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EXPERIÊNCIAS TRAUMÁTICAS E O TRANSTORNO BIPOLAR:

ASPECTOS NEUROBIOLÓGICOS, COGNITIVOS E CLÍNICOS

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Tese de Doutorado

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À memória de Lúcia Kauer, minha avó

À minha mãe, Maria Luiza, e ao meu pai, Vicente,

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Parte I

RESUMO

Experiências Traumáticas e o Transtorno Bipolar:
Aspectos Neurobiológicos, Cognitivos e Clínicos

Objetivo Geral: O objetivo geral desta tese é investigar os aspectos clínicos, neurobiológicos e cognitivos do transtorno bipolar associados à comorbidade ansiosa, e, mais especificamente, às experiências traumáticas.

Métodos: Pacientes ambulatoriais com diagnóstico de Transtorno Bipolar I ou II de acordo com DSM-IV foram recrutados para todos as estudos. No primeiro estudo transversal, 162 pacientes preencheram a escala WHOQOL-BREF, que avalia qualidade de vida. Estes foram divididos de acordo com a presença ou ausência de comorbidade com transtorno de ansiedade, para fins de comparação em relação à qualidade de vida e a variáveis clínicas. Para o segundo estudo, 163 pacientes tiveram sangue coletado para medida de BDNF sérico. Estes pacientes foram divididos de acordo com a presença ou ausência de experiência traumática, conforme os critérios A1 e A2 do DSM-IV, para fins de comparação em relação aos níveis séricos de BDNF e variáveis clínicas. Finalmente, para avaliar a memória emocional, recrutamos 20 pacientes eutímicos e 20 controles pareados por sexo, idade e anos de estudo. Os participantes foram designados a assistir a uma história de conteúdo emocional ou neutro. Uma semana depois um teste de memória foi aplicado.

Resultados: A presença de comorbidade ansiosa no TB está associada a escores mais baixos de qualidade de vida em todos os domínios da WHOQOL-BREF. A piora na qualidade de vida se mantém estatísticamente significativa no domínio psicológico, mesmo depois de controlar para o nível de depressão, como fator de confusão. A presença de comorbidade com transtorno de ansiedade no TB também se mostrou associada ao abuso e à dependência de álcool, à ciclagem rápida, à psicose, ao número de tentativas de suicídio e a um pior funcionamento. A presença de experiências traumáticas no TB está associada ao uso e ao abuso de álcool, à comorbidade com transtornos de ansiedade e a níveis séricos de BDNF mais baixos, em comparação com os pacientes sem eventos traumáticos. Em relação à função da amígdala, os controles normais, conforme o esperado, apresentaram melhor memória para a informação com impacto emocional. No entanto, esse mecanismo de aumento da memória para o conteúdo emocional em relação ao neutro, não foi observado no TB. Além disso, os pacientes bipolares não perceberam apropriadamente o impacto emocional da informação. De forma geral, os pacientes com TB tiveram um pior desempenho na evocação da memória, em comparação com os controles.

Discussão: Os resultados indicam que a presença tanto de comorbidade com transtorno de ansiedade quanto de experiências traumáticas no TB estão associadas à maior gravidade das variáveis clínicas. Isso pode ser explicado, em parte, pelos níveis reduzidos de BDNF associados a experiências traumáticas, e em parte, pela disfunção da amígdala, e consequentemente do processamento das emoções, observada no TB.

ABSTRACT

Traumatic Experiences and Bipolar Disorder:
Neurobiological, Cognitive and Clinical Aspects

Main Objective: The aim of this thesis is to examine the clinical, neurobiological and cognitive aspects of bipolar disorder when associated with anxiety comorbidity and, more specifically, with traumatic experiences.

Methods: Bipolar Disorder outpatients type I and II, as diagnosed by DSM-IV criteria, were recruited for all studies. In the first study, 162 patients were assessed using the WHOQOL-BREF, as quality of life measure. Subjects with and without anxiety comorbidity were compared in regards of quality of life scores and clinical features. In the second study, 163 patients had blood withdrawn for BDNF measure. The reported TE was assessed using DSM-IV A1 and A2 criteria. Subjects were divided in two groups according to presence or absence of lifetime TE. The levels of BDNF, comorbidity and other clinical features were compared between groups. Finally, in order to evaluate emotional memory, 20 euthymic bipolar patients and 20 sex, age and schooling years matched controls were recruited. Participants were shown a slide show of an emotionally neutral story, or a closely matched emotionally arousing story. One week later participants were assessed on a memory-recall test.

Results: Anxiety comorbidity in BD patients was associated with lower scores in all domains of quality of life. The impact of anxiety comorbidity on the psychological domain of the WHOQOL-BREF was kept, even when the current level of depression was added to the model as a confounding factor. Current anxiety comorbidity was also associated with lifetime alcohol abuse and dependence, rapid cycling, lifetime psychosis, number of suicide attempts, and a lower score in a functioning measure. Our results indicated that bipolar patients with a history of TE have alcohol abuse/dependence, anxiety comorbidity, and lower levels of serum BDNF compared with those without a history of TE. The results for emotional memory showed that, as expected, healthy controls presented a clear pattern of increased memory for the emotional content. In contrast, bipolar patients had no enhancement of memory for the emotional content as they recalled both neutral and emotional version in the same manner. The self report of emotional impact of emotional condition was significantly different from neutral condition in controls but not in patients. Bipolar patients also presented a lower overall recall rate than controls.

Discussion: The results suggest that either anxiety comorbidity or traumatic experiences in bipolar disorder are associated with a worse clinical presentation. Further, the results suggest that this may be in part explained by lower BDNF levels associated with traumatic events and in part by amygdala dysfunction and, consequently, impaired emotional memory circuitry observed in BD patients.

Lista de Abreviaturas

BD = do inglês *Bipolar Disorder*; transtorno bipolar.

BDNF= do inglês *Brain Derived Neurotrophic Factor*; fator neurotrófico derivado do cérebro.

CREB = do inglês *Cyclic AMP Response Element-Binding protein*; proteína ligadora ao elemento responsivo a AMPc.

CRH = do inglês *Corticotrophin Releasing Hormon*; hormônio Liberador de corticotrofinas.

DSM-IV = do inglês *Diagnostic and Statistical manual of Mental disorders*; manual diagnóstico e estatístico dos transtornos mentais.

GDNF = do inglês, *Glial cell line-Derived Neurotrophic Factor*; fator neurotrófico derivado das células gliais.

MAPK =do inglês, *Mitogen-Activated Protein Kinase;* proteína cinase ativada por mitógenos.

PI-3K = do inglês *Phosphatidylinositol-3 Kinase;* fosfatidilinisitol-3 cinase

PKC = do inglês *Protein Kinase C*; proteína cinase C.

PTSD = do inglês Posttraumatic Stress Disorder; transtorno de estresse pós-traumático.

TB = Transtorno Bipolar

TE = do inglês *Traumatic Event;* evento traumático.

TEPT = Transtorno de Estresse Pós-Traumático

TrkB = do Inglês *Tyrosine kinase-containing receptor B*; receptor com atividade tirosina cinase B.

WHOQOL-BREF= do inglês *World Health Organization Quality of life Instrument – Abbreviated version*; instrumento de qualidade de vida da organização mundial da saúde – versão abreviada.

INTRODUÇÃO

O transtorno bipolar afeta aproximadamente 1% da população (Belmaker, 2004), podendo chegar a 6,4% nas classificações que incluem formas atenuadas do transtorno (Judd et al., 2002; Katzow, Hsu, & Nassir Ghaemi, 2003). O TB é um transtorno do humor altamente incapacitante e com altas taxas de comorbidades psiquiátricas, as quais chegam a mais de 60% ao longo da vida (Sasson et al., 2003). Considerando os primeiros 288 pacientes bipolares incluídos no estudo da *Stanley Foundation Bipolar Network*, 65% apresentavam comorbidade psiquiátrica ao longo da vida, sendo que 42% apresentavam dois ou mais diagnósticos e 24% apresentavam três ou mais comorbidades (McElroy et al., 2001). Dentre as comorbidades, chama a atenção a presença de transtornos de ansiedade em pacientes com TB. Em pesquisas clínicas 24,0% a 79,2% dos bipolares apresentam pelo menos um transtorno de ansiedade ao longo da vida (McElroy et al., 2001); destes, 47% têm diagnóstico de dois ou mais transtornos (Henry et al., 2003b). Estudos epidemiológicos, como o *National Comorbidity Survey*, relatam que 92.9% dos pacientes bipolares tipo I apresentavam pelo menos um transtorno de ansiedade ao longo da vida, em comparação com 24.9% na população em geral (Kessler et al., 1997). A presença de transtornos de ansiedade em bipolares determina um subgrupo de pacientes com maior freqüência de estados mistos (McElroy et al., 1995), gravidade aumentada e instabilidade de sintomas, além de risco mais elevado de associação com transtornos por uso de substâncias psicoativas (Otto et al, 2006a) e com tentativas de suicídio (Simon et al., 2006). A

importância clínica do tema, despertou o interesse para investigação da comorbidade com transtornos de ansiedade no transtorno bipolar, sendo o passo inicial desta tese.

Embora estudos tenham demonstrado que a comorbidade com transtornos ansiosos está associada à maior gravidade de sintomas no TB, pouco foi investigado em relação aos desfechos funcionais, como qualidade de vida. Classicamente os ensaios clínicos apenas avaliavam a redução de sintomas; conceitos como qualidade de vida e funcionamento são recentes, adquirindo importância por serem os reais objetivos de um tramento. Qualidade de vida, segundo a Organização Mundial da Saúde, é um conceito amplo, que considera " a percepção do indivíduo da sua posição na vida, dentro do contexto cultural e sistema de valores em que ele vive, e em relação ao seus objetivos, expectativas, parâmetros e relações sociais" (The WHOQOL group.1998a). Ao contrário de medidas de funcionamento e de sintomas, que consideram os dados objetivos, as medidas de qualidade de vida consideram a experiência subjetiva de estar doente. É provável que a ansiedade tenha um impacto negativo no TB, acarretando mais problemas nas relações sociais e funcionamento, mas a magnitude desse impacto para o indivíduo pode ser difícil de avaliar. Medidas de qualidade de vida podem ser um instrumento relevante nessa avaliação. Evidências sugerem que o TB está associado à pior qualidade de vida, especialmente durante episódios depressivos (Gazalle et al., 2006). No entanto, pouco se sabe em relação ao impacto da comorbidade com transtornos de ansiedade na qualidade de vida de pacientes bipolares. Apenas um estudo recente demonstrou que pacientes com TB e comorbidade ansiosa apresentam pior qualidade de vida em relação àqueles sem a comorbidade (Otto et al., 2006a). Contudo, este e outros estudos utilizam escalas para medida de qualidade de vida que foram desenvolvidas para problemas clínicos,

apresentando resultados restritos à qualidade de vida relacionada ao estado de saúde física. A escala WHOQOL-BREF (The WHOQOL group.1998b), que inclui o conceito mais amplo de qualidade de vida, foi validada em português e demonstrou boa confiabilidade, consistência interna e validade do constructo (Fleck et al. 2000). Esta escala não foi avaliada em pacientes bipolares com comorbidade ansiosa.

Ao estudar os transtornos ansiosos em pacientes bipolares, destaca-se a alta prevalência do transtorno do estresse-pós traumático. Estudos demonstram altas taxas de prevalência de TEPT em amostras de pacientes bipolares, variando de 39% em amostras da comunidade (Henry et al., 2003b) a 7% em amostras clínicas (Perugi, Toni, & Akiskal, 1999). Indivíduos com TEPT também têm risco aumentado de apresentar TB, além de outras comorbidades de ansiedade (Vieira & Gauer, 2003). Ainda mais intrigante é a elevada taxa de experiências traumáticas entre pacientes bipolares, ainda que não desenvolvam o transtorno de estresse pós-traumático. Mueser et al. avaliaram a prevalência de TEPT em 275 pacientes com TB e esquizofrenia, e encontraram 43% de TEPT, chamando a atenção para o fato de que 98% apresentavam história de evento traumático (Mueser et al., 1998). A elevada prevalência motivou o estudo mais específico das experiências traumáticas no TB, uma vez investigados os transtornos ansiosos como um grupo. Pacientes com história de trauma tendem a ter sintomas mais graves, maior taxa de uso de substâncias psicoativas e maior número de hospitalizações (Leverich et al., 2002). Eventos de vida negativos têm sido associados com desenvolvimento do primeiro episódio do TB, e parecem favorecer recaídas, ainda que poucos estudos investiguem a associação (Johnson & Miller, 1997). Indivíduos que apresentaram eventos de vida negativos graves, avaliados prospectivamente, levaram três vezes mais tempo para obter

melhora dos sintomas (Johnson & Miller, 1997). A exposição ao trauma pode desencadear um sofrimento psíquico e uma resposta fisiológica ao estresse, que, embora não preencham os critérios para TEPT, têm repercussão clínica. Esta última foi avaliada por alguns estudos, os quais demonstraram que os pacientes com história de abuso na infância apresentam início precoce do TB, mais comorbidades associadas, e maior taxa de tentativas de suicídio (Leverich & Post, 2006). Outro estudo recente mostrou que quase metade dos pacientes bipolares avaliados relataram história de abuso físico ou sexual na infância, e estes apresentavam mais transtorno de abuso de substâncias, ciclagem rápida e tentativas de suicídio (Goldberg & Garno, 2005).

Ainda que as experiências traumáticas ocorram com freqüência em pacientes com TB, e tenham repercussões clínicas, a fisiopatologia dessa associação não é conhecida. As neurotrofinas, em especial o BDNF, parecem estar implicados na base fisiopatológica de diversas doenças neurodegenerativas e psiquiátricas. As características do BDNF o tornam um potencial mediador neurobiológico dos efeitos das experiências traumáticas. Evidências clínicas e pré-clínicas indicam que o BDNF desempenha papel fundamental na plasticidade neuronal e memória. O BDNF parece mediar os principais processos dependentes de estímulo externo, i.e. aprendizado, experiências, memórias. Ainda, a exposição ao estresse diminui os níveis de BDNF em modelos animais (Murakami et al., 2005). Por sua vez, os antidepressivos e os estabilizadores do humor são capazes de aumentar os níveis séricos de BDNF (Frey et al., 2006). Em pacientes com TB, os níveis séricos de BDNF estão diminuídos na depressão e na mania, correlacionando-se inversamente com a gravidade dos sintomas (Cunha et al., 2006). O polimorfismo para o gene do BDNF val66met, que produz uma substituição de uma valina por metionina na proteína proBDNF no códon

66, causando a redução da secreção de BDNF pela célula, tem sido associado ao desenvolvimento do TB (Neves-Pereira et al., 2002), embora os achados sejam controversos (Green et al., 2006; Kunugi et al., 2004). Curiosamente, ainda que dados de estudos com modelos animais de estresse indiquem alterações nos níveis séricos de BDNF, estes não foram avaliados em pacientes expostos a situações traumáticas ou com TEPT. Evidências indiretas, como o volume hipocampal reduzido em pacientes expostos eventos traumáticos precoces (Bremner et al., 2003; Stein et al., 1997) e o fato do polimorfismo do BDNF - val66met – estar associado à redução do volume do hipocampo em controles saudáveis (Szeszko et al., 2005), indicam uma possível relação entre trauma e BDNF. É possível que a exposição ao trauma desencadeie uma resposta neurobiológica que, em parte, altere os níveis de BDNF, culminando em uma apresentação clínica mais grave do TB. De fato, é sabido que o decréscimo nos níveis de BDNF em modelos animais correlaciona-se com elevação dos níveis de cortisol (Smith et al, 1995) e que alterações das corticotrofinas também são encontradas em pacientes com transtorno do estresse pós-traumático (Duval et al., 2004). Um estudo recente mostrou que pacientes deprimidos portadores do polimorfismo do BDNF têm maior atividade do eixo hipotálamo-hipófise-adrenal durante o teste de dexametasona-CRH (Schule et al., 2006). Em conjunto, essas evidências indicam que o BDNF é um possível mediador dos efeitos ambientais na psicopatologia.

Além das alterações neuroquímicas, a associação entre experiências traumáticas e TB também está sob influência do funcionamento dos circuítos envolvidos no processamento das emoções. É possível que o impacto e alta prevalência de eventos traumático no TB se deva a alterações na memória emocional e em estruturas relacionadas, como a amígdala. Há diversas razões para acreditar que o

processamento das emoções esteja alterado no transtorno bipolar. Muitos dos sintomas de humor presentes no transtorno bipolar envolvem vias comuns ao processamento emocional (Phillips, 2003). Há estudos sugerindo que a relação entre mania e depressão se deva mais ao aumento da intensidade das emoções, do que propriamente a emoções opostas, explicando de outra forma os estados mistos (Henry et al., 2003). O próprio BDNF, que parece estar alterado no TB, desempenha um papel importante na formação da memória de longa duração na amígdala e hipocampo (Shaltiel, Chen, & Manji, 2006). Estruturas sabidamente importantes para o processamento das emoções (Cahill, 1999), como córtex prefrontal, cingulado anterior, amígdala e estriado ventral mostraram alteração funcional em diferentes estudos de imagem em pacientes bipolares (Phillips, Drevets, Rauch, & Lane, 2003). Através de estudos pós-mortem, foi demonstrado no TB redução neuronal e das sinapses na região CA1 e CA2 do hipocampo, córtex cingulado e núcleo acumbens (Carlson et al., 2006). Em particular, a amígdala desempenha papel fundamental na modulação da memória emocional, atenção e percepção. O efeito de hormônios relacionados ao estresse, como epinefrina e glicocorticóides, sobre a memória parece ser mediado por processos que envolvem a amígdala (Cahill, Prins, Weber, & McGaugh, 1994). No TB, estudos de imagem estrutural mostraram volume aumentado da amígdala (Altshuler et al., 1998; Campbell & MacQueen, 2006), embora os achados não sejam universais. Aumento anormal no volume da amígdala foi detectado em adolescentes bipolares (BK Chen et al., 2004). Estudos de imagem funcional em bipolares constataram hiperativação do cingulado, amígdala e tálamo durante episódios de humor (Blumberg et al., 2000; CH Chen et al., 2006; Malhi et al., 2004).

Sabemos que o TB está associado a importante prejuízo cognitivo, o qual é mais acentuado durante episódios de humor, mas parece persistir durante a eutimia (Martinez-Aran et al., 2004b). Esse déficit cognitivo tem sido associado a um pior funcionamento social e ocupacional (Martinez-Aran et al., 2004a). As principais disfunções relatadas incluem prejuízo da função executiva e memória declarativa (Torres, Boudreau, & Yatham, 2007). No entanto, diferentes aspectos da função cognitiva, como a memória emocional, não foram avaliados no TB. A função da amígdala foi avaliada no TB apenas em tarefas de reconhecimento de faces. Nesses estudos, os pacientes bipolares, de uma forma geral, apresentaram maior dificuldade em identificar apropriadamente expressões faciais do que os controles saudáveis (Harmer, Grayson, & Goodwin, 2002; Lawrence et al., 2004). Além disso, bipolares eutímicos apresentaram hiperativação de regiões como amígdala, em contraste com a atividade diminuída no córtex pré-frontal em resposta a expressões faciais de medo (Yurgelun-Todd et al., 2000). No entanto, o estudo de pacientes com lesões na amígdala sugerem que o reconhecimento de faces e a memória emocional utilizam neurocircuítos diferentes (Brierley et al., 2004). O reconhecimento de faces parece não ser totalmente dependente da função da amígdala (Hamann & Adolphs, 1999), enquanto o aumento da memória para informação de conteúdo emocional parece ser dependente da integridade da função da amígdala (Cahill et al., 1994; Cahill, Babinsky, Markowitsch, & McGaugh, 1995). Isto foi demonstrado em estudos que utilizaram tarefas que especificamente comparavam a memória para dados emocionais com a memória para dados neutros (Cahill & McGaugh, 1995). Essas tarefas não foram avaliadas em pacientes bipolares.

Em função do exposto, parece-nos de grande interesse investigar o impacto dos transtornos de ansiedade no transtorno bipolar e, mais especificamente das experiências traumáticas. A avaliação de alterações neuroquímicas, como as neurotrofinas, e de alterações neurofuncionais, como a função da amígdala, ampliam o entendimento dessa complexa associação entre fatores ambientais e o TB, através da investigação em diferentes níveis da neurobiologia.

OBJETIVOS

O objetivo geral desta tese é investigar os aspectos clínicos, neurobiológicos e cognitivos do transtorno bipolar associado à comorbidade ansiosa, e mais especificamente, às experiências traumáticas.

Os objetivos específicos são:

1. Avaliar o impacto da comorbidade ansiosa na qualidade de vida e na gravidade da apresentação clínica de pacientes bipolares. Comparar pacientes bipolares com comorbidade de ansiedade com aqueles sem a mesma em relação a escores de qualidade de vida e variáveis de gravidade clínica.
2. Avaliar o impacto de experiências traumáticas na gravidade da apresentação clínica do transtorno bipolar. Comparar pacientes bipolares com experiências traumáticas com aqueles sem história de trauma em relação às variáveis de gravidade clínica.
3. Examinar a associação de experiências traumáticas com a redução nos níveis séricos de BDNF no transtorno bipolar. Comparar os níveis séricos de BDNF entre pacientes bipolares com e sem experiências traumáticas.
4. Examinar a memória emocional e função da amígdala em pacientes bipolares. Comparar o desempenho de pacientes bipolares com controles normais em uma tarefa dependente da amígdala, que avalia memória emocional.

Parte II

Capítulo I

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Anxiety Comorbidity and Quality of Life in Bipolar Disorder Patients

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Objective: To assess the impact of anxiety comorbidity on the quality of life of patients with bipolar disorder (BD).

Methods: We undertook a cross-sectional survey of 162 BD outpatients interviewed with the Structured Clinical Interview for DSM-IV. The primary outcome measure was quality of life, assessed with the 26-item WHO Quality of Life Instrument (WHOQOL-BREF).

Results: Anxiety comorbidity in BD patients was associated with lower scores in all domains of quality of life. The impact of anxiety comorbidity on the psychological domain of the WHOQOL-BREF was kept, even when the current level of depression was added to the model as a confounding factor. Current anxiety comorbidity was also associated with lifetime alcohol abuse and dependence, rapid cycling, lifetime psychosis, number of suicide attempts, and a lower score in the Global Assessment of Functioning measure.

Conclusion: Our findings suggest that anxiety comorbidity in BD patients is related to lower quality of life, particularly on the psychological domain. BD–anxiety comorbidity may be associated with such markers of illness severity as number of suicide attempts, rapid cycling, lifetime alcohol abuse, and psychosis. The recognition and treatment of anxiety comorbidity may help patients with BD to relieve their psychological pain and improve their overall quality of life.

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Information on funding and support and author affiliations appears at the end of the article.

Clinical Implications

- Anxiety comorbidity is highly prevalent among BD patients, with a great impact on quality of life, and warrants routine clinical assessment and better specific management.
- The comprehension of a relation between BD–anxiety comorbidity and quality of life suggests the importance of routine screening for other associated factors, such as suicide risk, rapid cycling, and alcohol abuse.
- Quality of life has increasingly become an outcome measure for treatment trials. Multiple factors, such as anxiety comorbidity, may affect quality of life and can be more specifically targeted in treatment interventions.

Limitations

- This study had a cross-sectional design, so no causative evidence could be taken.
- The anxiety disorders have been combined here, although they are not all alike.
- Investigation of a broad concept such as quality of life may be affected by other possible confounders not considered here.

Key Words*: bipolar disorder, quality of life, anxiety, comorbidity*

The clinical presentation of BD is usually associated with psychological suffering, functional impairment, interpersonal problems, and a substantial economic burden.[1,2] An emerging body of evidence shows that BD is associated with lower scores on quality of life.[3–6] Quality of life seems to be impaired during mood episodes[7] and in the

presence of subsyndromal symptoms,[8] but not in euthymic patients.[9] BD patients with higher scores for depression were reported to present lower scores for quality of life.[3,10] There is evidence that patients with bipolar depression present lower quality of life than unipolar patients,[3] but the level of depression does not seem to fully explain the lower quality of life among patients with BD.[10,11] Anxiety is a frequent complaint among patients with BD,[12] and anxious comorbidities are more prevalent among patients with BD than among patients with unipolar depression.[13,14] There is also evidence that generalized anxiety disorder, OCD, social phobia, and PTSD are associated with lower quality of life.[15,16] Therefore, the subjective experience of being anxious could be a concurrent factor for the determination of lower quality of life among patients with BD.

Epidemiologic studies have demonstrated that individuals with BD have higher rates of comorbid anxiety disorders than are found in the general population.[17,18] In the National Comorbidity Survey, 92.9% of the subjects who met criteria for lifetime BD I also met criteria for any lifetime anxiety disorder, compared with 24.9% of the general population sample.[18,19] Data from the Epidemiological Catchment Area Study showed that 21% of BD I and II patients had lifetime panic disorder and 21% had lifetime OCD.[19] Recent studies suggest that BD with comorbid anxiety may be associated with greater illness severity and poorer outcomes.[4,20,21] BD patients with comorbid anxiety have been described as more likely to present suicidal behaviour, substance abuse, more severe side effects from medication, and a longer time to achieve remission.[20–22] Frequently, more than one anxiety disorder is encountered in BD subjects,[23,24] which might be another factor affecting the prognosis. Thus BD comorbid with anxiety might lead to prominent problems in social relationships, employment, psychopathology, and global functioning in the long term. The magnitude of the impact of such impairments can be

difficult to assess. For this purpose, quality of life measures may be an interesting tool. Most quality of life instruments assess different domains, such as the physical, psychic, environmental, and social. Quality of life as defined by the WHO is a broad concept that considers "the individual's perception of his or her position in life, within the cultural context and value system he or she lives in, and in relation to his or her goals, expectations, parameters, and social relations."[25, page1570]

Intriguingly, few data to date examined the impact of anxiety comorbidity on the quality of life of individuals with BD. One recent study reported decreased quality of life in BD patients with anxiety comorbidity, compared with patients not suffering from anxiety comorbidity.[26] Therefore, the present study aims to evaluate whether BD patients with comorbid anxiety have lower quality of life and a more severe clinical presentation.

Methods

This study was a cross-sectional survey of 162 outpatients with BD, aged 18 years or older, consecutively recruited from the Bipolar Disorders Program of the University Hospital at the Federal University, Porto Alegre, Brazil, between 1 September 2003 and 15 January 2005. The subjects received a diagnosis based on the SCID-I.[27] We included patients with BD type I and type II at different stages of recovery. All patients gave written informed consent before entering in the study. The study was approved by the local ethics committee. We divided our sample into 2 major groups: patients with (*n* = 91) and without (*n* = 71) current comorbid anxiety disorder (that is, panic disorder with or without agoraphobia, agoraphobia without panic disorder, OCD, generalized anxiety disorder, social phobia, specific phobia, PTSD, and anxiety disorder not otherwise specified).

Quality of life was considered our primary outcome measure, and we assessed it with the 26-item WHOQOL-BREF,[28] a multidimensional, self-administered scale that covers 4 quality of life domains (psychological, environmental, social relationships, and physical health). Items are rated on a 5-point scale in which 1 indicates low, negative perceptions and 5 indicates high, positive perceptions. The instrument was previously validated in a Brazilian sample. The validation of the Portuguese version of the WHOQOL-BREF showed high rates of reliability, internal consistency, and construct validity.[28]

Assessments of demographic status and clinical psychopathological features were performed with a previously used, semistructured questionnaire.[10] Substance abuse or dependence, rapid cycling, and lifetime psychosis were assessed according to DSM-IV criteria. We assessed global functioning with the GAF measure and depressive symptoms with HDRS.[29]

Statistical Analysis

The 4 WHOQOL-BREF domains (physical, psychological, social and environmental) were analyzed separately. Descriptive analyses included calculation of proportions and respective 95%CIs for categorical variables. We calculated means, medians, SDs, and percentiles for continuous variables, and we used histograms and the Kolmogorov–Smirnov test to check variables for normality. The chi-square tests for heterogeneity were used to test differences in proportions. We applied the nonparametrical Kruskal–Wallis test to compare medians and the *t* test and ANOVA for heterogeneity to compare means. We used chi-square tests for heterogeneity for dichotomous outcomes such as substance abuse or dependence, rapid cycling, and psychosis. Continuous outcomes (age at onset, suicide attempts, and hospitalizations) were analyzed with ANOVA. Sex,

age, family income, and level of depression were controlled with a linear regression model.

Results

There were no statistical differences between anxious BD patients and the nonanxious BD subgroup in relation to sociodemographic variables (Table 1). The prevalence of overall current anxiety comorbidity in this sample was 56.1%. The most frequent anxiety disorder was specific phobia (32. 1%), followed by agoraphobia (17. 9%), social phobia (14. 8%), generalized anxiety disorder (11.7%), and panic disorder (11. 1%). The prevalence of OCD and PTSD was 10.6% and 10.5%, respectively.

Crude analysis showed that anxious BD patients had lower scores in all WHOQOL-BREF domains (Wald test, $P < 0.05$; see Table 2). After adjusting for age, sex, and family income, a significant impairment persisted in the psychological ($P = 0.031$) and social ($P < 0.001$) WHOQOL-BREF domains but not in the physical ($P = 0.300$) and environmental ($P = 0.062$) domains. However, after we added the level of depressive symptoms (according to the HDRS) as a confounder, only the psychological domain of the WHOQOL-BREF showed significant impairment (Wald test, $P = 0.002$), suggesting that comorbid anxiety may influence the quality of life of BD patients, regardless of the presence of depression.

Anxious BD patients had higher rates of suicide attempts (ANOVA, $P = 0.007$) than did non-anxious BD patients (Table 3). Anxious BD patients were more likely to present lifetime alcohol abuse and dependence (chi-square test, $P = 0.04$), rapid cycling (chi-square test, $P = 0.027$, and lifetime psychosis (chi-square test, $P = 0.021$). The group with anxiety comorbidity showed lower GAF scores (ANOVA, $P = 0.018$). Conversely,

we found no between-group differences in lifetime drug abuse or dependence, number of hospitalizations, and age at onset ($P > 0.05$).

Discussion

The present study showed that BD patients with current comorbid anxiety present lower quality of life scores. The effect of anxiety on the psychological domain of quality of life is kept, even when the level of depression is controlled for. This finding supports the notion that anxious comorbidity has a negative impact on quality of life in patients with BD, regardless of the presence of depression. Previous studies have shown that quality of life is inversely correlated with the level of depression. The magnitude of such correlation was reported to be in the order of –0.1 to –0.3[3] and up to –0.3 to –0.6.[11] According to these figures, one can argue that the correlation between depression and quality of life may be consistent but is far from being the sole explanation for the impaired quality of life found in patients with BD. Indeed, patients with bipolar depression are likely to present poorer quality of life than patients with unipolar depression,[3,11] even when the level of depression is matched between groups.[11] Our study suggests that the variance in quality of life among BD patients can be explained, at least in part, by anxiety comorbidity.

We also found that patients with comorbid BD and anxiety present more severe psychopathological features, namely, higher rates of alcohol abuse or dependence, lifetime psychosis, suicide attempts, and rapid cycling, as well as lower GAF scores. These findings accord with previous studies that found higher rates of alcohol abuse or dependence, elevated risk of suicide attempts, and impaired functioning in subjects with comorbid BD and anxiety.[4,21,30] Cassano et al[31] found an increased prevalence of panic disorder, OCD, and social phobia in subjects with affective psychosis, who were mostly

BD I patients. Further, they observed that patients with multiple anxiety disorders had more severe psychopathology and substance abuse.[31] A recent prospective study confirmed data showing greater severity and lower quality of life in BD patients with anxiety comorbidity, compared with patients without anxiety comorbidity after 1 year of follow-up.[26] Interestingly, the association between anxiety–BD comorbidity and rapid cycling is poorly discussed in the literature.[32] In a recent multisite study with a large sample of BD patients, MacKinnon et al[33] reported that rapid mood switching was associated with a higher risk of presenting anxiety disorders and substance abuse. Taken together, these findings show that comorbid anxiety may negatively influence the course of BD.

Although previous studies have reported an earlier age of onset, a higher prevalence of lifetime drug abuse or dependence, and a higher number of hospitalizations in subjects with comorbid BD and anxiety, we did not find such association. This discrepancy may be associated with different assessment methods and sample characteristics. We collected age-of-onset data retrospectively, so a recall bias should be considered. Further, we studied an exclusively outpatients sample of BD patients from an academic specialty centre in Brazil.

Qualitative differences between the subjective experience of suffering from unipolar and bipolar depression are difficult to grasp. Differential clinical features, such as a higher risk of suicide among BD patients, suggest that bipolar and unipolar depressions are not necessarily closely related. Early psychopathological descriptions highlighted the distinctive nature of the “inner turmoil” and incapacitation presented by patients who suffered from anxious melancholia.[34] In this same vein, the risk of suicide is increased in patients with unipolar depression and anxiety.[4,21] The psychological pain associated

with anxiety comorbidity in BD patients, expressed through lower scores in this quality of life domain, may be one of the variables influencing the higher rates of suicide attempts. It is reasonable to suppose that anxiety not only adds psychological suffering to patients with depression but may also even change the nature of the illness.[35] Our study's results support the notion that patients with BD who suffer from anxiety disorders are less satisfied with their lives and present more severe psychopathology.

BD patients who are not euthymic tend to present combined symptoms of depression, anxiety, and physical unrest.[36,37] Using the Ockham's razor, one may conclude that the symptoms of "manic-depressive" patients should be attributed to mania or depression until the contrary is proven. However, the literature rooted in the lore of general practioners suggests that symptoms of anxiety and depression are very difficult to tease apart.[38] Our findings are in line with these ideas. We found that the presence of anxious comorbidity correlated negatively with scores in the psychological and social domains of quality of life. However, when depression was controlled for, anxiety presented an independent effect only within the psychological domain of quality of life.

Our results showed a trend toward the association of anxiety comorbidity and poorer quality of life within the social domain. The data show that the deleterious effect of anxiety comorbidity in the social domain of the WHOQOL was influenced by the level of depression, but a trend indicates that this effect may also exist independent of it. This suggests that the added burden of anxiety may induce further damage in the way patients perceive their social lives. Acute episodes, as well as the burden of continuous subsyndromal symptoms, are likely to jeopardize social relationships.[39]

These results should be interpreted in the context of 3 significant limitations. First, other factors may influence quality of life, because it is a broad concept. To reduce

confounders, results were adjusted for age, sex, and family income, as well as for current depressive status. Further, in a previous study regarding other factors possibly associated with lower quality of life,[40] MacQueen et al. found no significant differences in quality of life scores between BD I patients with and without psychosis. Among studies examining alcohol dependence, quality of life seems to improve with a good response to treatment among these patients. Second, inherent to a cross-sectional design, only associations can be inferred from the data; no causative evidence can be taken. The severity of bipolar illness can increase susceptibility to comorbidity such as anxiety and can also decrease overall quality of life. Similarly, anxiety comorbidity may contribute to an adverse course of BD and lower quality of life. A recent prospective study confirmed previous data showing that anxiety comorbidity was associated with an adverse course of BD and decreased quality of life.[26] Third, although they have been combined here, not all anxiety disorders are alike. The limited number of subjects with each subtype of anxiety disorder precluded meaningful stratifications.

Despite these limitations, our study has essential strengths. It is the first study to use the WHOQOL-BREF to examine the impact of anxiety comorbidity in a sample of patients with BD. This instrument has undergone rigorous international development and is available in a wide variety of languages. It has been validated in Portuguese in a Brazilian sample. The WHOQOL-BREF uses a broader concept of quality of life than other previously frequently used scales, which had more specific concepts of health-related quality of life. Another core aspect of our study is the anxiety comorbidity diagnosis, which was accurately assessed with the SCID-I. To date, only few studies examined quality of life in BD patients with anxiety comorbidity. Our study confirms previous results highlighting the deleterious impact of anxiety comorbidity in BD.

In conclusion, the present study suggests that anxiety comorbidity may worsen the quality of life of patients with BD, particularly within the psychological domain. The added burden of anxiety may, in part, account for poorer outcomes, such as higher frequency of alcohol abuse, lifetime psychosis, increased number of suicide attempts, and rapid cycling. Despite the fair amount of evidence for the clinical relevance of BD–anxiety comorbidity, limited data focused on the therapeutic management of patients with comorbid BD and anxiety.[41] Further studies may help to validate interventions tailored to lessen the burden for BD patients who suffer from anxiety comorbidity.

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Table 1. Socio- demographics variables among bipolar patients.

VARIABLE	Bipolar patients		P value
	Anxiety (n=91)	*No-anxiety (n=71)*	
Socio- demographics			
Sex			0.60*
Men	38%	28.1%	
Women	62%	71.9%	
Age (years)			
Mean (SD)	43.1 (11.0)	42.0 (11.8)	0.52**
<40	38.0%	41.8%	0.88*
40-59	57.7%	53.8%	
≥60	4.2%	4.4%	

** Chi-square test; ** T-test; *** Kruskal Wallis test*

Table 2. Quality of life among bipolar patients with and without current anxiety comorbidity.

WHOQOL Domains	Crude analysis		Adjusted analysis*	
	Coefficient ($CI_{95\%}$)	*P value***	*Coefficient ($CI_{95\%}$)*	*P value***
Physical				
Anxiety	Reference	0.001	Reference	0.072
No- Anxiety	-0.3(-17.2; -4.7)		-0.1(-10.8; 0.5)	
Psychological				
Anxiety	Reference	0.001	Reference	0.001
No- Anxiety	-0.4 (-21.2; -9.3)		-0.2 (-14.2; -3.9)	
Social				
Anxiety	Reference	0.001	Reference	0.089
No- Anxiety	-0.2 (-18.6; -4.6)		-0.1(-12.3; 0.9)	
Environmental				
Anxiety	Reference	0.005	Reference	0.179
No- Anxiety	-0.2(-14.7; -2.1)		-0.1(-8.1; 1.5)	

* Adjusted for HAM-D

** Wald test

Table 3. Clinical features of bipolar patients with and without current anxiety comorbidity.

VARIABLE	Bipolar patients		P Value*
	Anxiety (n=91)	*No-anxiety (n=71)*	
Clinical Feature			
Lifetime substance use disorder			
Alcohol abuse	68.9 %	34.1 %	0.043 [a]
Alcohol dependence	74.1 %	25.9 %	0.040 [a]
Drug abuse	56.8 %	43.2 %	0.935 [a]
Drug dependence	58.3 %	41.7 %	0.817 [a]
Lifetime Psychosis	60.7 %	39.3 %	0.021 [a]
Rapid Cycling	68.9 %	31.1 %	0.027[a]
Age of onset	24.8 (12.1)	25.0 (11.9)	0.900 [b]
Nº of hospitalization	3.3 (3.0)	4.4 (4.5)	0.193 [b]
Nº of suicide attempt	2.3(2.4)	1.2 (1.4)	0.007 [b]
Global Functioning (GAF)	60.6(13.1)	65.6(13.5)	0.018 [b]

[a] *Chi-square test*; [b] *ANOVA test for heterogeneity*

Capítulo II

Artigo aceito na 'Bipolar Disorders: an International Journal of Psychiatry and Neurosciences' em Dezembro 2006.

Traumatic Life Events in Bipolar Disorder:

Impact on BDNF Levels and Psychopathology

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Abstract

Background: There is evidence that vulnerability to depression and anxiety disorders is markedly increased by traumatic life events. While childhood abuse has been reported to be associated with poorer outcomes in bipolar disorder, little is known about the neurobiological basis underlying this association. The aim of this study was to ascertain if bipolar patients who were exposed to traumatic event or events (TE) have lower Brain Derived Neurotrophic Factor (BDNF) levels and more severe psychopathology as indicated by increased comorbidity and other clinical features compared with those who were not exposed to TE.

Methods: One-hundred and sixty-three consecutive bipolar outpatients underwent structured clinical interviews for DSM-IV diagnosis and standard protocol to assess clinical features. The reported TE was assessed using DSM-IV A1 and A2 criteria. Subjects were divided in two groups according to presence or absence of lifetime TE. The levels of BDNF, comorbidity and other clinical features were compared between groups.

Results: After adjusting for confounders, results indicated that bipolar patients with a history of TE have alcohol abuse/dependence ($p<0.001$), anxiety comorbidity, and lower levels of serum BDNF ($p<0.01$) compared with those without a history of TE. There was no difference between the two groups in age of onset, presence of psychosis, other substance abuse and dependence, rapid cycling or suicide attempts.

Conclusion: Our findings suggest that TE is associated with significantly increased prevalence of alcohol and anxiety comorbidity as well as lower BDNF levels in bipolar patients. It is possible that decrease in BDNF levels may account for increased comorbidity but further prospective studies are required to confirm this.

Key words: bipolar disorder, traumatic life events, trauma, comorbidity, BDNF.

Introduction

There is strong evidence that vulnerability to depression and anxiety disorders is markedly increased by childhood abuse, including physical and sexual, as well as adulthood stressors. Epidemiological studies and clinical trials with large samples have revealed that stress and emotional trauma are associated with increased risk of psychopathology (1) and attempted suicide (2), particularly when experienced early in life (2,3). The impact of a traumatic event or events (TE) on mental health is not fully explained by genetic predisposition. A study of female twins showed that stressful life events, despite their clear positive interaction with the genetic liability to depression, continued to be significant predictors of onset of major depression even in the absence of a high genetic risk (4). In addition, the association between childhood abuse or traumatic life events and the development of Post Traumatic Stress Disorder (PTSD) is well known. As well, research data has shown a significant relationship between childhood trauma and other psychiatric disorders in later life including panic disorder (5), any anxiety disorder in children (6), eating disorders (7), Obsessive Compulsive Disorder (OCD) (8), substance abuse (1) and multiple personality disorder (9). Childhood maltreatment strongly predicts poor psychiatric and physical health outcomes in adulthood in that these individuals are more likely to become high utilizers of medical care and emergency services (10).

In comparison to the extensive literature on the links between adverse life events and depression, few studies examined the association between TE and their impact on bipolar disorder. These studies report that TE are highly prevalent among bipolar individuals, and are associated with the triggering of bipolar episodes and also with

poorer outcomes (11-13). Leverich et al. (14) examined the impact of childhood trauma on the course of bipolar illness and found that a history of physical or sexual abuse was associated with earlier onset of illness, increased comorbidity and higher rates of suicide attempts. A recent study (12) found a history of childhood abuse in half of patients with bipolar disorder, and in this sample it was associated with lifetime substance misuse comorbidity, rapid cycling and suicide attempts. Posttraumatic Stress Disorder comorbidity is also prevalent with variability in rates of PTSD between studies ranging from 7% to 19% for outpatient bipolar samples (15-17). One third of bipolar patients with a history of childhood abuse manifest comorbid adult PTSD (13) and bipolar patients with comorbid PTSD are more likely to present multiple axis I disorders, low social support and greater trauma exposure (17).

Notwithstanding the reported association of TE and an adverse course of bipolar disorder, little is known about neurobiological mediators of this interaction. The brain-derived neurotrophic factor (BDNF) may be a potential candidate. Alterations in BDNF levels and genes have been implicated in both mood disorders and stress (18). Brain-derived neurotrophic factor (BDNF) plays a diverse role in regulating neuronal survival, structure, and function including playing a critical role in the development and function of central serotonin neurons. Decreased BDNF levels have been reported among depressed patients (19). Indeed, three independent studies reported that serum BDNF levels were reduced in unipolar depressed patients and were negatively correlated with the severity of depressive symptoms (20). There are recent data suggesting the involvement of BDNF in the pathophysiology of bipolar disorder. For instance, serum BDNF levels were found to be negatively correlated with the severity of manic and depressive symptoms (21). In an animal model of mania, amphetamine decreased,

while lithium and valproate increased BDNF levels (22). In addition, family-based association studies have reported that polymorphisms in the BDNF gene may be involved in Bipolar Disorder (23, 24).

Intriguingly, to date there is no data about BDNF levels in patients with PTSD, or in those with a history of childhood abuse. However, studies have reported smaller hippocampal volumes in patients with early life stress, child sexual abuse (25), PTSD (26, 27) and depression when compared to normal controls (28). It is conceivable that TE may lead to adverse clinical outcome through a reduction in BDNF levels with a consequent reduction in hippocampal volumes. In fact, it has been found that BDNF val66met polymorphism is associated with decreased hippocampal volume in humans (29). Depressed women with a history of child abuse have an 18% smaller mean left hippocampal volume than non-abused women (30). Remarkably, these apparent differences in hippocampal size may be reversible with antidepressant treatment, consistent with a function of neurotrophic factors in both neural plasticity and neurotrophism within the hippocampus (18). Additionally, animal models of chronic and acute stress have demonstrated increased cortisol levels and decreased BDNF levels in the hippocampus (31). Taken together, these data suggest that BDNF might be neurobiological substrate that mediates the environmental effects on the psychopathology.

The aim of the present study, therefore, was to evaluate whether bipolar patients with a history of TE have lower BDNF levels and more severe psychopathology as indicated by increased comorbidity and other clinical features. Secondly, we aim to investigate whether the BDNF levels are affected by history of trauma independently of development of PTSD diagnosis.

Methods

One-hundred-sixty-three bipolar outpatients were consecutively recruited from the Bipolar Disorders Program of the University Hospital at the Federal University, Porto Alegre, Brazil, between September 2003 and August 2005. The subjects underwent a Structured Clinical Interview for DSM-IV (32) - Axis I (SCID-I) for diagnosis and a standard protocol to assess psychopathology and clinical features. Patients with bipolar disorder type I and type II were included and all patients gave written informed consent before entering the study. The present study was approved by the local ethical committee. The presence of substance abuse/dependence, anxiety comorbidity, rapid cycling and lifetime psychosis were determined using DSM-IV criteria (32). Anxiety comorbidity as a group included panic disorder with or without agoraphobia, agoraphobia without panic disorder, OCD, generalized anxiety disorder, social phobia, specific phobia, PTSD, and anxiety disorder NOS. Global functioning was assessed using the Global Assessment of Functioning (GAF) scale. Depressive and manic symptoms were assessed using the Hamilton Depression Rating Scale-17 items (HDRS), and Young Mania Rating Scale (YMRS), respectively.

The sample (n=163) was divided into two major groups: patients with (n=78) and without (n=85) lifetime exposure to a traumatic event (TE) for comparison purposes. The reported TE was assessed using DSM-IV A1 and A2 criteria. The DSM-IV definition of trauma, as used for the diagnosis of PTSD, includes objective (A1 - exposure to traumatic event) and subjective (A2 - presence of fear or helplessness) components. Criterion A1 and A2 from the PTSD module of the SCID was used to determine lifetime traumatic exposure even though many patients did not have PTSD comorbidity as the other symptoms for a diagnosis were not present. The reported trauma was grouped

into four major categories as follows (12,14): sexual abuse, physical abuse, psychological abuse, and `other traumatic events`. The latter category included loss of a close relative, car accident, or a personal accident.

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at 3000×*g* for 5 min, and serum was kept frozen at −80 ˚C until assayed. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluents and standard curve ranged from 7.8 to 500 pg of BNDF. Plates were then washed four times with wash buffer, monoclonal anti-BNDF rabbit antibody was added (diluted 1:1000 with sample diluents), and incubated for 3 h at room temperature. After washing, a second incubation with anti-rabbit antibody peroxidase conjugated (diluted 1:1000) for 1 h at room temperature was carried out. After addition of streptavidin-enzyme, substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin as a standard.

Statistical Analysis

Clinical features and comorbidity were compared between two groups, (i.e., presence or absence of TE), using Chi-square tests or *t*-tests as indicated in Tables 1 and 2. The BDNF levels were compared between groups using the one-way ANOVA test for heterogeneity. The individual differences were assessed using a post-hoc

Dunnett test if the ANOVA was significant. A Linear regression model was used in order to control for confounders; *p*-values <.05 were considered significant.

Results

The socio-demographic characteristics of BD patients are summarized in Table 1. BD patients with (n=78, 47.8%) and without (n=85, 52.1%) a history of TE did not differ in terms of gender, age or years of schooling. The ethnicity was assessed as white (n=135) and not white (n=25). The distribution of ethnicity was not different between patients with trauma and without trauma (p=0.079).

The prevalence of PTSD in this sample was 16.5%. Among the 163 bipolar patients, 59.1% were taking lithium, 32.9% valproate, 8.1% carbamazepine and 1.8% lamotrigine; 42.3% were taking antipsychotics and 15.3% were taking antidepressants. There was no significative difference between patients with and without trauma regarding antidepressant use (11.5% vs 18.8%; χ^2=4.04, df=5, p=0.671) and antipsychotic use (42.3% vs 41.1%, χ^2=3.7, df=4, p=0.439). Patients who who did not present a history of trauma when compared to those with history of trauma presented higher rates of use of Lithium (65.9% vs 41.0%, respectively) and a diminished rate of use of vaproate (22.4% vs 38.5%) (χ^2 =+ 7.94; df= 2; p = 0.019). Rates for the use of carbamazepine and lamotrigine did not differ between groups.

Clinical characteristics of the sample are shown in Table 2. After adjusting for confounders, which included gender, age, schooling years and HDRS scores, the bipolar patients with a history of TE were more likely to have alcohol abuse (p<0.001), alcohol dependence (p<0.001) and anxiety comorbidity (p<0.001). As expected, a history of TE was highly correlated to PTSD comorbidity (p<0.01). However, PTSD was not associated with alcohol abuse (p=0.654) or dependence (p=0.523) possible due to

limited number of subjects with this diagnosis in this sample. Patients with a history of TE had higher scores on the HDRS ($p<0.025$) but there was no difference between groups on the YMRS scores, presence of psychosis, age at onset of illness, other substance abuse and dependence, rapid cycling or suicide attempts. As well, the number of previous depressive episodes did not differ ($p=0.59$) between subjects exposed to traumatic events (depressive episodes, mean=9.0) and those not exposed to (depressive episodes, mean= 8.1). Also, the number of previous manic episodes did not differ between subjects exposed to traumatic events (manic episodes, mean=7.8) and those not exposed to (depressive episodes, mean= 7.3).

BDNF was found to be decreased in BD patients with a history of trauma ($P<0.002$). In a regression model controlled for depression and manic symptoms (HDRS and YMRS), sex, and age, trauma was related to decreased BDNF [β-0.265 Confidence Interval (-0.072;-0.019) $p=0.001$]. No correlation was found between HDRS scores and BDNF levels ($r=0.007$ $p=0.928$). As well, no difference in BDNF levels was found in patients with or without comorbid PTSD (one-way ANOVA test, $F= 0.842$; $p=0.360$), alcohol abuse ($p=0.123$) or alcohol dependence ($p=0.989$), rapid cycling ($p=0.704$), or history of suicide attempts ($p=0.527$). The prevalence of the subtypes of TE were 12.6% for sexual abuse, 6.9% for physical abuse, 6% for psychological abuse and 31.7% for `Other TE`. The latter includes loss of a close relative (10.3%), car accident (5.1%), personal accident, or being present in a life threatening situation for somebody else (16.3%). More than one trauma was spontaneously reported by 9.4% of subjects. These subjects were considered in both categories. The cumulative effect of trauma was not examined in this work. The type of trauma was considered as an independent variable in relation to BDNF levels. Among the different kinds of traumatic events, sexual abuse

had the strongest effect on BDNF levels in a covariate analysis (ANCOVA). Within the 22 patients who reported sexual trauma, 18 are women and 4 men. However, gender is not likely to influence the BDNF levels. The BDNF levels do not differ according to gender (p=0.932).

Discussion

Our results suggest that presence of lifetime TE is highly prevalent among bipolar individuals. Furthermore, those with history of TE are more likely to have alcohol abuse/dependence and anxiety comorbidity, PTSD, as well as more severe depressive symptoms. However, PTSD was not associated with alcohol abuse or dependence. This suggests that lifetime TE has an impact on the course of bipolar disorder independent of a PTSD diagnosis. These data are in agreement with previous reports indicating an increased incidence of comorbid disorders, including alcohol abuse/dependence, in bipolar patients with trauma (12, 14). While previous studies have reported increased suicide attempts, drug abuse, early age at onset and rapid cycling in the bipolar patients who experienced childhood abuse, we did not find such association in this sample. The reasons for this discrepancy may be related to characteristics of the sample and methods of data assessment. First, the TE was considered according to DSM-IV criteria, which could include both childhood and adulthood traumatic events since the time of the event was not assessed. The two major studies referred above assessed only childhood abuse. Second, our sample was outpatient bipolar subjects from an academic specialty centre, and our sample size was smaller than a previous study, which examined child abuse in bipolar disorder (14).

Besides a more severe clinical presentation, BD patients with a history of trauma also presented decreased serum BDNF levels. This is the first study to assess serum

BDNF levels in BD patients exposed to traumatic life events, as far as we know. Our findings confirmed our hypothesis that exposure to traumatic events would be associated with lower BDNF levels. In a recent previous study we showed that bipolar patients within the acute phases of the disorder (mania and depression) have lower levels of BDNF (21) whereas euthymic patients have BDNF levels at the same range as healthy control subjects. In the present study, traumatic events remained associated with lower BDNF levels even after controlling for manic and depressive symptoms. As well, no correlation between HDRS scores and BDNF levels was found in this sample. These data suggest that the exposure to TE has an effect independent of mood status on BDNF levels. The differences in BDNF levels were not better explained by other factors such as alcohol abuse or dependence, rapid cycling, suicide attempts or PTSD comorbidity as the exposure to traumatic events seems to have an independent effect on BDNF levels.

Among traumatic events, sexual abuse showed the strongest association with a reduction in BDNF levels. Accordingly with previous reports, the sexual trauma was more prevalent among females in our sample. However, the gender difference alone did not influence the BDNF levels. Previous clinical studies addressing differences across abuse subtypes, found suicidality was associated with sexual but not with emotional or physical trauma (12). In another study, comorbid adult PTSD was particularly associated with a history of sexual abuse (13). Childhood sexual abuse in particular has been repeatedly associated, in adulthood, with depression with physical complaints. (10). In this context, our results provide additional evidence suggesting that the sexual component a greatest impact on psychopathology and BDNF levels.

Significant limitations dictate that the results should be interpreted with caution. First, the reliability of bipolar patients' reports of past traumatic events may vary, given the possible association with recall bias and poor insight. The self-reported trauma requires caution for interpretation of the results, although Goodman et al. (33) observed good reliability in the longitudinal assessment of trauma histories among psychiatrically ill women. The possible bias involved is usually under report, particularly regarding early abuse (34). Second, the temporal and cumulative possible effects of trauma were not assessed nor considered in the analysis. The presence of a traumatic event was considered as a dichotomous variable: (i.e., lifetime presence or absence). In this context, only the association can be inferred from data, but no causative evidence can be taken. Third, it cannot be ruled out that the use of medication may have altered the levels of BDNF, since it is well established that psychotropic medications may change BDNF levels. Because patients with history of trauma seem to have a more severe clinical presentation, one may think they would be prescribed medication differently, which could be a potential source of bias. According to this rational, the patients with trauma would receive more medication. It has been shown that antidepressants, lithium and valproate increase BDNF levels. However, we found decreased levels of BDNF in those patients with trauma. This would be a bias against the results, which could indicate that the levels were even lower in those with trauma. In fact, there was no significant difference between patients with and without trauma regarding antidepressant and antipsychotic use. Patients who did not present a history of trauma presented higher rates of use of lithium, but also a diminished rate of use of vaproate in comparison to those with history of trauma. It has been demonstrated that lithium and valproate increase BDNF levels (22). Therefore, it is unlikely that medication would be

wholly responsible for the observed association with differences in BDNF levels. Finally, the BDNF was measured in serum. There may be other sources for serum BDNF, although they are not clearly known. However, it has been demonstrated that BDNF can cross the blood-brain barrier, and there is a high positive correlation (r = 0.81) between serum and cortical BDNF levels (35). Therefore, it has been suggested that the changes of plasma BDNF levels may partly reflect the changes of brain BDNF secretion (36).

It also must be acknowledged that the neurobiology of brain-derived neurotrophic factor (BDNF) is complex and influenced by a number of factors. BDNF has been implicated in the pathogenesis of mood disorders and in the mechanism of action of therapeutic agents such as mood stabilizers and antidepressants (18). In preclinical studies, BDNF expression has been shown to be regulated by stress responsive corticosteroids (37). Early life events may have long-term effects on adult health and well-being, in the form of repeated activation of stress-responsive biological mediators such as glucocorticoids and catecholamines (38,39). Notably, BDNF and other neurotrophic factors are believed to counteract the negative impact of stress hormones on the hippocampal volume (40). Early exposure to traumatic life events and PTSD, as well as depression, has been associated with HPA axis dysfunction (41). In fact, a recent article from Schule and colleagues showed that patients with BDNF met/met polymorphism had higher HPA axis activity during dexametasone/CRH test (42).

The exposure to traumatic life events could partially explain the increased comorbidity by lowering BDNF levels, which could also account for the severity of symptoms, decreased hippocampus volume, and cognitive impairment (43). Conversely, the genetic predisposition to reduced levels of BDNF could contribute to higher vulnerability to bipolar disorder and the neurobiological effects of traumatic

events. Indeed, studies have investigated the relationship between polymorphisms of BDNF gene and vulnerability to bipolar disorder. Some family-based association studies have shown that BDNF gene polymorphism val66met is associated with BD (44), but other studies could not confirm these results (45-47). No association was found in Japanese (45) and Chinese samples (46). One case-control study from the UK with 3000 individuals did not find increased risk for bipolar disorder in those with the polymorphism, but it was associated with rapid cycling (47). A recent study suggested another polymorphic region designated as BDNF-LCPR, which affects transcriptional activity of BDNF, is associated with susceptibility to BD (48). Further studies, prospective and investigating polymorphisms of BDNF and PTSD or lifetime TE could help to clarify and extend these initial observations.

The data presented may open some clinical and research perspectives. A large clinical trial for depression showed that, among those with a history of early childhood trauma, psychotherapy alone was superior to antidepressant monotherapy and combination therapy was marginally superior to psychotherapy alone (49). The effect of childhood trauma was not as robust as it was thought to be, since its impact on final remission was not detected in relation to baseline scores in recent erratum communication (49). However, there is no data regarding BDNF levels as an outcome of psychotherapy. One single study in panic disorder reported higher BDNF levels as a predictor of good response to cognitive behavior therapy (50). BDNF levels are also known to be increased by antidepressants (20) and mood stabilizers (22). These data in the future may help to match patients with an appropriate treatment. We highlight the need for future studies about response to treatment in specific bipolar subgroups of patients.

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Table 1. Demographic characteristics of the sample

Variable	*Bipolar Patients*		P value
	Absence of trauma (n=85)	*Presence of trauma (n=78)*	
Sex			0.370*
Men	31.1%	25.0%	
Women	68.9%	75.0%	
Age (years)			
Mean (SD)	43.01(11.21)	42.13(12.00)	0.616**
<40	35.6%	44.0%	0.413 *
40-59	61.1%	51.2%	
≥60	3.3%	4.8%	
Schooling (years)			
Mean (SD)	9.86(4.19)	9.09(4.27)	0.243**
0-8	36.0%	39.5%	0.187*
9-11	34.9%	43.2%	
≥12	29.1%	17.3%	

* χ^2 test; ** *t*-test

Table 2. Clinical features of bipolar disorder patients with and without history of trauma.

Variable	*Bipolar Patients*		P value
	Absence of trauma (n=85)	*Presence of trauma (n=78)*	
Age of Onset	25.02(11.7)	25.55(12.91)	0.771**
Number of Suicide Attempt	1.63(2.25)	2.16(1.86)	0.172**
Rapid Cycling			0.992*
Presence	26.4%	26.5%	
Absence	73.6%	73.5%	
Psychosis			0.739*
Presence	44.4%	49.0%	
Absence	55.6%	51.0%	
Alcohol Abuse			0.001*
Presence	21.1%	31.0%	
Absence	78.9%	69.0%	
Alcohol Dependence			0.001*
Presence	7.8%	26.2%	
Absence	92.2%	73.8%	
Drug Abuse			0.658*
Presence	75.6%	72.6%	
Absence	24.4%	27.4%	
Drug Dependence			0.665*
Presence	83.3%	85.7%	
Absence	16.7%	14.3%	
Anxiety Disorder			0.001*
Presence	45.6%	82.1%	
Absence	54.4%	17.9%	
GAF	63.42(15.62)	61.83(12.69)	0.464**
HDRS	8.71(6.57)	11.20(7.96)	0.025**
YMRS	4.80(5.95)	4.26(4.97)	0.531**

* χ^2 test; ** *t*-test

Figure 1. Difference in BDNF levels between bipolar disorder patients with and without history of trauma.

* ANOVA, p=0.002

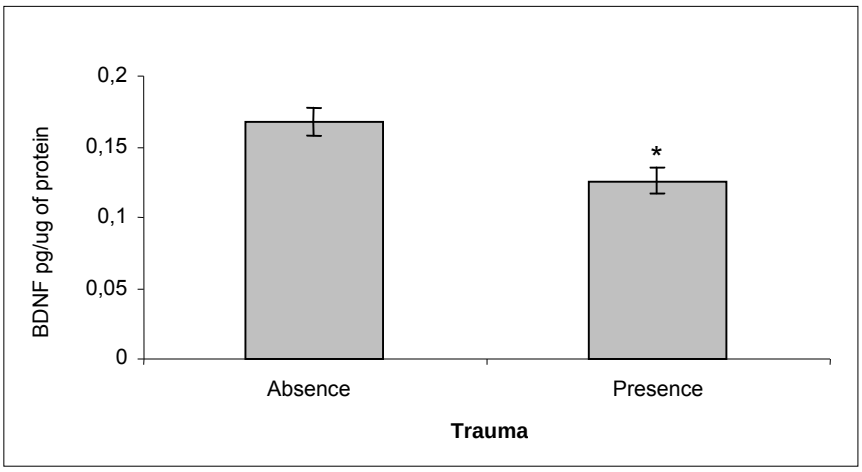
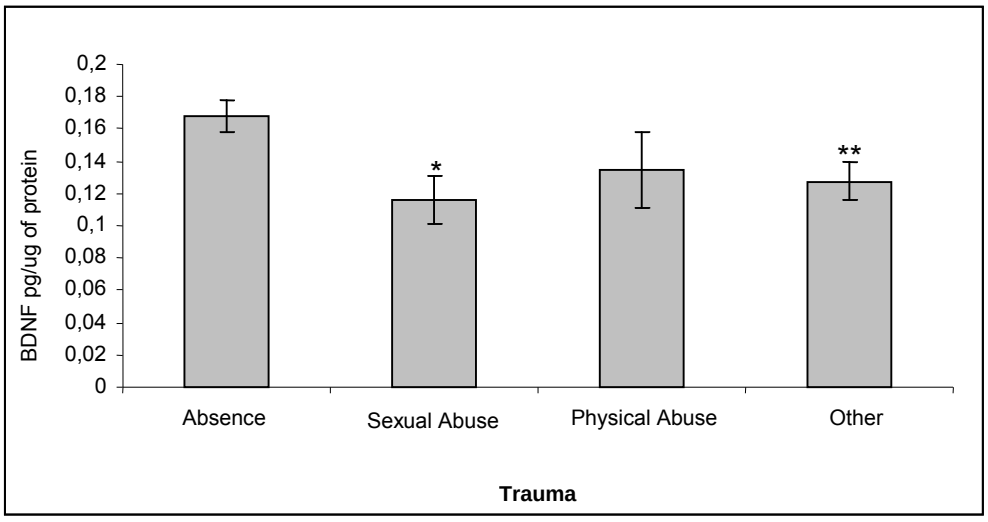


Figure 2. BDNF levels in bipolar disorder patients with history of different types of trauma.

* Different of absence of trauma; Post-test Dunnett, p= 0.020

** Different of absence of trauma; Post-test Dunnett, p= 0.014



Capítulo III

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Emotional memory in bipolar disorder

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Abstract

Background: Cognitive impairment has been well documented in bipolar disorder. However, specific aspects of cognition, such as emotional memory have not been examined in bipolar disorder.

Aims: To investigate episodic emotional memory in bipolar disorder, as indicated by performance on an amygdala-related cognitive task.

Method: Twenty euthymic bipolar patients and 20 matched controls were recruited. Participants were shown a slide show of an emotionally neutral story, or a closely matched emotionally arousing story. One week later, participants were assessed on a memory-recall test.

Results: In contrast with the pattern observed in controls, bipolar patients had no enhancement of memory for the emotional content of the story ($F=13.5$, $df= 2$, $p<0.001$). The subjective perception of emotional impact of emotional condition was significantly different from neutral condition in controls but not in patients.

Conclusions: Our data suggests that the physiological pattern of enhanced memory retrieval for emotionally-bound information is blunted in bipolar disorder.

Declaration of Interest: none.

Introduction

Cognitive impairment has been associated with significant deficits in social and occupational functioning in bipolar disorder [1, 2]. A recent meta-analysis indicated that euthymic bipolar patients when compared with healthy controls showed deficits in executive function, verbal and nonverbal episodic memory as well as in sustained attention [3]. However, specific aspects of cognitive function, such as emotional memory have not been examined in bipolar patients. There is evidence that memory for emotionally charged events may require specific neuroanatomical circuitries that include the amygdala. Previous studies have shown increased activity of amygdala in patients with bipolar disorder. Given this, bipolar patients would be expected to have enhanced perception of emotional stimuli and as a consequence, enhanced memory for emotional content. Therefore, we investigated emotional memory using a well validated amygdala-related cognitive task [4].

Methods

Twenty consecutive consenting stable euthymic bipolar I or II patients who met DSM-IV full remission criteria were recruited from the Bipolar Disorders Program of the University Hospital at the Federal University, Porto Alegre, Brazil. Patients were interviewed with the Structured Clinical Interview for DSM-IV Axis I Disorders [5]. Patients were referred by their psychiatrist when euthymic for at least a month, and remission was confirmed by clinical interview and life charting. Patients using regular β-blockers, benzodiazepines or stimulants were excluded. Occasional use of benzodiazepine was allowed (maximum 4mg lorazepam per week or equivalent), but all patients were asked to stop taking these medications at least 24 hours before memory task was performed.

None of the patients had significant concomitant medical illnesses or a history of substance abuse. The subjects were matched for sex, age, and schooling years with 20 healthy controls. Healthy controls were screened using the SCID (non patient version). Those with current psychiatric morbidity as well as lifetime mood disorders were excluded. We also excluded people using psychotropic medication, those with a previous history of psychological/psychiatric treatments, family history of mental illness, drug abuse and major health problems.

We used the Heuer & Heisenberg test modified by Cahill and others [4] to assess emotional memory. Bipolar disorder patients were randomly assigned to be exposed to a neutral story (n=10), or a closely matched but more emotionally arousing story (n=10). The controls were assigned to the same version of the story, neutral (n=10) or emotional (n=10), as their matched subjects. This assignment resulted in 4 groups: patient-neutral or patient emotional, control-neutral or control emotional. All procedures for the memory test were the same as previously described [4, 6, 7]. All participants had an individual explanation about study objectives and the informed consent was obtained. University Hospital Ethics Committee approved the protocol. The text with the explanation about the study was the same used by Cahill and others [4, 6, 8] and it was read to subjects in order to assure all participants were informed in the same manner. Subjects were told that the slide they watch might be emotionally arousing and that they will be recalled for another assessment a week later.

The stories were presented individually as a narrated slide show (11 slides, about 10 min), that could be neutral or emotional. Both stories were separable into three phases: the first phase including the slides 1–4, the second including slides 5–8, and the final from slides 9–11. The emotional and neutral stories differed primarily in the

slides 5-8, when the emotional elements were introduced in the emotional story, which will be referred from here on as phase 2. In the neutral version, no emotional element was introduced; the content was neutral across the 3 phases. Because the visual elements used in both stories were identical, differences in retention cannot be attributed to intrinsic differences in the visual elements. In both stories, a mother takes her young son to visit his father at the hospital where he works. In the neutral version, the son watches the staff conduct a practice disaster drill. In the emotional version, the boy is severely hurt in a car accident.

Immediately after viewing the slide show, each subject was asked to rate on a 0–10 scale how emotional he/she thought the story was. One week later participants were assessed on a memory-recall test. The testing session consisted of a questionnaire containing 76 questions of multiple choices. The questionnaire consisted of 5–8 questions for each slide, and was presented in the same order of the story. The questions were presented only once and the subject was asked to choose one answer and then go on to the next one.

Statistics. Statistical analyses were performed using the Statistical Package for Social Sciences version 13.0 (SPSS Inc. Chicago, IL, USA). Data for self-rating emotional scale and for the questionnaire of multiple choices (percentage of correct answers) are shown as mean±SD. A multivariate analysis of variance (MANOVA) with repeated measures was used to analyze the dependent variable: percent of correct answers in the three story phases from the multiple choice test (memory recall). The MANOVA with repeated measures included an effect for group (Bipolar x Control), an effect for condition (Neutral x Emotional) and an effect for phase (3 phases). A post-hoc ANOVA was carried out to examine differences within groups (neutral and emotional) in

the percent of correct answers between phases of the narrated story followed by post hoc Tukey test as appropriate. The differences in self-rating emotional scale scores between the groups in various phases were analyzed using ANOVA and post hoc Tukey tests. Continuous variables were tested using independent sample *t* tests, as indicated. Dichotomous demographic variables were tested using chi-square test. All tests were two-tailed with an α of 0.05 and $p<0.05$ was considered to indicate statistical significance.

Results

At the evaluation, all patients were taking mood stabilizers (lithium, n=3; valproate, n=7; carbamazepine, n=1; lithium and carbamazepine, n=3; lithium and valproate, n=5; valproate and carbamazepine, n=1). Half of patients were taking antipsychotics (risperidone, n=4; haloperidol, n=2; olanzapine, n=1; chlorpromazine, n=1; sulpiride, n=1; clozapine, n=1). Other medications used included lamotrigine (n=1), biperiden (n=1) and antidepressants (n=3, i.e. sertraline, citalopram and fluoxetine).There was no significant difference between emotional and neutral group regarding number of mood stabilizers used (one mood stabilizer was used by 7 vs 4 patients and two mood stabilizers by 3 vs 6 patients, respectively; p= 0.37). There were 5 patients in the emotional group and 5 patients in the neutral group that used antipsychotics. Antidepressants were used by one patient in the emotional group and 2 in the neutral group. As to the potential effects of medications, there was no difference between various medication groups (i.e. those on lithium, on divalproex or on Lithium plus divalproex) regarding self-rating scores ($F=2.2$, $df=2$, $p=0.14$), % of correct answers in phase 1 ($F=2.1$, $df=2$, $p=0.15$), % of correct answers in phase 2 ($F=0.06$, $df=2$, $p=0.93$), % of correct answers in phase 3 ($F=0.03$, $df=2$, $p=0.99$) and overall % of

correct answers (F=0.32, df=2, p=0.72). Similarly, there was no difference on any of these measures between those on antipsychotics or antidepressants and those who were not on these medications.

Demographic and clinical characteristics are shown in table 1. Fourteen of the patients were women, and six were men; they ranged in age from 19 to 66 years (mean=44.5); and their mean educational level was 10.8 years. The mean length of illness of bipolar patients was 18.8 years. They were closely matched by sex, age, schooling years to 20 healthy subjects who ranged in age from 18 to 65 years (mean= 42.9) and their mean educational levels was 12.1 years.

As expected, the overall percent of correct answers was lower in bipolar disorder patients compared with matched healthy controls (t=3.6, df= 38, p=0.001) (see Fig.1). The MANOVA with repeated measures showed an effect of phase (F=13.5, df= 2, p<0.001), effect of group (F=14.7,df=1,36, p<0.001), an interaction of a phase x condition (F=4.1, df=2, p=0.02) and an interaction of phase x group x condition (F=2.4, df= 2, p=0.03). When compared directly to controls, patients perform poorly regarding the enhancement of memory for emotional events, as indicated by scores in phase 2 of emotional version (F=5.2, df= 3,36, p=0.004). As well, there was a significant difference in perception of emotional impact of stories between groups as indicated by significant differences in emotional impact self-rating scale scores (F=5.6, df=3,36, p=0.003).
(Figure 1 about here)

The results for controls are presented separately in Fig.2. Consistent with previous studies that have used this task in healthy volunteers [6, 8], percentage of correct answers was enhanced in phase 2 of emotional version when compared to phase 1 and 3 (F=5.7, df=2,27, p=0.008). In the neutral version, there were no differences in

percentage of correct answers across phases within groups (F=1.0, df=2,27, p=0.35). There was significant difference in the percent of correct answers between the emotional and neutral group in emotional arousing phase 2 (t=2.1, df=18, p= 0.04). The emotional arousal content was associated with an increase in recall as indicated by the higher percent of correct answers. Self-rating for emotional arousal demonstrated a greater impact in the emotional version, as expected (p= 0.007). There was no difference between controls exposed to the emotional stimuli and the ones exposed to neutral stimuli regarding age (mean = 42.4 vs 43.5 years; p=0.86) and schooling years (mean 11.6 vs 12.7 years, p=0.98). There were more women in the emotional group (8 female: 2 male), as compared to the group exposed to neutral experience (6 female:4 male), but the difference was not statistically significant (p=0.62). (Figure 2 about here)

Results for bipolar patients exposed to neutral and emotional stimuli are shown in Fig.3. There was no difference in percent of correct answers between phases in the neutral group (F=2.5, df=2,27, p=0.1), as expected. Surprisingly, there was no difference between phases in the emotional group as well (F= 1.3, df= 2,27, p=0.27). Furthermore, there was no difference in the percent of correct answers between the emotional and neutral group in emotional arousing part, phase 2 (t=0.5, df=18, p= 0.57). The emotional arousal content was not associated with an increase in recall as reflected by the percent of correct answers. In addition, the expected subjective emotional impact was not observed, as demonstrated by absence of significant difference in self-rating scale scores between neutral and emotional group (p=0.23) (Fig 2b). Instead, bipolar patients were more likely to rate the neutral stimuli as of greater emotional impact, as compared to controls (mean =4.5±3.5 vs mean=2.5±2.5, respectively). There was no difference between the patients exposed to the emotional stimuli and the ones exposed

to neutral stimuli regarding length of illness (mean 21.3 vs 16.4 years, p=0.37), age (mean = 45.7 vs 43.2 years; p=0.72) and schooling years (mean 9.8 vs 11.9 years, p=0.22). Similar to the controls, there were more women in the emotional group.

(Figure 3 about here)

Discussion

This is the first study to test the impact of emotion on memory formation in bipolar patients in comparison with controls. As expected, controls showed a clear enhancement in memory for the emotional content of the story as compared to the neutral content. Controls also perceived accurately the emotional impact of the stories, as demonstrated by difference in self-ratings scores between the neutral and emotional version.

As expected, the overall recall rate in bipolar patients was significantly lower compared with controls. However, in contrast to the findings in healthy controls and our hypothesis, our results showed that the physiological pattern of enhanced memory retrieval for emotionally-bound information was blunted in patients with bipolar disorder. These findings were obtained in medicated bipolar patients, which is a potential source of bias. Drugs used to treat bipolar disorder may hamper different cognitive systems, and may impair emotional memory as well. However, it is unlikely that a non specific flattening of cognitive function as a whole would account for the higher rates of mislabeling of neutral information as emotional, which was found in bipolar patients. Further, bipolar patients perceived the neutral story as more emotionally charged as indicated by no difference in scores on the visual analogue self report scale between the neutral and the emotional versions. Since bipolar patients perceived the neutral content as more emotional and similar to the emotional version, one would have

expected an enhancement of memory in the phase 2 in both versions. However, the recall rate was similar in all phases in both versions in bipolar patients. This would suggest that the enhanced perception of emotional impact did not translate into enhancement of memory formation.

Amygdala-dependent memory task

When interpreting the results, the first consideration must be the neurocircuitry involved in this task. We used the Heuer and Reisburg task [9] modified by Cahill and others [4, 6-8], which compares memory for emotional arousing versus neutral information. It is well documented that the memory for an emotional arousing event is better than for neutral stimuli [10, 11]. There is evidence that the amygdala plays a crucial role in the enhancement of the strength of long-term memory for emotional events [12]. Further, previous studies that have used the modified Heuer and Reisburg test have shown that enhancement in memory associated with the emotional content is highly dependend on amygdala function [6]. For instance, memory enhancement induced by emotional arousal was absent 1) in healthy subjects using b-blockers [6]; 2) in a patient with a rare hereditary disorder that produces a bilateral brain damage confined to the amygdaloid complex [11]; 3) in temporal lobectomy patients with bilateral amygdala damage [13]; and 4) in short-term memory assessment [8]. These findings provide evidence that the amygdala might be a critical locus for emotional enhancement in memory in this task [6, 11]. Furthermore, in healthy volunteers, the degree of activity in the left amygdala during encoding was predictive of subsequent memory and was related to the emotional intensity of the experience [14]. Interestingly, patients with Alzheimer's disorder with moderate overall memory impairment did perform well in this test, and the extent of memory enhancement for emotionally charged content was similar in subjects and

controls [7]. Therefore, the poor performance of bipolar subjects on this task in the present study suggests that bipolar patients have emotional memory deficits which may be related to a dysfunctional amygdala circuitry.

Amygdala circuitry in bipolar disorder

Our findings are consistent with previous literature suggesting abnormalities in amygdala circuitry in bipolar disorder. For instance, many of the symptoms experienced by patients with bipolar disorder would appear to be associated with abnormalities in emotion processing [15, 16]. Further, emotional hyper-reactivity is a fundamental mood characteristic of manic and mixed states [17]. Moreover, structures known to take part in the emotional processing circuitry [4, 12] such as prefrontal cortex, subgenual anterior cingulate gyrus, the amygdala and ventral striatum have been reported to have structural and functional alterations in bipolar patients [18]. Of these, the amygdala is critically involved in modulating emotional memory, attention and perception [19]. Interestingly, enlarged amygdala volumes have been reported in structural imaging studies in bipolar disorder [20]. Abnormal age related increases in the amygdala volume have been found in bipolar adolescents [21]. Also, Magnetic Resonance Imaging (MRI) studies have reported enlarged amygdala volumes in bipolar disorder [22]. In addition to structural changes in this circuitry, functional neuroimaging studies indicate underactivity of the dorsal and ventral prefrontal cortex and increased activity in the dorsal anterior cingulate, amygdala [23, 24] and thalamus [25] during mood episodes. Increased metabolism within the right amygdala has been reported in depressed bipolar subjects. However, most of the functional imaging studies have investigated the activity of amygdala and temporal lobe in emotional processing in bipolar disorder using tests of facial expression recognition, but did not include emotional memory paradigms. The

available data from these studies demonstrated that manic and depressed subjects identify facial expressions less accurately than do euthymic bipolar or healthy comparison subjects [25]. Another study showed that euthymic and depressed bipolar patients present increased subcortical and ventral prefrontal cortical responses to both positive and negative emotional facial expressions as compared with healthy controls and major depression patients [26]. In euthymic patients, enhanced disgust [27] and impaired fearful facial expressions identification have been demonstrated [28]. The latter study also reported increased amygdala and reduced prefrontal cortical activation in response to facial expressions of fear.

Interestingly, the previously observed increased amygdala volume and increased activity of temporal lobe and amygdala during facial recognition task in euthymic bipolar patients [22, 25, 26, 29] did not translate into increased emotional memory formation in our study, as we expected. This is consistent with previous evidence that indicates that facial expression recognition and emotional memory formation require different neuroanatomical pathways [13, 30]. For instance, a study of patients with amygdala damage due to herpes simplex encephalitis suggested that recognition of facial emotion in adults does not have an absolute dependence on the amygdala [30]. Further, temporal lobectomy patients with bilateral amygdala damage have superior fear face perception but their ability to form enhanced emotional memories in the Heuer & Reisburg test [13] was severely compromised. Taken together, it would appear that the enlarged volumes and enhanced activity of the amygdala in bipolar disorder indicate an oversensitive but dysfunctional neural system for emotional processing.

Perception of emotional stimuli

Emotion, through amygdala, can influence encoding, attention and perception [19]. Although the memory test used here assessed the memory formation process as a whole, we further investigated the perception of the emotional content of the stories, as indicated by self-rating scores. Bipolar patients reacted differently than controls to the emotional impact of the stories. There was no difference between the scores for the emotional and for the neutral stimuli in self-report of emotional impact among patients, while for controls it was clearly different. This may suggest that bipolar patients may have an oversensitive emotional reaction to facts, which is not functional because it can be restrictive for the ability to focus on the real emotional content. The enhanced emotional memory is clearly adaptive, because emotional stimuli are generally more important for survival [12]. Previous studies have reported that bipolar patients are less able to accurately recognize emotions in human faces than healthy controls, which was thought to be associated with their impaired social skills [25]. Our results showed that this altered perception might not be restricted to facial expressions in bipolar patients, as their perception for facts in a simple story was also altered. One can speculate that this altered perception may lead bipolar patients to remember neutral stimuli as emotional and therefore be more susceptible to interpret life events as traumatic. This is consistent with the literature showing that stressful life events are associated with mood episodes.

Some limitations must be considered when interpreting this study. First, many factors have been reported to influence cognitive performance such as number of episodes, number of hospitalizations, age of onset, but studies also reported absence of such associations [31]. In order to minimize the impact of these confounding factors, we included length of illness in the assessment to ensure that groups were not different in

relation to illness variables. The length of illness was chosen because it has been reported to be associated with visuospatial and verbal memory impairments [32]. Second, these findings were obtained in medicated bipolar patients, which is a potential source of bias. Drugs used to treat bipolar disorder may hamper different cognitive systems, and may impair emotional memory as well. However, it is unlikely that a non specific flattening of cognitive function as a whole would account for the higher rates of mislabeling of neutral information as emotional, which was found in bipolar patients. Moreover, patients were medicated with a variety of combinations of medications, so that specific medications effects could not be determined with the number of subjects available. There were no baseline difference among the groups concerning the mood stabilizers, but we cannot exclude the influence of drugs on results, specifically when comparisons between patients and healthy controls are considered. Several studies have observed that lithium, valproate and atypical antipsychotics do not have significant effects on memory, but other studies have suggested that lithium may be potentially confounding for cognitive assessments [33]. Cognitive deficits are still evident in euthymic medication free patients [31]. This indicates that the use of medications is not wholly responsible for the observed deficits. Third, euthymic bipolar patients often present subsyndromal affective symptoms, which may affect performance on cognitive measures, specifically emotional memory. We have not used scales for mood symptoms, so that it was not possible to exclude the presence of this confounding factor. However, previous studies were able to demonstrate that cognitive impairment persisted in euthymic bipolar patients after controlling for mood symptomatology [32]. Fourth, there was no direct measure of attention in this study, and sustained attention deficits have been reported in euthymic bipolar patients. However, the task consisted of

a short presentation of slides and the test was administered by the investigator. Also, the self rating scores for emotional impact suggest that patients were sensitive to the content of the story.

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Figure Titles and Legends

Figure 1. Difference in overall recall performance, i.e. percent of correct answers, between patients (n=20) and healthy controls (n=20).

* significant difference between patients and controls (t=3.6, df=3,38, p=0.001)

Figure 2. a) Recall performance of **controls** exposed to the emotional (n=10) and neutral (n=10) condition. b) Emotional impact of the neutral and emotional version of the story for controls (self-rating emotional scale scores).

a) * Significant difference in percent of correct answers across phases in the emotional condition (p=0.008), but not in the neutral condition (p=0.35). b) * Significant difference in the subjective emotional impact of the story between neutral and emotional version (p=0.007).

Figure 3. a) Recall performance of **bipolar disorder** patients exposed to the emotional (n=10) and neutral (n=10) condition. b) Emotional impact of the neutral and emotional version of the story for patients (self-rating emotional scale scores).

a) Not significant difference in percent of correct answers across phases in both the neutral (p=0.1) and the emotional condition (p=0.27). b) Not significant difference in the subjective emotional impact of the story between neutral and emotional version (p=0.23).

Figure 1

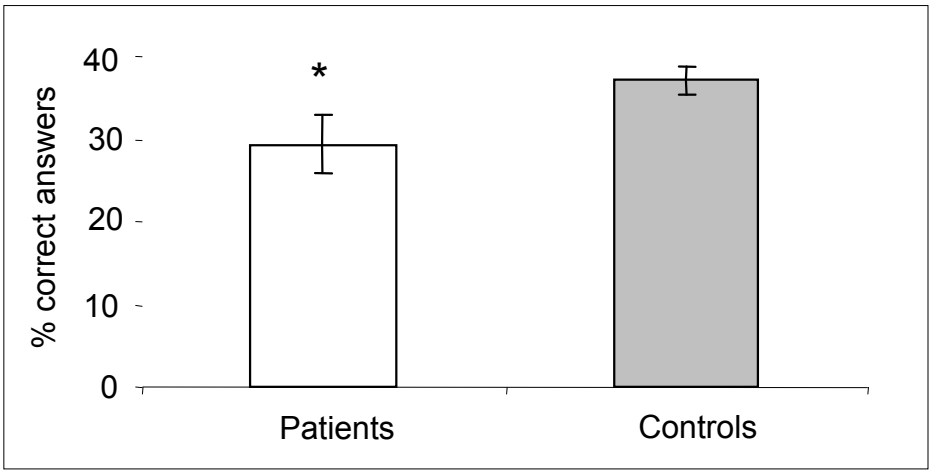


Figure 2.

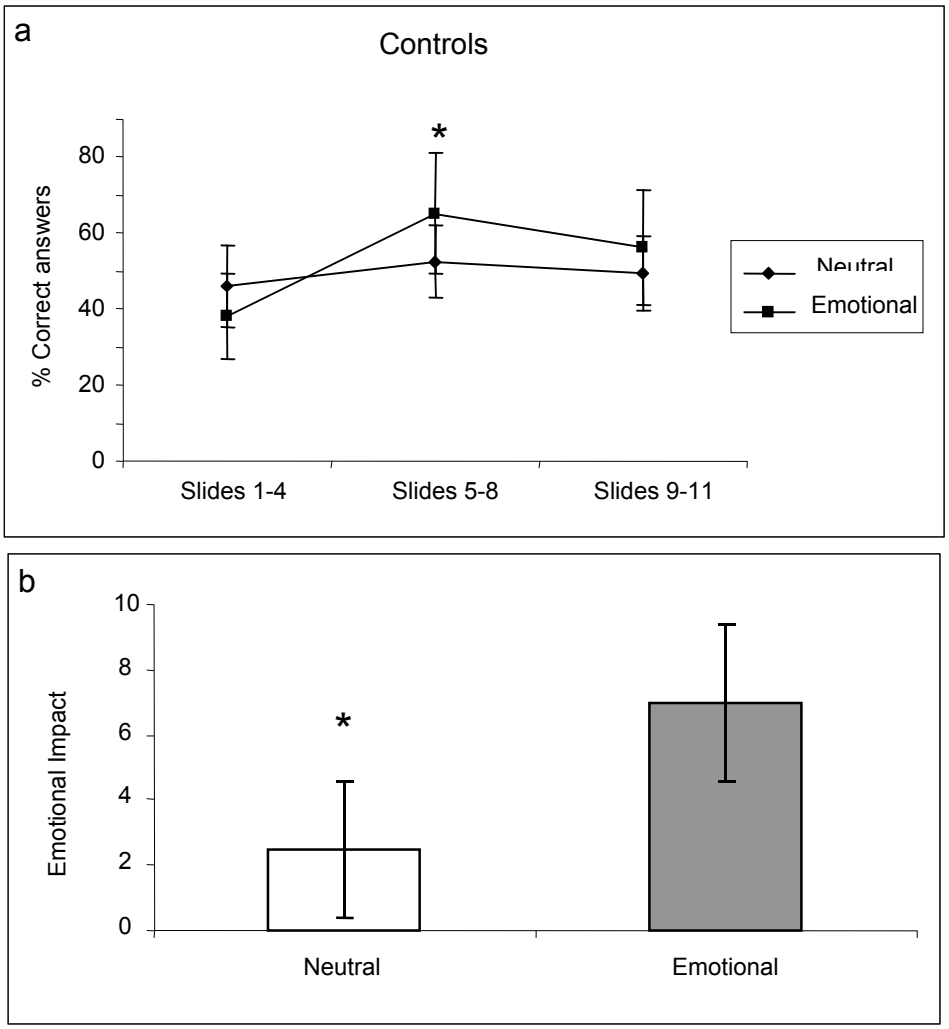
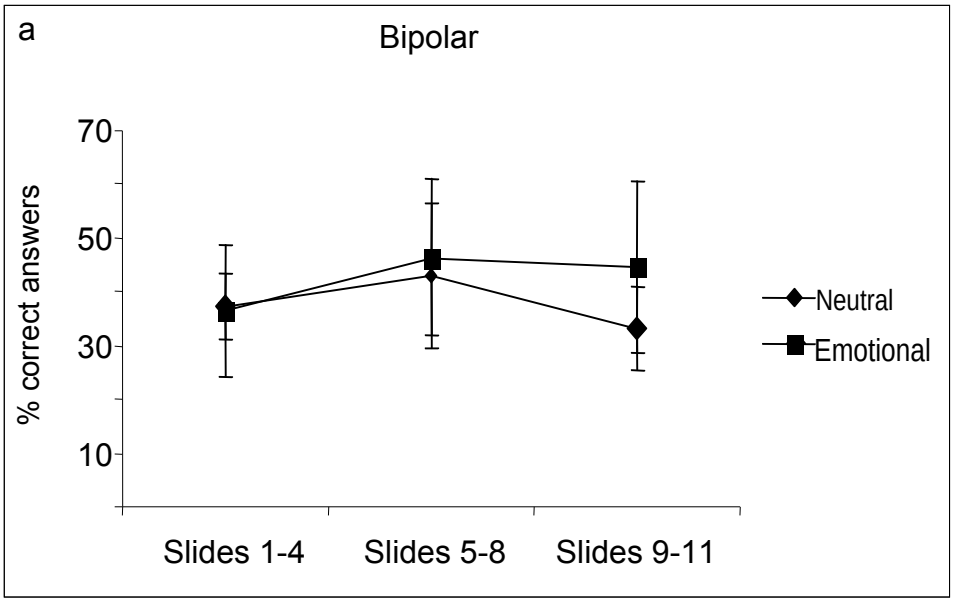

a
Controls
% Correct answers
80
60
40
20
0
*
Slides 1-4
Slides 5-8
Slides 9-11
Neutral
Emotional
b
Emotional Impact
10
8
6
4
2
0
*
Neutral
Emotional

Figure 3.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Bipolar
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50
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Slides 1-4
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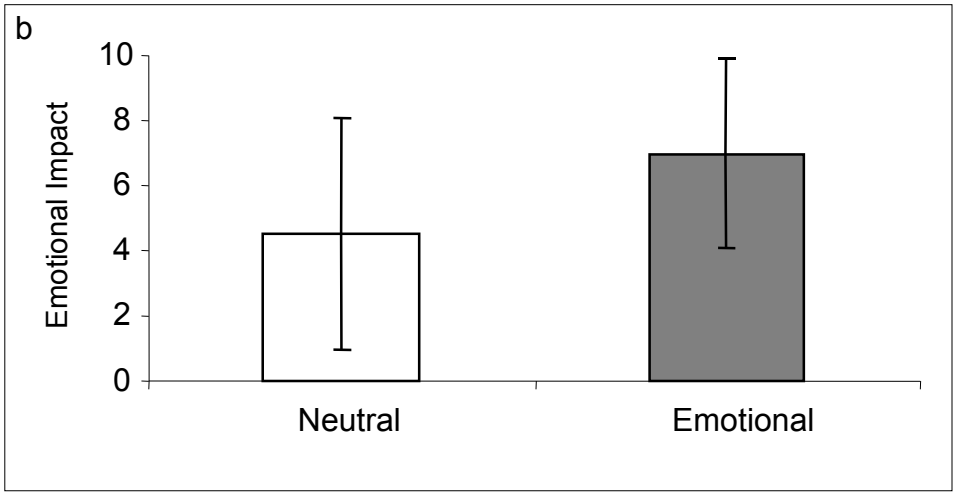
Emotional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Parte III

DISCUSSÃO

Os achados dessa tese demonstram que a presença da comorbidade ansiosa no transtorno bipolar está associada à pior qualidade de vida, à maior taxa de abuso e de dependência de álcool, à psicose, à ciclagem rápida, ao maior número de tentativas de suicídio e ao pior funcionamento. Os sintomas de depressão estão associados à pior qualidade de vida (Gazalle et al., 2006) e também à ansiedade, podendo ser um fator de confusão. No entanto, a análise controlada para os escores de depressão mostrou que a qualidade de vida permanece significativamente pior no domínio psicológico da escala WHOQOL-BREF em pacientes bipolares com ansiedade. Além disso, os resultados contrariam a idéia de que a qualidade de vida é apenas uma medida da depressão, indicando que é um conceito amplo e que pode ser influenciada por diversos fatores. Nossos resultados mostraram que a ansiedade é um desses fatores, e que a repercussão na qualidade de vida ocorre independentemente da presença do sintomas depressivos. Ainda mais, é provável que a comorbidade ansiosa aumente o sofrimento psíquico, conforme indicam os escores mais baixos neste domínio da escala de qualidade de vida, explicando, em parte, a elevada taxa de tentativas de suicídio entre esses pacientes. Esses dados reforçam a necessidade do estudo da associação entre as comorbidades ansiosas e o TB, e do desenvolvimento de tratamentos mais específicos. Destaca-se o fato de que não existe um único ensaio clínico desenhado para avaliar tratamento dos transtornos ansiosos em pacientes bipolares. No entanto, as evidências indicam que a ansiedade deve ser um importante

alvo de estratégias que visem não só aliviar sintomas, mas também melhorar o bem estar dos pacientes com TB.

Aproximadamente metade dos pacientes com TB relataram experiências traumáticas. Esses pacientes apresentavam maiores taxas de abuso e dependência de álcool, de comorbidade com ansiedade, incluindo TEPT e maior intensidade dos sintomas depressivos. A associação de experiências traumáticas com abuso e dependência de álcool pode estar relacionada ao risco aumentado de apresentar transtornos de ansiedade, os quais também se associam com uso do álcool, como descrito no primeiro estudo. Esse fato pode dever-se ao efeito ansiolítico do álcool por sua ação nos receptores gabaérgicos. Em relação à investigação da associação de experiências traumáticas no TB, é importante lembrar que o desenho transversal do presente estudo não permite concluir se o trantorno bipolar predispõe ao maior risco de exposição a situações de perigo ou o evento traumático contribui para o desenvolvimento e para maior gravidade do TB, ou, ainda, ambos. O mesmo raciocínio pode ser usado para interpretar o estudo da comorbidade ansiosa no TB. No entanto, dados de estudos prospectivos sugerem que a presença de abuso na infância está associado ao desenvolvimento de episódios de humor e ao início do TB em uma idade mais precoce (Leverich & Post, 2006); e confirmam que a presença de comorbidade ansiosa está associada ao pior funcionamento após um ano de observação (Otto et al., 2006b).

Outra constatação importante é o fato de que a presença de experiências traumáticas, mesmo que não seja feito o diagnóstico de TEPT, tem implicações na gravidade da apresentação clínica do TB. Na nossa amostra, enquanto 47.8% dos pacientes bipolares apresentavam história de trauma, apenas 16.5% preenchiam

critérios para o diagnóstico de TEPT. Isto sugere que o trauma em pacientes bipolares pode estar sendo subvalorizado e subtratado, em função de que muitos não apresentam o diagnóstico de TEPT. Nossos resultados alertam para a repercussão dessas experiências em relação à gravidade clínica e à redução nos níveis de BDNF. Os níveis séricos de BDNF estavam diminuídos nos pacientes que apresentavam história de eventos traumáticos em relação àqueles sem experiências traumáticas. Esse é o primeiro estudo a avaliar os níveis séricos de BDNF em pacientes com história de trauma. É possível que a maior gravidade da apresentação clínica em pacientes bipolares com experiências traumáticas se deva, em parte, à redução dos níveis de BDNF. Os dados da literatura pré-clínica corroboram nossos resultados. Em modelos animais de estresse o BDNF está reduzido (Murakami et al., 2005). A administração de corticosterona, assim como o estresse, reduz os níveis de BDNF, enquanto a remoção das adrenais aumenta a expressão de BDNF (Duman & Monteggia, 2006). Além disso, em pacientes com TB, os níveis de BDNF têm adquirido importância por estarem alterados na mania a também na depressão, correlacionando-se com a gravidade dos sintomas (Cunha et al., 2006). A presença do polimorfismo do gene do BDNF val66met tem sido associada ao desenvolvimento do TB (Neves-Pereira et al., 2002), com achados controversos (Green et al., 2006). Um estudo recente demonstrou que pacientes deprimidos com o polimorfismo do BDNF val66met apresentam alteração da atividade do eixo hipotálamo-hipófise-adrenal (Schule et al., 2006).

O conhecimento da base neurobiológica da associação entre o TB e experiências traumáticas, como o estudo do BDNF, abre perspectivas para o tratamento e prevenção do prejuízo associado a essa condição. O BDNF por ser parte

de uma ampla cascata bioquímica oferece diversos alvos para o estudo e desenvolvimento de futuros tratamentos. O grande desafio com o uso clínico das neurotrofinas é que não foi encontrada uma forma de administração viável, em que a substância cruze a barreira hemato-encefálica (Carlson et al., 2006). No entanto, a complexa regulação do BDNF permite que outras estratégias sejam investigadas. Por exemplo, sabe-se que o bloqueio dos receptores serotoninérgicos 5-HT2A bloqueia parcialmente os efeitos do estresse nos níveis de BDNF (Duman & Monteggia, 2006). A interleucina 1B também parece contribuir para regulação para baixo (*downregulation*) dos níveis de BDNF (Hasler et al., 2006). O BDNF apresenta afinidade pelo receptor TrkB (subtipo de receptor tirosina cinase) e, ao ligar-se, ativa uma sequência de reações altamente reguláveis, as quais envolvem PKC, PI-3K, MAPK e culminam na alteração da transcrição gênica através da ativação da CREB (Shaltiel et al., 2006). Medicamentos como lítio e antidepressivos parecem alterar diferentes etapas dessa seqüência (Warner-Schmidt & Duman, 2006), aumentando os níveis de BDNF (Chen B et al., 2001). Ainda hoje considerado um dos tratamentos mais eficazes para depressão, o ECT aumenta os níveis séricos de BDNF em pacientes deprimidos refratários (Bocchio-Chiavetto et al., 2006), além de, em modelos animais de eletrochoque, aumentar a expressão gênica do BDNF, quando administrado repetidamente, e regular vias neurotróficas (Zetterstrom et al., 1998). Mais interessante ainda são as evidências de que a redução dos níveis circulantes de corticóides pode ter efeito antidepressivo. De fato, medicamentos antagonistas do cortisol, os quais causam uma *up-regulation* dos receptores de glucocorticóides, se mostraram promissores no tratamento da depressão e sintomas cognitivos (Young, 2006). No entanto, ainda não é totalmente conhecida a via pela qual o cortisol parece diminuir os níveis de BDNF

(Smith et al., 1995). Além do BDNF, outras neurotrofinas parecem estar envolvidas na neuropatofisiologia do transtorno bipolar. Recentemente nosso grupo demostrou que o GDNF está aumentado na mania e na depressão, mas não em bipolares eutímicos (Rosa et al., 2006). Em conjunto, esses achados ampliam as possibilidades de desenvolvimento de novos tratamentos, avançando além da hipótese monoaminégica do TB.

Outro aspecto importante para compreendermos a associação das experiências traumáticas com o transtorno bipolar é o estudo da memória emocional e do funcionamento da amígdala. Surpreendentemente, o aumento da memória para a informação com conteúdo emocional não foi observado nos pacientes bipolares. A priori, poderíamos esperar que por apresentarem volume e atividade aumentados na amígdala, os pacientes bipolares seriam mais sensíveis ao impacto emocional e por conseqüência lembrariam mais os fatos associados à emoção. No entanto, nossos resultados constataram que isso é somente em parte verdade. Os pacientes com TB se mostraram sensíveis ao impacto emocional da história, mas aqueles que assistiram a história neutra, ao contrário dos controles, também se sentiram emocionalmente afetados. Assim, o aumento da sensibilidade do circuíto do processamento emocional não resultou em um eficaz aumento da memória. Ao contrário, os resultados indicam uma disfunção da amígdala. É possível que a sensibilidade aumentada ao conteúdo emocional dos fatos, seja disfuncional por impedir o foco no conteúdo realmente emocional, importante de ser lembrado. Pode-se especular que os pacientes com TB tenham uma predisposição a interpretar os fatos da vida como emocionais ou traumáticos. Esses dados estão de acordo com a literatura que mostra que eventos

estressantes estão relacionados ao desencadeamento de episódios de humor em pacientes com TB.

A interpretação dos resultados deve levar em consideração que a formação da memória emocional é um processo complexo, que envolve diversas etapas e outras estrututras cerebrais além da amígdala (Cahill, 1999). De fato, os pacientes bipolares apresentaram um pior desempenho global de memória em relação aos controles, o que era esperado. A literatura descreve prejuízo cognitivo no TB, principalmente da memória verbal e da função executiva. Esse fato deve ser atríbuído à disfunção de outras estruturas, como por exemplo o hipocampo e o córtex préfrontal. A amígada é uma estrutura com numerosas conexões para outras áreas cerebrais também envolvidas na função cognitiva, como córtex sensorial, hipocampo e córtex pré-frontal (Phillips et al., 2003). Sabemos que o impacto da emoção na formação da memória se dá através da modulação da amígdala sobre a consolidação da memória no hipocampo. A amígdala também parece modular memórias dependentes do estriado, que, em geral, são memórias implícitas. Estudos neuropatológicos no TB constataram redução das linhas de células neuronais no hipocampo (Benes et al., 1998). Há relatos de redução de células da glia e redução da densidade e volume no córtex cingulado anterior em pacientes bipolares (Phillips, 2003). Outros estudos demonstram redução da atividade no córtex pré-frontal no TB (Lawrence et al., 2004). As alterações observadas nessas outras estruturas podem estar contribuindo para o déficit cognitivo observado no TB.

Apesar desse estudo ter avaliado o processo de formação da memória como um todo, testando a lembrança dos fatos uma semana depois da tarefa, devemos lembrar que este engloba diversas etapas. Sabe-se que a amígdala modula as memórias

formadas no hipocampo principalmente aumentando a etapa da consolidação. No entanto, estudos demonstram que a amígdala também influencia o processamento emocional durante a aquisição, através de sua modulação da atenção e percepção. Estudos de neuroimagem confirmam que há a ativação da amígdala durante a aquisição da memória emocional, e que esse grau de ativação correlaciona-se com o aumento posterior da retenção da memória para o conteúdo emocional. Em contraste, os pacientes bipolares não apresentaram esse aumento da memória, em nossa amostra, embora estudos anteriores tenham mostrado aumento da atividade nessa estrutura em diferentes tarefas. É possível que as vias que partem da amígdala e modulam o aumento da consolidação no hipocampo estejam disfuncionais. A amígdala, ainda, tem papel importante na facilitação da atenção e da percepção de estímulos emocionalmente salientes, através do rápido *feedback* e estímulo de regiões do córtex sensorial. No reconhecimento de faces de medo, a amígdala parece modular a atenção e percepção detectanto o estímulo ameaçador através de vias subcorticais que passam pelo córtex visual. No entanto, a presença das vias subcorticais para detecção do estímulo foram questionadas, uma vez que a resposta da amígdala ao medo não é totalmente automática e depende da atenção. Os nossos resultados constatam uma alteração na percepção do impacto emocional da informação nos pacientes bipolares em comparação com os controles. Embora alteração da atenção seja descrita em pacientes bipolares, os escores da escala de impacto emocional subjetivo sugerem que os pacientes estavam sensíveis ao conteúdo da história. Além disso, a comparação foi feita entre as fases da história, além da comparação entre indivíduos. A alteração da função da amígdala no TB pode estar contribuindo para o desenvolvimento dos sintomas cognitivos e comportamentais. O estudo do papel da amígdala nos

transtornos do humor ainda é limitado pela dificuldade da análise volumétrica e mesmo funcional da amígdala em humanos, devido ao seu tamanho e localização. No entanto, são antigas as evidências de sintomas de humor e comportamentais das epilepsias de lobo temporal e, que somam-se aos relatos de casos de lesões degenerativas restritas à amígdala que estão associadas à perturbação emocional, compredominância de ansiedade, depressão e irritabilidade (Shibuyia-Tayoshi et al., 2005). Estudos de neuroimagem funcional no TB que incluam paradigmas de memória emocional vão ajudar a esclarecer quais vias também estão alteradas nesse transtorno.

Outro fato interessante em relação aos resultados do presente estudo é que essas alterações cognitivas foram encontradas em pacientes eutímicos. Esse fato tem duas implicações principais. Primeiro, esses dados reforçam a idéia de que não há uma recuperação total entre os episódios de humor no transtorno bipolar, como se acreditava inicialmente. Estudos têm demostrado que o prejuízo cognitivo pode se manter nos estados de eutimia. Segundo, essas alterações podem representar, em parte, a base neuroanatomica funcional para a manutenção da alternância dos episódios de humor, uma vez seriam um ponto vulnerável e desencadeante de episódios de humor, que se mantém nos estados de eutimia. É fato que mesmo com tratamento em doses terapêuticas, muitos pacientes ainda apresentam recorrência dos episódios de humor. É possível hipotetizar que o observado aumento do volume e da atividade da amígdala no TB leva à um aumento disfuncional da sensibilidade desse sistema em detectar o significado emocional dos fatos e em produzir estados afetivos. Além disso, o controle desses estados afetivos pode estar prejudicado, considerando os achados de redução do volume e atividade do córtex pré-frontal e do sistema dorsal.

Os sintomas tanto da fase maníaca quanto da fase depressiva, como labilidade de humor, distrabilidade e prejuízo cognitivo, podem estar associadas a essas disfunções.

As limitações dos estudos aqui discutidos já foram mencionadas nos capítulos anteriores. Aqui, discuto as perpectivas que surgem a partir destas. Primeiramente, estudos prospectivos poderiam confirmar os dados aqui apresentados e acrescentar a possibilidade de identificar fatores protetores ou de risco para os desfechos de gravidade clínica e de qualidade de vida. Além disso, estudos com pacientes no estágio inicial do TB, como amostras de pacientes que tiveram o primeiro episódio de mania, que são seguidos prospectivamente, poderiam esclarecer se a exposição ao trauma ocorre antes do início do TB, ou, ainda, se o próprio transtorno predispõe a maior exposição à situações potencialmente traumáticas. O estudo dos níveis séricos de BDNF no TEPT poderiam esclarecer se essa alteração ocorre em qualquer exposição ao trauma ou está relacionado à resposta ao trauma no TB mais especificamente. Além disso, a medida dos níveis de cortisol e da função do eixo hipotálamo-hipófise-adrenal no TB a sua associação com os níveis de BDNF pode começar a esclarecer a origem da alteração das neurotrofinas observada. Da mesma forma, a observação da evolução do prejuízo cognitivo desde os estágios iniciais do transtorno pode responder a questões importantes, como por exemplo, se o déficit observado é realmente encontrado apenas depois do desenvolvimento do TB e se a progressão do déficit cognitivo está associado aos episódios de humor ou à alterações neuroquímicas como os níveis de BDNF. A avaliação da memória emocional e função da amígdala em pacientes maníacos e deprimidos também pode esclarecer as diferenças entre as fases da doença. Embora difícil de executar, estudos com pacientes não medicados poderiam excluir os efeitos das medicações sobre a cognição. Exames de imagem

funcionais podem investigar o padrão de ativação da amígdala e de outras estruturas cerebrais durante o processo da memória emocional, clarificando nossos achados iniciais.

Em suma, os dados apresentados nesta tese demonstram a importância da comorbidade ansiosa no transtorno bipolar e em particular, das experiências traumáticas. Através da investigação da neurobiologia e da cognição, as possíveis vias fisiopatológicas dessa associação são indicadas, e inúmeras questões permanecem para serem esclarecidas em futuros estudos.

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