Quraishi & Frangou, 2002). Attentional processing, executive function, and verbal memory are the cognitive functions usually impaired in bipolar disorder (Ferrier, Chowdhury, Thompson, Watson, & Young, 2004). However, impairment in some domains (visual and working memory, and risk-taking behavior) did not remit during periods of euthymia, while in others did (selective attention, attentional shifting, verbal memory, verbal planning, processing

speed, and the elements of executive function as inhibitory control, response inhibition, or strategic thought) (Dixon, Kravariti, Frith, Murray, & McGuire, 2004).

The extent and magnitude is generally less severe and persistent than observed in schizophrenia or primary psychotic disorders (Daban et al., 2006). Some characteristics are shared by schizophrenia and bipolar disorder such as typical onset in early adult life, and excess of onset in the summer months (Takei et al., 1992). Furthermore, many studies have demonstrated an excess of life events prior to the onset of affective illness, and prospective studies have shown the importance of stressful life events in the three weeks preceding onset of a schizophrenic illness (Ventura, Neuchterlein, Lukoff, & Hardesty, 1989). The cognitive impairment presented by schizophrenia and bipolar disorder patients has been demonstrated to be shared in some aspects and exclusive in others (McGrath, Chappel, & Wright, 2001). Impaired working memory may act as a trait marker in schizophrenia, and as a state marker of acute psychosis in both schizophrenia and mania. Recognition that schizophrenia and bipolar disorder may fall on a continuum draws on the overlap in psychotic symptoms that occurs in these disorders (Moldin, 1999; Potash et al., 2001). Indeed, Seidman et al. (2002) proposed that bipolar I disorder patients with mania provide a stringent comparison group for examining the diagnostic specificity of cognitive dysfunctions in schizophrenia since these patients exhibit premorbid impairment and clinically marked disorganization similar to that shown in schizophrenia.

Identification of features of bipolar illness that may be predictive of its severity and course has been searched for, including the presence of psychotic symptoms during mood episodes (Goodwin, & Jamison, 1990). The psychotic features include delusions

and hallucinations and both can be mood congruent (include those entirely consistent with the thought content) or non-congruent (like guilt, sin, worthlessness, poverty and somatic health, or on the contrary thoughts of exceptional mental and physical fitness or special talents, wealth, or some kind of grandiose identity) (Fountoulakis, Gonda, Vieta, & Schmidt, 2009).

History of psychosis among bipolar patients have been associated with greater impairments of executive functioning and working memory (including spatial memory) (Glahn et al., 2007).The results of a recent meta-analysis suggested that psychosis during the course of BD is associated with poorer cognitive performance in a number of cognitive domains such as verbal memory, executive function (planning/reasoning), working memory and processing speed (Bora, Murat, & Pantelis, 2010). The review suggested that the effect of thought disorder and mood congruency on psychosis and cognition in BD should also be examined (Bora et al., 2010).

Performance in memory tests may be influenced by the type of information to be processed or by the affective state of the individual in the moment of the test (Jorm & Henderson, 1992; Blackburn, Roxborrough, Muir, Glabus, & Blackwood, 1990; Blaney, 1986; Breslow, Locsis, & Belkin, 1981). The phenomenon of mood congruence stated that information is best stored when its affective content corresponds to the affective state of the subject (Jorm & Henderson, 1992). The memory performance of depressed patients in different tasks is influenced by the affective state (Teasdal & Fogarty, 1979; Teasdale & Russel, 1983; Bora et al., 2010). The main evidence on the negative bias of depression were derived from studies with recollection of personal experiences during a depressive episode or studies with the same type of recall during mood induction (Jorm

& Henderson, 1992; Blaney, 1986; Teasdale & Russel, 1983; Teasdale,Taylor, & Fogarty, 1980; Snyder & White, 1982; Rholes, Riskind, & Lane, 1987; Sutton,Teasdale, & Broadbent, 1988).

There is little information on the emotional processing in bipolar disorder. A study with adolescents subclassified into high and low scores in a screening tool for bipolar disorder that targets mood-elevation symptoms showed that the high-score group presented facilitated recognition of surprised and neutral facial expressions and enhanced processing of positive versus negative information in emotional recognition memory and emotion-potentiated startle (Rock, Goodwin, & Harmer, 2010). Psychotic BD patients during mania presented poorer performances in many cognitive domains than non psychotic patients and there is no evidence of mood congruence between the content of the task and the patient´s state. Therefore we hypothesized that non psychotic patients (due to the purer nature of the phenomenology), besides better test performance than psychotic patients, would present mood congruence on a verbal memory task. The objective of this study was to evaluate attention and memory performance of acutely mania bipolar disorder patients with and without psychotic symptoms, comparing to a group of healthy participants. The investigation also aimed to assess the relation between levels of mania symptoms and the affective tone of a verbal memory task.

METHODS

A cross-sectional study was developed with 19 Bipolar I Disorder (BD-I) psychotic patients, 12 BD-I non-psychotic patients, and 27 healthy participants. Patients of the study were recruited from a psychiatric unit of a university hospital in the city of Porto Alegre/RS, Brazil. Healthy controls were individuals recruited from the community (age and education paired). Patients fulfilled the DSM-IV criteria for BD-I diagnosis, mania episode, ascertained by a senior psychiatrist. Exclusionary criteria were severe cognitive deficit (Mini Mental State Exame <10) (Folstein, Folstein, & McHugh, 1975) abuse of legal or illegal substances, illiteracy, and age lower than 20 or greater than 60.

For healthy community participants, inclusion criteria were age between 20 and 59 years and fully functional. Exclusion criteria were history of use of psychoactive drugs, psychiatric or neurological disorders, cognitive impairment and illiteracy.

Mania symptoms were rated with the Young Mania Rating scale (Young, Biggs, Ziegler, & Meyer, 1978) in the three groups. BD patients presented scores ≥12 and healthy controls ≤6. Number of episodes and duration of disease (in months) were recorded for each patient, but patients were at least during the second episode (Table 1). Psychotic symptoms were classified according to DSM-IV criteria for BD (presence of delusions and/or hallucinations), and corroborated by the items of the Young Mania Rating scale.

Of the 19 psychotic patients, 15 were on medication at the moment of evaluation (at the beginning of hospitalization): 3 were receiving lithium carbonate alone; 8 were using lithium carbonate associated with anticonvulsant and/or antipsychotic; 3 were

receiving anticonvulsant and antipsychotic; and 1 patient was using an antidepressant alone. Of the 12 non-psychotic patients, 10 were under treatment: 2 were receiving lithium carbonate alone; 4 were using lithium carbonate associated with anticonvulsant and/or antipsychotic; and 4 patients were receiving anticonvulsant and antipsychotic.

A set of cognitive tests was administered to assess attention, sustained attention, working memory, and episodic memory. A verbal episodic memory task with affective content (positive, negative, and indifferent) was also applied. Testing began with a visual recognition memory task. Assessment was administered at around 1 hour for each participant. The same instructions were given to all subjects to prevent subtle differences of interaction with the experimenter. The selected tests have been previously adapted and validated for the Brazilian population:

1. Word span: word lists with emotional content presented in a rate of one word/sec starting with the positive span and presented consecutively; the immediate recall was used. Higher scores represent better performance. The task evaluates verbal episodic memory (Ceitlin, Santos, Parizotto, Zanatta, & Chaves, 1995; Bertolucci et al., 2001).

2. Wechsler´s logical memory test (immediate and delayed recall): a short story to evaluate attention and verbal episodic memory (Wechsler, 1987; Chaves et al., 1999). Higher scores represent better performance.

3. Digit span: starting with two consecutive commands of 3 digits and progressively increases up to 2 commands of 10 digits. The test is interrupted when a participant fails to correctly repeat two consecutively commands. Higher scores represent better attention/memory processing. Evaluates attentional processing, sustained attention and working memory (Wechsler, 1987; Chaves & Izquierdo, 1992).

4. Visuospatial recognition span: white round tokens are displayed on a black board, starting from 1 and increasing up to 20 tokens. Each time a token is added to the board, the board is covered. The examinee has to identify the last added token (places are marked and the sequence is fixed). Higher scores mean better performance. This is a task developed to evaluate sustained visual attention and visual memory (Rebok, Brandt, & Folstein, 1990).

The study was approved by the Ethics Committee for Research of the Hospital de Clínicas de Porto Alegre. All participants or a legal guardian signed an informed consent.

STATISTICAL ANALYSIS

Descriptive statistics (mean, SD, and relative frequency) were calculated for demographic data, MMSE, and cognitive tests. A univariate general linear model (1-way ANOVA with Bonferroni post hoc) was designed for the evaluation of the effects of group (with and without psychotic symptoms, and healthy controls), and number of episodes on MMSE and cognitive tests. Variables with non parametric distribution were analyzed with Mann Whitney U test or Kruskall-Wallis. Correlation analyses were carried out with Spearman rho coefficient. The statistical analysis was carried out using Statistical Package for the Social Sciences for Windows (SPSS 14).

RESULTS

Groups did not present educational attainment difference (Table 1). Percentage of women was 63.2% among psychotic patients, 50% among non-psychotic patients, and 74.1% among healthy controls (Table 1). Ratings of mania symptoms are presented in Table 1. No difference of severity of mania symptoms was observed between the groups with and without psychotic symptoms.

No statistical difference was observed among the 3 groups in the scores of the Mini Mental State Exam. Mean score was 27.00 in the group of BD patients with psychotic symptoms, 28.4 in the group without psychotic symptoms, and 27.6 in the healthy control group (Table 1).

A significant difference was observed in the scores of the word span with positive tone among the three groups, controlling for number of mania episodes. Healthy controls presented lower scores than psychotic and non psychotic patients (Figure 1). Non psychotic patients presented higher mean scores.

There was a statistical tendency for BD patients with and without psychotic symptoms to perform poorer than healthy controls in the delayed recall of the logical memory test ($p = 0.069$). However, no difference was observed between these two groups of patients (Table 2).

We also analyzed the correlation between number of mania episodes with the Young Mania rating scale, duration of disease, and cognitive tests. Positive significant correlation was observed between number of episodes and duration of disease, and rating of mania symptoms (Young Mania rating scale) (Table 3). A positive significant

correlation was also observed between rating of symptoms and duration of disease (rho = 0.74; p = 0.000). Negative significant correlation was observed for the logical memory (immediate and delayed recall; rho= -0.27; p = 0.043 and rho= -0.32; p = 0.016), word span with indifferent content (rho = -0.28; p = 0.033), and visual recognition span (rho = - 0.32; p = 0.015) with number of episodes (Table 3).

DISCUSSION

This investigation was carried out to evaluate memory performance of type Bipolar I Disorder inpatients, during acute mania with and without psychotic symptoms, and to test mood congruence between a memory task and patients´ status. We hypothesized psychotic symptoms in BD patients would cause worst memory/attention performance and would prevent the mood congruence phenomenon. We observed that patients without psychotic symptoms showed better performance, while healthy controls presented the worst performance in the memory task with positive affective content – word span. The present finding suggests the existence of mood congruence phenomenon in symptomatic mania BD patients in a progressive way in which patients without psychosis showed the greatest congruence range and those with psychosis had the lowest range. One way to explain this observation would be to consider that the first group represents the purest manifestation of bipolar disorder. The phenomenon of mood congruence in depression has been demonstrated (Jorm & Henderson, 1992; Teasdale & Russel, 1983), but in BD there was still no evidence of such occurrence. Though, this

is the first report of this phenomenon. The study of Rock and co-workers (2010) suggested that students with the common adolescent bipolar phenotype (selected with a screening tool targeting mood-elevation symptoms) show positive emotional processing biases. However, they investigated remitted adolescents with bipolar and depressive disorders in the same group.

Bipolar disorder with psychotic symptoms may characterize a distinct manifestation of disease that might be associated with other features. However, psychotic symptoms did not correlate with the severity of manic symptoms, not even with number of episodes of mania. These findings suggest that psychotic symptoms may be related to the nature of bipolar disorder because they are manifested in patients with disease of shorter duration. Patients with psychotic symptoms may represent an intermediate manifestation of bipolar disorder, which tends to be close to that of schizophrenia. Schizophrenia and bipolar disorder have been considered separate entities or different manifestations of a single underlying pathological process (Demjaha, Maccabe, & Murray, 2011). It has been suggested that BD and schizophrenia share some susceptibility genes that can cause a predisposition to psychosis in general (Murray et al., 2004). Individuals with a parental history of nonaffective psychosis have an increased risk of bipolar disorder and those with parental affective psychosis have an increased risk of schizophrenia (Van Snellenberg & de Candia, 2009). Given the dopamine dysregulation implicated in schizophrenia and BD, antipsychotic drugs are effective in both disorders. Therefore, mood stabilizers are useful in treating certain schizophrenic patients, and similarly, antidepressants have a role in treatment of negative symptoms in schizophrenia (Demjaha et al., 2011). BD patients showed

increased right lateral ventricle volume in a lesser extent than in schizophrenia, and the laterality difference was opposite to that in schizophrenia, where ventriculomegaly is bilateral but more prominent on the left (Hallahan et al., 2011). Schizophrenia is additionally associated with extensive gray matter reductions, and hippocampus and amygdala reductions. In bipolar disorder, no generalized gray matter reductions as well as hippocampus or amygdala have been consistently reported (Hallahan et al., 2011; Hajek et al., 2009). A study with schizophrenia and BD-I patients also showed impaired mnemonic ability measured by spatial span (temporary storage and retrieval of visuospatial information),(Badcock, Michiel, & Rock, 2005). The authors speculated that similar changes observed in psychotic BD patients have also begun in parietal cortex, as the earliest deficits observed in adolescent schizophrenia patients, but suggested more restricted disruption of circuitry, including ventromedial prefrontal cortex (Thompson, Vidal, Giedd, & Gochman, 2001).

Besides this finding, we also observed poorer performance in the logical memory test delayed recall – which evaluates episodic memory. BD patients, regardless presence of psychosis, presented lower scores than healthy participants, corroborating the findings of the literature on impaired information processing observed in BD (Quraishi, & Frangou, 2002; Glahn et al., 2007; Albus et al., 1996; McGrath, Scheldt, Welham, & Clair, 1997; Sweeney, Kmiec, & Kupfer, 2000; Sax et al., 1999; Clark & Goodwin, 2004). Acutely manic patients consistently presented impairment of executive function, particularly abstract concept formation, set shifting and planning (Quraishi & Frangou, 2002; Glahn et al., 2007) and verbal and spatial working-memory tasks (Sweeney et al., 2000). Manic patients have shown faster reaction times, but made more

errors, which resulted in impaired overall performance (Sax et al., 1999). This pattern of dysfunction in attention may be a consequence of increased dopaminergic and noradrenergic activity (Clark & Goodwin, 2004). Despite our findings did not show cognitive differences between patients with and without psychotic symptoms, most evidence of the literature showed such differences. Cognitive dysfunction in psychotic affective disorders has been reported predominantly in chronic patients during acute episodes (Quraishi & Frangou, 2002). A recent meta-analysis suggested that psychosis during the course of BD is associated with poorer cognitive performance in a number of cognitive domains (verbal memory, executive function, working memory and processing speed) (Bora et al., 2010).

Considering the two groups of patients, we have observed that the greater the number of mania episodes, the lower the score of the logical memory (immediate and delayed recall), the word span with indifferent tone, and the visual recognition span. This suggests relation with the disease chronicity for the performance in these tests rather than to a hallmark of the disease, different from the finding of the word span with positive tone. We also observed the longer the duration of the illness, the higher the number of mania episodes and intensity of manic symptoms measured by the Young Mania rating scale, showing an expected relationship between them. Age at onset, total number of mood episodes, number of manic episodes, number of depressive episodes, and number and duration of hospitalizations have been associated with the degree of neurocognitive impairment among patients with bipolar disorder (Robinson et al., 2006). The analysis of relationships between clinical and neuropsychological variables indicated that patients with a longer duration of the illness, more manic episodes and

hospitalizations showed more verbal memory impairment (Cavanagh, Van Beck, Muir, & Blackwood, 2002).

Our patients were accessed during the first week of hospitalization (acute mania episode), and were all evaluated with the same battery of tests. Despite the use of the cutoff 10 for the MMSE as exclusion criterion to avoid patients with severe cognitive impairment, the lowest score observed was 25, demonstrating absence of global cognitive impairment in this sample. Fifty five percent of the patients were using lithium carbonate, and 42% were with an antipsychotic. Of those who presented psychotic symptoms, 58% were under medication at the moment of hospitalization. Low treatment adherence among BD patients is frequent and is a common feature in patients with chronic and recurrent illness, and even more prevalent among psychiatric patients due to impaired rationality or insight as well as the complex nature of illness (Colom et al., 2000). Treatment non-adherence is associated with poor treatment outcomes in BD (Colom et al., 2000), including relapse, hospitalization, suicide and poor functional outcomes. In our sample, of the patients without psychotic symptoms, 83% were using at least one drug. Most received lithium (50%), with combinations of antipsychotic (50%) and/or anticonvulsant (50%). The beneficial as well as the adverse neurobehavioral effects of antipsychotic treatments have been demonstrated (Reilly et al., 2007). On the other hand, lithium has been suggested as a neuroprotective drug (Tsaltas, Kontis, Boulougouris, & Papadimitriou, 2009).

The mean duration of disease was 130 and 191 months in the psychotic and non-psychotic groups, respectively, suggesting at least a decade of disease in each group. Moreover, the mean rating of symptoms in the Young Mania rating scale was 29.5 and

27.08 in the psychotic and non-psychotic groups, respectively, demonstrating similar intensity in both groups.

The present results should be interpreted with some limitations in mind. First, the study is based on a convenience sample and, therefore, the generalizability of these findings should be tested in other populations. Second, the sample size of the patients without psychotic symptoms is small. However, we performed a small number of statistical analyses to avoid bias. On the other hand, the study strength was the evaluation of patients during the acute phase (first week of hospitalization) and applied standardized protocol reducing confounding effects.

In conclusion, psychotic and non-psychotic BD-I patients during mania phase showed mood congruence phenomenon in a verbal memory task with positive tone in relation to a healthy control group. Markedly evidence of mood congruence was found in the non psychotic group of patients suggesting a purer manifestation of the disease. However, further studies are necessary to analyze the differential nature of the specific markers of the BD in these two manifestations.

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Table 1. Demographic and medical data of the sample

Variables	**BD patients - with psychotic symptoms (N = 19)**	**BD patients - without psychotic symptoms (N = 12)**	**Healthy controls (N = 27)**	**P value**
Age (mean± SD)	37.26±13.80	47.00±8.64	39.19±11.77	.663
Education (mean± SD)	10.79±3.98	11.00±3.08	10.19±3.38	.806
Sex Female (N,%)	12 (63.2%)	6 (50%)	20 (74.1%)	.431
Mini Mental State Examination (mean ± SD)	27.00±1.56	28.4±1.38	28.3±1.82	.644
Young Mania Rating scale (mean± SD)	29.53±3.28	27.08±3.40	0.81±1.07	.000
Number of episodes	4.80±4.89	7.08±4.68	--	.097
Disease duration (months)	130.21± 32.51	190.91±85.94	--	.038

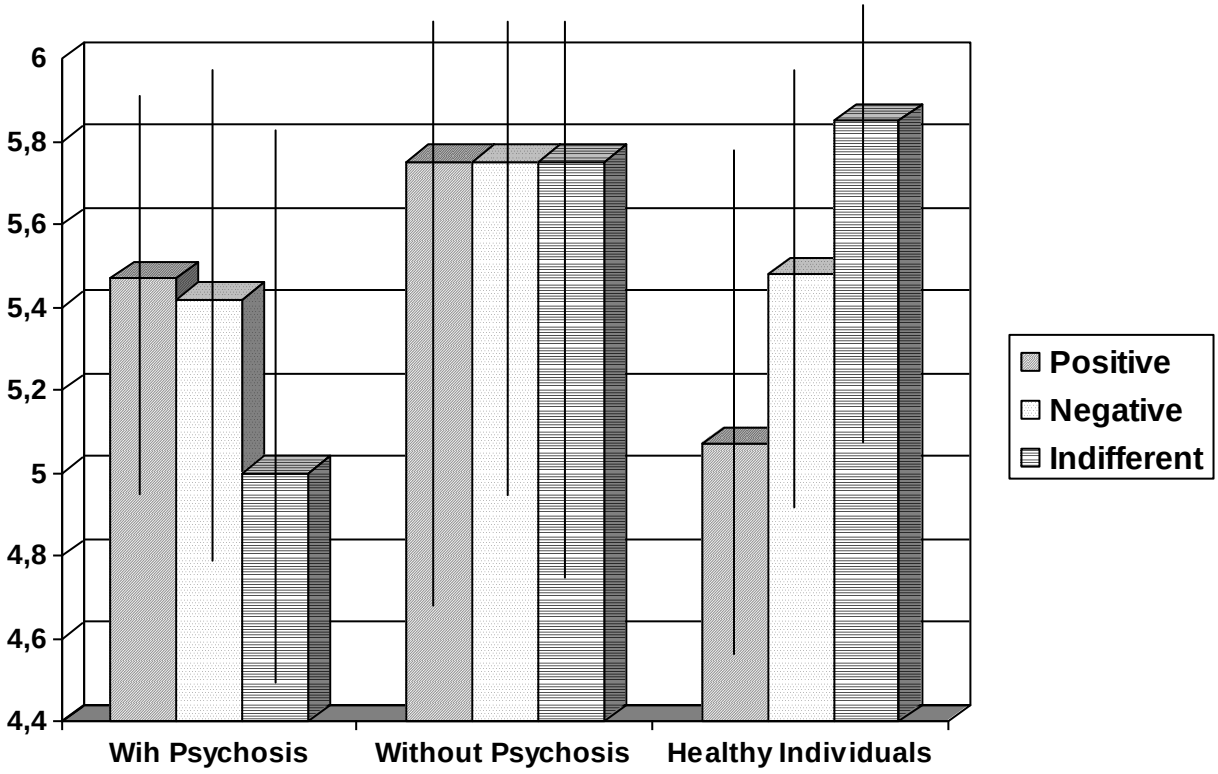

Figure 1. Mean and standard deviation of the Word Span in the studied groups. The three groups were significantly different in the positive words. The group without psychotic symptoms presented higher scores (p = 0.042; Bonferroni post-hoc test).

Table 2. Cognitive performance of the studied groups

Variables	**BD patients - with psychotic symptoms (N = 19)**	**BD patients - without psychotic symptoms (N = 12)**	**Healthy Controls (N = 27)**	**P value**
Logical memory (mean ± SD)				
Immediate Recall	6.63±1.34	6.58±1.51	7.48±1.50	.275
Delayed Recall	6.05±1.43a	6.08±1.78b	7.19±1.44c	.069
Digit span (mean ± SD)	6.11±2.11	6.00±2.86	5.78±2.01	.900
Visuospatial recognition span (mean ± SD)	7.32±2.45	8.50±3.37	9.63±3.30	.183

a,b≠c: *Bonferroni* post-hoc test (p = 0.045)

Table 3. Coefficient of correlation (rho) and p value of number of episodes, cognitive tests and the Young scale for the whole BD patient sample.

Tests	**Number of Episodes**	**Young Mania Rating scale**
Young scale	0.77 (p= .000)	--
Duration of disease	0.96 (p= .000)	0.74 (p = .000)
Word span Indifferent	-0.28 (p= .033)	-0.24 (p = .074)
Logical Memory immediate	-0.27 (p= .043)	-0.31 (p = .017)
Logical Memory delayed	-0.32 (p= .016)	-0.34 (p = .008)
Visual recognition span	-0.32 (p= .015)	-0.44 (p = .001)

PARTE III

DISCUSSÃO

Esta tese foi realizada para analisar o desempenho em tarefas de memória com e sem conteúdo afetivo de pacientes com Transtorno Bipolar, com mania agudamente sintomática, com e sem sintomas psicóticos. O objetivo foi compará-los a pacientes com TDM agudamente deprimidos e a um grupo de indivíduos saudáveis.

No primeiro estudo, avaliamos os desempenhos nos testes de memória e verificamos o fenômeno de congruência do humor. Pacientes com TB tipo I apresentaram escores mais altos no *span* de palavras com conteúdo positivo do que os pacientes TDM e controles saudáveis. Esse achado sugere a hipótese da congruência de humor na memória entre pacientes com TB. Evidência prévia semelhante ainda não havia sido demonstrada para os estados alterados do humor e do processamento da memória durante os episódios de mania no TB (dependência de estado ou congruência do humor).

O desempenho no *span* de palavras com conteúdo positivo foi afetado pelo número de episódios afetivos e pela duração da doença. Então, podemos supor que a tarefa foi influenciada pela gravidade do Transtorno Bipolar. Sugerimos que haja uma interconexão entre processamento de memória com viés positivo e os sintomas da doença (i.e., mania) no TB que é dependente da gravidade da doença.

No nosso estudo, nenhum efeito de congruência do humor para itens negativos foi encontrado nos pacientes com TDM. Não houve influência do número de episódios

ou duração da doença para este grupo. Pacientes com TDM apresentaram pior desempenho de memória do que os participantes saudáveis nos seguintes testes: memória lógica evocação imediata e tardia, *span* de dígitos e *span* de reconhecimento visuoespacial. Esses pacientes também apresentaram pior desempenho do que os pacientes com TB no *span* de dígitos e *span* de palavras com tom positivo. Além de testes de memória, os pacientes com TDM também apresentaram menores escores no MEEM, corroborando os dados anteriores sobre a deterioração cognitiva em pacientes com depressão (Airaksinen et al., 2004; Burt et al., 1995). Está bem estabelecido que os transtornos depressivos estão associados à disfunção cognitiva, distúrbios de memória, especialmente da memória episódica (Austin et al., 2001; Airaksinen et al., 2006).

Observamos também outros déficits de memória nos pacientes bipolares (teste de memória lógica e *span* de reconhecimento visuoespacial) em relação aos participantes saudáveis. Há atualmente evidências suficientes de que pacientes com TB apresentam comprometimento cognitivo nas fases agudas da doença as quais persistem durante os períodos interepisódios, mesmo quando o humor é eutímico (Robinson et al., 2006; Martínez-Arán et al., 2004a). Processamento de atenção, função executiv e memória verbal são as funções cognitivas geralmente comprometidas na doença bipolar (Ferrier et al., 2004).

No segundo estudo, avaliamos o desempenho de memória nos pacientes com TB tipo I internados, durante fase aguda com sintomas de mania com e sem sintomas psicóticos, com objetivo de testar a congruência de humor. Trabalhamos com a hipótese de que sintomas psicóticos em pacientes com TB poderiam causar pior desempenho da memória/atenção e impediria o fenômeno de congruência de

humor. Observamos que os pacientes sem sintomas psicóticos apresentaram melhor desempenho, enquanto os controles saudáveis apresentaram pior desempenho na tarefa de memória com conteúdo afetivo positivo – *span* de palavras. Esse achado sugere a existência do fenômeno de congruência de humor em pacientes bipolares sintomáticos de uma maneira progressiva na qual os pacientes sem psicose mostraram maior congruência e aqueles com psicose o menor efeito. Uma forma de explicar essa observação seria a de considerar que o primeiro grupo representa a mais pura manifestação do transtorno bipolar.

O fenômeno de congruência de humor na depressão já foi demonstrado (Jorm et al., 1992; Teasdale et al.,1983), mas no TB não havia ainda nenhuma evidência de tal ocorrência. O transtorno bipolar com sintomas psicóticos pode caracterizar uma distinta manifestação da doença que pode estar associada a outras características. No entanto, os sintomas psicóticos não se correlacionaram com a gravidade dos sintomas maníacos, nem mesmo com o número de episódios de mania. Esses dados sugerem que os sintomas psicóticos podem estar relacionados com a natureza da doença bipolar, porque eles se manifestam em pacientes com doença de duração mais curta. Os pacientes com sintomas psicóticos podem representar uma manifestação intermediária do distúrbio bipolar, que tende a ser próxima da esquizofrenia.

Além dessa constatação, também observamos pior desempenho no teste de memória lógica evocação tardia – que avalia a memória episódica. Pacientes com transtorno bipolar, independentemente de presença de psicose, apresentaram escores mais baixos do que os participantes saudáveis, corroborando os achados da literatura sobre o déficit de processamento de informação observado no TB (Quraishi et al., 2002;

Glahn et al., 2007; Albus et al., 1996; McGrath et al.,1997; Sweeney et al., 2000; Clark et al., 2004).

Em conclusão, nós encontramos o efeito de congruência do humor para o *span* de palavras com conteúdo afetivo positivo entre pacientes com transtorno bipolar, mas não observamos o mesmo entre os pacientes com TDM para os itens negativos. Pacientes com TDM apresentaram mais déficits de memória do que os pacientes com TB, enquanto os pacientes com TB também apresentaram déficits de memória em relação aos participantes saudáveis.

Os pacientes com TB psicóticos e não psicóticos, durante fase maníaca, mostraram fenômeno de congruência de humor em uma tarefa de memória verbal com tom positivo em relação a um grupo-controle saudável. Evidência nítida de congruência de humor foi encontrada no grupo não psicótico dos pacientes sugerindo uma manifestação mais pura da doença. No entanto, mais estudos são necessários para analisar a natureza diferencial dos marcadores específicos da BD nessas duas manifestações.

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6. ANEXOS

Testes aplicados

1. MINIEXAME DO ESTADO MENTAL

1. ORIENTAÇÃO TEMPORAL (0-5):
Ano, estação, mês, dia, dia da semana ..... ( )
2. ORIENTAÇÃO ESPACIAL (0-5):
Estado, rua, cidade, local, andar ..... ( )
3. REGISTRO (0-3):
Nomear: pente, rua, caneta ..... ( )
4. CÁLCULO (subtrair 7 a partir de 100) (0-5):
100 - 93 - 86 - 79 - 72 – 65 ..... ( )
5. EVOCAÇÃO (0-3):
Três pal. anteriores: pente, rua, azul ..... ( )
6. LINGUAGEM-1 (0-2):
Nomear um relógio e uma caneta ..... ( )
7. LINGUAGEM-2 (0-1):
REPETIR: NEM AQUI, NEM ALI, NEM LÁ ..... ( )
8.LINGUAGEM-3 (0-3):
Siga o comando: “Pegue o papel com a mão direita, dobre-o ao meio,
e coloque-o em cima da mesa” ..... ( )
9. LINGUAGEM-4 (0-1):
Ler e obedecer: FECHE OS OLHOS ..... ( )
10.LINGUAGEM-5 (0-1)
Escreva uma frase completa ..... ( )
11. LINGUAGEM-6 (0-1)
Copiar o desenho ..... ( )

TOTAL: .....

2. MEMÓRIA LÓGICA (Pequena história)

	Imediato	Recente (10')
1. Ana é uma empregada doméstica	( )	( )
2. tem 23 anos	( )	( )
3. e 3 filhos	( )	( )
4. há 30 dias	( )	( )
5. foi despedida do emprego	( )	( )
6. seu aluguel está atrasado 2 meses	( )	( )
7. e Ana não consegue outro emprego	( )	( )
8. alguns amigos	( )	( )
9. fizeram uma rifa de uma caixa de bombons	( )	( )
10. para angariar fundos para Ana.	( )	( )
TOTAL	.....	.....

3. *SPAN* DE PALAVRAS

POSITIVA	**NEUTRA**	**NEGATIVA**
Amor	Homem	Morte
Férias	Carro	Acidente
Sol	Flor	Assalto
Alegria	Livro	Doença
Festa	Casa	Fome
Vida	Panela	Dor
Saúde	Rua	Guerra
Juventude	Jardim	Incêndio
Liberdade	Cadeira	Violência
Música	Estrela	Miséria

TOTAL

4. *SPAN* DE DÍGITOS

Siga até errar duas sequências da mesma dupla.

5 8 2
6 9 4

6 3 9 4

7 2 8 6

4 2 7 3 1
7 5 8 3 6

6 1 9 4 7 3
3 9 2 4 8 7

5 9 1 7 4 2 8

4 1 7 9 3 8 6

5 8 1 9 2 6 4 7
3 8 2 9 5 1 7 4

2 7 5 8 6 2 5 8 4
7 1 3 9 4 2 5 6 8

Total de seq. corretas:

5. SPAN DE RECONHECIMENTO VISUAL

8 24 12 5 19 28 10 01 15 23 26 3 17 13

7. CONSENTIMENTO INFORMADO

AUTORIZAÇÃO PARA PARTICIPAR DE UM PROJETO DE PESQUISA

Nome do estudo: **ESTUDO DO DESEMPENHO DE MEMÓRIA COM E SEM CONTEÚDO AFETIVO DE PACIENTES COM TRANSTORNOS DO HUMOR**

Instituição: Hospital de Clínicas de Porto Alegre (HCPA)

Pesquisadores responsáveis: Vera B. D. Santos, Márcia L. F. Chaves

Telefones para contato: Enfa. Vera Beatriz Delgado dos Santos: 33598710/33598711

Nome do participante:_____

1. OBJETIVO DESTE ESTUDO

Atualmente, os problemas mentais com depressão ou com 'mania' (quando uma pessoa fica mais 'alegre' do que seria esperado e muito 'ativada') afetam aproximadamente de 1% a 3% da população mundial, sendo um problema crônico que interfere com as relações afetivas e familiares. Existem informações de que esses problemas afetam a memória desses pacientes de formas variadas, especialmente se o que tiver de ser aprendido e lembrado contém afeto (uma boa lembrança, uma estória alegre, uma imagem agradável etc.). Devido à importância desses tipos de problemas, vamos estudar como pessoas com depressão e com mania executam testes de memória com e sem conteúdo afetivo.

2. EXPLICAÇÃO DOS PROCEDIMENTOS

O(A) Sr(a). irá responder perguntas sobre sua pessoa (dados de identificação como idade, escolaridade etc.) e alguns testes de memória com palavras, algumas estórias, entre outros.

3. POSSÍVEIS RISCOS E DESCONFORTOS

O possível desconforto é a aplicação das perguntas e dos testes de memória e o tempo dispensado na entrevista.

4. DIREITO DE DESISTÊNCIA

O(A) Senhor(a) pode desistir de participar a qualquer momento, com garantia de que não sofrerá qualquer tipo de prejuízo em função de sua decisão.

5. SIGILO

Todas as informações obtidas neste estudo poderão ser publicadas com finalidade científica, preservando-se o completo anonimato dos participantes.

6. CONSENTIMENTO

Declaro ter lido – ou me foi lido – as informações acima antes de assinar este formulário. Foi-me dada ampla oportunidade de fazer perguntas, esclarecendo plenamente minhas dúvidas. Por este instrumento, tomo parte, voluntariamente, do presente estudo.

Porto Alegre, _____ de _____ de _____.

_____

Assinatura do paciente

_____

Assinatura da testemunha

_____

Assinatura do pesquisador responsável