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O IMPACTO DO TRAUMA NA INFÂNCIA NA NEUROBIOLOGIA, COGNIÇÃO E MORFOLOGIA CEREBRAL EM CRIANÇAS EM IDADE ESCOLAR E EM PACIENTES APÓS O PRIMEIRO EPISÓDIO DE MANIA

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SUMÁRIO

PREFÁCIO

O presente trabalho surgiu a partir da ideia de investigar os efeitos do trauma na neurobiologia e cognição em crianças. Assim, realizamos um estudo sobre o prejuízo cognitivo associado a história de trauma em crianças que integrou a dissertação de mestrado da aluna, executada no Programa de Pós-Graduação em Psiquiatria desta universidade (Bücker et al., 2012). A partir destes resultados, vimos a importância de estudar as alterações neurobiológicas associadas ao trauma nesta mesma amostra, a fim de auxiliar no entendimento dos mecanismos envolvidos no prejuízo associado às experiências adversas na infância. Avaliamos uma amostra de crianças sem diagnóstico de transtorno psiquiátrico para controlar os resultados para possíveis fatores de confusão, como, por exemplo, a cronicidade da doença, uso de medicação psiquiátrica a longo prazo e hospitalização.

Com a realização do doutorado sanduíche na University of British Columbia, no Canadá, surgiu a oportunidade de estudar os efeitos do trauma em uma amostra de pacientes com Transtorno de Humor Bipolar no início da doença, logo após o primeiro episódio de mania. Este estudo faz parte de uma coorte que investiga a progressão do transtorno bipolar. Nessa amostra, investigamos a associação do trauma ao prejuízo cognitivo em pacientes bipolares no início da doença e em controles saudáveis. Também avaliamos as mudanças na morfologia cerebral em pacientes bipolares após o primeiro episódio de mania com história de trauma na infância comparados àqueles sem trauma e a controles saudáveis sem trauma.

Enfim, esta trajetória uniu o aprendizado obtido através das experiências no Programa de Pós-Graduação em Psiquiatria e no doutorado sanduíche no exterior, dando continuidade ao estudo realizado durante o mestrado e resultou em três artigos científicos que serão apresentados nesta tese na seguinte ordem:

- Brain-derived neurotrophic factor and inflammatory markers in school-aged children with early trauma.
- The impact of childhood trauma on cognitive functioning in patients recently recovered from a first manic episode: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM).
- Childhood maltreatment and corpus callosum volume in recently diagnosed patients with Bipolar I Disorder: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM).

1. Bücker J, Kapczinski F, Post R, Ceresér KM, Szobot C, Yatham LN, *et al.* (2012): Cognitive impairment in school-aged children with early trauma. *Comprehensive Psychiatry* 53: 758–764.

ABREVIATURAS E SIGLAS

BD- do inglês, *Bipolar Disorder*

BDNF- do inglês, *Brain Derived Neurotrophic Factor*, fator neurotrófico derivado do cérebro

BMI- do inglês, *Body Mass Index*

CBA- do inglês, *Cytometric Bead Array*

CC- corpo caloso

CT- do inglês, *childhood trauma*

CTQ- do inglês, *Childhood Trauma Questionnaire*

CVLT-II- do inglês, *California Verbal Learning Test – Second Edition*

DSM-IV- do inglês, *Diagnostic and Statistical Manual of Mental Disorders*; manual diagnóstico e estatístico dos transtornos mentais

ES- do inglês, *effect size*

GAF- do inglês, *Global Assessment of Functioning*

HAM-D-29- do inglês, *Hamilton Depression Rating Scale, 29-item version*

HPA- eixo-hipotálamo-pituitária-adrenal

IL- interleucina

IV- do inglês, *intracranial volume*

K-BIT- do inglês, *Kaufman Brief Intelligence Test*

K-SADS-E- do inglês, *Kiddie Schedule for Affective Disorders and Schizophrenia Epidemiologic Version*

MDD- do inglês, *major depressive disorder*

MINI- do inglês, *Mini International Neuropsychiatric Interview*

MRI- do inglês, *magnetic resonance imaging*

NAART- do inglês, *North American Adult Reading Test*

IQ- do inglês, *Intelligence Quotient*

OCD- do inglês, *obsessive-compulsive disorder*

OD- do inglês, *optical density*

PTSD – do inglês, *post-traumatic stress disorder*

QI- Quociente de Inteligência

STOP-EM- do inglês, *Systematic Treatment Optimization Program for Early Mania*

TEPT- Transtorno de Estresse Pós-Traumático

THB- Transtorno de Humor Bipolar

TNF-α- Fator de Necrose Tumoral Alfa

YMRS- do inglês, *Young Mania Rating Scale*

WISC-III- do inglês, *Wechsler Intelligence Scale for Children – III Edition*

RESUMO

A exposição a eventos traumáticos durante a infância está associada a um prejuízo na cognição, neurobiologia e morfologia cerebral. No entanto, não se sabe se o trauma está relacionado a essas mudanças em amostras que não apresentam potenciais fatores de confusão como idade avançada, cronicidade do transtorno psiquiátrico e múltiplos episódios de humor. O impacto do trauma na infância foi avaliado em duas amostras diferentes nesta tese: 1) crianças com e sem história de trauma; 2) pacientes com diagnóstico de THB logo após a recuperação do primeiro episódio de mania com e sem história de trauma na infância e controles saudáveis com e sem história de trauma na infância. Os resultados sugerem que o trauma está associado a mudanças na neurobiologia, cognição e morfologia cerebral. Crianças com trauma apresentaram aumento nos níveis de BDNF, TNF-α, IL-6 e IL-10 comparadas com crianças sem trauma. No entanto, após a exclusão de crianças com história de doença inflamatória, apenas os níveis de BDNF e TNF-α permaneceram aumentados em crianças com trauma. Na população com transtorno bipolar, a história de trauma na infância foi associada a uma diminuição no QI, atenção auditiva e memória verbal e memória de trabalho enquanto um padrão diferente foi observado nos controles saudáveis com história de abuso infantil. Pacientes com THB e trauma também apresentaram menor volume total do CC em comparação aos pacientes com THB e sem trauma, com diferenças significativas também na região anterior do CC. Por outro lado, não encontramos diferenças significativas entre o volume do CC nos pacientes com ou sem trauma em comparação aos controles saudáveis. Estes achados reforçam a extensão e gravidade do

impacto negativo do trauma na infância, em diferentes etapas do desenvolvimento, afetando tanto aspectos cognitivos, como neurobiológicos e de morfologia cerebral.

Palavras-chave: trauma na infância, transtorno de humor bipolar, cognição, corpo caloso, citocinas e BDNF.

ABSTRACT

Exposure to traumatic events during childhood is associated with impairment in cognition, neurobiology and brain morphology. However, it is unknown if trauma is related to these changes in samples that do not show the potential confounds of advancing age, chronicity of psychiatry disorder and multiple mood episodes. We evaluated the impact of childhood trauma in two different samples: 1) children with and without childhood trauma; 2) pacients with a BD diagnosis recently recovered from a first manic episode with and without childhood trauma and healthy controls with and without childhood trauma. The results suggest that childhood trauma is associated to changes in neurobiology, cognition and brain morphology. Children with trauma showed higher levels of BDNF, TNF-α, IL-6 e IL-10 compared to children without trauma. However, after excluding children with history of inflammatory disease, only BDNF and TNF-α levels remained increased in children with trauma. In BD patients, the childhood trauma was associated to a decreased IQ, auditory attention, verbal memory, and working memory and a different pattern was observed in healthy subjects with a history of childhood abuse. The total CC volume was found to be smaller in BD patients with trauma compared to BD patients without trauma and differences were more pronounced also in the anterior region of the CC. On the other hand, we did not find significant differences in the CC volume of patients with/without trauma compared to the healthy subjects. These findings reinforce the extent and severity of the negative impact of childhood trauma in different stages of development, affecting cognitive aspects, as well as neurobiological and brain morphology.

Keywords: childhood trauma, bipolar disorder, cognition, corpus callosum, citokines and BDNF.

1. INTRODUÇÃO

1.1 Trauma na infância

A violência contra a criança é um fenômeno complexo e multifatorial, com consequências graves para o desenvolvimento infantil, sendo considerada um problema de saúde pública (Gomes et al. 2002). A Organização Mundial de Saúde define o trauma na infância como a presença de abuso físico ou emocional, abuso sexual, negligência ou tratamento negligente, exploração comercial ou qualquer outro tipo de exploração, que resulte em danos reais ou potenciais para a saúde, sobrevivência, desenvolvimento ou dignidade da criança em uma relação de responsabilidade, confiança ou poder (Report of the Consultation on Child Abuse Prevention, 1999). O trauma na infância também é definido como a presença de abuso sexual, físico e emocional, negligência física e emocional (Marques,1994; Bernstein et al., 2003) e pode ser considerado precoce quando ocorre antes dos 6 anos de idade (Tardivo, 2005). O abuso sexual é um fenômeno universal, considerado a forma mais grave, recorrente e geradora de efeitos negativos para o desenvolvimento das vítimas e que atinge todas as idades, níveis sociais e econômicos, etnias, religiões e culturas (Pfeiffer & Salvagni, 2005).

A incidência de trauma na infância na população em geral é alta com uma estimativa de 35% na América do Norte (Gorey & Leslie, 1997), com índices maiores em crianças de 2 a 17 anos de idade (71%) (Finkelhor et al., 2007), resultando em um custo anual superior a US$100 bilhões (Wang & Holton, 2007). A frequência de abuso sexual na infância é maior nas mulheres (7%-36%) do que nos homens (3%-29%) (Olafson, 2011). Estudos sugerem que até 82% dos pacientes com diagnóstico de doença mental

grave apresentam história de trauma na infância (Larsson et al., 2013a) e que a maioria dos pacientes com transtorno de humor que são atendidos no sistema público de saúde relatam a vivência de eventos traumáticos durante a infância (Lu et al., 2008).

O processo de recuperação após a vivência traumática ainda não é bem compreendida, apesar das altas taxas na população e das consequências negativas desta experiência (Stige et al., 2013). O abuso sexual está correlacionado com uma série de transtornos mentais como depressão, transtornos alimentares e do sono (Chen et al., 2010) e a piores desfechos clínicos como o prejuízo na saúde mental e física, pior funcionamento e aumento de abuso de substâncias na população adulta em geral (Dube et al., 2001; Dube et al., 2002) e em adultos com diagnóstico de transtorno de humor (Lu et al., 2008). Estudos mostram também que a exposição a experiências adversas durante a infância podem ter um impacto negativo na resposta ao tratamento em pacientes com Transtorno de Humor Bipolar (THB) (Marchand et al., 2005). Um estudo de Sugaya et al., (2012), mostrou que o risco para o desenvolvimento de transtorno psiquiátrico em adultos é relacionado à frequência de abuso físico sofrido na infância, sugerindo uma relação de dose-resposta entre essas duas variáveis. Pacientes com transtorno de humor reportam, em geral, maior frequência de abuso físico e sexual, mais incidência de experiências traumáticas ao longo da vida e sintomas de estresse pós-traumático que àqueles com outros transtornos psiquiátricos como, por exemplo, esquizofrenia (O'Hare et al., 2013).

Pode-se especular então que existem diferentes "janelas" de vulnerabilidade em que experiências negativas precoces podem induzir em um aumento da susceptibilidade para o desenvolvimento de transtorno mental no futuro (Goldberg & Garno, 2005). O

aumento da frequência e o acúmulo de experiências severas adversas durante a infância podem também contribuir para o desencadeamento de um mecanismo de resposta patológica, podendo ser reativados no futuro por eventos de estresse de menor gravidade ou podem predispor a uma maior exposição a eventos adversos ao longo da vida (Leverich et al., 2002b; Horesh & Iancu, 2010). O trauma na infância pode também ocorrer antes do início do THB, podendo assim, desencadear o primeiro episódio, que é frequentemente associado a estressores psicossociais (Vieira et al., 2003).

1.2 Transtorno de Humor Bipolar

O THB é a 6ª causa de incapacidade no mundo entre a faixa etária dos 15 aos 44 anos (Murray & Lopez, 1996). Este transtorno afeta aproximadamente 1% a 2,4% da população (Belmaker, 2004; Merikangas et al., 2011), podendo chegar a 6,4% nas classificações que incluem formas atenuadas do transtorno (Judd et al., 2002; Katzow et al., 2003). Estudos populacionais sugerem que o início dos sintomas ocorre geralmente entre o fim da adolescência e o início da idade adulta (Weissman, 1991). Setenta e cinco por cento dos pacientes maníacos apresentam sintomas psicóticos durante o curso da doença, fazendo com que o THB seja um dos mais comuns transtornos psicóticos, com uma prevalência ao longo da vida semelhante à esquizofrenia (Tohen, 1990).

Pacientes com THB apresentam pior desempenho cognitivo mesmo durante períodos de eutimia (Goodwin & Jamison 1990; Bora et al, 2009; Torres et al., 2007; Robinson et al, 2006), e este déficit é associado a um pior funcionamento social e ocupacional (Martinez-Aran et al., 2004a) e parece ser progressivo e também é associado

aos anos de doença e ao número de episódios (Kapczinski et al., 2008; Kauer-Sant'Anna et al, 2009; Torrent et al, 2012).

1.3 Trauma e Transtorno de Humor Bipolar

A associação entre trauma na infância e o desenvolvimento de transtorno psiquiátrico, como por exemplo o THB, tem sido reportado em diferentes estudos (Etain et al., 2010; Horesh & Iancu, 2010; Larsson et al., 2013b; Watson et al., 2013). A incidência de trauma na infância é mais frequente e severa em pacientes com THB em comparação a controles saudáveis, com uma alta frequência de abuso emocional e negligência no grupo de pacientes (Leboyer et al., 2007; Etain et al., 2010; Fowke et al., 2012). Além de predispor o paciente ao THB, o trauma na infância pode também modular a expressão clínica e o curso da doença, aumentando a vulnerabilidade dos sintomas durante seu desenvolvimento (Hammersley et al., 2003; Etain et al., 2008; Daruy-Filho et al., 2011).

No entanto, uma limitação é que a maioria dos estudos avaliam os eventos adversos de forma retrospectiva, limitando assim as conclusões sobre a causa e efeito do trauma na infância e THB e o risco para um potencial viés de memória não pode ser subestimado neste caso (Daruy-Filho et al., 2011). Uma hipótese sobre a causa e efeito do trauma na infância e THB sugere que crianças com vulnerabilidade hereditária ou ambiental para a doença, podem ser mais expostas a eventos traumáticos (Daruy-Filho et al., 2011).

Presença de trauma na infância em pacientes com THB parece estar relacionada ao aumento da progressão da doença e é também considerado um alto fator de risco para a cronicidade da doença, impactando na sua fisiopatologia (Daruy-Filho et al., 2011; Angst et al., 2011). Existem evidências sugerindo que pacientes com THB que foram expostos ao trauma na infância além de serem mais sintomáticos (Neria et al., 2005), apresentam maior número de hospitalizações psiquiátricas (Carballo et al., 2008), início precoce da doença (Garno et al., 2005; Larsson et al., 2013b), história positiva de psicose (Savitz et al., 2009) e aumento da frequência e gravidade de alucinações e psicose (Hammersley et al., 2003). Trauma na infância e THB também estão associados a sintomas depressivos recorrentes na vida adulta, juntamente com baixos níveis de funcionamento pré-mórbido, baixa aderência ao tratamento e taxas mais altas de história forense (Conus et al., 2010). Eventos adversos na infância são considerados um fator de risco para suicídio e tentativas de suicídio em THB em comparação com aqueles sem trauma (Halfon et al., 2013; Dilsaver et al., 2007; Garno et al., 2005; Leverich & Post, 2006; Brown et al., 2005; Carballo et al., 2008). Pacientes com THB e história de trauma na infância também parecem apresentar comorbidades com várias doenças clínicas, como alergias, artrite, asma, síndrome da fadiga crônica, irregularidades menstruais crônicas, fibromialgia, hipotensão arterial, síndrome do cólon irritável e enxaqueca (Post et al., 2013).

O curso do THB em pacientes com história de trauma na infância também inclui ciclagem rápida (Garno et al., 2005; Leverich & Post, 2006), maior prevalência de transtornos afetivos em parentes de primeiro grau (Carballo et al., 2008), gravidade dos episódios maníacos (Leverich et al., 2002b) especialmente em pacientes com história de

abuso físico na infância (Levitan et al., 1998), juntamente com agressividade e impulsividade (Daruy-Filho et al., 2011) e menor duração dos estados de eutimia em comparação a pacientes sem história de trauma na infância (Leverich et al., 2002b). Os pacientes com THB e trauma apresentam atraso na aderência ao tratamento em comparação aos pacientes sem trauma (Leverich et al., 2002b) e esse atraso pode contribuir para o aumento da incidência de abuso de substâncias e álcool nestes pacientes, em parte como uma tentativa de automedicação (Leverich & Post, 2006).

Transtorno de Estresse Pós-Traumático (TEPT) é também uma das consequências mais frequentes do trauma na infância (Brown et al., 2005) e é fortemente e, talvez, diretamente, associada ao THB e vice-versa (Maniglio, 2013). As taxas de pacientes com THB que também apresentam TEPT variam de 11% a 24% (Goldberg & Garno, 2005; Quarantini et al., 2010), enquanto que na população geral as taxas variam de 3% a 5% (Kessler et al., 2005). Em torno de um terço dos pacientes com THB e com história de trauma na infância, especialmente abuso sexual, desenvolvem também TEPT (Goldberg & Garno, 2005).

A frequência do trauma na infância parece ser importante para o curso da doença. Leverich et al. (2003) e Leverich, Perez et al. (2002a), mostraram que pacientes que relataram a incidência única ou rara de abuso físico apresentaram menos tentativas de suicídio que àqueles que apresentaram maior frequência de trauma na infância. Contudo, história de abuso sexual na infância, mesmo ocorrendo uma única vez, está associado ao aumento da incidência de tentativas graves de suicídio.

A exposição a eventos adversos é comum também em amostras de crianças com THB, com um impacto negativo no prognóstico da doença. Um estudo com adolescentes

com THB mostrou que 53% destes pacientes apresentavam história de maus-tratos e que o trauma na infância estava associado ao atraso no diagnóstico, maior número de hospitalizações psiquiátricas e diminuição na resposta ao tratamento (Marchand et al., 2005). Crianças com THB são mais susceptíveis a apresentarem um maior número de familiares com história de abuso de álcool, que está relacionada com maior desorganização parental e um maior risco de trauma na infância (Etain et al., 2008). História de abuso também está correlacionada com TEPT, psicose, transtorno de conduta e história familiar de transtorno de humor em jovens com THB (Romero et al., 2009).

Estudos têm relatado a presença de trauma na infância em até metade das amostras de pacientes com THB (Goldberg & Garno, 2005; Garno et al., 2005; Etain et al., 2010), mostrando a importância de explorar este aspecto durante o tratamento destes pacientes (Conus et al., 2010). No entanto, a prevalência de presença de trauma na infância medido por questionários autoaplicáveis é maior do que a prevalência de trauma mensurada através de prontuários médicos, provavelmente porque os médicos não investigam frequentemente sobre a presença de trauma nos seus pacientes (Shannon et al., 2011).

Garno et al. (2005), avaliaram pacientes com THB e história de trauma na infância. O tipo de trauma mais frequente nesta amostra foi o abuso emocional, relatado por 37% dos pacientes. Vinte e quatro por cento referiram história de abuso físico, 24% de abuso emocional, 21% de abuso sexual e 12% de negligência física. Além disso, um terço destes pacientes apresentaram uma combinação de diferentes tipos de trauma e um aumento para o risco de suicídio e ciclagem rápida. Outro estudo também relatou uma

maior frequência de abuso emocional e negligência em pacientes com THB, em comparação a outros tipos de trauma (Fowke et al., 2012).

O prejuízo associado ao trauma está bem documentado no THB, entretanto não está claro se as alterações cognitivas, neurobiológicas ou na morfologia cerebral, estão presentes no início da doença, quando os efeitos da cronicidade do transtorno ainda não estão presentes. Também seria importante avaliar crianças com trauma e sem transtorno psiquiátrico para investigar os efeitos do trauma antes mesmo da manifestação da doença mental, para auxiliar na compreensão dos mecanismos envolvidos nos efeitos deletérios do abuso infantil.

1.4 Trauma na infância e marcadores biológicos

Trauma na infância pode contribuir para uma inflamação crônica em transtornos psicóticos (Suvisaari & Mantere, 2013) e também está associado com níveis elevados de citocinas por-inflamatórias na vida adulta (Danese, et al., 2009). As citocinas são proteínas produzidas por células do sistema imune e do sistema nervoso sendo fatores centrais nos processos inflamatórios (Goncharova et al., 2007). Estas proteínas têm atividades biológicas específicas que variam de acordo com a interação entre mediadores pró e anti-inflamatórios (Coelho et al., 2013). Citocinas como as interleucinas IL-6, Il-8, IL-12p70, IL-1β, e o fator de necrose tumoral (TNF-α), apresentam uma ação pró-inflamatória, enquanto a interleucina IL-10, apresenta uma atividade anti-inflamatória. Essas proteínas provocam a produção do cortisol e a hiperatividade do eixo-hipotálamo-pituitária-adrenal (HPA), sendo um estímulo para a inflamação (Watson et al., 2004). As

citocinas também modulam o controle da neuroplasticidade, resiliência celular e o controle da apoptose, que são funções do sistema nervoso central (Munoz-Fernandez et al., 1998). A resposta inflamatória é parte de uma resposta complexa do sistema imunológico a estímulos nocivos, tais como a patogênese, o dano celular ou os estressores ambientais (Coelho et al., 2013).

Estudos têm mostrado que história de trauma na infância está associado a alterações nos níveis de citocinas e a um estado inflamatório crônico independente de comorbidades clínicas (Coelho et al., 2013). Este estado inflamatório crônico pode ser relacionado ao aumento nos níveis de plasma/soro de citocinas pró-inflamatórias em estudos com pacientes com história de trauma, bem como a resultados inconsistentes em relação aos mediadores anti-inflamatórios (Coelho et al., 2013). A revisão sistemática de Coelho et al. (2013) mostrou também que além de uma associação entre trauma na infância e resposta inflamatória, as consequências a longo prazo das experiências traumáticas no início da vida são aumento do risco para a manifestação de psicopatologia na vida adulta.

O Fator Neurotrófico Derivado do Cérebro (BDNF) é um membro das neurotrofinas, uma família de proteínas estruturalmente relacionadas. Um grande número de estudos demonstrou que o BDNF desempenha um papel diverso na regulação da estrutura e função neuronal, tanto no desenvolvimento quanto no sistema nervoso central do adulto (Savitz et al., 2007; Perroud et al, 2008). O impacto deletério das experiências traumáticas precoces parece ser modulado pela variabilidade genética individual e está relacionado a alterações do BDNF (Rattiner et al., 2005; Aguilera et al., 2009). Esta neurotrofina parece mediar os principais processos dependentes de estímulo externo,

como aprendizado, experiências e memórias, bem como regular tanto a função sináptica de curto e longo prazo.

Eventos que ocorrem cedo na infância podem ter efeitos a longo prazo, reativando repetidamente os mediadores biológicos que respondem ao stress, e acredita-se que o BDNF neutraliza o impacto negativo dos hormônios do stress. O BDNF é mais fortemente expresso no hipocampo (Yan et al. 1997) e danos nesta estrutura cerebral resultam em expressão reduzida do mRNA do BDNF em outras áreas do cérebro (Rybakowski et al., 2003). Baixa expressão do BDNF também foi considerado um preditor de menor volume do hipocampo esquerdo em uma amostra de primeiro episódio de psicose, demonstrando que o estresse pode ativar mudanças biológicas que podem influenciar as estruturas cerebrais no primeiro episódio de psicose, como por exemplo, através dos níveis de BDNF (Mondelli et al., 2011).

Kauer-Sant'Anna et al (2007) avaliou o impacto da história de trauma na infância nos níveis séricos de BDNF em pacientes com THB. Este estudo mostrou que o abuso sexual estava associado a níveis séricos mais baixos de BDNF, podendo ser um responsável pelas comorbidades psiquiátricas. Entre os eventos traumáticos, o abuso sexual apresentou uma associação mais forte com a redução dos níveis de BDNF. Estes dados sugerem que o componente sexual do trauma na infância tem um maior impacto na psicopatologia e nos níveis séricos de BDNF. Por outro lado, a predisposição genética para redução dos níveis de BDNF também poderia contribuir para uma maior vulnerabilidade ao THB e aos efeitos neurobiológicos dos eventos traumáticos (Kauer-Sant'Anna et al., 2007).

O polimorfismo para o gene do BDNF val66met, que produz uma substituição de uma valina por metionina na proteína proBDNF no códon 66, está relacionada com os níveis reduzidos de secreção de BDNF pela célula (Egan et al., 2003). Trauma na infância e o polimorfismo do gene do BDNF val66met tem sido associado com alterações em pacientes psiquiátricos em vários estudos. A baixa atividade do alelo Met do gene do BDNF (val66met) e a presença de história de trauma na infância, podem estar associadas ao o transtorno obsessivo-compulsivo (Hemmings et al., 2013) e a maior severidade, cronicidade e idade de início precoce no THB (Liu et al., 2010; Miller et al., 2013). Pacientes com depressão maior e controles saudáveis com história de trauma na infância e que são portadores do polimorfismo do gene do BDNF val66met, apresentaram redução do volume do hipocampo (Carballedo et al., 2013). Além disso, a presença do trauma na infância e do polimorfismo do BDNF (val66met) parecem impactar mais fortemente a sintomatologia depressiva em sujeitos saudáveis (Aguilera, et al., 2009), mostrando que os efeitos adversos do trauma podem ser notados mesmo em sujeitos que não apresentam um transtorno psiquiátrico.

Até onde sabemos, não há, porém, estudos que avaliam os níveis de BDNF e citocinas em uma amostra de crianças com trauma comparadas a crianças sem trauma. Todos os estudos relatados foram conduzidos em amostras de adultos com história de trauma na infância.

1.5 Trauma e prejuízo cognitivo em pacientes com Transtorno de Humor Bipolar

O estudo das funções cognitivas e a relação dessas funções com áreas cerebrais é um dos campos da neuropsicologia. O prejuízo das funções cognitivas é uma característica central no THB (Chaves et al., 2011; Hellvin et al., 2012; Leboyer & Kupfer, 2010) e as principais funções prejudicadas são: memória verbal, funcionamento executivo e déficits na atenção (Martinez-Aran et al, 2004b; Malhi et al., 2007), não somente durante os episódios de humor (Kurtz et al., 2009) mas também durante a eutimia (Torres et al., 2007). Esses prejuízos variam de acordo com a duração da doença, número de episódios, uso de medicação, psicose, comorbidades, entre outros fatores (Kapczinski et al., 2009; Robinson & Ferrier, 2006), e podem ser identificados mesmo em pacientes que estão no início da doença (Hellvin et al., 2012).

A memória verbal se refere a memória na forma de linguagem e pode ser de curta e longa duração (Toulopoulouand & Murray, 2004). O funcionamento executivo é considerado o aspecto mais complexo da cognição e é o responsável pelas capacidades de resolver problemas, utilizar conceitos abstratos, gerenciar as habilidades cognitivas, planejamento, monitoramento e flexibilidade cognitiva (Elliott, 2003). A atenção pode ser sustentada, dividida ou seletiva. A atenção sustentada ajuda na detecção e resposta a determinadas mudanças nos estímulos apresentados. A atenção dividida é a capacidade de atendermos dois ou mais estímulos ao mesmo tempo e de forma eficiente. A atenção seletiva nos permite um foco sobre um aspecto mais específico de um estímulo apresentado (Nabas & Xavier, 2004).

Funções cognitivas também são sensíveis às experiências ambientais (Knudsen, 2004) e Quociente de Inteligência (QI) elevado está associado com uma diminuição ao risco de exposição a eventos traumáticos (Breslau et al., 2006). Do ponto de vista do

desenvolvimento, o trauma na infância tem potencialmente uma alta chance de amplos e nocivos efeitos na função cognitiva e na neurobiologia. Alguns estudos apontam para diferenças encontradas em cada tipo de trauma como o pior desempenho visuoespacial, linguagem, QI e função executiva naqueles com história de maus-tratos ou abuso sexual. Àqueles com história de negligência, apresentam pior desempenho na atenção auditiva e integração visual-motora (Scarborough et al., 2009; Pears & Fisher, 2005; De Bellis et al., 2009).

Estudos avaliaram as consequências do trauma na função cognitiva em pacientes com psicose e THB. Pacientes com psicose e história de trauma na infância apresentam prejuízo cognitivo principalmente em velocidade do processamento, memória de trabalho, função executiva, aprendizagem, memória verbal, atenção, concentração, linguagem e inteligência verbal, na fase crônica da doença e até mesmo após o primeiro episódio de psicose (Lysaker et al., 2001; Schenkel et al., 2005; Shannon et al., 2011a; Aas et al., 2011; Aas et al., 2012). Somente dois estudos encontraram resultados negativos ou inconclusivos entre cognição e trauma na infância em primeiro episódio de psicose (Aas et al., 2011; Sideli et al., 2013), com o último e maior estudo mostrando um efeito do trauma na infância na função cognitiva em controles saudáveis mas não em pacientes (Sideli et al., 2013).

Pacientes com THB e altas taxas de eventos adversos na infância, apresentaram pior desempenho na memória, fluência verbal e flexibilidade cognitiva (Savitz et al., 2007; Savitz et al., 2008). Quando avaliado o impacto dos diferentes tipos de trauma na cognição nos pacientes com THB, os abusos físico e sexual parecem estar associados ao prejuízo na função executiva, percepção, habilidades viso-espaciais e verbais enquanto o

prejuízo na memória de trabalho está relacionada somente com o abuso físico (Aas et al., 2012).

O único estudo que avaliou os efeitos do trauma na cognição em pacientes no início da doença bipolar mostrou que esses pacientes apresentaram uma pior performance cognitiva em comparação aos pacientes sem história de trauma (Aas et al., 2011a). No entanto, somente pacientes com psicose foram incluídos neste estudo. Além disso, a presença de um tamanho pequeno da amostra (20 pacientes com trauma e 9 pacientes sem trauma) e a ausência de um grupo controle podem limitar a discussão desses achados. Portanto, é importante avaliar a presença de trauma na infância em amostras de pacientes com THB em estudos neuropsicológicos especialmente se estes pacientes foram expostos a altas taxas de eventos estressores (Savitz et al., 2008).

Alguns importantes mecanismos podem estar envolvidos no prejuízo cognitivo em pacientes com THB e história de trauma na infância. Estudos indicam que história de trauma na infância (Savitz et al., 2007; Shaltiel et al., 2007; Kurnianingsih et al., 2011) e a presença do polimorfismo do gene do BDNF estão associados com prejuízo cognitivo, especialmente na memória no THB. De forma semelhante, pacientes com psicose e portadores do polimorfismo do gene do BDNF val66met, com história de trauma na infância, especialmente abuso físico e abuso emocional, demonstraram prejuízo cognitivo em comparação àqueles pacientes que não eram portadores do polimorfismo do BDNF (val66met) (Aas et al., 2013). Neste estudo o prejuízo cognitivo foi mais proeminente na função executiva/fluência verbal, memória de trabalho e habilidades verbais. Estes resultados demonstram que o polimorfismo do gene do BDNF val66met modula a associação entre abuso na infância e déficit cognitivo em psicose e que os fatores

ambientais são importantes para avaliar o prejuízo cognitivo nestes pacientes (Aas et al., 2013).

A hiperatividade do eixo HPA também tem sido descrito no THB e àqueles pacientes com mais tempo de doença, maior número de episódios e características psicóticas, parecem apresentar ainda maior desregulação do eixo HPA (Daban et al., 2005; Jabben et al., 2011). Estudos em controles saudáveis mostraram que um evento estressor e posterior excesso de cortisol pode ser um dos mecanismos subjacentes do prejuízo cognitivo (Liston et al., 2009; Beluche et al,. 2010). Estudos que avaliaram pacientes com esquizofrenia (Saffer et al., 1985; Lupien et al., 2000) e depressão maior (Zobel et al., 2004; Egelandet al., 2005; Reppermund et al., 2007), mostraram uma associação entre a resposta do eixo HPA e função cognitiva. No entnato, somente um estudo avaliou a função do eixo HPA na associação entre sintomas depressivos e funcionamento cognitivo no THB (Werf-Eldering et al., 2012). Os resultados mostraram que as mudanças na atividade do eixo HPA parecem não explicar a associação entre a severidade dos sintomas depressivos e o prejuízo cognitivo no THB (van der Werf-Eldering et al., 2012).

A partir do exposto, faz-se importante a investigação da associação entre prejuízo cognitivo e trauma na infância em pacientes com THB, principalmente no início da doença, devido a escassez de dados na literatura. Avaliar pacientes no início da doença, também pode auxiliar no entendimento dos mecanismos envolvidos nos efeitos deletérios do trauma quando pode-se controlar os potenciais fatores de confusão como, por exemplo, a cronicidade da doença.

1.6 Influência do transtorno de humor bipolar e do trauma na infância em estruturas do cérebro

A infância é um período de grande vulnerabilidade e é a fase mais importante para a maturação cerebral (Toga et al., 2006). Assim, fatores ambientais, como por exemplo, o trauma na infância, podem causar significativas mudanças na maturação do sistema nervoso central (Etain et al., 2008). Estudos pré-clínicos têm demonstrado que o abuso infantil promove mudanças a longo prazo na reativação ao estresse e desenvolvimento do cérebro (Heim e tal., 1997; Kaufman et al., 2000). Diferentes formas de trauma na infância podem afetar o sistema nervoso central de forma diferente, dependendo da severidade e da cronicidade dos eventos (Etain et al., 2008; Sugaya et al., 2012).

Muitas pesquisas foram dedicadas ao estudo dos efeitos do trauma na anatomia do cérebro. Estudos de neuroimagem em crianças, adolescentes e adultos com história de trauma encontraram alterações estruturais em diversas regiões cerebrais, como por exemplo no hipocampo, corpo caloso (CC), córtex pré-frontal e amígdala (Bremner et al., 2002; Grassi-Oliveira et al., 2008; Edmiston, et al., 2011; Rinne-Albers et al., 2013). Por exemplo, a relação entre as vivências traumáticas na infância e redução de volume da amígdala e hipocampo foi observada em uma amostra de pacientes em primeiro episódio de psicose (Hoy et al., 2011). Os resultados demonstraram que a história de trauma na infância foi um preditor significativo de menor volume do hipocampo esquerdo e menor volume direito e total da amígdala. Em outro estudo relevante em pacientes com primeiro episódio de psicose (Aas, 2012), o abuso infantil estava associado ao pior funcionamento

cognitivo (função executiva, linguagem e inteligência verbal) e menor volume da amígdala que parece mediar a relação entre história de trauma e prejuízo cognitivo.

Estudos de neuroimagem em pacientes em primeiro episódio maníaco são limitados e se tem poucas informações sobre quais mudanças cerebrais podem estar presentes no início da doença. No entanto, a redução de substância branca parece ser o achado mais proeminente em pacientes no início da doença bipolar (Vita et al., 2009; De Peri et al., 2012). Estudos mostram também que pacientes com THB e mais tempo de doença apresentam mudanças no volume do CC em comparação a controles saudáveis (Lloyd et al., 2013). Apesar dos pacientes com THB apresentarem altas taxas de prevalência de trauma na infância, até onde sabemos, não existem estudos de neuroimagem que avaliaram os efeitos do trauma na infância em pacientes com THB.

O trauma na infância é sabidamente associado a menor volume do CC (Grassi-Oliveira et al., 2008; Rinne-Albers et al., 2013) e De Bellis et al. (1999), mostrou que a redução do CC foi o achado anatômico mais significativo em uma amostra de crianças com trauma na infância e TEPT (De Bellis et al., 1999). O CC é a maior estrutura de substância branca do cérebro humano e conecta os dois hemisférios do cérebro, permitindo que eles troquem informações, desempenhando um papel crucial na cognição (Li et al., 2014). A redução do tamanho do CC tem sido associada com a dimunição da comunicação entre os hemisférios cerebrais (Clarke et al., 1994).

Os mecanismos envolvidos na redução do CC a partir do trauma na infância podem estar relacionados a uma forma alternativa e adaptativa do organismo de lidar com eventos estressores. Grassi-Oliveira et al. (2008) descreve que uma criança nascida em um ambiente com altos níveis de estresse, terá de modificar as estruturas psicológicas e

neurológicas para se adaptar as experiências de toxicidade durante a infância. No entanto, em estágios inicias do desenvolvimento, essas modificações e rearranjos podem se tornar potencialmente prejudiciais principalmente se utilizadas fora do contexto ou em um ambiente traumático.

Estudos com ratos também mostraram que os efeitos de experiências traumáticas na infância podem ser mediados através de diferentes mecanismos. Em um estudo de Juraska and Kopcik (1988), os autores dividiram ratos em um ambiente "complexo" e em um ambiente de "isolamento". No "ambiente complexo" 12 ratos do mesmo sexo foram alojados em uma gaiola, junto com alguns objetos de madeira, plástico e metal. Estes ratos também ficavam 30 minutos por dia em campo aberto com acesso a novos brinquedos. Já os ratos do "ambiente de isolamento", foram alojados na mesma sala, mas em gaiolas individuais e menores e podiam enxergar o ambiente fora da gaiola. Os ratos do sexo feminino que estiveram em um "ambiente complexo" apresentaram um aumento significativo de axônios mielinizados comparados com àqueles que estiveram em um "ambiente isolado" (Juraska and Kopcik, 1988). Já os ratos do sexo masculino tiveram um aumento do diâmetro dos axônios mielinizados, quando expostos a um "ambiente complexo", comparado com àqueles que estiveram em um "ambiente isolado", mostrando, neste caso, a importância da diferença de gênero. Este resultado corrobora com a hipótese de que o trauma na infância pode afetar o desenvolvimento do CC também nos humanos. A partir desses dados, pode-se pressupor que existe uma associação entre trauma na infância e volume do CC, mas ainda não se sabe se esta relação pode ser de causa e efeito (Teicher et al., 2004).

Teicher et al., (2004), também discute que os estudos em animais ajudam a esclarecer em parte esta relação de causa e efeito já que os sujeitos são distribuídos randomicamente entre os grupos. Isto ajudaria a eliminar as hipóteses de que indivíduos com redução do volume cerebral apresentam maior risco de vivenciarem uma experiência traumática na infância ou de que a redução do volume cerebral pode ser herdada e que prejuízo semelhante nos familiares pode aumentar o risco de trauma na infância (Teicher et al., 2004).

A partir do exposto, parece-nos de grande interesse investigar o impacto do trauma na infância nas alterações neuroquímicas, neurofuncionais e neurocognitivas, principalmente no início do THB, quando os efeitos da medicação, múltiplos episódios e psicose ainda não apresentaram prejuízos tão significativos. A avaliação destas alterações ampliam o entendimento relacionado aos efeitos do trauma na infância.

2. OBJETIVOS

2.1 Objetivo geral

Estudar o impacto do trauma na infância na cognição, neurobiologia e morfologia cerebral em pacientes com transtorno de humor bipolar após o primeiro episódio de mania e em uma amostra de crianças sem transtornos psiquiátricos.

2.2 Objetivos específicos

-Comparar os níveis plasmáticos de BDNF, citocinas pró-inflamatórias (IL-6, Il-8, IL-12p70, IL-1β, TNF-α) e anti-inflamatórias (IL-10) em crianças com trauma em relação a crianças sem trauma.

-Investigar o impacto do trauma na infância na cognição em pacientes que se recuperaram recentemente de seu primeiro episódio de mania. Comparar o desempenho cognitivo entre pacientes com THB após o primeiro episódio de mania e com história de trauma na infância com àqueles sem história de trauma e com controles saudáveis com e sem história de trauma.

-Avaliar a relação entre trauma na infância e a morfologia do CC no THB. Comparar o volume do CC entre pacientes com THB após o primeiro episódio de mania e com história de trauma na infância com àqueles sem história de trauma e com controles saudáveis sem história de trauma.

3. Artigo

3.1 Artigo 1 – submetido ao Biological Psychiatry

Brain-derived neurotrophic factor and inflammatory markers in school-aged children with early trauma

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Abstract:

Background: Childhood trauma (CT) has been associated with alterations in BDNF and cytokines levels in adults. However, the impact of maltreatment on these levels earlier in development remains unclear. In this study, we investigated the association between CT and changes in BDNF and cytokines plasma levels in children with and without trauma.

Methods: We recruited 36 children with trauma between 3 and 12 years of age and 26 children without trauma. The presence or absence of CT was based on a clinical interview and by Criteria A of DSM-IV criteria for PTSD. Blood samples were drawn from all children to assess BDNF, IL-12p70, IL-6, IL-10, IL-1β, IL-8 and TNF-α. ANCOVA was performed with psychiatric symptoms and BMI as covariates in order to evaluate group differences in plasma levels.

Results: After adjusting for confounders, results indicated that children with trauma showed increased levels of BDNF, TNF-α, IL-6 and IL-10 (all $p<.05$) when compared with those without trauma. IL-12p70, IL-8 and IL-1β levels were not statistically different between groups. However, after excluding children with history of inflammatory disease, only BDNF and TNF-α levels remained increased in children with trauma ($p<.05$).

Conclusions: children with trauma have increases in the neurotrophin BDNF as well as in pro- and anti-inflammatory cytokines. The BDNF and IL-10 increases may be an attempt to neutralize the negative effects of trauma in early life, while TNF-a and other cytokine increases may reflect increases in inflammation. How these changes

associated with trauma relate to biological changes and illness trajectory later in life remain to be further studied.

Keywords: Trauma, BDNF, cytokines, children

Introduction

Childhood trauma (CT), here defined as physical abuse, sexual abuse, emotional abuse, and neglect (1), has been described as one of the most severe environmental stressor and a critical event for investigation (2) in the prevention of psychiatric illness. CT also has been found to be associated with poor outcomes in adults (3, 4) and children (5) in several domains as well as alterations in biological markers, particularly in brain-derived neurotrophic factor (BDNF) (6) and inflammatory cytokines (7).

BDNF is a member of the neurotrophins' family and is important for brain development, plasticity, and maintenance of neurons in adult life (8), and plays a critical role in the formation of long term memory and other cognitive processes (9). A growing body of evidence indicates that patients with psychiatric illness have altered peripheral BDNF levels, especially those with bipolar disorder (BD) (10), schizophrenia (11) and post-traumatic stress disorder (PTSD) (12).

The impact of CT on BDNF levels has also been reported in patients with psychiatric disorders. Our group has previously shown that the history of childhood abuse was associated with lower levels of serum BDNF in adult patients with BD, which may account for increased psychiatric comorbidity (6). Reduced BDNF expression was also

found in first-episode psychosis patients with a history of CT, through a pathway that may involve increased inflammation (13). Similar findings have been reported in animal models. For instance, an association between life long reduced *Bdnf* gene expression in prefrontal cortex and early life stress has been reported in a study with a rat model of infant maltreatment by a caregiver (14).

CT appears to interact with *BDNF* val66met polymorphism to confer predisposition to cognitive impairments, changes in brain volumes and psychiatric symptoms (15). For instance, carriers of the met allele exposed to high level of childhood abuse showed increased risk to develop obsessive-compulsive disorder (OCD) (16). In samples of Schizophrenia spectrum disorder, BD (17) and major depressive disorder (MDD) patients (18), those with CT and carriers of the met allele showed cognitive impairment and reduced brain volumes. Furthermore, *BDNF* val66met seems to moderate the effect of CT on adult depressive symptoms in a healthy population (19), showing that the deleterious effect of CT might be noted even in subjects without a psychiatric disorder.

Cytokines are important proteins for the development of a normal brain and have the ability to mediate key steps in cellular immunity and influence behavior (20). Chronic exposure to elevated inflammatory cytokines and the associated persistent alterations in neurotransmitter systems can lead to depression and other psychiatric disorders (20), and CT may have long-term effects on activation of stress-responsive biological mediators.

Similarly, pro-inflammatory cytokines have been proposed to be associated with symptomatology and disease progression in BD (21, 22), as a trait marker in schizophrenia (23), and are possibly involved in the pathophysiology of MDD (24).

Studies have also shown that CT may have an important role in the cytokines' changes in patients with psychiatric disorders (7, 25, 26) and in healthy subjects (26), suggesting that these alterations may precede the development of a stress-related psychiatric disorder (27).

To date, however, no study has examined both cytokine and BDNF levels in children with a history of trauma to evaluate whether alterations are present in early life, a crucial period for development and vulnerability of the brain. Our group has previously evaluated a sample of children and showed cognitive impairment in those with a history of trauma compared with those without trauma (5). However, it is currently unknown what neurobiological changes occur as a result of childhood trauma and how they might confer vulnerability to cognitive impairment or psychiatric symptoms. Therefore, the objective of this study was to examine the impact of childhood trauma on biomarkers in children with a history of early trauma and compare them with children without trauma. We hypothesized that the experience of maltreatment would be associated with increases in pro-inflammatory cytokines and decreases in BDNF levels in school-aged children.

Methods and materials

Patients with trauma were drawn from a Child Protection Program and a foster care home in south Brazil. Children with early trauma between the ages of 3-12, that had experienced sexual abuse, maltreatment, and/or neglect (i.e., trauma), were recruited. We considered early trauma as a trauma before the age 4 years. Children that had unstable

clinical illness, physical disabilities or neurological illness were excluded. The presence of childhood trauma was based on a clinical interview by a trained psychiatrist and a standardized psychiatric examination based on criterion A1 of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for PTSD and adapted from PTSD module of Kiddie Schedule for Affective Disorders and Schizophrenia Epidemiologic Version (K-SADS-E) structured interview to include also in the examples sexual abuse and neglect. A perfect age and sex match proved difficult to recruit; nevertheless, the groups were highly similar.

Children without a trauma history were recruited from a community primary health care center within the same catchment area, as well as a nearby school and pediatric clinic. Written informed consent was obtained from all parents or guardians in accordance with the Declaration of Helsinki and was obtained after the nature of the procedures had been fully explained. For those with a legal guardian, we also obtained a court authorization allowing us to invite the child to participate in the study. After informed consent was obtained from the parent or guardian, a puppet show was used to explain study procedures to the children, and their assent to participate was also obtained. A local ethics committee approved the study protocol.

Psychiatric status was assessed using a structured interview that was designed in accordance with DSM-IV criteria (K-SADS-E) and modified to incorporate DSM-IV, Text Revision criteria. The same psychiatrist completed all psychiatric interviews and was trained to administer the K- SADS-E. The psychiatrist was not blinded, given the fact that the children with trauma were recruited separately in time and place from the children without trauma.

Clinical and sociodemographic variables were assessed using a standardized protocol and were obtained from the best sources available, including an interview with the child, the parents, or guardians and a medical record review. All participants had blood samples collected for biochemical analyses at the time they were enrolled into the study. Body mass index (BMI) scores were calculated using each child's weight, height, sex and age, recommended by American Journal of Clinical Nutrition's (28, 29).

We used a 2-subtest short form of the Wechsler Intelligence Scale for Children – III Edition (WISC-III): the Vocabulary and Block Design subtests, to generate an IQ score.

Distribution of BDNF and cytokines

IL-6, IL-8 and BDNF showed a non-normal distribution, therefore, we applied a log transformation, which resulted in significant improvement in the distribution. We also detected an outlier in IL-10 and IL-1β and we changed the score to be one unit above the next highest score in the data set to reduce the impact of this value in the analyses, as recommended by Field (2009) (30).

We controlled the BDNF and cytokines analyses for subsyndromal symptoms due to the fact that these neurotropic and inflammatory markers are altered in patients with psychiatric disorders (10-12, 22-24). Of note, even though children in our sample did not meet criteria for a psychiatric disorder, the group with trauma reported subsyndromal symptoms. We also analyzed these data without controlling for subsyndromal symptoms, and the results did not change. Thus, results controlled for subsyndromal symptoms were reported for consistency. We also controlled for BMI due to significant differences between groups.

Biochemical assays

Four milliliters of blood were withdrawn from each subject by venipuncture into a vacuum tube with anticoagulant. The blood was centrifuged at 4000g for 10 min and plasma was kept frozen at - 80 °C until assayed. BDNF plasma levels were measured by sandwich-ELISA using a commercial kit according to the manufacturer's instructions (Millipore, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 hrs at 4 °C with the samples diluted 1:100 in sample diluent and standard curve ranging from 7.8 to 500 pg of BNDF. Plates were then washed four times with buffer followed by the addition of biotinylated mouse anti-human BNDF monoclonal antibody (diluted 1:1000 in sample diluent), which was incubated for 3 hrs at room temperature. After washing, a second incubation with streptavidin- horseradish peroxidase conjugate solution (diluted 1:1000) for 1 hr at room temperature was carried out. After addition of 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.

Cytokines measurement

The concentration of plasma cytokines was determined by flow cytometry using the BD™ Cytometric Bead Array (CBA) Human Inflammatory Cytokine Kit (BD Biosciences, San Diego, CA). The CBA kit employed allows the discrimination of the following cytokines: IL-12p70, IL-6, IL-10, IL-1β, IL-8 and TNF-α. Sample processing and data analysis were performed according to the manufacturer's instructions. Briefly, plasma samples were incubated with the six cytokine capture beads for 1.5 hrs, then washed and incubated for more 1.5 hrs with PE-conjugated detection antibodies both

incubations at room temperature and protected from light. Afterwards, samples were washed and sample data were acquired using a FACS Calibur flow cytometer (BD Biosciences, San Diego, CA). Results were generated in graphical and tabular format using the BD CBA Analysis Software FCAP Array™ (BD Biosciences, San Diego, CA). This methodology has been described previously (21).

Statistical Analysis

All statistical analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA). To assess demographic and clinical group differences, the chi-square test was used to compare categorical variables between children with trauma and comparison subjects, and by ANOVA to compare continuous variables. Plasma levels of each of the biomarkers were assessed for normality using visual inspection of histograms and the Shapiro-Wilk test. Data from these variables that were found to be skewed were adjusted using logarithmic (ln) transformation. The main comparisons of plasma levels of BDNF and cytokines between the two groups (children with and without trauma) were performed in a model with psychiatric symptoms and BMI as covariates (ANCOVA). Partial correlation analyses were carried out to determine the correlation between plasma levels and duration of trauma, age of onset of trauma and length of time since trauma cessation, after controlling for psychiatric symptoms. All statistical tests were 2 tailed with a significance threshold of $\alpha = 0.05$.

Results

Demographics

As shown in Table 1, there were 36 children with trauma and 26 children without trauma. There were no differences between these groups in years of education, IQ, age, and gender (all $p > .38$). However, children with trauma showed higher BMI compared to their controls ($p < .05$). 19.4% of children with trauma reported sexual abuse, whereas 52.8% and 91.75% reported physical abuse and neglect, respectively. More than a half (52.8%) of these children had been exposed to more than one type of trauma.

Twenty-seven of children with trauma showed subsyndromal psychiatric symptoms (75%) and 4 (11.11%) were taking methylphenidate. No children met the criteria for a psychiatric diagnosis according to DSM-IV, Text Revision; therefore, we report the presence of psychiatric symptoms according to K-SADS-E and clinical interview. The subsyndromal symptoms of children with trauma were depression (n=6), mania (n=2), psychosis (n=1), anxiety (n=10), irritability (n=8), attention-deficit/hyperactivity disorder (n=6), conduct disorder (n=14), drug abuse (n=1), language delay (n=3), enuresis (n=7), encopresis (n=1), and sleep disturbance (n=4). No children without trauma showed psychiatric symptoms or met the criteria for a psychiatric diagnosis according to DSM-IV. Four children with trauma (11.1%) and 5 children without trauma (19.2%) showed infectious or inflammatory disease, such as migraine (n=1), respiratory disease (n=7) and thyroid disease (n=1). The information related to age at onset of trauma, duration of trauma and length of time since trauma cessation are reported in Table 1.

Group differences in BDNF and cytokines measurements

As detailed in Table 2, there were significant differences in TNF-α, IL-1β, IL-6, IL-10 and BDNF levels (all $p < .05$) between children with and without trauma. Post-hoc

analysis showed significantly greater levels of these parameters in those with trauma. There were no differences in IL-12p70, and IL-8 levels between children with and without trauma (all p>.05). We also conducted analyses excluding children that were taking medication, but this did not change the results.

Furthermore, considering that even if not acute, infectious and inflammatory diseases may be a confounding factor, we performed further analyses removing children who had these conditions. The results of controlled analysis show that only TNF-α [F(1, 47)= 9.23, p= .004, Effect Size (ES)=-.15] and BDNF [F(1,48)=4.19, p=.04. ES=-.53] levels remained significantly different between groups, with greater levels in patients with trauma.

For the partial correlation analyses, we included only children with trauma and used the variables "duration of trauma", "age of onset of trauma" and "length of time since trauma cessation" to correlate with BDNF and cytokines levels, partialling out psychiatric symptoms and BMI. The only significant finding was a positive correlation between IL-6 and age of onset of trauma r= .36; p=.03).

Discussion

Our results demonstrate that children with trauma showed increased levels of BDNF, the inflammatory cytokines TNF-α, IL-1β and IL-6 and the anti-inflammatory IL-10 when compared with those without trauma. These parameters were not correlated with the duration of trauma, the age of onset of trauma and the length of time since trauma cessation, except for a positive correlation between IL-6 and age of onset of trauma. However, sample size may limit interpretation of exploratory analysis such as correlation

with multiple clinical features. IL-12p70 and IL-8 levels were not associated with trauma in our sample. When we excluded children with diseases that might reflect infection or inflammation from our analysis, only TNF-α and BDNF levels remained increased in patients with trauma. Thus, the higher levels of BDNF and TNF-α in children with trauma compared with those without trauma are the strongest findings in this study.

A previous study (31) evaluated the role of chronic family stress on cytokines levels in children with and without asthma. However, the term "chronic family stress" was considered a broad term, focusing, for example, on family relationships, friendships, school, and home life over the period of the past 6 months although this included neglect, physical, sexual and emotional abuse.

A growing body of evidence indicates that adults with a history of childhood trauma and psychiatric disorders show decreases in BDNF (6) and increases in cytokines levels (7, 25, 26) and a history of CT may result in damage to immune system functioning, leading to a permanent chronic inflammatory state (32). Lower BDNF expression in adulthood does seem to be related to poorer cognitive performance (33), smaller hippocampal volumes (13), and increased psychiatric comorbidity (6).

Thus while previous studies found lower levels of BDNF in adults with a history of CT (6, 13), we found the opposite in our child sample. The reasons for this difference remain to be further explored. However, early life stressors may initially engender BDNF increases either directly or as a compensatory mechanism. In adulthood, in conjunction with persistent increases in inflammatory cytokines and aging such counter regulatory attempts may fail and BDNF deceases. This would be consistent with similar observations that BDNF levels were decrease late but not early in the course of BD (22).

It would be helpful to study the same patients longitudinally in order to assess this possibility. It is also possible that resilience may have played role in the BDNF increases, as these children where no longer in there adverse environments and were in a potentially relatively enriched environment.

A growing body of evidence suggests that stress and traumatic events may have effects on BDNF expression through the modulation of epigenetic mechanisms, including DNA methylation and histone modifications (14, 34). Recent studies have also suggested that different genotypes may differentially interact with epigenetic mechanisms in determining the expression levels of some proteins (35). It is possible that this gene x environment interaction plays a key role in the BDNF levels assessed in our sample, although BDNF subtype were not available in this same. However, other evidence suggests that while the Val66met allele of proBDNF maybe associated with cognitive dysfunction in adults (15), with further aging it may confer relative protection against the development of dementia (36), again suggesting different BDNF relationships over the life span.

Enriched environments increase BDNF expression in mice (37), and differently affecting female and male (38). We used the variable "time since trauma cessation" in our analysis as a potential indicator of an enriched environment, as in this period the children were living with current caregivers or in foster care homes removed from their earlier traumatic experiences. However, we did not see a significant relationship between increases in BDNF levels and time since trauma cessation, possibly due to the small sample size or an inadequate characterization of environmental enrichment.

The pro-inflammatory IL-6 is a cytokine involved in inflammation and infection responses, as well as in the regulation of metabolic, regenerative and neural process (32). Increased IL-6 is considered to be one of the most consistent findings in psychiatric disorders (39), especially in BD patients (21). Our findings are in agreement with previous studies that have reported increased levels of IL-6 in subjects with a history of CT, especially in women with migraine (40) and in schizophrenia patients (25). The TNF-α, a pro-inflammatory cytokine, has also been found to be increased in studies that evaluated the history of CT. For instance, schizophrenia patients (25), first-episode psychosis patients (26) and women with migraine (40) that had a history of early life adversity showed higher levels of TNF-α when compared with those patients without a history of childhood stress. The higher levels of pro-inflammatory cytokine IL-1β in the group with trauma is also partly consistent with the literature, which shows that MDD patients with trauma had increased levels compared with those without trauma and healthy controls (7), although one study did not observe these changes is patients with schizophrenia (25).

The increases in anti-inflammatory cytokine IL-10 in association with CT are of interest in relationship to increases in the other pro-inflammatory cytokines. These higher levels of IL-10 may represent an attempt to increase compensatory and protective mechanisms in our sample of children with trauma.

Several previous reports did not find increase in IL-10 associated with CT in first-episode psychosis and schizophrenia patients (26, 41). However, IL-10 has been reported increased in studies of psychiatric disorder patients (where CT was not investigated), but in whom many other indices of inflammation were elevated as in our cohort (22, 42). The

increases in IL-6, IL-1β and IL-10 may be closely related to inflammatory disease in our sample, since the significance of these increases disappeared when we excluded the patients with direct or indirect evidence of associated inflammation. However, there is a very large literature associating childhood adversity to not only a variety of inflammatory conditions in both psychiatrically ill and non-psychiatrically ill patients, but also to a great many other medical illnesses and syndromes (43).

Neurotrophins and the inflammatory system can interact in different ways and the higher levels of BDNF may reduce the immune injury in the brain in an inflammatory condition (44). Nonetheless, the higher levels of IL-6, TNF-α and IL-1 β may reflect underlying inflammatory processes that will culminate in worse psychiatric and medical outcomes in these children. In a study evaluating BD patients in early compared to late stages of the illness (22), lower levels of BDNF were found only in the late stage of the disease compared to healthy controls. All interleukins, including IL-6, IL-10 and TNF-α, were increased in the early stage, whereas only IL-10 was decreased in the late stage of the illness.

Our study has several merits. It has examined a clinically relevant sample consisting of children with and without a history of early trauma and the results were controlled for age, gender, years of education, IQ, BMI, and the presence of subsyndromal symptoms. However, the results need to be considered within a framework of some limitations. First, the small sample size reduced the statistical power of this study for sub-analyses. The impact of different kinds of trauma, namely physical, sexual and emotional on plasma levels could not be examined and may warrant investigation in future studies. Another important limitation is the absence of a specific instrument to

quantify aspects such as the severity and intensity of trauma. We included some indirect quantitative information such as duration of trauma, the age of onset of trauma and the length of time since trauma cessation in an attempt to mitigate this limitation. Lastly, we also did not include the assessment of *BDNF* val66met polymorphism in our analysis, nor epigenetic alterations on the genes involved or the associated histone modifications. These parameters would be useful in futures studies, particularly in light of the association of poor outcomes in patients with a history of CT.

In conclusion, we identified increased levels of BDNF, as well as the pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and the anti-inflammatory cytokine IL-10 in children with a history of trauma compared with those without trauma. These results suggest that the children with trauma may be in a pro-inflammatory state and the higher levels of BDNF and IL-10 are possibly an attempt to compensate for or neutralize the negative effects of early trauma. Future studies in this direction may help to understand why some of those exposed to trauma show better outcomes than others, and to determine a neurobiological basis of 'windows' in development at certain ages that may allow for optimal intervention.

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Table 1. Demographic characteristics of the sample:

	Children with trauma (n=36)	Children without trauma (n=26)	F/ df	p
Characteristics	Mean ± SD	Mean ± SD		
Years of education	2.88±1.68	3.26±1.80	.72/ 1	.39
Age	9.44±2.07	8.96±2.23	.76/ 1	.38
Premorbid IQ[1]	94.14±10.74	95.21±15.03	.10/ 1	.75
BMI[2]	18.24±2.55	15.91±1.97	14.04/58	.00
Age at onset of trauma	3.11±3.31	-	-	-
Duration of trauma (years)	5.02±3.50	-	-	-
Length of time since trauma cessation (years)	1.44±2.03	-	-	-
Gender	**M/F** 22/14	**M/F** 15/11	**X^2/ df** .073/ 1	**p** .79

1- 1 child with trauma and 3 children without trauma did not perform this subtest because they were younger than 6 years and WISC-III are not valid for that age range

2- data was missing for 1 child with trauma and 2 children without trauma

Table 2. BDNF and cytokines levels of children with trauma and children without trauma

	Children with trauma (n=36)	Children without trauma (n=26)	ANCOVA[a] F/ p	Effect Size
	Mean ± SD	Mean ± SD		
BDNF[1]	1.42±.25	.89±.57	6.29/ .01	.51
TNFα[3,4]	3.61±.55	3.46±.43	10.92/.00	.15
IL-12p70[3,4]	3.24±.40	3.15±.26	.77/ .38	.13
IL-10[3,4]	1.67±.34	1.42±.24	6.24/.01	.39
IL-8[2,4]	.87±.31	.72±.20	3.47/.06	.27
IL-6[2,4]	.58±.14	.50±.09	7.43/.00	.32
IL-1beta[3,4]	2.16±.82	1.88±.33	4.48/.03	.21

a controlling for psychiatric symptoms and BMI

1- Log-transformed data. Original data as ng/ml
2- Log-transformed data. Original data as pg/ml
3- Data as pg/ml
4- Data were missing for 1 child without trauma

3.2 Artigo 2 - publicado no Journal of Affective Disorders, 2013 Jun;148(2-3):424-30.

The impact of childhood trauma on cognitive functioning in patients recently recovered from a first manic episode: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM).

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Abstract:

Background: Both bipolar disorder (BD) and childhood trauma are associated with cognitive impairment. People with BD have high rates of childhood trauma, which confer greater overall disease severity, but, it is unknown if childhood trauma is associated with greater neurocognitive impairment in BD patients early in the course of their illnesses. In this study, we investigated the impact of childhood trauma on specific cognitive dysfunction in patients who recently recovered from their first episode of mania. **Methods:** Data were available for 64 patients and 28 healthy subjects matched by age, gender and pre-morbid IQ, recruited from a large university medical center. History of childhood trauma was measured using the Childhood Trauma Questionnaire. Cognitive function was assessed through a comprehensive neuropsychological test battery. **Results:** Trauma was associated with poorer cognitive performance in patients on cognitive measures of IQ, auditory attention and verbal and working memory, and a different pattern was observed in healthy subjects. Limitations: We had a modest sample size, particularly in the group of healthy subjects with trauma. **Conclusions:** Childhood trauma was associated with poorer cognition in BD patients who recently recovered from a first episode of mania compared to healthy subjects. The results require replication, but suggest that the co-occurrence of trauma and bipolar disorder can affect those cognitive areas that are already more susceptible in patients with BD.

Key words: Bipolar disorder; childhood trauma; first-episode mania; cognition.

Introduction:

Childhood trauma is a complex experience that can include emotional, physical and sexual abuse as well as emotional and physical neglect (Dannlowski et al., 2012). It is associated with a higher number of negative life events in adulthood and with psychiatric disorders at all stages of development (Etain et al, 2008; Igarashi et al, 2010; Nanni et al, 2012). The rate of childhood maltreatment in the general population is high and in Canada has been estimated to be around 20% (Hébert et al., 2009).

Childhood trauma-related dysfunction can also be observed in healthy adults without diagnosed psychiatric illness (Dannlowski et al, 2012), both in physical health outcomes (Widom et al., 2012) and in cognitive function, especially memory (Majer et al., 2010). The negative consequences of trauma can even be observed during childhood (Nolin & Ethier, 2007). In a study by Bücker et al (2012) children who have experienced trauma but do not meet full criteria for psychiatric disorder showed attention impairment. Another study (De Bellis et al., 2009) that compared neglected children with and without PTSD did not find major significant differences in neurocognitive abilities between these two groups; however, when compared to healthy subjects, the neglected children demonstrated significantly lower neurocognitive outcomes and academic achievement.

History of trauma is more common in patients with psychotic disorders compared with the general population (Aas et al., 2011a), and, in patients with bipolar disorder (BD) (Read et al., 2005; Etain et al., 2008; Fisher et al., 2010 and 2011). The presence of multiple types of trauma also occurs more frequently in bipolar patients than in comparison subjects (Etain et al., 2010). History of maltreatment increases the risk and severity of the illness in adult life in psychotic populations (Schäfer et al., 2011; Alvarez

et al., 2011; Hoy et al., 2011) and childhood abuse and neglect are also associated with worsening clinical course in BD (Daruy-Filho et al., 2011).

It is well established that patients with BD show cognitive deficits in sustained attention, verbal and visual memory, executive function, processing speed and verbal fluency even during euthymic periods (Bora et al., 2009; Torres et al., 2007; Robinson et al., 2006). Studies with patients recently recovered from the first episode of mania show that similar, albeit less severe cognitive impairments are also present early in the course of illness (Nehra et al., 2006; Torres et al., 2010; Hellvin et al., 2012).

Both childhood trauma and BD have been associated with adverse effects on cognitive functions such as verbal and visual recall, verbal fluency and cognitive flexibility (Savitz et al., 2008). Furthermore, a history of childhood trauma is also associated with poorer cognitive performance in working memory, executive function, language and verbal intelligence in patients with first episode affective psychosis (Aas et al., 2011a). However, no studies to date have investigated the impact of childhood trauma on cognition in first episode mania samples.

Although BD patients who recently recovered from a first manic episode have impairments in various domains of cognition, the magnitude of impairment is smaller compared with those that who had multiple episodes. However, it is unknown if other risk factors such as a history of childhood trauma confers additional cognitive burden in this population. Therefore, the objective of this study is to examine the impact of childhood trauma on cognitive function in patients who recently recovered from their first manic episode in comparison to healthy subjects. It is important to study this kind of sample to verify if the cognitive impairment, present early in the course of illness, may be

exacerbated further by trauma-related dysfunction. This could direct treatment or rehabilitative efforts toward individuals with the highest susceptibility to cognitive impairment.

To analyze the data, we adopted two different strategies. First, we categorized individuals into dichotomous "trauma" versus "no trauma" groups and compared cognitive functioning between three different groups: patients with trauma, patients without trauma, and healthy subjects without trauma. In the second approach, we used scores on a validated scale of childhood trauma as a continuous variable and evaluated the linear relationship between cognitive functioning and trauma severity in both patients and comparison subjects. Based on the existing literature, we hypothesized that the experience of trauma would be associated with specific cognitive impairment especially in verbal memory and auditory attention in both patients and healthy subjects.

Subjects and methods

Patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (DSM-IV-TR) criteria for bipolar I disorder and were recruited from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) at Vancouver Hospital Health Sciences Centre and affiliated sites, as well as community and hospital referrals from physicians and psychiatrists. Diagnosis of bipolar I disorder was based on a clinical interview by a trained psychiatrist and a standardized psychiatric examination using the Mini International Neuropsychiatric Interview (MINI) (Sheehan, et al., 1998). Description of the full longitudinal study protocol can be found elsewhere (Yatham et al., 2009; Torres et al., 2010).

Healthy volunteers matched to patients on age, gender, and premorbid IQ were recruited by advertisement from the same geographical area. Written informed consent was obtained from all patients and healthy subjects in accordance with the Declaration of Helsinki and the study protocol was approved by the ethics committee of the University of British Columbia. Participants consisted of patients aged 16-34 who had experienced their first episode of mania within the 3 months preceding enrollment, and who may also have been experiencing comorbid history of substance or alcohol abuse. Psychiatric status at baseline was assessed using clinical rating scales, including the Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale, 29-item version (HAM-D-29) (Williams et al., 1988). Healthy subjects were screened using the MINI and excluded if they had a personal or family history of major Axis I psychiatric disorder. The sample in this study was obtained from a larger longitudinal study and includes patients and comparison subjects who received cognitive assessments and a history of childhood trauma interview.

Cognitive Assessment

Neuropsychological measures were selected to assess the following seven domains which have been demonstrated to be relevant to BD (Burdick et al., 2011; Yatham et al., 2010): 1) Intellectual Ability; 2) Attention; 3) Processing speed; 4) Verbal memory; 5) Nonverbal Memory; 6) Executive function; 7) Working memory. Premorbid IQ was assessed using the North American Adult Reading Test (NAART) full scale IQ (Blair & Spreen, 1989), and IQ was assessed with the Kaufman Brief Intelligence Test (K-BIT) (Kaufman & Kaufman, 1990). Processing speed was measured using the Trial-Making Test A time to completion (Reitan & Wolfson, 1993), Stroop Test word and

color naming trials number correct (Golden, 1978) and Letter Fluency number correct (Lezak, 2004). Attention was evaluated using CANTAB rapid visual information processing (RVIP) discriminability score (Robbins et al., 1994), and California Verbal Learning Test – Second Edition (CVLT-II) trial 1 words recalled (Delis et al., 2000). Working memory was measured using Wechsler Memory Scale-Third Edition (Wechsler, 1997) letter/number sequencing, CANTAB spatial working memory (SWM) between errors and strategy score. Executive function was evaluated using Stroop color/word trial number correct, Trial Making-Test B Time, CANTAB Intra-/extra-dimensional (IED) set-shifting task number of extra-dimensional shifting errors, and CANTAB stockings problems solved in minimum number of moves. Verbal memory was measured using CVLT-II recall trials 1-5, and CVLT-II short and long delayed cued and free recall. Nonverbal memory was assessed using CANTAB spatial recognition memory percent correct, CANTAB pattern recognition memory percent correct, and CANTAB paired associate learning total errors adjusted score.

All tests were administered and scored by trained research assistants. Patients were tested when they were judged to be cooperative and clinically stable, and Table 1 confirms that on average, patients showed a low level of mood symptoms. For each cognitive measure, raw scores were converted into standardised z-scores (obtained from test manuals) based on demographics-adjusted normative data for each test.

Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire (CTQ) is a reliable and valid 28-item self-report questionnaire, developed by Bernstein et al. (1994) and is defined as trauma occurring before the age of 18 years. It is administered to assess maltreatment

during childhood, including emotional, physical, and sexual abuse as well as emotional and physical neglect, and also yields a weighted total CTQ score. Items are rated on a five-point Likert scale from 1 (‘‘never true’’) to 5 (‘‘very often true’’), according to the frequency with which each event occurred. The overall total score has a range of 25 to 125 and reflects the severity of overall trauma exposure. Cutoff scores for none to low, low to moderate, moderate to severe and severe to extreme exposure are provided for each scale. Incidence of childhood trauma was determined by using cutoffs for each CTQ subscale score that indicated a moderate to severe level of exposure, according to the manual (Bernstein, 1994). Subjects were considered to have a history of trauma if 1 or more subscales met the cutoff criteria. Furthermore, the reliability of the CTQ has been demonstrated in patients with BD (Etain, 2010).

Statistical Analysis

All statistical analyses were conducted using SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA). To assess demographic and clinical group differences, the chi-square test was used to compare categorical variables and t test to compare continuous variables between patients and comparison subjects. For each cognitive measure we used analysis of variance (ANOVA) to compare cognitive functioning between patients with and without trauma and healthy subjects without trauma. We excluded the healthy subjects with trauma in this analysis due to small sample size in this group. The relationship between cognitive variables and CTQ total score was assessed using Pearson correlation coefficients within both the patient and comparison subject groups. In the latter analysis, which treated CTQ scores as a continuous variable, we included the healthy subjects with trauma. Where necessary, we also conducted analyses using

nonparametric tests or after transformation of specific variables, but the results did not change. For the main analyses described above, we elected not to adjust for multiple comparisons due to 1) the specific hypothesis that trauma would be selectively associated with memory dysfunction, and 2) because there was interest in evaluating the overall pattern of cognitive tasks that would be associated with trauma. Partial correlation analyses were carried out to determine the correlation between CTQ score and cognitive measures after controlling for residual mood symptoms (controlling variables were YMRS and HAMD). Multiple regression analysis was conducted to determine the cognitive functions most strongly associated with CTQ scores in our regression models. All statistical tests were 2 tailed and had a significance threshold of $\alpha = .05$. Data are presented as means ± SDs.

Results

Demographics:

Overall, there were 26 patients with trauma, 38 patients without trauma, 19 healthy subjects without trauma and 9 healthy subjects with trauma. Patients and controls showed a history of emotional, physical, and sexual abuse as well as emotional and physical neglect. Patient demographic and illness characteristics are presented in Table 1. Patients and healthy subjects were similar in age ($p=.92$), gender ($p=.82$), years of education ($p=.30$) and current and premorbid IQ ($p=.10$; $p=.69$, respectively). We also present these data in two different groups, patients with trauma and patients without trauma. These two groups showed differences in age at illness onset ($p=.03$) and the Global Assessment of Functioning Scale ($p<.01$), with patients with trauma showing earlier onset of disorder and poorer functioning.

Distribution of Cognitive variables:

The CANTAB Intra-/extra-dimensional (IED) set-shifting task number of extra-dimensional shifting errors measure showed a non-normal highly skewed distribution, even after applying various transformations. Thus, nonparametric statistics were applied in the analysis of this variable. However, because the results from analyses using nonparametric statistics were the same as those using parametric statistics, results for the latter were reported for consistency.

Group differences in cognitive functioning

In this first step we only compared cognitive performance in the patients with and without trauma and healthy subjects without trauma due to the small sample size of healthy subjects with trauma (n=9).

We used ANOVA to analyze group differences but we only reported on the contrasts that showed significant differences between the trauma versus no trauma patient groups. The only significant difference between cognition in patients with trauma and without trauma, as a dichotomous variable, was in CVLT-II trial 1. In this subtest, patients with trauma showed poorer performance compared to patients without trauma ($t_{61}=2.33$, $p=.02$, effect size (ES)= 0.60). This difference was not noted between patients without trauma and healthy subjects ($t_{54}=-0.48$, $p=.63$, ES= -0.13). Patients with trauma also showed poor performance in this subtest compared to healthy subjects ($t_{43}=-2.76$, $p<.01$, ES= -0.83).

Correlational and Regression Analyses

The correlational analyses for patients and healthy subjects are presented in two tables (Table 2 and 3). For analysis of healthy subjects, we included those with trauma

and used the CTQ total score as a continuous variable to correlate with neurocognitive results. The CTQ total score, especially in the healthy subject group, showed a skewed distribution and contained one outlier (one of the healthy subjects scored 92). Because there was no obvious reason to exclude this individual, we opted to change the CTQ score to the highest score in the healthy subject group plus one, as recommended by Field (2009). Due to the continued skewed distribution, we conducted a logarithmic transformation on CTQ scores and the distribution was significantly improved; however, because the raw and log-transformed data yielded the same results in all analyses, the untransformed data are presented for consistency. Table 2 reveals the correlations between the CTQ total score and cognitive variables and clinical features in patients. Correlations between Global Assessment of Functioning (GAF) and CTQ total score were significant ($r=-.26$, $p=.04$). There were no significant associations between CTQ total score and age at illness onset, total score YMRS or total score HAMD (all r's $p>.06$). There was no significant association between CTQ and number of previous depression, number of previous hypomanias, age at depression onset or age at mania onset (all r's $p>.15$; data not shown).

There was a modest negative significant correlation between CTQ total score and K-Bit IQ ($r=-.29$, $p=.02$). Apart from several scattered correlations between cognitive variables and CTQ scores, the most consistent and significant associations were observed between higher CTQ scores and poorer verbal memory and auditory attention performance as indexed by various CVLT-II variables (see Table 2). In order to help rule out the possibility that the association between each of these cognitive variables and CTQ scores was due to residual symptoms, we partialled out the effects of YMRS and HAMD.

The magnitude of the correlations remained similar and relatively unchanged. Specifically, the following variables continued to be significantly associated with CTQ scores: K-Bit IQ (r=-.29, p=.02), CVLT-II trial 1 (r=-0.32, p=.01) and CVLT-II short delay free recall (r=0.27, p=.03).

A regression model constructed to evaluate the strongest independent cognitive predictor(s) of CTQ scores. In this analysis, the strongest cognitive predictors of CTQ scores within each cognitive domain (KBIT IQ, CVLT-II trial 1, Spatial working memory strategy score, CVLT short delay free recall) were entered simultaneously as predictors into a regression equation using CTQ scores as the dependent measure. The results indicated that the only CVLT-II trial 1 scores remained as a significant predictor of CTQ scores (B=-.33, SE= 1.20, p=.009).

The results in table 3 reveal the correlations between cognitive variables and CTQ total score in healthy subjects. There were only two significant correlations between cognitive function and CTQ scores: in executive functioning and nonverbal memory. The subtests were Stockings of Cambridge (p=.02) and pattern recognition (p<.01), respectively. There were no significant associations between other cognitive subtests and CTQ total score (all r's p>.10).

Discussion

To our knowledge, this is the first report to investigate a possible relationship between childhood maltreatment and cognitive impairment in BD patients recently recovered from a first-episode of mania. One previous study (Aas et al., 2011a) also investigated the effects of childhood maltreatment on cognition in a small sample of

first episode patients with BD; however, this study was restricted to patients with psychosis and had a small sample size (20 patients with trauma and 9 without trauma) and did not include a comparison subject group. The results in this previous study showed poorer performance in language, visuo-construction and perceptual domains in patients with trauma compared to patients without trauma. Although both studies showed diminished cognitive functioning associated with trauma, the pattern of cognitive abilities affected was different between them. One possible reason for this difference may be that their patients had psychosis and this may lead to a different pattern of findings in patients with BD (Szoke et al., 2008; Martinez-Aran et al., 2008). Other study differences that may have influenced findings include our larger sample size, our conceptualization and analysis of trauma as a continuous variable, and the use of different trauma questionnaires and definitions in the two studies.

Our results showed that trauma in patients was especially associated with decreased IQ, auditory attention (which was the strongest predictor of CTQ), verbal memory, and working memory. Moreover, these associations were not merely a function of mood symptoms. These trauma-related cognitive impairments were also different from those observed in healthy subjects with childhood trauma, suggesting that the pattern of cognitive impairment may differ when both conditions co-occur. This result is consistent with the literature, which shows that childhood trauma has been associated with worse cognitive performance in BD in a more established stage of the illness (Savitz et al., 2008).

The cognitive deficit, especially in verbal memory, may be particularly relevant to BD. This domain is also considered a candidate bipolar endophenotype given large

reported deficits in BD patients (Arts et al., 2008; Balanzá-Martínez et al., 2008). In our study, the negative influence of trauma on memory functioning was revealed by the small, albeit consistent association between CTQ scores and multiple CVLT-II scores. These data thus suggest that the childhood trauma-related changes observed in patients may be due to cognitive impairment in domains of known vulnerability in BD. Furthermore, our findings imply a possible association of childhood trauma with a more severe cognitive impairment, and this influence may be detectable early in the course of illness, after a first episode of mania.

There are some potential brain mechanisms that may be related with childhood trauma and worse memory performance in BD, including the influence of BDNF (brain-derived neurotrophic factor). BDNF is a member of the neurotrophins, found throughout brain areas that can be critical for the control of cognition (Ernfors et al., 1990). Serum BDNF levels are reduced during manic and depressive episodes (Fernandes et al., 2011), in first episode of psychosis (Mondelli, 2011) and in BD patients who had a traumatic life events (Kauer-Sant'Anna et al., 2007). A growing body of evidence indicates that lower levels of BDNF and low activity in the Met allele of the BDNF gene (val66met) are associated with cognitive decline, especially memory, in patients with history of childhood trauma (Savitz et al., 2007; Shaltiel et al., 2007; Kurnianingsih et al., 2011).

Another potential brain mechanism is HPA (hypothalamic-pituitary-adrenal) axis dysfunction. Stress exposure and abnormal levels of the primary HPA axis hormone cortisol are associated with cognitive impairments in a variety of clinical samples (McEwen, 2004; Yehuda et al., 2005; Osterberg et al., 2009). In a first episode

psychosis sample, a more blunted cortisol response was associated with a more severe deficit in verbal memory (Aas et al., 2011b). It would be useful if future studies on childhood trauma also assessed BDNF and HPA axis dysfunction in first episode mania sample in order help clarify the mechanisms that may be involved regarding the negative effect of childhood stress in cognition.

The reasons for the different patterns of trauma-related cognitive impairment in patients and healthy subjects are unclear. The effects of childhood stress on cognition in healthy people has been previously associated with poorer cognitive performance in short-term and non-verbal memory (Bremner et al., 1995; Navalta et al., 2006; Majer et al., 2010), perceptual abilities (Aas et al., 2011a) and, executive function (Spann et al., 2012). Our results are partly consistent with these previous studies. On the other hand, trauma may be more strongly related to BD (Brown et al., 2005; Garno et al., 2005) even in the first episode of mania. The role of BD can be crucial to determine the cognitive performance in patients with a history of trauma.

The significant correlation between CTQ total score and cognitive performance was, both in patients and healthy subjects, more evident when we analyzed trauma as a continuous variable. This likely occurred because the categorization results in loss of information and reduced statistical power (Streiner, 2002). For this reason we feel that conceptualizing trauma as a continuous variable appears most appropriate. Many previous studies investigating the effect of childhood trauma on cognition with the same questionnaire have also employed a correlational approach (Savitz et al., 2007; Spann et al., 2012; Aas et al., 2012).

When we correlated the childhood trauma scale with illness characteristics, our results showed that high rates of history of childhood trauma were associated with more deficits in functioning. These findings are consistent with previous studies suggesting that adults with a history of childhood trauma are associated with increased disability in adulthood (Lysaker at al., 2001; Gil et al., 2009). When we compared patients with and without trauma, those with trauma showed earlier onset of the disorder, in accordance with other studies in BD in the later stages of the illness (Dienes et al., 2006; Grandin et al., 2007; Carballo et al., 2008; Daruy-Filho et al., 2011).

On the other hand, in our study there were no significant associations between childhood trauma and severity or number of previous hypomanic or depressive symptoms in the patient group. Several studies in BD, but not in first episode mania patients, reported a strong association between severity of symptoms and childhood trauma (Leverich et al., 2002; Garno et al., 2005). It is possible that more severe symptoms may be associated with childhood trauma as the illness progresses, but not in the first episode of mania.

The reported associations were demonstrated in a sample of patients in their first episode of mania and healthy subjects and they were not confounded by group differences in age, verbal intelligence or education. Nevertheless, others possible confounders, including age of onset of trauma, duration and type of trauma and comorbidity with other psychiatric disorders, were not evaluated in this study.

Some limitations of this study must be mentioned. First, although larger than prior studies, we nevertheless had a modest sample size, particularly in the group of healthy subjects with trauma. The modest sample size also prevented the comparison between

variables that showed potential importance in previous studies with childhood trauma such as gender (Fisher et al., 2009; Aas et al., 2011a) and type of trauma (Pears et al., 2008; Scarborough et al., 2009). Therefore, our findings will need to be replicated in larger samples. Another limitation is the large number of cognitive tasks and the possibility that some of the correlations were obtained by chance. We chose not to apply corrections for multiple testing because the goal was to observe the overall pattern of findings across a broad range of cognitive measures, and because we had a directed hypothesis (e.g. most of the cognitive variables associated with CTQ were from CVLT-II). The correlations were generally modest but nonetheless still significant, likely because this was a first-episode sample. The magnitudes of the correlations might be expected to increase in a more established sample.

Lastly, the use of the CTQ can be problematic in several regards. One important point is the risk of potential recall bias as childhood trauma history was based on retrospective self-report. Also, specific ages of the trauma were not available from the CTQ. Future studies that investigate specific ages at which the abuse and neglect occurred would be important to verify if the early trauma would be more harmful in this kind of sample.

Nonetheless, this report is noteworthy in several respects. It is the first study that investigated the association between childhood trauma and cognition in a first episode of mania compared to healthy subjects. Our main finding showed that trauma is associated with poor cognitive performance, especially in IQ, auditory attention, verbal memory and working memory, in patients, and different domains are implicated in

healthy subjects. This suggests that the co-occurrence of trauma and bipolar disorder, can affect those cognitive areas that are more susceptible in these patients.

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Conflict of Interest:

Joana Bücker and Leonardo Silveira received a scholarship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil. Prof Kauer-Sant'Anna has received research grants from CNPq-INCT-TM, CNPq Universal, CAPES, SMRI, NARSAD, Astra-Zeneca, Eli Lilly and Fipe-HCPA. Dr Bond has received research grants from or is on speaker / advisory boards for the Canadian Institutes of Health Research (CIHR), the UBC Institute of Mental Health / Coast Capital Depression Research Fund, the Canadian Network for Mood and Anxiety Treatments (CANMAT), the Canadian Psychiatric Association, Pfizer, AstraZeneca, Janssen-Ortho, Bristol-Myers Squibb, and Otsuka. Dr Lam has received research funds from or is on ad-hoc speaker / advisory boards for AstraZeneca, Biovail, Bristol-Myers Squibb, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Canadian Psychiatric Association Foundation, Eli Lilly & Co., Litebook Company, Lundbeck, Lundbeck Institute, Mochida, Pfizer, Servier, St. Jude's Medical, Takeda, and UBC Institute of Mental Health / Coast Capital Savings. Dr Yatham has received research grants from or is on speaker / advisory boards for AstraZeneca, Bristol-Myers Squibb,

Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Eli Lilly & Co., Forest, GlaxoSmithKline, Janssen, Lundbeck, Michael Smith Foundation for Health Research, Novartis, Otsuka, Pfizer, Ranbaxy, Servier, and the Stanley Foundation. Jan-Marie Kozicky and Dr Torres declare that they have no conflicts of interest.

Role of funding source

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Tables

Table 1. Demographic and Illness Characteristics of the Sample

	Patients with trauma (n=26)	Patients without trauma (n=38)	t, df	Patients with Bipolar Disorders (n=64)	Healthy Subjects (n=28)	t, df
Characteristic *a*	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Years of education	14.21±1.91	14.26±2.31	0.09, 62	14.24±2.13	14.78±2.50	-1.04, 89
Age	22.57±3.17	23.10±5.05	0.51, 61.64	22.89±4.36	22.78±4.90	0.10, 90
Premorbid IQ NAART	105.35±6.82	107.34±7.36	1.09, 62	106.53±7.15	107.1842±7.07	-0.40, 90
IQ (K-BIT)	103.58±9.89	105.05±10.43	0.57, 61	104.44±10.12	108.14±9.56	-1.63, 89
Age at illness onset, y	18.27±4.12	21.11±5.65	2.18, 60*	19.91±5.52		
Age at mania onset, y	22.50±3.28	23.00±4.98	0.48, 60.79	22.79±4.33		
Age at depression onset, y	16.78±3.32	19.31±6.99	1.21, 15.92	17.84±5.23		
Number of previous depressives episodes	1.36±1.63	0.95±1.54	-1.02, 61	1.11±1.57		
Number of previous hypomanic episodes	0.54±1.60	0.34±1.47	-0.50, 62	0.42±1.52		
Young mania rating scale	2.00±4.19	1.18±1.84	-0.93, 31.67	1.52±3.02		
Hamilton depression rating scale	8.35±9.13	5.47±6.07	-1.40, 39.96	6.64±7.53		
Brief Psychiatric Rating Scale	24.30±6.57	21.55±3.94	-1.90, 37.88	22.70±5.33		
Global Assessment of Functioning Scale	61.65±12.60	70.66±12.09	2.88, 62*	67.00±12.99		
	M/F	**M/F**	**X2, df**	**M/F**	**M/F**	**X2, df**
Gender	10/16	18/20	0.50, 1	28/36	11/17	0.16, 1

*p<.05
a Some illness characteristics and cognitive values were missing for 3 patients and some premorbid socioeconomic status and cognitive values were missing for 1 healthy subject.

Table 2. Correlation between CTQ total score, cognition and clinical features in patients with and without trauma

Trauma			
	N	**r**	**r2**
Clinical features			
Global assessment of functioning	64	-.26*	.06
Age at illness onset	62	-.24	.06
Total score YMRS	64	.22	.05
Total score HAMD	64	.22	.05
Intelligence Quotient			
Kbit vocabulary	63	-.20	.04
Kbit IQ	63	-.29*	.08
Kbit matrices	63	-.27*	.07
Processing speed			
TMT-A	63	.02	<.001
FAS verbal fluency	63	.06	.004
Stroop word	63	-.11	.01
Stroop color	63	-.10	.01
Attention			
Rapid visual information processing	61	-.11	.01
CVLT trial 1	63	-.36*	.13
Working memory			
Letter/number sequencing	63	-.15	.02
Spatial working memory between errors	61	-.14	.02
Spatial working memory strategy	61	-.25*	.06
Executive			
TMT-B	63	-.13	.02
Stroop interference	63	-.12	.01

Intra-/extra-dimensional task	61	.08	.01
Stockings of Cambridge	61	-.19	.04
Verbal Memory			
CVLT trials 1-5	63	-.21	.04
CVLT short delay free recall	63	-.31*	.10
CVLT short delay cued recall	63	-.29*	.08
CVLT long delay free recall	62	-.25*	.06
CVLT long delay cued recall	62	-.25*	.06
Nonverbal memory			
Pattern recognition	62	-.05	.002
Spatial recognition	61	.03	<.001
Paired associates	61	-.12	.01

*p<0.05

Table 3: Correlation between CTQ total score and cognition in healthy subjects with and without trauma

Trauma			
	N	**r**	**r2**
Intelligence Quotient			
Kbit vocabulary	28	.03	.001
Kbit IQ	28	.03	.001
Kbit matrices	28	.03	<.001
Processing speed			
TMT-A	28	.03	<.001
FAS verbal fluency	28	.21	.04
Stroop word	28	-.25	.06
Stroop color	28	-.10	.01
Attention			
Rapid visual information processing	28	.02	<.001
CVLT trial 1	28	.02	<.001
Working memory			
Letter/number sequencing	28	-.05	.003
Spatial working memory between errors	28	-.31	.10
Spatial working memory strategy	28	-.28	.08
Executive			
TMT-B	27	.14	.02
Stroop interference	28	.08	.01
Intra-/extra-dimensional task	28	-.14	.02
Stockings of Cambridge	28	-.45*	.20
Verbal Memory			
CVLT trials 1-5	28	-.14	.02
CVLT short delay free recall	28	.08	.01

CVLT short delay cued recall	28	-.19	.04
CVLT long delay free recall	28	-.06	.003
CVLT long delay cued recall	28	-.05	.003
Nonverbal memory			
Pattern recognition	28	-.50*	.25
Spatial recognition	28	-.04	.002
Paired associates	28	.12	.01

*$p<0.05$

3.3. Artigo 3 – publicado no Journal of Psychiatric Research, 2014 Jan;48(1):65-72.

Childhood maltreatment and corpus callosum volume in recently diagnosed patients with Bipolar I Disorder: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM)

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Abstract:

Childhood trauma (CT) has been associated with abnormalities in the corpus callosum (CC). Decreased CC volumes have been reported in children and adolescents with trauma as well as adults with CT compared to healthy controls. CC morphology is potentially susceptible to the effects of Bipolar Disorder (BD) itself. Therefore, we evaluated the relationship between CT and CC morphology in BD. We using magnetic resonance imaging in 53 adults with BD recently recovered from their first manic episode, with (n=23) and without (n=30) CT, defined using the Childhood Trauma Questionnaire (CTQ) and 16 healthy controls without trauma. ANCOVA was performed with age, gender and intracranial volume as covariates in order to evaluate group differences in CC volume. The total CC volume was found to be smaller in BD patients with trauma compared to BD patients without trauma ($p<0.05$). The differences were more pronounced in the anterior region of the CC. There was a significant negative correlation between CTQ scores and total CC volume in BD patients with trauma ($p=0.01$). We did not find significant differences in the CC volume of patients with/without trauma compared to the healthy subjects. Our sample consists of patients recovered from a first episode of mania and are early in the course of illness and reductions in CC volume may occur late in the course of BD. It might mean there may be two sources of CC volume reduction in these patients: the reduction due to trauma, and the further reduction due to the illness.

Keywords: bipolar disorder, first episode mania, corpus callosum, childhood trauma, magnetic resonance imaging.

Introduction

Childhood maltreatment, such as neglect, sexual and physical abuse, is highly prevalent in patients with psychiatric disorders (Arnow, 2004; De Bellis et al., 2011; Fowke et al., 2012). The long term negative consequences of childhood traumatic experiences in adults with mental illness comprise poor outcomes in various domains, including changes in brain morphology, particularly in the hippocampus (Woon & Hedges, 2008), amygdala (Vermetten et al., 2006), prefrontal cortex (Treadway et al., 2009) and corpus callosum (Villarreal et al., 2004).

Among various brain regions, corpus callosum (CC) is of particular interest given its key function in mediating communication between the right and left cerebral hemispheres and in co-ordinating a number of major cognitive processes, including, attention, arousal, emotion, and higher cognitive abilities (Giedd et al., 1996; Badaruddin et al., 2007). The development of the CC starts in utero, progresses during childhood and early adolescence by a process of myelination and is only completed in early adult life (Giedd et al., 1996; De Bellis, 2005). Therefore, this region may be particularly vulnerable to the effects of stress and trauma during development. The genu, splenium and body of CC have been shown to increase in size from 5 to 8 years of age and continue into early adolescence, accounting for most of the white matter tract increases in the developing brain during this period (Lebel & Beaulieu, 2011). Structural and functional reorganization of the CC, particularly the isthmus, has been reported to occur between 6 and 8 years of age (Westerhausen et al., 2011). Thus, new challenges and experiences during this period are likely to have a significant impact on the development of the CC (Lebel & Beaulieu, 2011). It can be inferred that different regions of the CC

might have different windows of vulnerability to early negative experience, which can result in a reduction in CC size and potential impairment in communication between the two cerebral hemispheres (Clarke & Zaidel, 1994; Teicher et al., 2004).

The most consistent finding in children and adolescents, who experienced psychological trauma seems to be structural abnormalities of the corpus callosum (Rinne-Albers et al., 2013). Decreases in anterior and posterior regions of CC have been reported in maltreated children and adolescents compared to healthy subjects, especially in rostral body, splenium, rostrum and isthmus (De Bellis & Keshavan, 2003; Jackowski et al., 2008). A more recent study reported significant correlations between the degree of exposure to childhood peer verbal abuse with increased mean and radial diffusivity and decreased fractional anisotropy in the CC (Teicher et al., 2010). Childhood trauma is also reportedly associated with delayed myelination of the CC (Kaplow & Widom, 2007). However, a recent study showed no differences in CC mid-sagittal area in adolescents with trauma compared to those without (Mehta et al., 2009). Similar findings have been reported with animal models. An association between CC volume reduction and early life stress has been reported in a few studies with animals (Sánchez et al., 1998; Jackowski et al., 2011), especially in non-handled male rats (Berrebi et al., 1988) and male primates (Coe et al., 2002). On the other hand, others studies have reported no changes in CC with early trauma (Spinelli et al., 2009). Overall, the evidence seems to suggest a potentially causal relationship between early trauma and CC volume.

Furthermore, the neurobiological consequences of early stress may have an important role in the emergence of psychiatric disorders during the course of brain development (Teicher et al., 2003). Findings of smaller CC volume in psychiatric patients

related to maltreatment have led to the hypothesis that childhood trauma is associated with a reduction in CC size in these individuals (Kitayama et al., 2007; Van Harmelen et al., 2010). Smaller CC areas also have been largely associated with posttraumatic stress disorder (PTSD) in children (De Bellis et al., 1999; De Bellis et al., 2002) and adults with trauma (Kitayama et al., 2007). Meta-analyses of magnetic resonance imaging (MRI) findings in pediatric samples with PTSD, who had experienced maltreatment, provide evidence of smaller CC volume compared to controls (Karl et al., 2006). This finding is however limited by the fact that PTSD is not the most common consequence of childhood maltreatment and only one third of children who experienced childhood maltreatment develop PTSD (Widom, 1999).

There is reportedly a high prevalence of childhood trauma in patients with psychotic disorders (Larsson et al., 2012), and the frequency of adverse life event appears to be higher and more severe in adults with a diagnosis of bipolar disorder (BD) compared with individuals with no psychiatric diagnoses (Kennedy et al., 2002; Nerila et al., 2005). Traumatic experiences may be considered a predictor of BD (Brietzke et al., 2012) and are strongly associated with a worse clinical presentation, such as, early onset of the disorder (Leverich et al., 2002; Daruy-Filho et al., 2011), high risk for developing alcohol and other substance abuse disorders (Leverich & Post, 2006; Daruy-Filho et al., 2011), rapid cycling (Post et al., 2001) and suicide attempts (Carballo et al., 2008; Daruy-Filho et al., 2011). However, the neurobiological consequences of childhood trauma on a maturing brain in BD patients remain unclear and could be a potential risk factor or disease modifier in BD (Etain et al., 2008).

There are few studies assessing CC volumes in BD. Decreased size of the CC in established BD patients compared to age-matched controls has been reported (Coffman et al., 1990; Brambilla et al., 2004; Arnone et al., 2008; Walterfang et al. 2009a; Walterfang et al., 2009b); in BD patients with first episode of mania compared to healthy subjects (Atmaca et al., 2007), there was a reduction in the areas of total CC, genu, anterior body, posterior body and isthmus and youths with BD showed smaller middle and posterior callosal regions compared to healthy controls (Lopez-Larson et al., 2010). On the other hand, there are studies in children and adolescents with BD that reported no significant differences in CC area, suggesting that CC abnormalities possibly appear late in the course of bipolar disorder (Yasar et al., 2006; Baloch et al., 2009). A meta-analysis of five studies evaluating CC volume in BD compared to healthy controls, reported a significant effect size (-0.52, 95% CI = -0.82, -0.21) for decreased volume in BD (Arnone et al., 2008), after controlling for age and gender. However, none of these studies evaluated the prevalence and possible influence of childhood trauma on CC morphology in BD.

Although patients with BD demonstrate a high prevalence of childhood trauma and negative effects of such stress, such as poorer cognition even early in the course of illness (Bücker et al., 2013), morphometric studies in this population have not reported or controlled for child maltreatment. The present study examined the relationship between childhood trauma and CC volume in adults with BD, recently recovered from a first episode of mania. We hypothesized that the experience of childhood trauma would be associated with decreased CC volume in BD patients early in the course of illness, compared to BD patients without trauma and matched healthy controls.

Subjects and methods

The subjects for this study were drawn from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) Project, details of which have been published elsewhere (Yatham et al., 2009; Torres et al., 2010). Briefly, patients between the ages of 16-34, who experienced their first manic or mixed episode within 3 months preceding enrolment, and met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, (DSM-IV-TR) criteria for bipolar I disorder were recruited. Diagnosis of bipolar I disorder was based on a clinical interview by a trained psychiatrist and a standardized psychiatric examination using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients presenting with a history of major medical or neurological illness underlying their manic symptoms or any contraindications to Magnetic Resonance Imaging (MRI) were excluded.

Healthy volunteers matched to patients on age, gender, premorbid and IQ, were recruited by advertisement from the community. Healthy subjects were screened using the MINI and excluded if they had history of major Axis I psychiatric disorder in themselves or first-degree relatives. There were only 5 healthy controls with trauma but they were excluded from the analysis due to the small sample size. Therefore, we included only healthy controls without a history of trauma based on Childhood Trauma Questionnaire (CTQ) scores (see description of measure below). Written informed consent was obtained from all patients and healthy subjects in accordance with the Declaration of Helsinki and the informed consent of the participants was obtained after the nature of the procedures had been fully explained. The study protocol was approved

by the ethics committee of the University of British Columbia Clinical Research Ethics Board.

Psychiatric status at baseline was assessed using clinical rating scales, including the Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale, 29-item version (HAM-D-29) (Williams et al., 1988). Clinical and sociodemographic variables were assessed using a standardized protocol.

MRI Protocol and Data Extraction

All patients and healthy controls had a cerebral MRI scan at enrolment. T1-weighted MR images were acquired on a Philips Achieva 3.0 Tesla scanner (Amsterdam, The Netherlands) using a three-dimensional axial inversion recovery-weighted spoiled gradient recalled sequence and the following parameters: FOV = 25.6 cm, matrix = 256 × 256, isotropic voxels (1 × 1 × 1 mm3), autoshim, TR/TE = autoset shortest, T/R head coil, flip angle = 8 degrees, and 1 mm thick contiguous 180 slices of the whole brain.

Corpus Callosum - Region of Interest

CC measurements were done in the midsagittal section using the Freesurfer v5.1 software. The CC in the midsagittal section was segmented automatically, using Freesurfer, with the CC highlighted in blue. By automatically drawing 4 lines perpendicular to the antero-posterior line passing through the maximum curvature of CC, Freesurfer divides the CC into five equal segments. For better anatomical delineation of the CC, the two anterior segments were combined to represent the anterior CC and the two posterior segments were combined to denote posterior CC. The CC was thus divided into 3 parts in this analysis: anterior, central and posterior in a 2:1:2 ratio, as described previously (Serpa et al., 2012). These 3 parts of the CC correspond approximately to the

following areas described by Witelson (1989): The anterior part corresponds to rostrum, genu, anterior rostral body, posterior rostral body and part of anterior midbody; the central part corresponds to part of anterior midbody and part of posterior midbody; and the posterior part corresponds to isthmus, part of posterior midbody and splenium. We decided to analyze the subregions of the CC, rather than analyze only the whole CC, because the callosal variation in BD patients, maltreated children and maltreated adolescents is more pronounced in some regions than others (De Bellis & Keshavan, 2003; Atmaca et al., 2007; Jackowski et al., 2008) and morphological abnormalities in specific corpus callosum areas are thought to be associated with abnormalities in corresponding cortical regions (Witelson,1989).

Figure 1. – The areas of Corpus Callosum:

(Insert figure 1 here)

Childhood Trauma Questionnaire

Traumatic experiences were recorded with the Childhood Trauma Questionnaire (CTQ) which is a reliable and valid 28-item self-report questionnaire (Bernstein et al., 1994). It asks participants to rate the estimated frequency of maltreatment experienced during childhood and is defined as trauma occurring before the age of 18 years. It assesses five types of childhood trauma: emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse, and also yields a total CTQ score. Items are scored 1-5 on a Likert scale ranging from ‘‘never true” to ‘‘very often true’’, according to the frequency with which each event occurred. Each scale score is evaluated by summing the 5 item scores on that scale and a summary score assesses overall trauma with scores ranging from 25 to 125. Higher scores indicate higher levels of childhood trauma and cut

off scores have been set for each type of trauma at four levels of maltreatment: None, Low, Moderate and Severe according to the manual (Bernstein et al., 1994). Subjects were considered to have a history of trauma if 1 or more subscales met the cut off criteria (moderate or severe). Furthermore, the reliability of the CTQ has been demonstrated in patients with BD (Etain et al., 2010).

Statistical Analysis

All statistical analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA). To assess demographic and clinical group differences, the chi-square test was used to compare categorical variables between patients and comparison subjects and ANOVA to compare continuous variables. To compare Intracranial Volume (ICV) between three groups, we used an analysis of variance (ANOVA). For each CC measure we used analysis of covariance (ANCOVA) to compare CC volumes between patients with and without trauma and healthy subjects without trauma controlling for age, gender and ICV. Pairwise comparisons were used to assess the differences between these three groups. Partial correlation analyses were carried out to determine the correlation between CTQ score and CC volumes after controlling for intracranial volume. An exploratory analysis was conducted in patients with and without trauma to evaluate the difference between the types of trauma (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect) and CC volumes. For this purpose, we used analysis of covariance (ANCOVA) controlling for age, gender and ICV and partial correlation analyses after controlling for intracranial volume. All statistical tests were 2 tailed with a significance threshold of $\alpha = 0.05$. Data are presented as means ± standards deviations (SDs).

Results

Demographics:

Included in this study were 23 patients with trauma, 30 patients without trauma and 16 healthy subjects without trauma. The history of childhood trauma could include emotional, physical, and sexual abuse as well emotional and physical neglect. 43.5% (n=10) of patients with trauma reported moderate to severe levels of emotional abuse, whereas 13% (n=3) reported moderate to severe levels of physical abuse. Sexual abuse rates were 26% (n=6) and physical neglect rates were 26.1% (n=6). The most commonly reported trauma was emotional neglect, with a prevalence of 52.1% (n=12). 43.48% (n=10) of patients with trauma had been exposed to more than one type of trauma (data not shown).

Patient demographic and illness characteristics are presented in Table 1. There were no significant group differences in age, gender, years of education and current and premorbid IQ between patients with trauma, patients without trauma and healthy subjects. There were no significant differences between patients with trauma and without trauma in age at illness onset, age at mania onset, age at depression onset, lithium use and divalproex use and patients were not taking other medications. Patients had very low sub-threshold symptomatology as indicate by rating scale scores; YMRS 3.70 (5.85), HAM-D 6.89 (8.80).

Distribution of CC volumes:

The anterior, central and posterior CC volumes showed a non-normal distribution only in the healthy subjects group. We applied a log transformation and the distribution was significantly improved. However, because the results from analyses using

transformed data were the same as those using original data, results for the latter were reported for consistency and interpretability.

Group differences in ICV and CC measurements

There was a non-significant trend suggesting a difference in the ICV volumes between patients with trauma, patients without trauma and healthy subjects, which justifies controlling for this in our analyses (table 1). Regardless, comparison of CC volumes was adjusted for age, gender and intracranial volume (table 2).

As detailed in Table 2, there were significant differences in the total volume of CC. On further analysis, we found a significant difference in the anterior region of CC. Post-hoc analysis showed that this was due to a significantly smaller CC volume in BD patients with trauma compared to patients without trauma. There were trends although no statistically significant group differences in central and posterior areas of the CC. The total volume of the CC in the three groups is also reported in Figure 2.

The exploratory analysis showed that there were significant differences in BD patients with emotional abuse compared to patients without emotional abuse in the posterior ($p=.009$) and total volume of CC ($p=.014$) and there were significant differences in BD patients with sexual abuse compared to patients without sexual abuse in the central region of CC ($p=.009$). There were no significant differences between groups in CC volumes for physical abuse, emotional neglect or physical neglect (all $p>.05$) in our sample. Patients with trauma showed smaller CC volume compared to patients without trauma in all significant results (data not shown).

Partial correlation analyses

We included BD patients with trauma and without trauma and used the CTQ total score as a continuous variable to correlate with CC volumes, partialling out ICV. The CTQ total score showed a skewed distribution and we conducted a logarithmic transformation on CTQ scores and the distribution was significantly improved; however, because the raw and log-transformed data yielded the same results in all analyses, the untransformed data are presented for consistency.

There was a significant negative correlation between CTQ total scores and total volume of CC (r= -.35; p=.01). We also found a significant negative correlation between CTQ scores and posterior (r= -.29; p=.03), and anterior (r= -.35; p=.01) areas of CC. There was no significant correlation between central CC (r= -.20 p=.13) and CTQ total score. We conducted the partial correlational analyses only in the patient group as history of trauma was ruled out in the healthy subjects. The correlation between CTQ total score and total CC volume in patients with and without trauma is also reported in Figure 3.

The analysis between different types of trauma showed that there was a significant negative correlation between CTQ sexual abuse score and central area of CC (r= -.27; p=.04). We also found a significant negative correlation between CTQ emotional abuse score and posterior (r=-.42; p=.002), anterior (r=-.31; p=.02) and total volume of CC (r=-.42; p=.002). There were no significant correlations between physical abuse, emotional neglect or physical neglect and CC volumes (all p>.05) (data not shown).

Discussion

To the best of our knowledge, this study represents the first investigation of the impact of childhood trauma on brain morphology in early BD. Our main finding is a

significant reduction in total and regional volumes of the CC in BD patients with trauma compared with those without trauma. Therefore, in patients with early BD, childhood stress/trauma seems to affect this important brain region, possibly even before the psychiatric illness can manifest its effects. The hypothesis that differences in CC sizes might be a consequence of traumatic events and might not be a consequence of psychiatric illness per se was previously reported (Teicher et al., 2004). Our finding of decreased volumes of anterior region of the CC further supports the existing literature that trauma during the developing years can negatively impact the maturation of the genu and the body of the CC (Lebel & Beaulieu, 2011). However, with the absence of a control group with trauma, it is not possible to establish a hypothesis about the relationship between childhood trauma and CC volumes in this study. Nonetheless, during the course of the illness, bipolar disorder might be related to decreased cc volumes and this reduction might be mediated by a history of childhood trauma.

Also, the CC volume in patients had a significant negative correlation with the CTQ, particularly the anterior, posterior and total volume of CC. This is in line with earlier studies reporting significant negative correlations between sexual abuse and isthmus volume in girls, while neglect and sexual abuse was correlated similarly with reductions in the anterior midbody of CC (Teicher et al., 2004). Another study reported a significant negative correlation between the duration of maltreatment and areas of anterior and posterior midbody and splenium of CC in individuals with PTSD (De Bellis et al., 1999). A more recent study reported a significant association between the magnitude of verbal abuse and decreased fractional anisotropy of CC (Teicher et al., 2010). Anatomic abnormalities in specific callosal areas (i.e. anterior and posterior areas)

may be related to diminished connectivity between specific cerebral hemispheric regions, such as orbital prefrontal and inferior premotor, pre-frontal regions, the premotor, supplementary motor, the superior temporal, posterior parietal and the occipital and inferior temporal cortical regions (Witelson 1989 and Giedd et al 1994), which were reported to be abnormal in bipolar patients (Soares and Mann 1997) and children with trauma (De Bellis et al., 2002; Govindan et al., 2010; McCrory et al., 2011). Taken together, these studies appear to indicate that the severity of trauma could have a significant negative impact on the development of particular areas of CC and could underlie some of the interhemispheric connectivity and cognitive deficits in these individuals (Brambilla et al., 2004; Hinkley et al., 2012). Despite the modest sample size, our results also showed that emotional abuse and sexual abuse were especially associated with decreased CC volumes. This result is consistent with the literature, which shows that depending on the type of trauma, the impact on brain volume might be different (Heim et al., 2013; Sheffield et al, 2013).

We, however, did not find significant differences in the CC volume of remitted patients with/without trauma compared to the healthy subjects. A possible explanation for this could be that our sample consists of patients recovered from a first episode of mania and are early in the course of illness. A study by Walterfang et al. 2009a, reported a significant global reduction in callosal thickness in well-defined remission of illness BD patients compared to healthy controls. However, these patients were older (mean of age was 43 years) when compared to patients from our sample (age ranging from 21-23 years). An earlier study reported smaller middle and posterior CC regions in youth with early onset BD (Lopez-Larson et al., 2010) compared to controls. However, this was in a

sample of currently manic patients, with a mean YMRS score of 20.8±9.5. Our sample consisted of remitted early BD patients (YMRS score 3.70±5.85). It is likely that CC volume in remitted patients with early BD may not be much different from matched healthy controls and the reductions in CC volume may occur later in the course of BD. It might mean there may be two sources of CC volume reduction in these patients. First, there is the reduction due to trauma, and second there is the further reduction due to the illness.

We used correlational analysis and direct group comparisons to analyze the data. For the first, the total CTQ score was included as a continuous variable and for the latter we separated patients into two groups, those with and without trauma, according to the cut off point on the CTQ scale previously described (Bernstein et al., 1994). With trauma as a categorical variable, we found reduced volume in anterior and total CC in those patients with trauma. When we analysed trauma as a continuous variable, we found that trauma in patients was particularly negatively associated with posterior, anterior and total CC volume. These findings support our hypothesized association between the experience of childhood trauma and decreased CC volumes. As mentioned earlier, this has been identified consistently in children or adults with a history of trauma (Teicher et al., 2003) and these abnormalities have been reported both in total CC and in specific regions of the CC in these individuals (McCrory et al., 2010).

CC volume is associated with higher cognitive ability and increased myelination is associated with increased cognitive capacity during adolescence (Giedd et al., 1999). Thus, a reduction in CC size could lead to decrease in inter-hemispheric communication, and result in cognitive impairment in specifics areas, such as, attention, arousal,

language, and memory (Brambilla et al., 2004). Furthermore, patients with BD have been previously reported to have cognitive impairments such as decreased verbal and visual recall, verbal fluency and cognitive flexibility (Savitz et al., 2008). It would be interesting to evaluate in a future study, the relationship between these cognitive domains, childhood trauma and CC volumes in order to clarify if the association between childhood maltreatment and impaired cognition in BD would be mediated by smaller CC volumes.

The study has certain merits. The sample consisted of stable first episode mania patients and thus results were not confounded by age, hospitalization, disease chronicity and the effects of long-term psychiatric medication, which may affect brain morphology (Brambilla et al., 2005). Further, the three groups were matched for age, gender, years of education and current and premorbid IQ, and the group difference analyses controlled for age, gender and ICV, which may confound between-subject comparisons in MRI analysis (Ge et al., 2002a; Ge et al., 2002b).

There are some limitations to the present study. First, we used a modest sample size that reduced the statistical power of this report. However our sample was still larger than other reports of first episode of mania (Atmaca et al., 2007; Chen et al., 2012) or those that have reported childhood trauma and brain MRI (Choi et al., 2012; Herringa et al., 2012) and we were still able to detect CC volume group differences. Another limitation is the absence of a control group with a history of childhood trauma in the analyses, which could help clarify if CC volumes are related only to maltreatment and not to BD. Another limitation is that there may be specific ages when childhood trauma could affect specific parts of the brain morphology, and CC seems to be reduced with childhood sexual abuse at ages 9–10 years (Andersen et al., 2008). However, the CTQ did not

evaluate specific ages at which the abuse and neglect occurred and hence this could not be analysed. Another limitation related to the use of the CTQ is the risk of potential recall bias as childhood trauma history was based on retrospective self-report. Further, the severity of maltreatment on CC volumes could not be analyzed due to a small sample size and may merit investigation in future studies. And finally, the segmentation of CC into 3 regions, unlike the routinely reported segmentation, was a limitation of the software available to us and makes it potentially difficult to compare our findings with future studies.

In conclusion, we identified a reduced CC volume in BD patients recovered from a first episode of mania with a history of childhood trauma compared to BD patients without trauma, but not to healthy subjects. The findings possibly indicate that callosal abnormalities might be more related to childhood maltreatment than bipolar illness early in its course. To further investigate this, the inclusion of a sample of healthy controls with childhood trauma would be needed to fully understand the impact of trauma and Bipolar Disorder on CC volume in patients with a first episode of mania.

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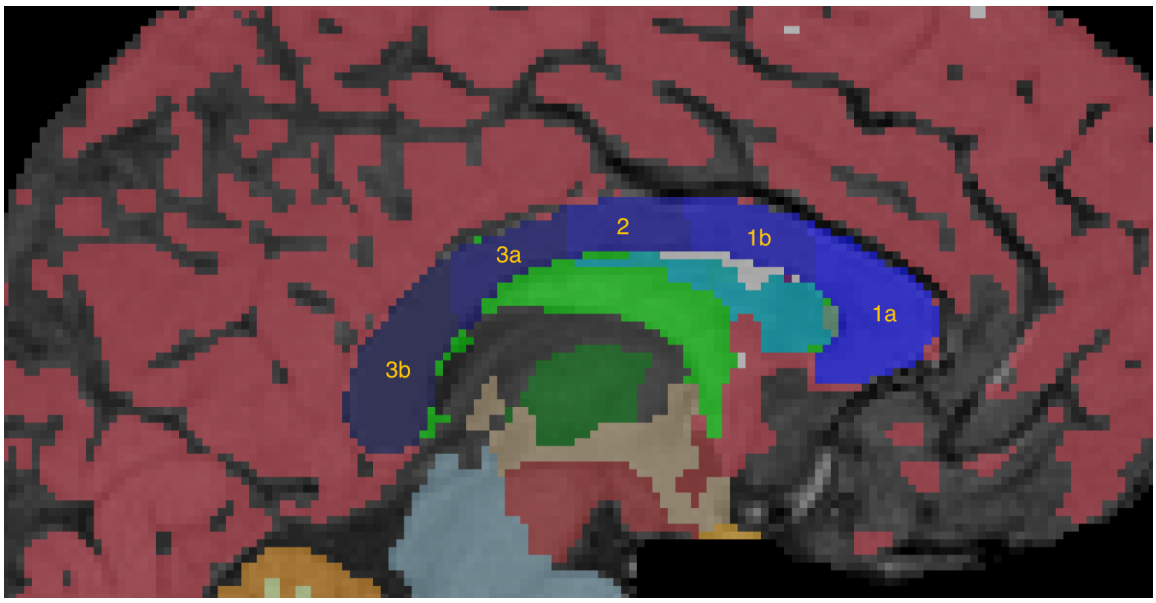
Figure 1- the areas of the Corpus Callosum



1a+1b= anterior

2= central

3a+3b= posterior

Figure 2: Total CC volumes of patients with trauma, patients without trauma and healthy subjects

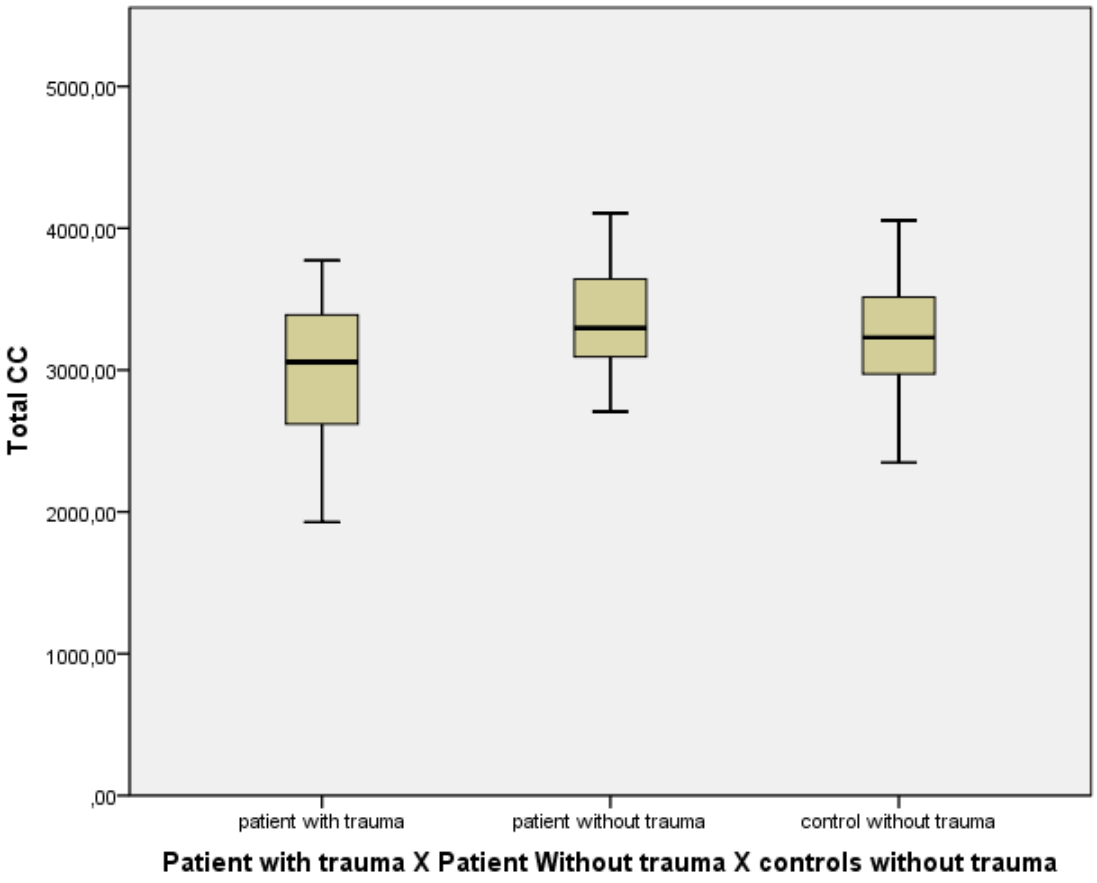


Figure 3: Correlation between CTQ total score and total CC volume in patients with and without trauma:

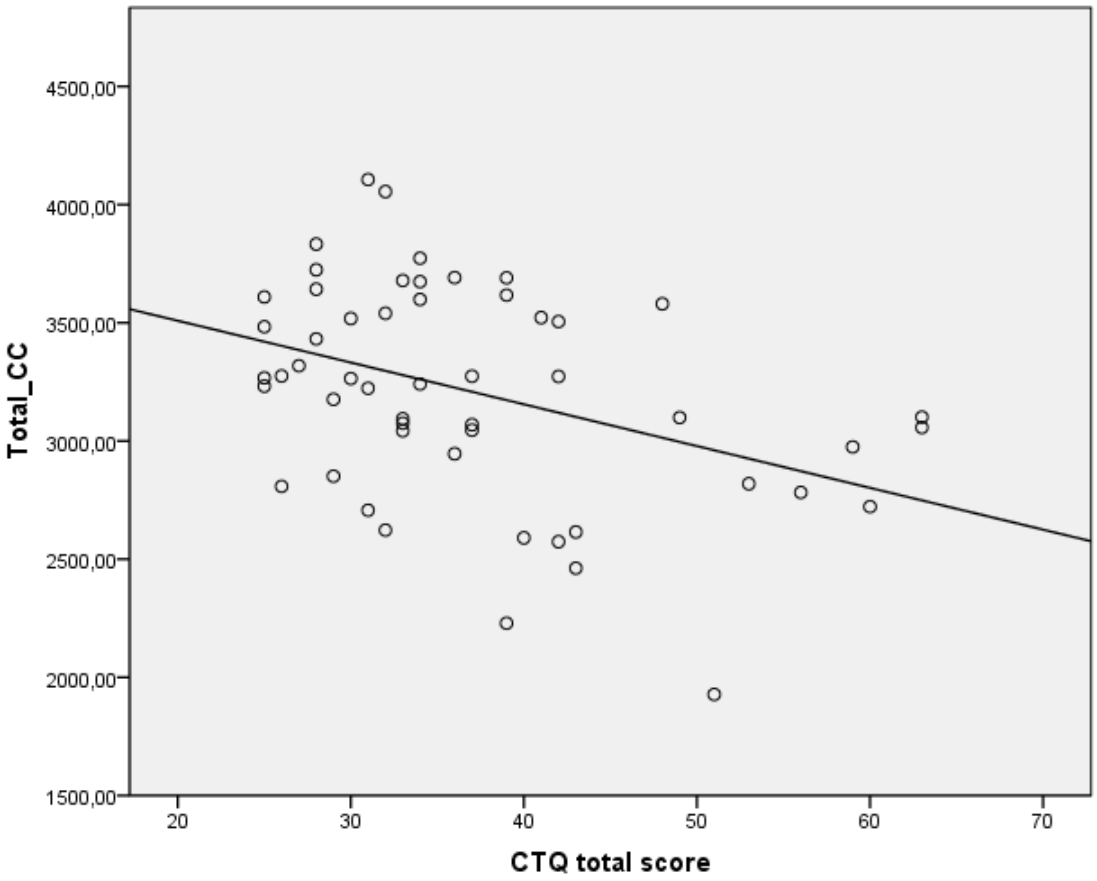


Table 1. Demographic Characteristics of the sample:

	BD Patients with trauma (n=23)	BD Patients without trauma (n=30)	Healthy Controls (n=16)	F, p
Characteristics *a*	Mean ± SD	Mean ± SD	Mean ± SD	
Years of education	13.97±1.93	14.10±2.41	13.80±1.85	.09, .90
Age	22.08±3.11	23.50±5.30	21.50±4.41	1.23, .29
Premorbid IQ NAART	108.91±7.05	106.00±9.00	105.36±7.07	1.17, .31
IQ (K-BIT)	108.83±7.13	103.52±11.84	106.57±9.18	1.88, .16
ICV	1528869.69±144012.60	1572401.33±122758.35	1637167.31±147720.47	2.99, .057
Age at illness onset, y	18.17±3.84	20.93±5.84		3.83, .056
Age at mania onset, y	22.00±3.21	23.37±5.18		1.22, .27
Age at depression onset, y	17.12±3.08	19.50±7.19		1.49, .23
Lithium dose, mg	916.66±230.48	923.07±134.80		.007, .93
Divalproex dose, mg	1156.25±436.68	884.61±241.85		3.78, .06
Gender	**M/F** 10/13	**M/F** 14/16	**M/F** 8/8	**X^2, p** .163, .92

a Some demographic characteristics were missing for 1 patient and 2 healthy subjects.

Table 2. CC volumes of patients with trauma, patients without trauma and healthy subjects

	Patients with trauma (n=23)	Patients without trauma (n=30)	Healthy Controls (n=16)	ANCOVA[a] F/ p	Posthoc	Effect Size
	Mean ± SD	Mean ± SD	Mean ± SD			P+ x P-
Total Corpus Callosum	2994.26±491.34	3372.06±352.69	3231.93±441.24	4.13/ .020*	P+*<P-*, HC	-.40
Posterior	1289.43±208.39	1447.86±168.14	1405.68±240.65	2.83/ .066	P+<P-, HC	-.38
Central	437.78±102.35	486.10±62.76	449.43±76.63	2.41/ .098	P+<P-, HC	-.27
Anterior	1267.04±231.17	1438.10±193.70	1376.81±183.47	3.86/ .026*	P+[#]<P-[#], HC	-.37

a controlling for ICV, age and gender
* p=.03 between patients with trauma and patients without trauma
[#] p=.01 between patients with trauma and patients without trauma
P+: patient with trauma
P-: patient without trauma
HC: healthy controls
x: versus

4. CONSIDERAÇÕES FINAIS:

A partir dos dados apresentados, nossos resultados sugerem que o trauma na infância está associado a mudanças na neurobiologia, cognição e morfologia cerebral. Crianças com trauma apresentaram aumento nos níveis de BDNF, TNF-α, IL-6 e IL-10 comparadas com crianças sem trauma. No entanto, depois de excluir crianças com doenças inflamatórias, somente os níveis de BDNF e TNF-α permaneceram aumentados nas crianças com trauma. Nos outros dois artigos apresentados nesta tese, nós avaliamos uma amostra de pacientes com THB após o primeiro episódio de mania comparado a controles saudáveis. O trauma esteve associado com um pior desempenho no QI, atenção auditiva e memória verbal e de trabalho nos pacientes e um padrão diferente foi observado nos controles saudáveis. Pacientes com THB e trauma também apresentaram menor volume total do CC em comparação aos pacientes sem trauma, com diferenças significativas também na região anterior do CC. Outro dado importante foi que altos escores da CTQ estavam correlacionados com menor volume total do CC nos pacientes. Por outro lado, não encontramos diferenças significativas entre o volume do CC nos pacientes com ou sem trauma em comparação aos controles saudáveis.

As conclusões gerais que podem ser retiradas dos resultados apresentados é que a amostra com trauma na infância apresentou prejuízos ou então diferenças significativas em relação a amostra sem trauma. Estes resultados nem sempre estiveram associados ao transtorno psiquiátrico por si só e o trauma parece ter um efeito independente nesses achados já que, por exemplo, nos pacientes com THB, o trauma parece ter afetado o CC possivelmente antes mesmo da doença manifestar o seu efeito e o trauma também esteve

associado ao prejuízo cognitivo na amostra de controles saudáveis. O mesmo ocorreu na amostra de crianças em que a presença de trauma parece ter um efeito significativo nos níveis de BDNF e citocinas, idependente dos sintomas psiquiátricos. Assim, não é surpresa que em muitos estudos, os piores desfechos estão relacionados a pacientes com história de trauma na infância. Outro ponto importante é que a literatura indica que o trauma infantil tem um efeito independente também na etiologia do THB e que o entendimento destes mecanismos no desenvolvimento da doença pode ser útil para a elaboração de estratégias de prevenção e tratamento (Liu et al., 2010).

Nós avaliamos uma amostra após o primeiro episódio de mania e os resultados achados não apresentam fatores de confusão como uso de medicação psiquiátrica a longo prazo, hospitalização e cronicidade da doença. Também avaliamos uma amostra de crianças que havia sido recentemente abusada e os resultados obtidos não foram confundidos pela presença de transtorno psiquiátrico. Até onde sabemos, este é o primeiro estudo que avalia uma possível relação entre o abuso infantil e prejuízo cognitivo em pacientes com THB logo após a recuperação do seu primeiro episódio de mania e também é o primeiro estudo que investiga o impacto do trauma na infância na morfologia do cérebro no início do THB. Este estudo também é o primeiro que avalia os níveis de BDNF e citocinas em uma amostra de crianças com presença de trauma.

Apesar do estudo apresentar dados consistentes e de acordo com achados científicos atuais, ele também apresenta algumas limitações. Além das limitações específicas de cada artigo, a principal seria o número de sujeitos incluídos em cada análise. O tamanho modesto de amostra impediu a comparação entre variáveis que apresentaram importância para uma maior compreensão desses resultados. Outro ponto

importante seria averiguar se existe alguma relação entre trauma na infância, função cognitiva, volume do CC e níveis de BDNF e citocinas na mesma amostra.

Outro cuidado importante na interpretação desses dados é a ausência de um estudo de seguimento. Existem evidências de que o trauma na infância está associado com efeitos adversos nos desfechos clínicos, funções cognitivas, neurobiologia e estruturas cerebrais. No entanto, até onde sabemos, nenhum estudo demonstrou uma relação causal forte entre o trauma na infância e um desfecho desfavorável, como por exemplo, o desenvolvimento de um transtorno psiquiátrico. Outra questão que ainda não está clara é por que os eventos traumáticos na infância podem predispor algumas pessoas à morbidade, e o mesmo não ocorre com outras. É importante que futuras pesquisas, através de um estudo de seguimento, tentem focar na influência das sequelas neurobiológicas do abuso infantil na etiologia dos transtornos psiquiátricos, em especial no THB, a fim de esclarecer o papel do trauma na infância no surgimento e evolução da doença.

Outro ponto importante é que o aumento nos níveis de BDNF na amostra de crianças com trauma divergem dos resultados encontrados no estudo de Sant'Anna et al. (2007), em que os níveis desta neurotrofina estavam diminuídos nos pacientes com THB e história de trauma. Podemos especular que talvez possa existir uma janela para a intervenção durante o desenvolvimento infantil já que a plasticidade neural é maior durante esta fase. Outro ponto importante é que a co-ocorrência de THB e trauma pode afetar os níveis de BDNF de forma diferente em comparação a crianças com trauma, mas sem diagnóstico de um transtorno psiquiátrico. Talvez a presença do THB possa influenciar na diminuição dos níveis de BDNF em pacientes com história de trauma na

infância. Além disso é importante lembrar que aumento e diminuição do BDNF depende do local ou região cerebral em que isso ocorre e por isso ainda não podemos dizer o que seria mais adaptativo; a associação desta alteração biológica com desfechos negativos ou positivos em estudos logitudinais vai esclarecer melhor esta questão.

O reconhecimento do trauma na infância como um evento adverso com negativas consequências também pode ser importante para criar projetos efetivos de prevenção e estratégias de tratamento que evitem a ocorrência das experiências adversas na infância e minimizem seu impacto. Seria importante também investigar o contexto no qual esses traumas podem ocorrer para auxiliar no desenvolvimento de estratégias de intervenção precoce (Conus et al., 2010).

Certamente a grande complexidade do tema abordado e as limitações específicas deste estudo implicam em um achado preliminar. Assim, futuros estudos são necessários para replicar estes dados e acrescentar a avaliação da efetividade de estratégias terapêuticas nestas amostras, levando em consideração a fisiopatologia do trauma.

Em suma, os dados apresentados nesta tese sugerem que efeitos deletérios do trauma na infância são detectáveis em crianças em idade escolar e ficam ainda mais evidentes no início do THB, demonstrados a partir da investigação da cognição, neuroimagem e neurobiologia.

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