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Dante Galileu Guedes Duarte

CORRELATOS NEURAIS DO TRAUMA INFANTIL E COMPORTAMENTO SUICIDA EM ADULTOS PORTADORES DE TRANSTORNO BIPOLAR

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Medicina Molecular da Faculdade de Medicina da Universidade Federal de Minas Gerais como pré-requisito para obtenção do título de Doutor em Ciências da Saúde.

Orientador: Humberto Corrêa Silva Filho.

Co-Orientadora: Maila de Castro Lourenço das Neves.

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RESUMO

INTRODUÇÃO: O Transtorno Afetivo Bipolar (TAB) é um transtorno psiquiátrico relacionado a altas taxas de tentativas de suicídio. O trauma infantil (TI) é um dos principais fatores que contribuem para o aparecimento e a gravidade do comportamento suicida (CS) em pacientes com TAB. Alguns estudos de neuroimagem detectaram alterações morfológicas em regiões cerebrais que compõem o sistema fronto-límbico (*frontolimbic network*) dos adultos com TAB que sofreram maus-tratos na infância e tentaram suicídio ao longo da vida. Todavia, os achados são heterogêneos e ainda pouco replicáveis. **OBJETIVOS:** Avaliar o volume de substância cinzenta (VSC) em componentes das redes neurais da região fronto-límbica relacionados ao TI e ao CS em pacientes com TAB, levando em conta variáveis clínicas e sociodemográficas. **MÉTODOS:** Foram avaliados 40 pacientes portadores de TAB tipo I e 20 controles. O TI foi avaliado pelo Questionário sobre Traumas na Infância (CTQ) e história de CS pelas Escalas de Suicídio de Beck (ideação, intencionalidade e letalidade suicida). Utilizamos a morfometria baseada no voxel para processamento das imagens de ressonância magnética do crânio. **RESULTADOS:** Os pacientes bipolares apresentaram correlação inversa entre gravidade do trauma e de seus subtipos, e VSC no córtex pré-frontal dorsolateral direito e tálamo direito. O grupo de indivíduos bipolares com história de tentativa de suicídio apresentou alteração do VSC no cíngulo anterior direito a qual foi mais proeminente em relação à alta-letalidade suicida. Outros achados de anormalidades no VSC foram localizados no córtex orbito-frontal e ínsula no grupo com alta letalidade suicida. **CONCLUSÃO:** O presente trabalho sugere que TI e CS estão relacionados a anormalidades morfológicas em redes neurais que compõem o sistema fronto-límbico de pacientes bipolares. Os achados contribuem para o fortalecimento de uma psiquiatria preventiva e para o desenvolvimento de um modelo neurobiológico de entendimento dessa complexa relação de variáveis.

Palavras-chave: transtorno bipolar; comportamento suicida; trauma infantil; neuroimagem; morfometria baseada no voxel.

ABSTRACT

BACKGROUND: Bipolar Disorder (BD) is a psychiatric disorder associated with high rates of suicide attempts (SA). The childhood-maltreatment (CM) is one of the main factors contributing to the onset and severity of suicidal behavior in patients with BD. Some neuroimaging studies have detected morphological changes in brain regions that make up the fronto-limbic network of adults with BD who suffered childhood-maltreatment and lifetime history of suicide attempt. However, the findings are heterogeneous and poorly replicable. **OBJECTIVES:** To evaluate gray matter volume (GMV) in regions of the the fronto-limbic network related to CM and SA in patients with BD. **METHODS:** We assessed 40 patients with BD type I and 20 healthy controls. The CM was assessed by childhood trauma questionnaire (CTQ) and suicide behaviour by Beck's suicide scales. Voxel-based morphometry (VBM) was used for processing magnetic ressonance images. **RESULTS:** Bipolar patients showed an inverse correlation between total score of CTQ and trauma subtypes and GMV in the right dorsolateral prefrontal cortex and the right thalamus. The group of bipolar patients with SA history showed alteration of GMV in the right anterior cingulate cortex, which was more pronounced in the high-lethality subgroup. Other findings of abnormalities in GMV were located in the orbitofrontal córtex and insula in high-lethality group. **CONCLUSION:** This study suggests that traumatic experiences in childhood and suicidal behavior are related to morphological abnormalities in neural networks that make up the fronto-limbic system in bipolar patients. The findings are crucial to the development of a science of preventative psychiatry and to the design of a neurobiological model.

Keywords: childhood-maltreatment; suicide behavior; bipolar disorder; voxel-based morphometry

SUMÁRIO

LISTA DE ABREVIATURAS

BA -   Área de Brodmann

BD –   Bipolar Disorder

BDNF –   Fator Neurotrófico Derivado dos Neurônios

C -   Indivíduos controle

CA -   Comissura anterior

CID 10 -   Classificação Estatística Internacional de Doenças e Problemas Relacionados à Saúde décima edição

CM –   *Childhood-maltreatment*

CP -   Comissura posterior

CPF -   Córtex Pré-Frontal

CS –   Comportamento Suicida

CTQ -   *Childhood Trauma Questionnaire* ou Questionário sobre Trauma na Infância

DLPFC -   Córtex pré-frontal dorsolateral

DARTEL -   *Diffeomorphic Anatomical Registration using Exponentiated Lie álgebra*

DP -   Desvio-padrão

EUA -   Estados Unidos da América

FLN –   Sistema Fronto-límbico

GMV –   *Gray Matter Volume*

HPA –   Eixo Hipotálamo-Hipófise-Adrenal

MINI PLUS - *Mini-International Neuropsychiatric Interview* – versão Plus

OFC -   Córtex orbitofrontal

OMS –   Organização Mundial de Saúde

PFC -   Córtex pré-frontal

ROI –   *Regions of Interest* ou Regiões de Interesse

SA –   *Suicide Attempts*

TAB -   Transtorno Afetivo Bipolar

TI-   Trauma Infantil

UFMG –   Universidade Federal de Minas Gerais

VBM –   *Voxel-based Morphometry*

VSC –   Volume de Substância Cinzenta

1 INTRODUÇÃO

O Transtorno Afetivo Bipolar (TAB) é uma doença crônica, recorrente e com alta herdabilidade, caracterizada primariamente por variações patológicas do humor e acometimento da funcionalidade (GOODWIN; JAMISON, 2010). Tem uma prevalência de 1% ao longo da vida e não tem predileção por sexo. Fatores genéticos, epigenéticos e psicossociais parecem estar envolvidos na sua etiologia, que ainda não foi claramente desvendada (SADOCK; SADOCK, 2007). Além dos fatores supracitados, desde Kraepelin (1921), a importância dos estressores ambientais na variação individual do curso clínico do TAB era conhecida.

O entendimento da fisiopatologia do TAB é um grande desafio atual, com implicações na sua identificação precoce, prevenção e estratégias de tratamento. Um consistente conjunto de evidências indica a existência de fatores genéticos na suscetibilidade para as doenças afetivas. A maioria dos estudos realizados com gêmeos, permite estimar a herdabilidade do transtorno afetivo bipolar em aproximadamente 70% (LIMA; SOUGEY; VALLADA, 2004). Entretanto, os dados disponíveis até o momento não identificam de modo inequívoco genes de vulnerabilidade e a demonstração dos fatores genéticos continua inconclusiva (AAS *et al.,* 2016).

Visando a agregar conhecimento na pesquisa neurobiológica do TAB, outras abordagens têm se somado aos estudos de genética molecular. Particularmente no estudo de uma patologia complexa e polimórfica como o TAB alguns autores (SCHULZE, 2010; DARUY-FILHO *et al*., 2011; AAS *et al.,* 2016), têm proposto descompartimentar o seu fenótipo completo em sub-fenótipos, tais como: bipolares com comportamento suicida (CS) (MALHI *et al*., 2013), início precoce da doença, alteração do ritmo circadiano, *déficits* neuropsicológicos e sintomas psicóticos (NEVES *et al.,* 2016). Outra importante abordagem seria a exploração dos efeitos de vivências ambientais para a formação e caracterização do fenótipo bipolar (AGNEW-BLAIS AND DANESE, 2016).

Nesse sentido os modelos estresse-diátese têm tentado elucidar a complexa interação gene-ambiente para a gênese dos transtornos psiquiátricos (CASPI; MOFFITT, 2006). Seguindo esse modelo, Caspi *et al.* (2002) foram os primeiros a mostrar que o genótipo afeta a influência do fator ambiental – trauma infantil (TI) – sobre uma doença mental. Os autores mostraram que o polimorfismo funcional no gene que codifica a monoamina oxidase A modulava o efeito desse trauma no desenvolvimento de transtorno de personalidade antissocial e transtorno depressivo.

Vale lembrar que as evidências concernentes ao modelo estresse-diátese em pacientes bipolares permanecem escassas e heterogêneas, mas em crescimento exponencial (TEICHER; TOMODA; ANDERSEN, 2006). Alguns fatores ambientais parecem aumentar o risco de desenvolvimento de TAB, como: TI (LEVERICH *et al.,* 2002; HAMMERSLEY *et al.,* 2003;

GARNO, *et al.,* 2005a; 2005b; LEVERICH; POST, 2006), eventos estressantes ao longo da vida (TSUCHIYA; BYRNE; MORTENSEN, 2003), infecções por vírus (SALVATORE *et al.,* 1997; FRANK *et al.,* 2005), uso de maconha (VAN LARR *et al.*, 2007) e complicações obstétricas (KINNEY *et al.,* 1998).

1.1 Trauma Infantil e Transtorno Afetivo Bipolar

O TI é um dos fatores ambientais mais estudados e com maior impacto na incidência do TAB - sofrer dois ou mais tipos de trauma triplica o risco de ser bipolar com *odds ratio* = 3.14 (1.52-6.47) (LEBOYER *et al.,* 2007). Além disso, está associado às principais causas de morbidade e de mortalidade nos Estados Unidos da América (EUA) com redução da expectativa de vida, levando a altos custos em saúde. Essa afirmativa é sustentada pelo trabalho de Fellitti *et al.* (1998), que estudou 19.000 indivíduos da população americana.

Todas as revisões e meta-análises realizadas até o momento sobre TI no TAB (ALLOY *et al.,* 2005; ALLOY *et al.,* 2006; ETAIN *et al.,* 2008; FISHER; HOSANG, 2010; DARUY-FILHO *et al.,* 2011; DEVRIES, 2014; AAS *et al.,* 2016) esclarecem que os eventos traumáticos na infância associam-se a seu pior desfecho clínico, com: aparecimento precoce, aumento de ciclagem rápida, piora das funções cognitivas e dos sintomas psicóticos, comorbidade com abuso de substâncias, transtorno de pânico, e, principalmente, aumento da incidência e maior gravidade do CS. Defendem também que existe uma piora da funcionalidade nos períodos inter-episódicos.

Esses estudos apontam que história de TI foi identificada em mais da metade de pacientes bipolares, com números em torno de 37% para abuso emocional, 24% abuso físico, 24% negligência emocional, 21% abuso sexual e 12% negligência física. Mais de um terço sofreram combinação de diferentes tipos de trauma. Os números são maiores quando comparados aos transtornos depressivos unipolares (HYUN; FRIEDMAN; DUNNER, 2000) e a indivíduos sadios (AAS *et al.,* 2016).

O conceito de TI utilizado no presente trabalho foi o proposto por Bernstein *et al.* (1994) que divide as experiências traumáticas em ativas: abuso físico (agressões corporais em uma criança, ocasionadas por um adulto ou pessoa mais velha que representava um risco ou resultou em lesão), abuso emocional (agressões verbais dirigidas a uma criança ou qualquer humilhação ou comportamento humilhante dirigido para uma criança por um adulto ou mais pessoas), abuso sexual (contato sexual ou conduta entre uma criança com menos de 18 anos e uma pessoa adulta ou mais velhos), e passivas: negligência física (falha do cuidador para fornecer para uma criança necessidades físicas básicas) e negligência emocional (fracasso dos cuidadores para atender as necessidades emocionais e psicológicas das crianças) (GRASSI-OLIVEIRA; STEIN; PEZZI,

2006). A partir da literatura, é necessário considerar também disfunções familiares (exemplo: uso de drogas, doença mental, comportamento criminoso, agressões entre pais) e condições socioeconômicas paternas dentro do conceito de TI (FELITTI *et al.,* 1998; FISHER; HOSANG, 2010).

As evidências neurobiológicas mais robustas das consequências dos maus-tratos até o presente momento incluem modificações epigenéticas em genes que regulam três importantes sistemas: a) sistema de resposta ao estresse (cortisol), com redução dos receptores de glicocorticoides e hiperativação do eixo hipotálamo-hipófise-adrenal (HPA) (VAN HEERINGEN; MANN, 2014) b) sistema regulador das neurotrofinas, particularmente afetando a expressão do fator neurotrófico derivado dos neurônios (BDNF) e seu receptor TRKB (HASHIMOTO, 2010) e c) sistema serotoninérgico com redução da expressão do gene transportador de serotonina, associado à menor inervação serotoninérgica e a um "cérebro hiposerotoninérgico" (BOLDRINI *et al*., 2008; PARSEY *et al*., 2006). Além dessas alterações, o TI induz a modificações duradouras em processos inflamatórios (interleucinas e fatores de necrose tumoral entre outros) em diversos diagnósticos psiquiátricos (BAUMEISTER *et al.,* 2015; COELHO *et al.,* 2014; TURSICH *et al.,* 2014), incluindo o TAB (MUNKHOLM *et al.,* 2013). Uma explicação plausível seria que a alteração desses sistemas precocemente na vida da criança levaria ao aumento da carga alostática (KAPCZINSKI *et al.,* 2008) e à elevada toxicidade cerebral (TURECKI *et al.,* 2012), provocando consequências de longo prazo nas trajetórias do desenvolvimento neural (WATTS-ENGLISH *et al.,* 2006).

O cérebro humano continua se desenvolvendo durante a infância por meio de processos de remodelamento sináptico, mielinização e apoptose programada (GRAAF-PETERS; HADDERS-ALGRA*,* 2006). A influência do "ambiente" na plasticidade neural é evidente, e a substância cinzenta é menos dependente da herdabilidade e se desenvolve de uma forma não linear, sendo mais afetada pelos estressores que a substância branca (GILMORE *et al.,* 2010). Seguindo esse raciocínio, a literatura indica que existem períodos de maior sensibilidade – janelas de vulnerabilidade - em que algumas regiões encefálicas são mais susceptíveis aos efeitos do trauma (TEICHER; SAMSON, 2013). O hipocampo é mais sensível em idades de 3 a 5 anos, corpo caloso de 9 a 10 anos e regiões frontais de 14 a 16 anos (ANDERSEN *et al.,* 2008). O tipo, a intensidade e a frequência do abuso representam variáveis importantes para o grau de influência na neuroplasticidade (TURECKI *et al.,* 2012).

O conjunto de evidências atuais em neuroimagem morfológica utilizando ressonância magnética detectaram alterações anatômicas em regiões cerebrais que compõem o sistema fronto-límbico (*frontolimbic network* – FLN) dos adultos que sofreram maus-tratos na infância (HART; RUBIA, 2012; TEICHER; SAMSON, 2013). O FLN é formado pelas regiões frontais (córtex pré-

frontal - PFC; e orbito-frontal - OFC), cíngulo anterior e estruturas subcorticais, tais como amígdala, hipocampo (e giro parahipocampal), insula, tálamo e núcleo caudado (PHILLIPS; LADOUCEUR; DREVETS, 2008). O comprometimento da modulação frontal (hipoativa) sobre o sistema límbico (hiperativo) - *top-down regulation* – produz perturbações significativas, que se manifestam clinicamente como flutuações extremas de humor, impulsividade aumentada, desregulação emocional e resposta desadaptativa a estressores (STRAKOWSKI *et al.,* 2012). O modelo FLN de regulação do comportamento é coerente com a fenomenologia do TAB (TORRES; BOUDREAU; YATHAM, 2007) e fornece uma estrutura teórica útil para a compreensão do CS nessa população (ETAIN *et al*., 2008; MALHI *et al.,* 2013).

Vários estudos em adultos que sofreram TI acharam alterações em áreas cerebrais que compõem o FLN, tanto utilizando métodos de seleção de regiões de interesse (*regions of interest* – ROI) com hipóteses *a priori* (COHEN *et al.*, 2006; MEHTA *et al*., 2009; MORANDOTTI *et al.,* 2013; TOTTEHAN *et al.,* 2010), quanto métodos que permitem um mapeamento automático do cérebro inteiro por meio da morfometria baseada no voxel (voxel-based morphometry – VBM) (TOMODA *et al.,* 2009a; 2009b; VAN HARMELEN *et al.,* 2010; SHEFFIELD *et al.,* 2013; CHANEY *et al.,* 2014;). Esses achados foram confirmados pela primeira meta-análise de neuroimagem estrutural por VBM em TI (LIM; RADUA; RUBIA, 2014) com uma amostra de 331 indivíduos e 12 artigos. Todavia, os resultados não são homogêneos na literatura, a qual demonstra alterações também em giro temporal superior e córtex auditivo (TOMODA *et al.,*2011), corpo caloso (TEICHER *et al.*, 2004) e córtex visual (TOMODA *et al.,* 2012) em adultos abusados quando menores de idade.

Os trabalhos que estudaram especificamente amostra de bipolares que sofreram TI são muito raros e os achados concernem o corpo caloso (BUCKER *et al.,* 2014), PFC, hipocampo e amígdala (KAPCZINSKI *et al.,* 2008; HART; RUBIA, 2012). Mais conhecimentos são necessários para esclarecer essa intricada rede de inter-relações. Todavia, como descrito anteriormente, alterações nessas estruturas são consistentes com os atuais modelos neurobiológicos de compreensão da doença bipolar e sua propensão ao ato suicida (TORRES; BOUDREAU; YATHAM, 2007; STRAKOWSKI *et al.,* 2012; TOWNSEND; ALTSHULER, 2012). Ademais, essas regiões foram associadas a *déficits* em muitos domínios cognitivos dos bipolares, tais como, atenção, concentração, resposta inibitória, resolução de problemas e memória verbal e de trabalho (BRIETZKE *et al.,* 2012). Tudo indica que esses sujeitos expressam um fenótipo especializado e desadaptativo (fenocópia) resultado das influências dos estressores ambientais, ou seja, "ecofenótipos" (TEICHER; SAMSON, 2013).

O presente trabalho justifica-se pela necessidade de aprofundar o estudo do TI no TAB e sua associação com CS. Torna-se importante esclarecer melhor a influência do trauma e seus subtipos

no curso clínico desfavorável dessa enfermidade (AGNEW-BLAIS; DANESE, 2016). Indo mais além, um modo estratégico de abordagem é homogeneizar a população de bipolares em tipo I e em sub-fenótipos. O de eleição foi o CS que, além de prevalente nesses indivíduos, parece apresentar relação transnosográfica com o TI, ou melhor, terem mecanismos fisiopatológicos comuns independentes do diagnóstico (VAN HEERINGEN *et al.,* 2014)

1.2 Comportamento Suicida e Transtorno Afetivo Bipolar

O conceito de comportamento suicida do presente trabalho foi baseado em Mann *et al.* (2003): um ou mais atos lesivos autodirecionados com intenção de acabar com a própria vida. Mais de 800 mil pessoas morrem por suicídio todos os anos. Se levarmos em conta a ideação e as tentativas de suicídio os números são de 10 a 20 vezes maiores[1]. Entre os brasileiros, são aproximadamente 12 mil mortes por ano, levando em conta o ano de 2012 (último dado consolidado pela Organização Mundial de Saúde – OMS). Estima-se que quase a totalidade das vítimas de suicídio tenham um transtorno psiquiátrico, sendo que o TAB tem o maior risco absoluto (NORDENTOFT; MORTENSEN; PEDERSEN, 2011). Esse relevante tema de alta prevalência pode ser em grande parte prevenível, e para isso é importante a busca por neuromarcadores que sinalizariam os casos de maior vulnerabilidade.

Referindo-se ao CS, estudos de neuroimagem e *post-mortem* acharam alterações estruturais em diversas regiões cerebrais: PFC, OFC, cíngulo anterior, insula, tálamo amygdala, hipocampo e córtex parietal em diferentes diagnósticos e no TAB (JOLLANT *et al.*, 2011; MALHI *et al.,* 2013; TURECKI, 2014; VAN HEERIGEN; MANN, 2014), entretanto os achados são heterogêneos e necessitam de replicação (VAN HEERIGEN *et al.,* 2014). Uma revisão de estudos de neuroimagem mostrou diferenças em regiões cerebrais entre grupo de pacientes bipolares comparados de acordo com presença e ausência de CS (Figura 1).

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[1] Disponível em: <http://who.int/mental_health/suicideprevent>. Acesso em: 10 fev. 2016

Figura 1: Áreas cerebrais mostrando alterações entre pacientes bipolares
com e sem história de CS
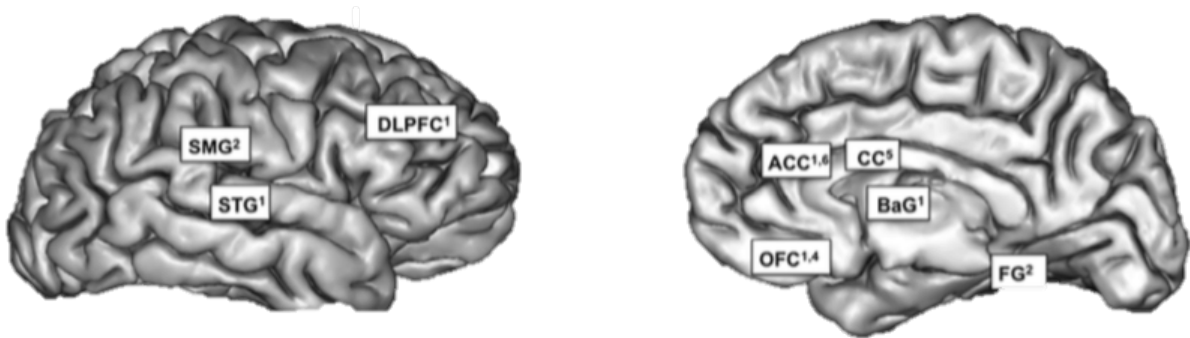
Nota: ACC: córtex cingulado anterior; BaG: ganglio basal; CC: corpo caloso; DLPFC: córtex pré-frontal dorsolateral; FG: giro fusiforme; OFC: córtex orbitofrontal; SMG: giro supramarginal; STG: giro temporal superior.
Fontes: 1. Benedetti *et al.* (2011); 2. Giakoumatos *et al.* (2013); 3. Lijffijt *et al.* (2014); 4. Mahon *et al.* (2012); 5. Matsuo *et al.* (2010); 6. Matsuo *et al.* (2009).
Adaptado com autorização de Hozer e Houenou (2016)

Diante da diversidade de regiões cerebrais candidatas, uma forma crescentemente utilizada em estudos de neuroimagem para aprofundar o entendimento sobre o suicídio é subdividi-lo quanto à letalidade dos atos (alta e baixa letalidades) (SOLOFF *et al.*, 2012; GIAKOUMATOS *et al.,* 2013). Suspeita-se que os indivíduos com alta letalidade têm características neurobiológicas comuns àqueles que morreram por suicídio (OQUENDO *et al.,* 2003; VAN HEERINGEN; MANN, 2014).

Apesar das anormalidades morfológicas identificadas poderem servir para funções diversas, elas são componentes de circuitos cerebrais envolvidos na autovaloração, impulsividade e regulação do humor. Alterações nessas regiões são particularmente relacionadas a prejuízos em alguns domínios cognitivos: memória verbal e de trabalho, tomada de decisão, resolução de problemas, controle inibitório e funções executivas (FERGUSSON; WOODWARD; HORWOOD, 2000; MALHI *et al.,* 2013) e fenótipos comportamentais especializados: elevados traços de ansiedade, instabilidade emocional, impulsivo-agressividade e baixo limiar a fracassos e frustrações (REILLY-HARRINGTON *et al.,* 1999; BREZO *et al.,* 2006). Estudos longitudinais apontam que essas características conjuntamente podem predizer o CS em pacientes bipolares (ENNS *et al.*, 2006; BREZO *et al.*, 2008b).

O modelo de suicídio atual relevante para o TAB foi proposto por Malhi *et al.* (2013). Postula-se que o CS ocorre no contexto de um estressor. O sistema de autoavaliação ou autovaloração é engajado no sentido de tomar conhecimento da experiência e determinar uma resposta emocional e comportamental adequada para cada estímulo diferente. Ele envolve a representação de si mesmo, do outro e da situação como um todo, e no TAB é comprometido por alterações cognitivas e emocionais. Com isso, pode gerar um sentimento de derrota/fracasso ou de "aprisionamento", e que juntamente com uma pequena habilidade de criar soluções de fuga ou
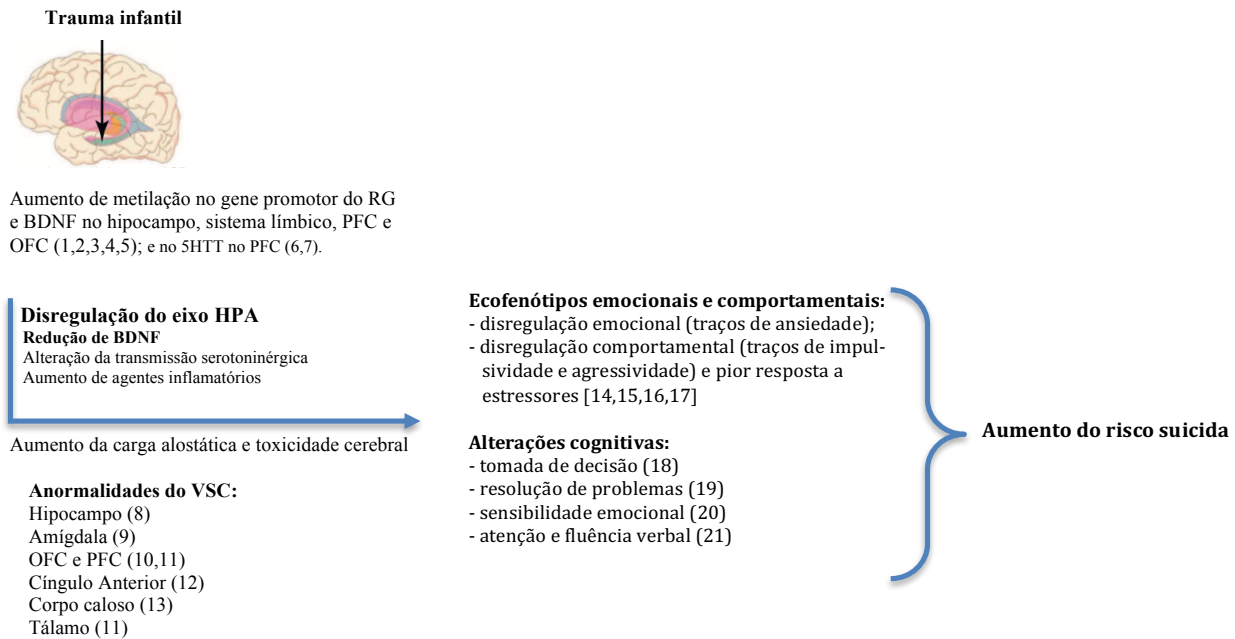
coping, leva a um aumento da sensação de desesperança. No paciente bipolar, a avaliação interativa desses fatores aumenta o sentimento de derrota e de impossibilidade de escapar em tal extensão que o cenário do CS é ativado. Finalizando o raciocínio do modelo, o autor adiciona o aumento da disregulação emocional e do humor próprio da enfermidade contribuindo negativamente para o processo suicida.

1.3 Trauma Infantil e Comportamento Suicida no TAB

A associação entre TI com seus subtipos e CS em pacientes bipolares foi extensivamente demonstrada na nossa revisão e meta-análise (artigo 1) e em outros estudos recentes (ALLOY *et al.,* 2005; ALLOY *et al.,* 2006; ETAIN *et al.,* 2008; FISHER; HOSANG, 2010; DARUY-FILHO *et al.,* 2011; DEVRIES, 2014; AAS *et al.,* 2016; AGNEW-BLAIS; DANESE, 2016). Os artigos argumentam também que essa associação não é específica ao TAB, pois investigações recentes mostraram que TI está associado ao aumento do risco de suicídio em outros diagnósticos.

Uma explicação vigente é que TI e CS em TAB apresentariam duas vias de associação com influências mútuas e não lineares. Uma via seria específica ao TAB e mediada pelo seu pior desfecho clínico conforme descrito anteriormente (ETAIN *et al.,* 2008). A outra, seria a via transnosográfica e não específica a nenhum diagnóstico psiquiátrico, em que o TI levaria a pior autorregulação emocional, agressividade, impulsividade, comprometimento do senso de valoração e da capacidade de resolução de problemas (YATES; CARLSON; EGELAND, 2008; MUEHLENKAMP *et al.,* 2010). Almejando unir os achados atuais, segue abaixo um modelo integrativo da influência do TI e a associação com CS (Figura 2). Para maiores detalhes sobre estudos moleculares em animais, humanos e *post-mortem*, vide o artigo de Turecki *et al.* (2012).

Figura 2: Modelo explicando o aumento do risco suicida
em indivíduos expostos ao trauma infantil[2]

Trauma infantil

Aumento de metilação no gene promotor do RG
e BDNF no hipocampo, sistema límbico, PFC e
OFC (1,2,3,4,5); e no 5HTT no PFC (6,7).

Disregulação do eixo HPA
Redução de BDNF
Alteração da transmissão serotoninérgica
Aumento de agentes inflamatórios

Aumento da carga alostática e toxicidade cerebral

Anormalidades do VSC:
Hipocampo (8)
Amígdala (9)
OFC e PFC (10,11)
Cíngulo Anterior (12)
Corpo caloso (13)
Tálamo (11)

Ecofenótipos emocionais e comportamentais:
- disregulação emocional (traços de ansiedade);
- disregulação comportamental (traços de impul-
 sividade e agressividade) e pior resposta a
 estressores [14,15,16,17]

Alterações cognitivas:
- tomada de decisão (18)
- resolução de problemas (19)
- sensibilidade emocional (20)
- atenção e fluência verbal (21)

Aumento do risco suicida

Nota: Abreviaturas: BDNF: fator neurotrófico derivado dos neurônios; PFC: córtex pré-frontal; HPA: eixo hipotálamo, hipófise, adrenal; OFC: córtex órbitofrontal RG: receptor de glicocorticoide; 5HTT: transportador de serotonina; VSC: volume de substância cinzenta.
Fontes: 1. Mcgowan *et al.* (2009); 2. Merali *et al.* (2006); 3. Ernst *et al.* (2009a); 4. Ernst *et al.* (2009b); 5: Alt *et al.* (2010); 6. Bolddrini *et al.* (2008); 7. Parsey *et al.* (2006); 8. Vythilingam *et al.* (2002); 9. Weniger *et al.* (2008); 10. Tomoda *et al.* (2009a); 11. Duarte *et al.* (2016); 12. Kitayama; Quinn; Bremner (2006); 13. Teicher *et al.* (2004); 14. Brezo *et al.* (2006); 15. Fergusson; Woodward; Horwood (2000); 16. Brezo *et al.,* (2007); 17. Brezo *et al.* (2008b); 18. Jollant *et al.* (2005); 19. Speckens; Hawton (2005); 20. CHA *et al.* (2010); 21. Keilp *et al.*, 2001.
Adaptado de Turecki et al., 2012

Diante do exposto, nossa hipótese é que eventos precoces na infância como TI podem alterar a morfologia cerebral em pacientes portadores de TAB predispondo a um fenótipo especialmente susceptível ao CS. Para testar tal hipótese quatro estudos foram conduzidos. Artigo 1: uma revisão sistemática e meta-análise sobre TI e CS em pacientes com TAB; Artigo 2: investigou os tipos de TI e sua relação com CS na nossa amostra; o Artigo 3: avaliou o VSC de bipolares e controles e sua associação com gravidade e tipo de TI, o Artigo 4: verificou o VSC nessa população e a associação com CS (ideação, intenção, letalidade e método suicida).

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[2] A exposição ao TI aumenta a metilação no promotor do RG, BDNF e transportador de serotonina, levando a desregulação do eixo HPA, das neurotrofinas e desnervação serotoninérgica, o que altera a arquitetura cerebral e leva ao desenvolvimento de ecofenótipos emocionais, comportamentais e cognitivos, que por sua vez, aumenta o risco suicídio.

1.4 Artigo 1: Childhood-Maltreatment in Bipolar Patients with Suicidal Behaviour: Systematic Review and Meta-Analysis

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Childhood-Maltreatment in Bipolar Patients with Suicidal Behaviour:

Systematic Review and Meta-Analysis

Dante G.G. Duarte[a*], Raoul Belzeaux[b], Emilie Rancourt[b], Humberto Correa[a], Gustavo Turecki[b],

Stéphane Richard-Devantoy[b]

a: Mental Health Department, Federal University of Minas Gerais, Brazil

b: McGill University, Department of Psychiatry & Douglas Mental Health University Institute, McGill Group for Suicide Studies, Montréal (Québec), Canada

Correspondence to: Dr. Dante Galileu Guedes Duarte, Mental Health Department, Federal University of Minas Gerais. Avenida Prof. Alfredo Balena, 190 sl 2002, Santa Efigenia, Belo Horizonte, Minas Gerais, Brazil. Fax: 55-34-3216 3020, E-mail: dantegalileu@gmail.com

ABSTRACT

The diagnosis of bipolar disorder carries a high risk for suicidal behaviour. Childhood abuse is a well-established distal risk factor for suicidal behaviour. Therefore, the objective of this study was to examine the association between childhood abuse and vulnerability to suicide attempts in bipolar disorders. A literature review was performed using Medline, Embase, and PsycInfo databases. Nine studies met the selection criteria. In the meta-analysis, the Childhood Trauma Questionnaire (CTQ)

was used to assess childhood maltreatment in three different studies, which were analyzed by using a random-effects model to account for the likely variations of true effect sizes between the included studies. Compared to bipolar non-attempters, bipolar suicide attempters had experienced childhood abuse significantly more frequently and had higher total CTQ scores (g=-0.64, 95%CI [-0.86 – -0.41], Z=-5.62, p<0.001) and CTQ sub-scores (sexual abuse: g=-0.62, 95%CI [-0.85 – -0.39], Z=-5.45; physical abuse: g=-0.55, 95%CI [-0.77 – -0.32], Z=-4.87; emotional abuse: g=-0.55, 95%CI [-0.77 – -0.32], Z=-4.87; physical neglect: g=-0.29, 95%CI [-0.51 – -0.07], Z=-2.64; emotional neglect: g=-0.37, 95%CI [-0.59 – -0.15], Z=-3.35). Our findings suggest that childhood-maltreatment may contribute to increased risk of suicidal behaviour among bipolar subjects, an observation that is consistent with similar associations among other psychiatric conditions.

Key words: suicidal behaviour; vulnerability; childhood-maltreatment; bipolar disorder.

INTRODUCTION

Bipolar disorder (BD) is one of the psychiatric diagnoses strongly associated with risk of suicidal behaviour (SB), ranging from 10 to 15% of death by suicide (Nordentoft et al., 2011). Suicidal behaviour is complex and multifactorial, resulting from the interaction of environmental and biological factors (Turecki et al., 2012). Among distal environmental risk factors of suicide behaviour, childhood-maltreatment (CM) plays an important role. CM is a global highly prevalent burden that has serious life-long effects, yet is a very difficult concept to study because of the associated social stigma. World Health Organization (WHO) data shows that 25% of all adults report having been physically abused as children, and one in five women and one in thirteen men report having been sexually abused as a child (World Health Organization, 2014).

CM is generally defined by sustained or repeated exposure to events that usually involve a betrayal of trust (De Bellis et al., 2001). Active examples of CM include childhood sexual and physical abuse and various forms of emotional abuse. Passive examples include emotional and physical neglect (Teicher and Samson, 2013).

Strong evidence suggests that the effect of CM depends on timing, type, and severity of exposure (Teicher and Samson, 2013) and has cumulative effects over time (Danese et al., 2012; Felitti et al., 1998). However, some controversy persists about what types of adversity may contribute to SB in patients with BD. In addition, efforts to better understand the interactions between CM and SB are hampered by the lack of consensus in CM nomenclature and definitions.

While a number of reviews have examined the potential association between BD and CM in general (Alloy et al., 2005, 2006; Etain et al., 2008; Fisher & Hosang, 2010; Daruy-Filho et al., 2011; Aas et al., 2016; Agnew-Blais and Danese, 2016), they tended to focus on combinations of different forms of child abuse and have accepted diverse methods for assessment of CM. Thus, they did not adequately explain the specific role of each subtype of CM in the suicidality of bipolar subjects. Despite the importance of the topic, only two meta-analysis have been previously published on this topic. One showing an association between sexual abuse and suicide attempt; this study used data from highly heterogeneous populations with diverse nationalities, diagnoses, assessment protocols, and study qualities (Devries et al., 2014). Another meta-analysis has shown an association of childhood maltreatment and unfavourable clinical outcomes, including suicide behaviour, in bipolar disorder (Agnew-Blais and Danese, 2016). Despite the highly quality of those both studies, they have included different assessment protocols to evaluate CM and a more general concept of maltreatment. To date, no meta-analyses have specifically examined the association between CM and SB in bipolar patients with a stringent concept of maltreatment and with only one assessment protocol trying to make results more uniform and homogeneous. One way to assess CM is to use the Childhood Trauma Questionnaire (CTQ), which is a standard form to assess meaning taken from traumatic experiences in childhood.

Establishing an empirical relationship between CM and SB in bipolar individuals would help patients and their families gain a better understanding of their symptomology as well as affording valuable clinical opportunities to potentially prevent and manage suicidal behaviour in this specific population. Within this context, we sought to conduct (1) a review of studies on CM (physical and emotional negligence and physical, emotional, and sexual abuse) using the Childhood Trauma Questionnaire (CTQ) and (2) a meta-analysis aimed at clarifying the relationship between the type of childhood-maltreatment experienced based on CTQ and the vulnerability to suicidal behaviour in bipolar disorders.

METHODS AND MATERIAL

Data sources

A systematic literature search of MEDLINE, Embase, and PsycInfo databases was performed for human studies published until 2016 and published in English or French. The Medical Subject Heading (MeSH) term "suicide" was combined with the MeSH terms "bipolar disorder", and "child abuse" (adults survivors of child abuse), and with the Title/Abstract (TIAB) terms "CTQ", "child abuse", "child neglect", "child maltreatment", "childhood abuse", "childhood maltreatment", "sexual abuse", "physical abuse", "emotional abuse", and "family conflict". An

iterative process was used to ensure that all relevant articles were obtained. Bibliographical references of the selected papers and existing reviews were manually searched to identify additional potential studies.

Study selection

Abstract selection was based on the **Strengthening the Reporting of Observational studies in Epidemiology** (STROBE) checklist (Von Elm et al., 2008) which describes items that should be included in reports of cohort studies. Abstracts identified through the literature search were independently evaluated by two reviewers (DGGD and SRD) and selected by a consensus from all authors.

Studies that met the following inclusion criteria were included in this systematic review: 1) original articles published in an English- or French -language peer-reviewed journal; 2) included assessment of childhood-maltreatment using CTQ; 3) included at least two groups of patients, of which at least one had a history of suicide attempt; and 4) suffered bipolar disorder according to DSM criteria. A suicide attempt was defined as any act carried out with a certain intent to die and different from non-suicidal self-injury (Mann, 2003). Full articles were then obtained for final review. The study selection process is shown in **Figure 1**.

Of the 401 originally identified abstracts, 9 studies met the inclusion criteria for this systematic review (see **Table 1**). The quality of each study was assessed independently by two reviewers (DGGD and SRD) using the Crombie criteria adapted by Petticrew et al. (Petticrew et al., 2006).

Although eligible, three studies were not included, because precise means and standard deviations were not available in the papers and could not be obtained directly from the authors.

Data extraction and analyses

A standardized form was used to extract data, which included authors, date of publication, study design, settings, study population, childhood-maltreatment scale, definition of suicidal behaviour, and childhood trauma questionnaire (CTQ) scores (mean and SD). CTQ scores and CTQ sub-scores were explored in at least three different studies. We controlled the data for possible confounders: 1) age, 2) gender, 3) level of depression and 4) level of mania.

Analyses were performed using Comprehensive Meta-Analyses Version 2.0 (Biostat, Englewood, NJ, USA), and IBM SPSS Version 20 (IBM Corporation, Chicago, IL, USA).

Two groups were compared: suicide attempters (patients with a history of suicide attempt), patient controls (i.e., patients with no personal history of suicidal behaviour but with a history of bipolar disorders).

We used a random-effects model to account for the likely variations of true effect sizes between the included studies (Riley et al., 2011). Pooled Hedges' *g* effect sizes for the subjects' CTQ scores, depression and mania ratings were computed (Hedges et al., 1985). The obtained effect sizes are usually considered small if <0.3, moderate if comprised between 0.4-0.8, and large if >0.8 (Egger et al., 2001).

Heterogeneity was assessed using the Q statistics and the I^2 index (Cooper et al., 2009). Values of *p* <0.10 for the former and >35% for the latter were deemed as indicative of study heterogeneity. Finally, we used funnel plots, Rosenthal's Fail-Safe N (Rosenthal, 1979) and Egger's Regression Intercept (Egger et al., 1997) to test for the presence of publication bias (Cooper et al., 2009).

RESULTS

Systematic review

Table 1 summarizes the nine studies (Garno et al., 2005; Pompili et al., 2009; Etain et al., 2013; Janiri et al., 2014; Li et al., 2014; Watson et al., 2014; Bernegger et al., 2015; Cakir et al., 2016; Duarte et al., 2016) included in the systematic literature review. The design of all identified studies was cross-sectional. The rate of men ranged from 31.3 to 39.8 %. Childhood-maltreatment was tested with the CTQ.

Overall, the main findings in patients suffering from bipolar disorders were:

1) A higher rate of suicide attempts in those who experienced childhood abuse;

2) Higher total CTQ scores and higher CTQ sub-scores in suicide attempters compared to non-attempters.

Meta-analysis

A total of three studies were included, comprising **398** participants, of whom **116** were suicide attempters (mean age = 42.7 ± 11.9 years; 27.3 % males), and **282** were patient controls (43.6 ± 11.6 years; 44.5 % males.

Suicide attempters had significantly higher CTQ total scores, sexual abuse CTQ sub-scores, physical abuse CTQ sub-scores, emotional abuse CTQ sub-scores, physical neglect CTQ sub-scores, and emotional neglect CTQ sub-scores than patient controls (**Figure 2**), all representing moderate to small effect sizes. Mean age, gender, depression, and mania level did not differ between the two groups, thus ruling out these variables as confounding factors.

Total CTQ between suicide attempters vs. patient controls

Suicide attempters had significantly higher CTQ total scores than patient controls, with a moderate effect size (Hedges' g=-0.64, 95%CI [-0.86 – -0.41], Z=-5.62, p<0.001). The Fail-Safe N, i.e., the number of unpublished or missing null-findings that would be needed to render the results non-significant, was 19. Heterogeneity did not exceed that which was expected by chance (Q=1.3; df=2; p=0.5; I^2=0), implying that the variance among the effect sizes was not greater than expected by sampling error. A funnel plot was generated and the Egger's regression intercept was assessed and both indicated that there was no publication bias.

CTQ sexual abuse between suicide attempters vs. patient controls

Suicide attempters had significantly higher CTQ sexual abuse scores than patient controls, with a moderate effect size (Hedges' g=-0.62, 95%CI [-0.85 – -0.39], Z=-5.45, p<0.001). The Fail-Safe N was 17. Heterogeneity did not exceed that which was expected by chance (Q=0.5; df=2; p=0.7; I^2=0). The funnel plots were reasonably symmetrical, suggesting a low risk of publication bias, and the more conservative Egger's regression intercept suggested no publication bias.

CTQ physical abuse between suicide attempters vs. patient controls

Suicide attempters had significantly higher CTQ physical abuse scores than patient controls, with a moderate effect size (Hedges' g=-0.55, 95%CI [-0.77 – -0.32], Z=-4.87, p<0.001). The Fail-Safe N was 12. Heterogeneity did not exceed that which was expected by chance (Q=0.9; df=2; p=0.6; I^2=0). The funnel plots were reasonably symmetrical, suggesting a low risk of publication bias, and the more conservative Egger's regression intercept suggested no publication bias.

CTQ emotional abuse between suicide attempters vs. patient controls

Suicide attempters had significantly higher CTQ emotional abuse scores than patient controls, with a moderate effect size (Hedges' g=-0.55, 95%CI [-0.77 – -0.32], Z=-4.87, p<0.001). The Fail-Safe N was 201. Heterogeneity did not exceed that which was expected by chance (Q=0.2; df=2; p=0.8; I^2=0). The funnel plots were reasonably symmetrical, suggesting a low risk of publication bias, and the more conservative Egger's regression intercept suggested no publication bias.

CTQ physical neglect between suicide attempters vs. patient controls

Suicide attempters had significantly higher CTQ physical neglect scores than patient controls, with a small effect size (Hedges' g=-0.29, 95%CI [-0.51 – -0.07], Z=-2.64, p=0.008). The Fail-Safe N was 1. Heterogeneity did not exceed that which was expected by chance (Q=0.6; df=2; p=0.7; I^2=0). The funnel plots were reasonably symmetrical, suggesting a low risk of publication bias, and the more conservative Egger's regression intercept suggested no publication bias.

CTQ emotional neglect between suicide attempters vs. patient controls

Suicide attempters had significantly higher CTQ emotional neglect scores than patient controls, with a moderate effect size (Hedges' *g*=-0.37, 95%CI [-0.59 – -0.15], Z=-3.35, p=0.001). The Fail-Safe N was 5.

Heterogeneity exceeded that expected by chance at p<0.05 only, implying that the variance among the effect sizes was greater than expected by sampling error (Q=444; df=2; p<0.001; I^2=99.5). The study by Bernegger (Bernegger et al., 2015) was likely responsible for the heterogeneity. After excluding this study (Bernegger et al., 2015), the heterogeneity disappeared and the main results remained significant. The funnel plots were reasonably symmetrical, suggesting a low risk of publication bias, and the more conservative Egger's regression intercept suggested no publication.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis on the association between CTQ scores and vulnerability to SB in bipolar disorders. Overall, we found that compared to patient controls, bipolar suicide attempters had experienced significantly more CM and had higher total CTQ scores and higher CTQ sub-scores. Our meta-analysis of three studies showed a significant but moderate effect size of higher CTQ scores among suicide attempters compared to patient controls in bipolar patients.

These findings suggest that CM may be related to increased vulnerability to SB in bipolar patients. Accordingly, some longitudinal studies have highlighted the association between CM and SB in bipolar diagnoses as a primary outcome (Ernst et al., 1993; Leverich et al., 2003; Enns et al., 2006; Brezo et al., 2008) and other longitudinal studies suggest a relationship between CM and SB mediated by increased drug misuse or dependence (Fergusson et al., 2008; Sugaya et al., 2012). Furthermore, three recent reviews have addressed the impact of CM in clinical outcomes of bipolar diagnosis (Maniglio et al., 2013; Aas et al. 2016; Agnew-Blais and Danese, 2016). Although, all evidence above-mentioned plus the results of the present work bring data upon a strong association between CM and SB in bipolar disease, we cannot state there is a causal mechanism or a cause-effect phenomena within this variables.

The association between SB and CM is multifactorial and begins since early in life. Parental figures, caregivers, and other close relatives provide social support during early developmental stages, which is essential for healthy emotional regulation and stress resilience (Labonté and Turecki, 2012). The experience of repetitive acts of abuse or negligence from such figures signals a

hostile environment that may trigger brain modifications in key response systems, such as the hypothalamic–pituitary–adrenal axis, serotoninergic and sympathetic nervous systems (Bremner, 2003; Watts-English et al., 2006). These may adversely affect the nature and trajectory of normal brain development (Pechtel et al., 2011), particularly the late maturation of limbic–thalamic– cortical structures (Giedd et al., 2010), which may then induce the development of personality and cognitive traits, making abused individuals particularly vulnerable to SB (Turecki et al., 2012). A variety of studies have shown a relationship between CM and disrupted neurodevelopment (Teicher et al., 2003 and 2006; Widom et al., 2007; Grassi-Oliveira et al., 2008), generating ecophenotypes across different psychiatric diagnoses (phenotypic specialization) (Turecki et al., 2012; Teicher and Samson, 2013).

This biological process may not be specific to BD, as some recent investigations have shown that CM is associated with an increase in the risk of SB in patients with schizophrenia (Roy et al., 2005), alcoholism (Roy et al., 2003), personality disorders (Bierer et al., 2003), or substance abuse (Roy et al., 2004), as well as in subjects from the general population (Brown et al., 1999; Dube et al., 2001; Nelson et al., 2002;). In individuals having experienced CM, BD emerges earlier (Leverich et al., 2002) with greater severity (Etain et al., 2013), more comorbidity (Leverich et al., 2006), more suicidal behaviour (Garno et al., 2005; Duarte et al., 2015), and responds less favorably to treatment (Garno et al., 2006; Agnew-Blais and Danese, 2016)).

Our findings are in agreement with the conclusions made by Daruy-Filho et al., (2011) and Aas et al., (2016). Assessment of CM usually requires the use of different instruments due to the heterogeneity of definition regarding CM, i.e., childhood abuse, trauma, adversities and early stress, each to varying degrees of severity. This shows the fragility of constructs describing a complex issue. To minimize discrepancies, the use of clinical interviews and validated questionnaires should be encouraged. Although there is currently no clear evidence of its superiority over other tools, the widespread use of CTQ in research centres and its reliability in both clinical and research settings may make it a useful instrument for professionals in clinical and research practice (Roy and Perry 2004).

Some limitations of this meta-analysis should be considered when interpreting the results. First, participants in some studies were on medication while in other studies they were not. Moreover, it was not possible to separate CTQ scores from low- and high-lethality attempters or from violent and non-violent suicide attempters, because none of the studies distinguished these groups. Of note, we were able to rule out the effects of several variables (e.g., the intensity of depressive and mania symptoms, age, and gender). Since the studies included in the present review evaluated CM retrospectively, conclusions about cause and effect are not possible and the potential impact of memory bias should be considered. Thus, an alternative explanation for the association

between CM and SB must also be taken into consideration: children with hereditary or environmental vulnerability to BD and to SB could also be more likely to be abused and neglected and/or be more susceptible to drug misuse. Further studies will be required to clarify the neurobiological mechanisms underlying the association between CM and SB in bipolar populations. Meta-analyses have often been criticized for combining heterogeneous studies, for their potential of publication bias, and for the inclusion of poor-quality trials. In the present study, however, these concerns were addressed by the objective examination of both publication bias and heterogeneity. An additional limitation is the small number of studies in some analyses, and this may have caused an artificially high effect size (Button et al., 2013). One final limitation is the combined analysis of multiple tasks with the assumption that they measure the same core component of childhood-maltreatment, which may partly explain the heterogeneity observed in several contrasts.

Our findings suggest that a subset of CM types may contribute to the development of suicidal behaviour in bipolar subjects. These findings also highlight the importance of recognizing maltreatment as an etiological risk factor, which is crucial to develop science-based preventative psychiatry, to design effective therapeutic regimens, and to delineate an accurate nosology.

STATEMENT OF INTEREST

None to declare.

REFERENCES

Agnew-Blais, J., Danese, A., 2016. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry, 3, 342-349.

Alloy, L.B., Abramson, L.Y., Smith, J.M., Gibb, B.E., Neeren, A.M., 2006. Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: mediation by cognitive vulnerability to depression. Clinical Child and Family Psychology Review 9, 23–64.

Alloy, L.B., Abramson, L.Y., Urosevic, S., Walshaw, P.D., Nusslock, R., Neeren, A.M. 2005. The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. Clinical Psychology Review 25, 1043–1075.

Aas, M., Etain, B., Bellivier, F., Henry, C., Lagerberg, T., Ringen, A., Agartz, I., Gard, S., Kahn, J.P., Leboyer, M., Andreassen, O.A., Melle, I., 2014. Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders. Psychol Med. 44, 1653-1662.

Aas, M., Henry, C., Andreassen, O.A., Bellivier, F., Melle, I., Etain, B., 2016. The role of childhood trauma in bipolar disorders. Int J Bipolar Disord 4, 1-10.

Bernegger, A., Kienesberger, K., Carlberg, L., Swoboda, P., Ludwig, B., Koller, P., Kapusta, N.D., Martin Aigner, M., Haslacher, H., Schmöger, M., Kasper, S., Schosser, A., 2015. Influence of sex on suicidal phenotypes in affective disorder patients with traumatic childhood experiences. PLoS ONE 10(9): e0137763. doi:10.1371/journal.pone.0137763.

Bierer, L.M., Yehuda, R., Schmeidler, J., Mitropoulou, V., New, A.S., Silverman, J.M., Siever, L.J., 2003. Abuse and neglect in childhood: relationship to personality disorder diagnoses. CNS Spectr 8: 737–754.

Bremner, J.D., 2003. Long-term effects of childhood abuse on brain and neurobiology. Child and Adolescent Psychiatric Clinics 12, 271-292.

Brezo, J., Paris, J., Vitaro, F., Hébert, M., Tremblay, R.E., Turecki, G., 2008. Predicting suicide attempts in young adults with histories of child- hood abuse. Br J Psychiatry 193, 134–139.

Brown, J., Cohen, P., Johnson, J.G, Smailes, E.M., 1999. Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. J Am Acad Child Adolesc Psychiatry 38, 1490–1496.

Cakir, S., Durak, R.T., Ozyildirim, I., Ezgi Ince, E., Vedat Sar, V., 2016. Childhood trauma and treatment outcome in bipolar disorder, Journal of Trauma & Dissociation 17, 397-409.

Cooper, H., Hedges, L. V. & Valentine, J. C., 2009. The Handbook of Research Synthesis and Meta-Analysis, New York, U.S., Russell Sage Foundation Publications.

Danese, A., McEwen, B.S., 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiological Behavior, 106, 29–39.

Daruy-Filho, L., Brietzke, E., Lafer, B., Grassi-Oliveira, R., 2011. Childhood maltreatment and clinical outcomes of bipolar disorder. Acta Psychiatrica Scandinavica 124, 427–434.

De Bellis, M.D., 2001. Developmental traumatology: the psychobiological development of maltreated children and its implications for research, treatment, and policy. Developmental Psychopathology 13, 539–564.

Devries, K.M., Mak, J.Y., Child, J.C., Falder, G., Bacchus, L.J., Astbury, J., Watts, C.H., 2014. Childhood sexual abuse and suicidal behavior: a meta-analysis. Pediatrics 133, 1331–44.

Duarte, D.G.G., Neves, M.C., Albuquerque, M.R., Neves, F.S., Corrêa H.S., 2015. Sexual abuse and suicide attempt in bipolar type I patients. Revista Brasileira de Psiquiatria 37, 35-38.

Duarte, D.G.G., Neves, M.C., Albuquerque, M.R., Souza-Duran, F.L., Busatto, G., Corrêa, H., 2016. Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: a voxel-based morphometric study. J. Affect. Disord. 197, 74-80.

Dube, S.R., Anda, R.F., Felitti, V.J., Chapman, D.P., William, D.F., Giles, W.H., 2001. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. JAMA 286, 3089–3096.

Egger, M., Davey Smith, G., Altman, D., 2001. Systematic Reviews in Health Care: Meta-Analysis in Context, London, BMJ Publishing Group.

Egger, M., Smith, D.G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ. 315, 629-34.

Enns, M.W., Cox, B.J., Afifi, T.O., De Graaf, R., Ten Have, M., Sareen, J., 2006. Childhood adversities and risk for suicidal ideation and attempts: a longitudinal population-based study. Psychol Med. 36, 1769–1778

Ernst, C., Angst, J., Földényi, M., 1993. The Zurich Study. XVII. Sexual abuse in childhood. Frequency and relevance for adult mor- bidity data of a longitudinal epidemiological study. Eur Arch Psychiatry Clin Neurosci. 242, 293–300.

Etain, B., Henry, C., Bellivier, F., Mathieu, F., Leboyer, M., 2008. Beyond genetics: Childhood affective trauma in bipolar disorder. Bipolar Disorders 10, 867–876.

Etain, B., Aas, M., Andreassen, O.A., Lorentzen, S., Dieset, I., Gard, S., Kahn, J.P., Bellivier, F., Leboyer, M., Melle, I., Henry, C., 2013. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. Journal of Clinical Psychiatry 74, 991- 998.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson D.F., Spitz, A.M., Valerie Edwards, V., Koss M.P., Marks, J.S., 1998. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine 14, 245-258.

Fergusson, D.M., Boden, J.M., Horwood, L.J., 2008. The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study. Drug Alcohol Depend. 96:165–77.

Fisher, H. L., Hosang, G. M., 2010. Childhood maltreatment and bipolar disorder: A critical review of the evidence. Mind & Brain — The Journal of Psychiatry 1, 750–785.

Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2005. Impact of childhood abuse on the clinical course of bipolar disorder. British Journal of Psychiatry 186, 121-125.

Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2006. Course of bipolar illness after history of childhood trauma. Lancet 367, 1040-2.

Grassi-Oliveira, R., Stein, L.M., Lopes, R.P., Teixeira, A.L., Bauer, M.E., 2008. Low plasma brain-derived neurotrophic factor and childhood physical neglect are associated with verbal memory impairment in major depression–a preliminary report. Biol Psychiatry 64, 281–285.

Hedges, L.V., Olkin, I., 1985. Statistical Methods for Meta-analysis, London, Academic Press.

Janiri, D., Sani, G., Danese, E., Simonetti, A., Ambrosi, E., Angeletti, G., Erbuto, D., Caltagirone, C., Girardi, P., Spalletta, G., 2015. Childhood traumatic experiences of patients with bipolar disorder type I and type II. J Affect Disord. 175, 92–97.

Labonté, B., Turecki, G., 2012. Epigenetic Effects of Childhood Adversity in the Brain and Suicide Risk. In: Dwivedi Y, editor. The Neurobiological Basis of Suicide.1st ed. CRC Press, New York.

Leverich, G.S., McElroy, S.L., Suppes, T., Keck, P.E., Denicoff, K.D., Nolen, W.A., 2002. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biological Psychiatry 51, 288–297.

Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. J Clin Psychiatry 2003; 64: 506–15.

Leverich, G.S., Post, R.M., 2006. Course of bipolar illness after history of childhood trauma. Lancet 367, 1040–1042.

Li, X.B., Liu, J.T., Zhu, X.Z., Zhang, L., Tang, Y.L., Wang, C.Y., 2014. Childhood trauma associates with clinical features of bipolar disorder in a sample of Chinese patients. J Affect Disord. 168, 58–63.

Lindenmayer, J. P., Czobor, P., Alphs, L., Nathan, A. M., Anand, R., Islam, Z., et al., 2003. The InterSePT scale for suicidal thinking reliability and validity. Schizophr Res. 63, 161-70.

Maniglio, R., 2013. Prevalence of child sexual abuse among adults and youths with bipolar disorder: a systematic review. Clin Psychol Rev. 33, 561–73.

Mann, J. J., 2003. Neurobiology of suicidal behaviour. Nature Reviews. Neuroscience. 4, 819-828.

Mann, J.J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., Hegerl, U., Lonnqvist, J., Malone, K., Marusic, A., Mehlum, L., Patton, G., Phillips, M., Rutz, W., Rihmer, Z., Schmidtke, A., Shaffer, D., Silverman, M., Takahashi, Y., Varnik, A., Wasserman, D., Yip, P., Hendin, H., 2005. Suicide prevention strategies: a systematic review. J. Am. Med. Assoc. 294, 2064–2074

Nordentoft, M., Mortensen, P.B., Pedersen, C.B., 2011. Absolute Risk of Suicide After First Hospital Contact in Mental Disorder. Arch Gen Psychiatry 68, 1058-1064.

Nelson, E.C., Heath, A.C., Madden, P.A., Cooper, M.L., Dinwiddie, S.H., Bucholz, K.K., Glowinski, A., McLaughlin, T., Dunne, M.P., Statham, D.J., Martin, N.G., 2002. Association between self-reported childhood sexual abuse and adverse psychosocial outcomes: results from a twin study. Arch Gen Psychiatry 59, 139–145.

Nerila, Y., Bromet, E.J., Carlson, G.A., Naz, B., 2005. Assaultive trauma and illness course in psychotic bipolar disorder: findings from the Suffolk county mental health project. Acta Psychiatrica Scandinavica 111, 380-383.

Osman, A., Bagge, C. L., Gutierrez, P. M., Konick, L. C., Kopper, B. A. & Barrios, F. X., 2001. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. Assessment. 8, 443-54.

Petticrew, M. & Roberts, H., 2006. Systematic reviews in the social sciences: a practical guide, Oxford, Blackwell.

Plutchik, R., Van Praag, H., 1989. The measurement of suicidality, aggressivity and impulsivity. Prog Neuropsychopharmacol Biol Psychiatry. 13 Suppl, S23-34.

Pompili, M., Iliceto, P., Innamorati, M., Rihmer, Z., Lester, D., Akiskal, H.S., Girardi, P., Ferracuti, S., Tatarelli, R., 2009. Suicide risk personality traits in physically and/or sexually abused acute psychiatric inpatients: a preliminary study. Psychol Rep. 105, 554-68.

Riley, R.D., Higgins, J.P. & Deeks, J.J., 2011. Interpretation of random effects meta-analyses. BMJ. 342, d549.

Rosenthal, R., 1979. The File Drawer Problem and Tolerance for Null Results. Psychological Bulletin. 86, 638-641.

Roy, A., 2005. Reported childhood trauma and suicide attempts in schizophrenic patients. Suicide Life Threat Behav 35, 690–693.

Roy, A., 2003. Distal risk factors for suicidal behavior in alcoholics: replications and new findings. J Affect Disord 77, 267–271.

Roy, A., 2004. Relationship of childhood trauma to age of first suicide attempt and number of attempts in substance dependent patients. Acta Psychiatr Scand 109: 121–125.

Roy, C.A., Perry, J.C., 2004. Instruments for the assessment of childhood trauma in adults. J Nerv Ment Dis. 192, 343–51.

Sugaya, L., Hasin, D.S., Olfson, M., Lin, K.H., Grant, B.F., Blanco, C.J., 2012. Child physical abuse and adult mental health: a national study. Journal of Trauma Stress. 25, 384-92.

Teicher, M.H., Andersen, S.L., Polcari, A., Anderson, C.M., Navalta, C.P., Kim, D.M., 2003. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 27,33–44.

Teicher, M.H., Tomoda, A., Andersen, S.L., 2006. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? Ann N Y Acad Sci 1071, 313–323.

Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. American Journal of Psychiatry 170, 1114–1133.

Turecki, G., Ernst, C., Jollant, F., Labonté, B., Mechawar, N., 2012. The neurodevelopmental origins of suicidal behavior. Trends in Neurosciences 35, 14-23.

Von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2008. The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement: guidelines for reporting observational studies. Journal of Clinical Epidemiology. 61, 344-349.

Watson, S., Gallagher, P., Dougall, D., Porter, R., Moncrieff, J., Ferrier, N., Young, A.H., 2014. Childhood trauma in bipolar disorder. Australian & New Zealand Journal of Psychiatry 48, 564–570

Watts-English., T., Fortson, B.L., Gibler, N., Hooper, S.R., and DeBellis, M.D. 2006. The psychobiology of maltreatment in childhood. Journal of Social Issues 62, 717–736.

Widom, C.S., Dumont, K., Czaja, S.J., 2007. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry 64, 49–56.

Williams, J.M., Broadbent, K., 1986. Autobiographical memory in suicide attempters. J Abnorm Psychol. 95, 144-9.

World Health Organization, 2014. Global status report on violence prevention 2014. WHO Press, Switzerland.

Table 1: Review of Studies Exploring Childhood Abuse in Patients with Suicidal Behaviours with Bipolar Disorders

Authors	Study type and population	Medication	Suicidal Behaviour			Childhood abuse (type and tools)	Results
			Definition	Source of information	Period Assessed		
Duarte et al., 2016 Brasil	- Cross-sectional study - Outpatients with diagnosis of BD-I (n=39) (DSM-IV). ○ SA (n=20) ○ PC (n=19)	Yes [a,b,c,d]	Suicide attempt	MINI-Plus	Lifetime history of SA	CTQ	- SA > PC: Higher total CTQ scores and higher CTQ sub-scores (emotional, physical and sexual abuse; emotional and physical neglect)
Cakir et al., 2016 Turkey	- Cross-sectional study from an ongoing follow-up project - Outpatients with diagnosis of BD-I (n=135) (DSM-IV). ○ SA (n=21) ○ PC (n=114)	Yes [a,b,c,d]	Suicide attempt	SCID-I	Lifetime history of SA	CTQ	- SA > PC: Higher total CTQ scores and higher CTQ emotional neglect sub-score
Bernegger et al., 2015 Austria	- Cross-sectional study - Inpatients or outpatients with either major depressive (n=211) or BD (n= 44) (DSM-IV-TR) ○ SA BD (n= 12) (17,1%) ○ PC BD (n= 32) (17,3%)	NA	Suicide attempt	VI-SURIAS SBQ-R	Lifetime history of SA	CTQ	- SA > PC: Higher total CTQ scores and higher CTQ sub-scores (emotional, physical and sexual abuse; emotional and physical neglect) in females.
Janiri et al., 2014 Italy	- Cross-sectional study - Outpatients with diagnosis of BD-I (n=58) or II (n=46) (DSM-IV) (n=104) ○ SA BD I (n=12) ○ PC BD I (n=46) ○ SA BD II (n=14) ○ PC BD II (n=32)	Stable medication for a minimum of six months	Suicide attempt	Semi-structured questionnaire	Lifetime history of SA	CTQ	- SA BDI > PC BDI: Higher total CTQ scores and higher CTQ sub-scores for emotional and sexual abuse. - SA BDII > PC BDII: Higher total CTQ scores and higher CTQ sub-scores for emotional abuse. -Emotional abuse: independent predictor of lifetime suicide attempts in BD patients.
Li et al., 2014 China	-Cross-sectional study -Outpatients with diagnosis of bipolar disorder type I (DSM-IV) ○ SA (n=31) ○ PC(n=101)	NA	Suicide attempt	SCID-I	Lifetime history of SA	CTQ-SF	- SA > PC: Higher total CTQ scores and higher CTQ sub-scores (emotional, physical and sexual abuse, as well as emotional and physical neglect), but not statistically significant (p > 0.05)
Watson et al., 2014 England	- Cross-sectional study - Outpatients with diagnosis of bipolar disorder I (n=31), II (n=25) or NOS (n=4) (DSM-IV) ○ SA (n=31) ○ PC (n=24)	Stable medication for a minimum of four weeks	Suicide attempt	Semi-structured questionnaire	Lifetime history of SA	CTQ	- SA > PC: Higher total CTQ scores and higher CTQ emotional abuse sub-score
Etain et al., 2013 France Norway	- Cross-sectional study - In and outpatients with diagnosis of bipolar disorder (type I, type II, or NOS) (n=587) (DSM-IV) ○ SA (n=211) ○ PC (n=376)	Yes [a]	Suicide attempt	SCID-I	Lifetime history of SA	CTQ	- SA > PC: Higher total CTQ scores and higher CTQ sub-score (emotional, physical and sexual abuse). - Emotional and sexual abuse were independently associated with increased frequency of a history of suicide attempt

Study						Results

Pompili et al., 2009 Italy
 - Cross-sectional study
 - Inpatients with psychiatric disorder (DSM IV-TR) (n=62) (15% bipolar disorder I, 26% bipolar disorder II, 7% major depressive epi- sode, 15% psychosis, and 8% other specified diagnosis)
   o HSR (n=20)
   o LSR (n=42)
	Yes	Suicide attempt	Minnesota Multiphasic Personality Inventory-2 (MMPI-2)	Lifetime history of SA	CTQ	- HSR > LSR: Higher risk of suicide report more often history of physical or sexual abuse.
						 -Patients who reported physical abuse by family members were more likely to be at higher risk for suicide. Being insulted – 6 times; bruises or marks – 9 times; and punishment with a belt or hard object – 20 times more likely to be at higher risk for suicide.

Garno et al., 2005 USA - Cross-sectional study - Out and inpatients with diagnosis of bipolar disorder (n= 100) (DSM-IV)	Yes	Suicide attempt	SADS	Lifetime history of SA	CTQ	- SA > PC: A near-significant relationship between lifetime suicide attempts and history of sexual abuse.

Abbreviations : CTQ : Childhood Trauma Questionnaire; SADS Schedule for Affective Disorders and Schizophrenia ; SBQ-R: Revised Suicidal Behaviours Questionnaire (Osman et al., 2001); SCID: Structured Clinical Interview for DSM-IV Axis I disorders; SPS : Suicide Probability Scale ; SRC: Suicide Risk Scale (Plutchik et al., 1989); SSI: Suicide Intent Scale ; VASA: Violence and Suicide Assessment Scale; VLL: Verbal List Learning; VLMT: Verbaler Lern- and Merkfähigkeitstest ; VI-SURIAS : Viennese Suicide Risk Assessment Scale; SA: Suicide attempters (i.e. patients with a history of suicide attempt); PC: Patient Controls (i.e. patients with no history of suicide attempt); NA: Non-Available; HSR: Higher suicidal risk; LSR: Lower suicidal risk; NOS: not otherwise specified.

[a] Antipsychotic medication; [b] Antidepressant medication; [c] Anxiolytic medication; [d] Mood Stabilizers (lithium, valproic acid, or carbamazepine).

Figure 1. Flow chart
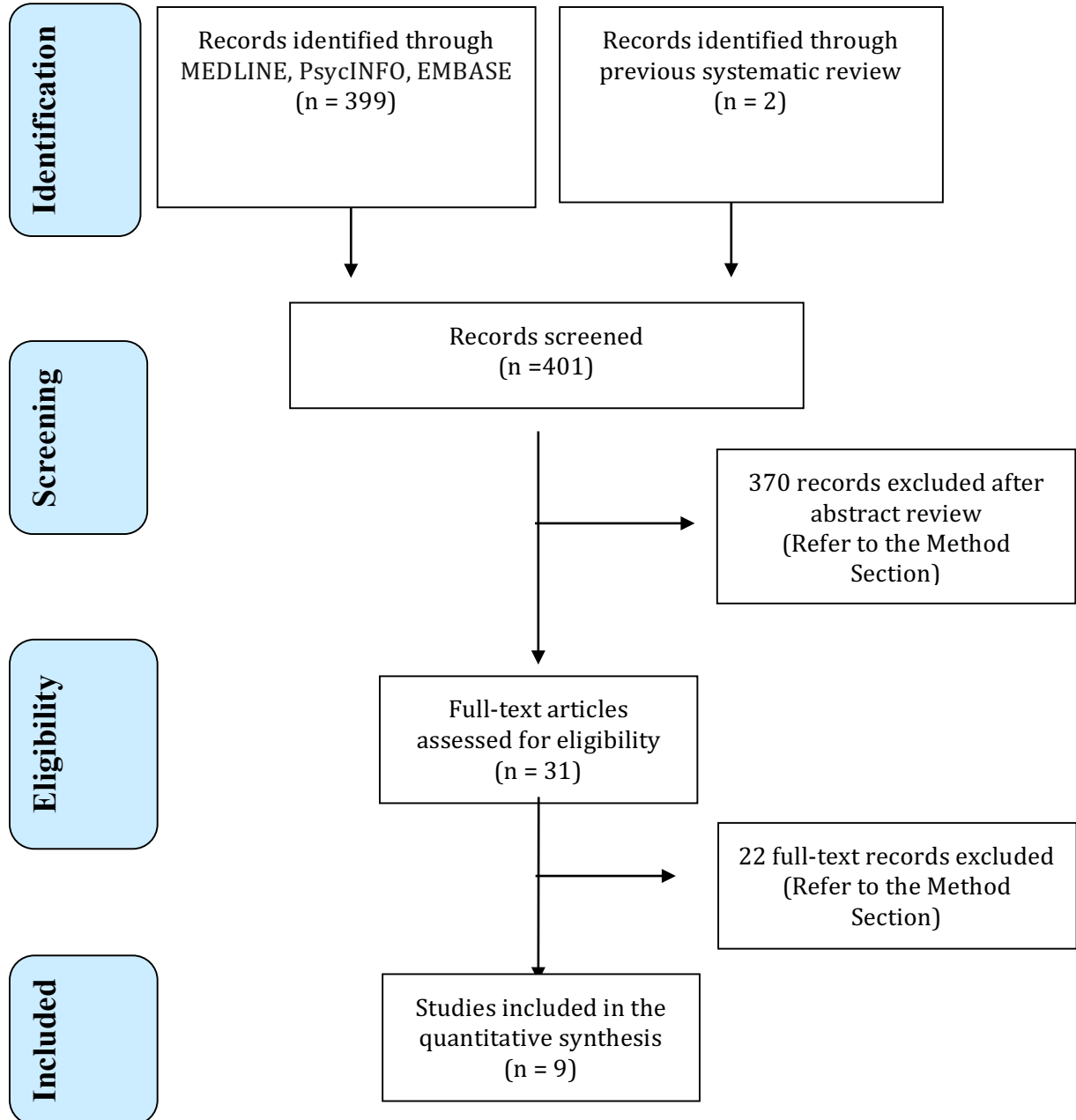
Figure 2: Comparison of the CTQ Total Score (A), CTQ Sexual Abuse Sub-score (B), CTQ Physical Abuse Sub-score (C), CTQ Emotional Abuse Sub-score (D), CTQ Physical Abuse Sub-score (E), and CTQ Emotional Abuse Sub-score (F) between Suicide Attempters and Patient Controls in Bipolar Patients.
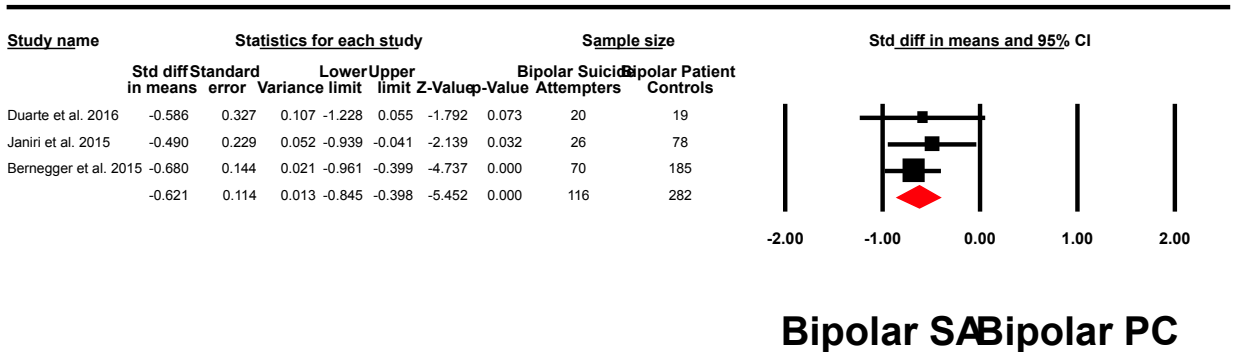
A.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Bipolar Suicide Attempters	Bipolar Patient Controls
Duarte et al. 2016	-0.410	0.317	0.101	-1.032	0.211	-1.294	0.196	20	19
Janiri et al. 2015	-0.838	0.232	0.054	-1.293	-0.383	-3.610	0.000	26	78
Bernegger et al. 2015	-0.608	0.142	0.020	-0.887	-0.328	-4.265	0.000	70	185
	-0.637	0.113	0.013	-0.860	-0.415	-5.620	0.000	116	282

Hedges's g and 95% CI

-2.00 -1.00 0.00 1.00 2.00

Bipolar SA   Bipolar PC

CTQ Total

Results indicate that suicide attempters had a significantly higher CTQ Total Score relative to patient controls.

B.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Bipolar Suicide Attempters	Bipolar Patient Controls
Duarte et al. 2016	-0.586	0.327	0.107	-1.228	0.055	-1.792	0.073	20	19
Janiri et al. 2015	-0.490	0.229	0.052	-0.939	-0.041	-2.139	0.032	26	78
Bernegger et al. 2015	-0.680	0.144	0.021	-0.961	-0.399	-4.737	0.000	70	185
	-0.621	0.114	0.013	-0.845	-0.398	-5.452	0.000	116	282

Std diff in means and 95% CI
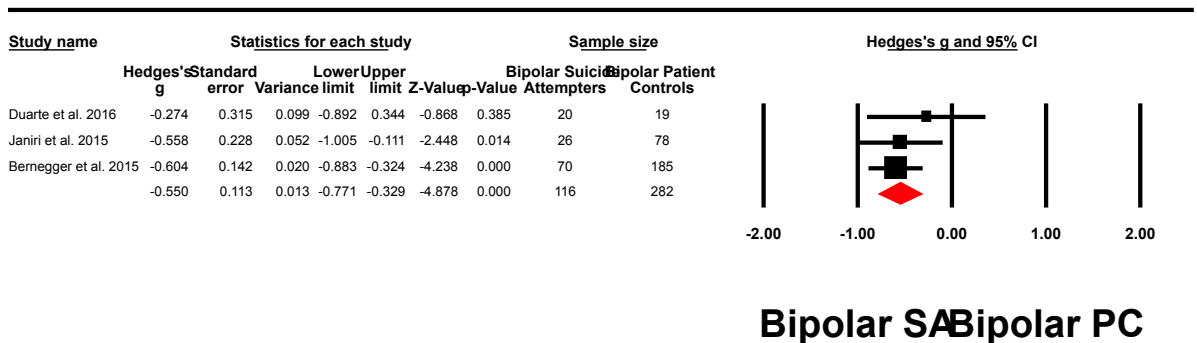
-2.00 -1.00 0.00 1.00 2.00

Bipolar SA   Bipolar PC

CTQ Sexual Abuse

Results indicate that suicide attempters had a significantly higher CTQ Sexual Abuse SubScore relative to patient controls.

C.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Bipolar Suicide Attempters	Bipolar Patient Controls
Duarte et al. 2016	-0.274	0.315	0.099	-0.892	0.344	-0.868	0.385	20	19
Janiri et al. 2015	-0.558	0.228	0.052	-1.005	-0.111	-2.448	0.014	26	78
Bernegger et al. 2015	-0.604	0.142	0.020	-0.883	-0.324	-4.238	0.000	70	185
	-0.550	0.113	0.013	-0.771	-0.329	-4.878	0.000	116	282

Hedges's g and 95% CI
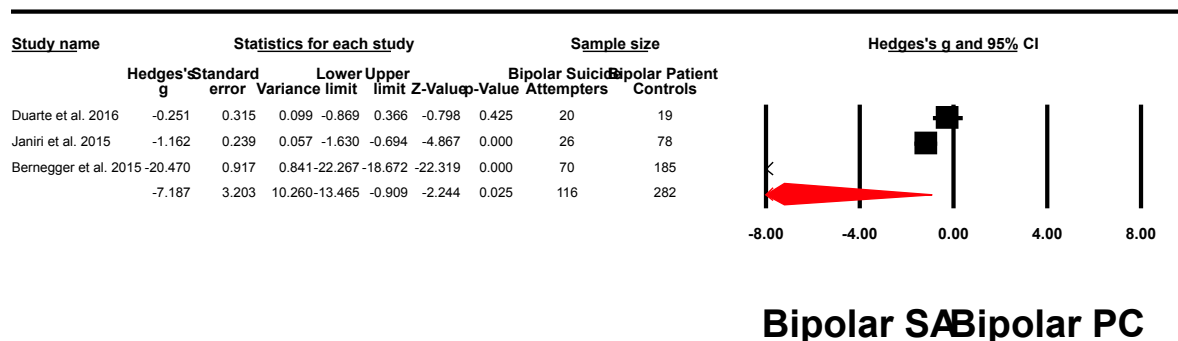
-2.00 -1.00 0.00 1.00 2.00

Bipolar SA   Bipolar PC

CTQ Physical Abuse

Results indicate that suicide attempters had a significantly higher CTQ Physical Abuse SubScore relative to patient controls.
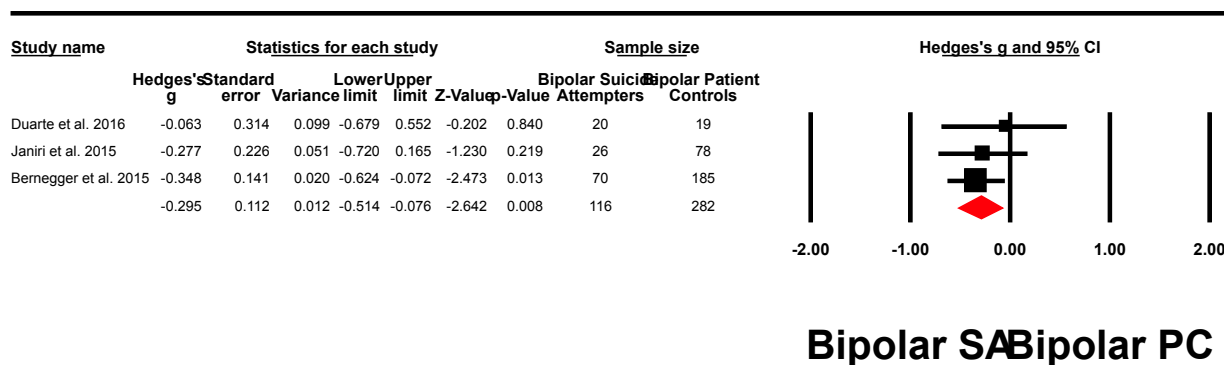
D.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Bipolar Suicide Attempters	Bipolar Patient Controls
Duarte et al. 2016	-0.251	0.315	0.099	-0.869	0.366	-0.798	0.425	20	19
Janiri et al. 2015	-1.162	0.239	0.057	-1.630	-0.694	-4.867	0.000	26	78
Bernegger et al. 2015	-20.470	0.917	0.841	-22.267	-18.672	-22.319	0.000	70	185
	-7.187	3.203	10.260	-13.465	-0.909	-2.244	0.025	116	282

Statistics for each study — *Sample size* — *Hedges's g and 95% CI*

Bipolar SA   Bipolar PC

CTQ Emotional Abuse|

Results indicate that suicide attempters had a significantly higher CTQ Emotional Abuse SubScore relative to patient controls.
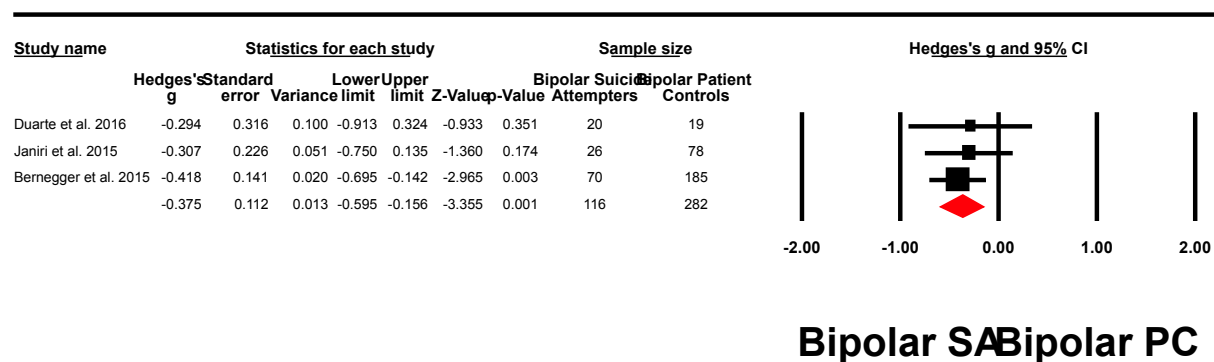
E.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Bipolar Suicide Attempters	Bipolar Patient Controls
Duarte et al. 2016	-0.063	0.314	0.099	-0.679	0.552	-0.202	0.840	20	19
Janiri et al. 2015	-0.277	0.226	0.051	-0.720	0.165	-1.230	0.219	26	78
Bernegger et al. 2015	-0.348	0.141	0.020	-0.624	-0.072	-2.473	0.013	70	185
	-0.295	0.112	0.012	-0.514	-0.076	-2.642	0.008	116	282

Statistics for each study — *Sample size* — *Hedges's g and 95% CI*

Bipolar SA   Bipolar PC

CTQ Physical Neglect

Results indicate that suicide attempters had a significantly higher CTQ Physical Neglect SubScore relative to patient controls.

F.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Bipolar Suicide Attempters	Bipolar Patient Controls
Duarte et al. 2016	-0.294	0.316	0.100	-0.913	0.324	-0.933	0.351	20	19
Janiri et al. 2015	-0.307	0.226	0.051	-0.750	0.135	-1.360	0.174	26	78
Bernegger et al. 2015	-0.418	0.141	0.020	-0.695	-0.142	-2.965	0.003	70	185
	-0.375	0.112	0.013	-0.595	-0.156	-3.355	0.001	116	282

Statistics for each study — *Sample size* — *Hedges's g and 95% CI*

Bipolar SA   Bipolar PC

CTQ Emotional Neglect

Results indicate that suicide attempters had a significantly higher CTQ Emotional Neglect SubScore relative to patient controls.

2 OBJETIVOS

2.1 Objetivo geral

Avaliar a associação entre trauma infantil, comportamento suicida e o VSC em componentes das redes neurais da região fronto-límbica de pacientes adultos portadores de Transtorno Bipolar do Tipo I.

2.2 Objetivos específicos

✓ Correlacionar as variáveis sociodemográficas e clínicas entre subgrupos de pacientes bipolares e controles (C), levando em conta os fatores TI e CS;

✓ Avaliar os escores totais e os subtipos na escala de TI e sua associação com CS;

✓ Comparar o VSC entre pacientes com TAB e C, entre pacientes com TAB que sofreram TI com aqueles que não sofreram e com C e entre pacientes com TAB que tentaram suicídio com aqueles que não tentaram e com C;

✓ Correlacionar o VSC e a gravidade de cada tipo de TI;

✓ Subdividir o grupo de suicidas entre alta e baixa letalidades da tentativa e realizar comparação volumétrica cerebral com os não suicidas e C. Avaliar nesses subgrupos: perfil sociodemográfico, clínico e características do CS (número de tentativas, ideação suicida na admissão, intenção da tentativa de suicídio mais letal e métodos suicidas);

✓ Analisar os dados obtidos no estudo, em contraste com os relatados na literatura nacional e internacional.

3 MATERIAIS E MÉTODOS

A metodologia está detalhadamente descrita nos artigos da presente tese.

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (UFMG) sob o número ETIC 0431.0.203.000-10 (Anexo).

4 RESULTADOS

4.1 Artigo 2: Sexual Abuse and Suicide Attempt in Bipolar type I Patients

Revista Brasileira de Psiquiatria, 2015, 37(2), 180-182
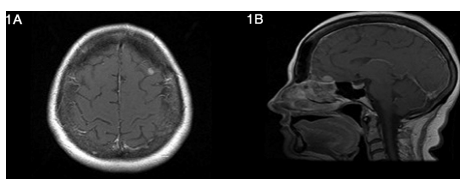
Figure 1 A) Small meningioma in the left frontal high convexity. B) At 1 year, a new meningioma was visible in the cribriform plate of the ethmoid.

agitated, sleepless, and exhibiting signs of memory loss over the previous 2 months.

She had no history of alcohol or other drug abuse, and no prior psychiatric history. Blood tests, serologies, drug screening, and electroencephalography (EEG) showed no abnormalities.

The patient had been on citalopram 20 mg/day for 1 month as prescribed by her geriatrician. We decided to switch her medication to quetiapine 50 mg/day, and requested a head computed tomography (CT) scan and advice from the neurology service.

After 2 weeks, the patient was more communicative and said that her husband had been filming her at home. Head CT showed no abnormalities, and she was discharged from the neurology service. However, we insisted that a magnetic resonance imaging (MRI) scan of the brain should be performed and increased the dose of quetiapine to 100 mg/day.

At 1-month follow-up, the patient was asymptomatic and asked: "How could I believe that my husband wanted to harm me?" MRI showed a small meningioma in the left frontal high convexity (Figure 1A) and she was referred for neurosurgical evaluation, but the neurosurgeon recommended watchful waiting.

The patient returned after 1 year, still on regular quetiapine therapy (100 mg/day). Although well, she complained of headaches and memory lapses. There were no signs or symptoms of intracranial hypertension. Blood tests, serologies, and EEG remained normal. Nevertheless, we requested another MRI scan, which showed enlargement of the frontal meningioma and emergence of a new tumor in the cribriform plate of the ethmoid (Figure 1B). Two weeks later, the patient came to evaluation in a very agitated state, asking why we had "posted what she had told us on Facebook." After a 30-day course of olanzapine 5 mg/day, the patient improved substantially. Olanzapine was well tolerated and the patient did not experience adverse effects. When last seen in August 2014, she was well and remained on olanzapine 5 mg/day.

Meningiomas are benign neoplasms of the central nervous system, highly prevalent among elderly women.[1] Benign cerebral tumors such as these may not cause any symptoms other than psychiatric manifestations until they are quite large. Analyses of correlation between peritumoral edema and coexistence of psychiatric symptoms have indicated that the underlying pathophysiological mechanism is likely related to disruptions in intracerebral pathways rather than with a mass effect of meningioma on intracranial pressure.[2] Indeed, headache, papilledema, and focal neurological signs often arise only when the meningioma has reached an advanced stage. Often, the correct diagnosis is established only after intracranial hypertension has caused irreversible cerebral damage.[2,3]

Meningiomas can cause delusions, especially when located in the cerebral convexities.[2,4] Based on the case reported herein, a low dose of olanzapine seems to be safe and effective for the treatment of such clinical presentations.

When an older adult with no history of mental illness develops psychiatric symptoms, other medical conditions should be considered in the differential diagnosis. Severe diseases may be overlooked if this recommendation is disregarded.[5]

Joao P. Maia-de-Oliveira,[1,2,3] Lizie E. Brasileiro,[3]
Carlos E. Correia,[3] João P. Machado-de-Sousa,[1,2]
Jaime E. Hallak[1,2]
[1]Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil. [2]National Science and Technology Institute for Translational Medicine (INCT-TM). [3]Universidade Federal do Rio Grande do Norte (UFRN), Natal, RN, Brazil

Disclosure

The authors report no conflicts of interest.

References

1 Whittle IR, Smith C, Navoo P, Collie D. Meningiomas. Lancet. 2004;363:1535-43.
2 Lampl Y, Barak Y, Achiron A, Sarova-Pinchas I. Intracranial meningiomas: correlation of peritumoral edema and psychiatric disturbances. Psychiatry Res. 1995;58:177-80.
3 Maurice-Williams RS, Dunwoody G. Late diagnosis of frontal meningiomas presenting with psychiatric symptoms. Br Med J (Clin Res Ed). 1988;296:1785-6.
4 Hunter R, Blackwood W, Bull J. Three cases of frontal meningiomas presenting psychiatrically. Br Med J. 1968;3:9-16.
5 Maia-de-Oliveira JP, Pinto JP, Alexandre V, Machado-de-Sousa JP, Morais SL, Chaves C, et al. A false case of clozapine-resistant schizophrenia. Case Rep Med. 2010;2010:534027.

Sexual abuse and suicide attempt in bipolar type I patients

Bipolar disorder (BD) is the psychiatric diagnosis that carries the highest risk for suicide behavior. Many different factors are associated with suicide behavior in BD, such as genetics,[1] first-episode bipolarity,[2] and early life adversities (ELA).[3] However, specifically concerning

Table 1 Sociodemographic parameters, clinical features, and childhood trauma events of 47 bipolar patients stratified by history of suicide attempt

Variable	Suicide (n=23)	No suicide (n=24)	p-value
Female gender	14 (60.8)	14 (58.3)	0.86
Age	43.1±12.2	39.3±10.6	0.27
Marital status			
Married/living with partner	8 (34.8)	10 (41.6)	
Single/divorced/widowed	15 (65.2)	14 (48.4)	0.63
Educational attainment, years	11.9±4.2	11.3±5.1	0.65
Age at first mood episode, years	26.7±9.6	25.1±8.4	0.52
History of psychiatric hospitalization	15 (65.2)	15 (62.5)	0.85
At least one comorbid diagnosis	14 (60.8)	12 (50.0)	0.45
Alcohol abuse or dependence	9 (39.1)	6 (25.0)	0.30
Physical negligence	7.7±3.4	8.1±4.3	0.71
Emotional negligence	10.3±5.9	9.4±6.2	0.54
Physical abuse	8.9±5.5	7.3±4.6	0.17
Emotional abuse	9.6±5.1	9.0±4.5	0.71
Sexual abuse	11.2±8.2	6.9±5.1	**0.03**
Total	47.7±22.1	41.0±18.5	0.29

Data presented as n (%) or mean ± standard deviation.

ELA, some controversy persists about what types of adversity would contribute or not to suicidal behavior in patients with BD.[3] Within this context, we conducted a study of all early life stressors (physical and emotional negligence and physical, emotional, and sexual abuse) and their associations with suicide behavior in BD.

We enrolled 47 BD type 1 (BD-I) patients aged 18 to 65 years. All patients lived in Belo Horizonte or neighboring areas and were receiving regular follow-up at the Núcleo de Transtornos Afetivos, Universidade Federal de Minas Gerais (UFMG). Our routine patient assessment protocol is fully detailed elsewhere.[1] Briefly, the diagnosis was established using a structured diagnostic interview (Mini International Neuropsychiatric Interview, MINI-PLUS). We only included BD-I patients in euthymia, defined as a score < 8 in the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D). We also evaluated the frequency, intent, and lethality of suicide attempts, using Beck's Suicide Intent Scale. For the purpose of this study, ELA was assessed using the Childhood Trauma Questionnaire.[4]

The study was approved by the UFMG Research Ethics Committee. Written informed consent was obtained from all participants after a complete description of the study had been provided.

Overall, 23 patients (48.9%) in our sample had a history of at last one previous suicide attempt, with mean frequency of 1.67±0.89, and 24 (51.1%) did not. No significant statistical differences were found concerning socio-demographic and/or clinical characteristics between the suicidal or non-suicidal groups in variables classically associated with suicidal behavior, such as gender and comorbidities (Table 1).

Using the Shapiro-Wilk *W* and Mann-Whitney *U* tests and binary logistic regression, we found that BD-I patients with a lifetime suicide attempt exhibited significantly higher scores for sexual abuse (z = -2.093; p = 0.036, r = -0.31) than BD-I patients without a history of suicide attempt. However, we failed to find differences in any of the other ELA factors studied (Table 1).

Furthermore, we constructed a logistic regression model with the sexual abuse score. The results showed that sexual abuse contributed significantly to suicidal behavior ($\chi^2_{(1)}$ = 4.69, df = 1, n=47; p = 0.03) in this population, accounting for 9.5% (Cox and Snell R^2) to 12.7% (Nagelkerke R^2) of the variance of the dependent variable. The Exp(β) and confidence interval was 1.102 (95% confidence interval 1.001-1.214).

A large body of evidence is currently available to help explain the link between ELA, particularly sexual abuse, and suicidal behavior (mediated for example by impulsivity and aggressivity), as well the molecular epigenetic mechanisms underlying those behaviors.[5] To our knowledge, this was the first study to assess ELA and suicidal behavior in a Brazilian BD sample. Even considering some limitations (retrospective design and small sample size), our findings reinforce the idea that identifying child sexual abuse in BD patients may help psychiatrists define high-risk groups for suicidal behavior, and highlights the need to address this hidden epidemic.

Dante G. Duarte,[1] Maila de C. Neves,[1] Maicon R. Albuquerque,[2] Fernando S. Neves,[1] Humberto Corrêa[1]
[1] Mental Health Department, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. [2] Physical Education Department, Universidade Federal de Viçosa (UFV), Viçosa, MG, Brazil.

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Disclosure

The authors report no conflicts of interest.

References

1 Neves FS, Malloy-Diniz LF, Romano-Silva MA, Aguiar GC, de Matos LO, Correa H. Is the serotonin transporter polymorphism (5-HTTLPR) a potential marker for suicidal behavior in bipolar disorder patients? J Affect Disord. 2010;125:98-102.
2 Neves FS, Malloy-Diniz LF, Barbosa IG, Brasil PM, Corrêa H. Bipolar disorder first episode and suicidal behavior: are there differences according to type of suicide attempt? Rev Bras Psiquiatr. 2009;31:114-8.
3 Leverich GS, Post RM. Course of bipolar illness after history of childhood trauma. Lancet. 2006;367:1040-2.
4 Grassi-Oliveira R, Stein LM, Pezzi JC. [Translation and content validation of the Childhood Trauma Questionnaire into Portuguese language]. Rev Saude Publica. 2006;40:249-55.
5 Labonté B, Turecki G. Epigenetic effects of childhood adversity in the brain and suicide risk. In: Dwivedi Y, editor. The neurobiological basis of suicide. Boca Raton: CRC Press; 2012. p.256-84.

New-onset panic attacks after deep brain stimulation of the nucleus accumbens in a patient with refractory obsessive-compulsive and bipolar disorders: a case report

New-onset panic attacks (PA) have been described in patients with obsessive-compulsive disorder (OCD) receiving deep brain stimulation (DBS), mostly during the intraoperative period or a few weeks after device implantation.[1,2] We report the case of a 39-year-old, right-handed man with severe treatment-refractory OCD and bipolar disorder type I (BD-I), beginning at age 17 (without any other psychiatric disorder), who developed late-onset PA after DBS implant placement.

The patient presented with obsessions of doubt, cleaning, and disgusting thoughts accompanied by checking and cleaning compulsions, with an intense need for reassurance and avoidance. Due to poor response to multiple drugs and to cognitive-behavioral therapy (Table 1), the patient underwent surgical evaluation for DBS. Implantation was performed after the patient and relatives had signed an informed consent form and following authorization from the Federal Council of Medicine. At baseline, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score was 36[3] and the Beck Depression Inventory (BDI) score was 35.[4]

Bilateral DBS electrodes were inserted through the anterior limb of the internal capsule into the nucleus accumbens (NAcc) near the anterior commissure (Figure 1).

Table 1 Medications previously taken by the patient

Medication	Maximum dose (mg)	Duration
Clozapine	400	15 years
Fluoxetine	80	14 years
Valproate	2000	3 years
Lithium	1200	16 years
Clomipramine	250	3 years
Sertraline	200	2 years
Paroxetine	80	1 year
Fluvoxamine	300	6 years
Citalopram	60	7 months
Haloperidol	5	6 months
Risperidone	6	3 years
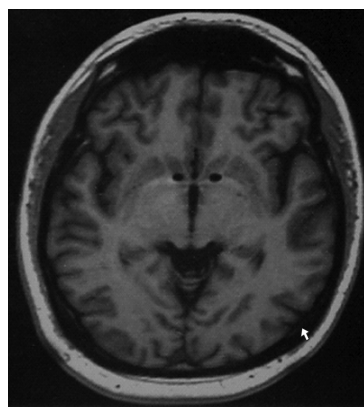
Figure 1 Magnetic resonance imaging scan showing the deep brain stimulation electrodes (Medtronic model 3387) inserted bilaterally through the anterior limb of the internal capsule into the nucleus accumbens near the anterior commissure. Cartesian coordinates of the distal end of the deepest contact relative to the mid-commissural point were: left and right: 6 mm lateral to midline, 3 mm anterior to mid-commissural point, and in the anterior commissure-posterior commissure plane.

Intraoperative evaluation of the DBS electrodes was carried out using bipolar stimulation at each contact. Pulse width and stimulation frequency ranged from 90 to 210 μs and 100 to 180 Hz, respectively. Voltage varied between 0 and 4 V, while bilateral stimulation was 3+/0-, 3+/1-, 3+/2-, and 0+/3-. The patient did not notice any change in mood or anxiety during stimulation. Testing occurred for approximately 2 to 4 minutes at each setting and the voltage was turned off before testing each contact. The patient was discharged from the hospital with the DBS regulated at 4.2 V, 150 μs, 150 Hz both sides, LL 3+, zero and 1 Neg, RR 7+, 4 and 5 Neg. Final adjustment was performed after several trials with on-off checking. Five months after surgery, the patient had experienced significant improvement of both OCD (Y-BOCS = 17) and depression (BDI = 9). Suddenly, within 12 hours of a follow-up visit involving a parameter adjustment for better control of OCD symptoms (4 V, 180 μs, 120 Hz both sides, LL C+, zero and 1 [-], RR C+, 4 and 5 [-]), the patient began to have

4.2 Artigo 3: Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: a voxel-based morphometric study

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Research paper

Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: A voxel-based morphometric study

Dante G.G. Duarte [a,*], Maila de Castro Lourenço Neves [a], Maicon R. Albuquerque [b], Fábio L. de Souza-Duran [c], Geraldo Busatto [c], Humberto Corrêa [a]

[a] *Mental Health Department, Federal University of Minas Gerais, Brazil*
[b] *Federal University of Viçosa, Brazil*
[c] *Laboratory of Neuroimage in Psychiatry, Research in Applied Neuroscience, Support Care of the University of São Paulo, Brazil*

A R T I C L E   I N F O

A B S T R A C T

Background: Childhood maltreatment (CM) may be related to clinical expression and outcome of bipolar disorder (BD). Several neuroimaging studies have detected brain morphological changes in specific neural networks of adults who suffered maltreatment in their childhood. We investigated alterations in gray matter volume (GMV) to determine a possible neuroanatomical basis of vulnerability in patients with CM having type I BD (BD-I).

Methods: We assessed 39 euthymic DSM-IV BD-I patients with (n=20) and without (n=19) a history of CM and 20 healthy controls without maltreatment as defined by the Childhood Trauma Questionnaire (CTQ). Voxel-based morphometry (VBM) was used to compare GMV differences between patients and controls and perform linear correlations in overall BD group between GMV and CTQ scores.

Results: BD-I patients had significant negative correlations between CTQ total score and GMV in the right dorsolateral prefrontal cortex (PFC) and the right thalamus; between physical abuse and GMV in the right dorsolateral PFC; between physical neglect and GMV in the thalamus bilaterally; and between emotional neglect and GMV in the right thalamus.

Limitations: Pharmacological treatment could have altered GMV findings. Results emerged only when using SVC approach. CTQ, a retrospective self-report, has the risk of potential recall bias. The cross-sectional design limits longitudinal and neurodevelopmental inferences.

Conclusions: The severity of self-reported CM in BD-I patients is associated with morphological changes in GMV of specific neural networks relevant to responses to stress and to modulate emotional behavior.

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1. Introduction

Childhood maltreatment (CM) is a global epidemic, which can have serious life-long effects on its victims. CM is a very difficult concept to study because of the huge social stigma that accompanies it. A generally used definition for maltreatment states that it is characterized by sustained or repeated exposure to events that usually involve a betrayal of trust (De Bellis, 2001). Active examples of CM include sexual and physical abuse and various forms of emotional abuse. Passive examples include emotional and physical neglect (Teicher and Samson, 2013). Indeed, household dysfunction (e.g., household member use of substance, mental illness, criminal behavior, mother treated violently) and parental socioeconomic status play an important role in CM and should be considered part of this complex issue (Felitti et al., 1998). The estimated prevalence of CM among Western societies is between 10% and 15% (Lutz and Turecki, 2014).

CM is among the strongest predictors of physical health problems, life expectancy (Anda et al., 2009; Danese and McEwen, 2012; Dong et al., 2004; Dube et al., 2001; Yang et al., 2013), psychiatric pathology (Cutajar et al., 2010; Green et al., 2010; Hanson et al., 2013; Scott et al., 2010; Sugaya et al., 2012; Teicher and Samson, 2013; Widom et al., 2007), and severity of the clinical course (Lutz and Turecki, 2014; Tomoda et al., 2012). Strong evidence suggests that the effect of CM depends on timing, type, and severity of exposure (Teicher and Samson, 2013) and has cumulative outcome over time (Danese and McEwen, 2012; Felitti et al., 1998). Phenotypic expression of psychopathology may be strongly influenced by exposure to maltreatment, leading to a constellation

of ecophenotypes (Teicher and Samson, 2013; Turecki et al., 2012). In bipolar disorder (BD), for instance, the disease emerges earlier (Leverich et al., 2002; Maguire et al., 2008) with greater severity (Etain et al., 2013), more comorbidity (Leverich and Post, 2006), more suicidal behavior (Duarte et al., 2015; Garno et al., 2005), and a less favorable response to treatment (Garno et al., 2006).

BD is highly heritable mental illness known to have polygenetic variants with a wide array of complex interactions involved in the etiology, yet poorly clarified (Schulze, 2010). Further studies are needed; a major challenge remains to understand how negative early-life events can interact with genes expression and affect brain morphology and functioning over extended periods of time in such effect size detectable in neuroimaging studies (Dannlowski et al., 2012; Lutz and Turecki, 2014). One possible mechanism is the disruption of key stress-response systems during early stages of child development, such as the hypothalamic–pituitary–adrenal axis, serotonin and catecholamine systems, and neurotrophic factors, which significantly influence stress handling, arousal, and emotional behavior and can contribute to increased allostatic load (Danese and McEwen, 2012) and long-term negative consequences in brain development (Bremner, 2003; Turecki et al., 2012, 2014; Watts-English et al., 2006).

Several magnetic resonance imaging studies have investigated brain volume abnormalities that are associated with CM suggesting that frontal–temporal–limbic areas may be the most compromised. These studies have either investigated changes in brain regions of interest selected *a priori* (Bücker et al., 2014; Cohen et al., 2006; Mehta et al., 2009; Morandotti et al., 2013; Tottenham et al., 2010) or employed methods that enable an automated evaluation of the entire brain, such as voxel-based morphometry (VBM) (Chaney et al., 2014; Tomoda et al., 2011; Tomoda et al., 2012; Sheffield et al., 2013; Van Harmelen et al., 2010). The first meta-analysis of VBM studies regarding CM was recently published (Lim et al., 2014). The authors examined individuals (n=331) with many different psychiatric diagnoses from 12 different MRI studies, all of whom had been exposed to CM. Their findings revealed gray matter volume (GMV) abnormalities in individuals who had been exposed to CM compared with healthy controls (HC); these gray matter (GM) abnormalities were located in a network of brain regions that are considered to be critical for regulating responses to stress and to modulate emotional behavior, including the prefrontal cortex (PFC), lateral temporal cortex, insula, and temporo-limbic regions (Lim et al., 2014).

BD is a psychiatric diagnosis most often associated with a history of CM (Nerila et al., 2005; Sugaya et al., 2012). Our group and others have documented the presence of subtle GM abnormalities in patients with BD relative to HC as assessed with VBM in several brain regions, including the PFC (orbitofrontal, right ventral, and dorsolateral prefrontal cortex), temporal cortex, thalamus, anterior cingulate cortex, insula, corpus callosum, precentral gyrus, amygdala, and hippocampus (Azevedo-Marques et al., 2011; Houenou et al., 2011; Matsuo et al., 2009; Nery et al., 2015; Neves et al., 2015; Nortje et al., 2013; Radenbach et al., 2010; Selvaraj et al., 2012).

In this study, we aimed to investigate GMV correlates of self-report CM in euthymic patients with BD-I. We hypothesized that maltreatment type and degree perpetrated in BD-I patients' childhood is related to greater GMV alterations in regions previously implicated in BD [specifically PFC (orbitofrontal and dorsolateral prefrontal cortex), amygdala, hippocampus, and thalamus] and in regulating responses to stress and to modulate emotional behavior (Hart and Rubia, 2012; Lim et al., 2014; Teicher and Samson, 2013).

2. Methods

2.1. Study sample and assessment schedules

Forty-seven patients with BD-I aged between 18 and 65 years were screened. We recruited right-handed patients with BD-I in the *Núcleo de Transtornos Afetivos* (a tertiary service specialized in affective disorders) from the Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil. None of the participants received any financial incentives. All patients were interviewed by a psychiatrist who used the Mini International Neuropsychiatry Interview Plus (MINI-Plus) and were required to score > 40 on the Edinburgh Inventory (Oldfield, 1971). For the purpose of studying BD-I apart from the current mood episode effect, we included only patients with BD-I being in remission defined as not meeting criteria for any mood episode in the last 2 months (Tohen et al., 2009) and presenting scores below 8 on the Young Mania Rating Scale (Vilela et al., 2005) and on the 21-item version of the Hamilton Depression Rating Scale (Williams, 1988). Current mood episode is a potential confound factor in a retrospective trauma assessment and its stabilization decreases the possibility of affecting study findings (Scherk et al., 2008; Daruy-Filho et al., 2011; Etain et al., 2013). Twenty HC were screened using MINI-Plus and were excluded if they had a history of a major Axis I psychiatric disorder and/or a history of trauma on the basis of Childhood Trauma Questionnaire (CTQ) scores. Trying to avoid any confounder we only accepted score of 25, it means the minimum score of the questionnaire. Exclusion criteria were [1] presence of active tobacco, alcohol, and drug use disorders in the last 12 months, [2] serious medical condition that adversely affected the central nervous system, [3] current neurological disorders, and [4] lifetime history of head injuries. Of the 47 patients initially evaluated, one was excluded for use of a pacemaker; three for not being right-handed; one for alcohol abuse; and one for absence on exam day and our inability to contact him/her. Afterward, two of the remaining patients were excluded because of image acquisition artifacts, thereby leaving a total of 39 eligible patients.

The Research and Ethics Committee of UFMG approved the study in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from all participants after a complete study description was provided.

2.2. Childhood trauma assessment

CM was assessed by a valid self-report questionnaire CTQ that evaluates frequency, intensity, and type of trauma (Bernstein et al., 1994). CTQ is a widely used screening tool that aims to detect experiences of childhood abuse and neglect in adults and adolescents (Grassi-Oliveira et al., 2014). Reliability of CTQ has been demonstrated in patients with BD (Etain et al., 2010). CTQ was validated and translated by Grassi-Oliveira et al. (2006) in Brazil. The questionnaire assesses five types of childhood trauma (five subscales): emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Household dysfunction is also assessed by CTQ: "My parents were too drunk or high to take care of the family", "I knew that there was someone to take care or me and protect me", "People in my family looked out for each other". This questionnaire can be used as a categorical and/or continuous variable (Etain et al., 2010; Dannlowski et al., 2012). Participants rate items on CTQ using a 1–5-point scale, ranging from "never true" to "very often true." Each CTQ subscale yields five items; responses range from 5 (no maltreatment) to 25 (severe maltreatment). The five CM subtypes are summed for a CTQ total score 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). Patients were considered to have a history of trauma if one or more sub-scales met the cut-off criteria (moderate or severe).

2.3. Image acquisition

Brain imaging data were acquired with a 1.5-T Phillips MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands) using a T1-3D SPGR sequence. Contiguous axial images across the entire brain were acquired with the following parameters: TE=6 ms,   TR=35 ms,   flip   angle=45°,   acquisition matrix=288 × 288, and voxel size=0.85 mm × 0.85 mm × 1 mm (190 slices).

2.4. Image processing and analysis

VBM analysis was carried out using Statistical Parametric Mapping Version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) and Matlab 2009b (http://www.mathworks.com/index.html). Briefly, we analysed all MRI datasets to place the anterior commissure at the origin of the three-dimensional Montreal Neurological Institute (MNI) coordinate system. The images were then segmented into GM and white matter using the unified segmentation procedure described by Ashburner and Friston (2005). The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007) was then used to spatially normalize the segmented images. This procedure maximizes the localization sensitivity and accuracy by registering individual structural images to an asymmetric custom T1-weighted template derived from the participants' own structural images rather than a standard T1-weighted template based on a different sample (Ashburner, 2007). These fully normalized images were resliced with trilinear interpolation to a final voxel size of $1.5 \times 1.5 \times 1.5$ mm^3. An additional "modulation" step consisted of multiplying each spatially normalized GM image by its relative volume before and after normalization; this ensured that the total amount of GM in each voxel was preserved. Finally, the resulting GM images were smoothed using an 8-mm isotropic kernel at full-width half-maximum to ensure normal distribution of the data as required by subsequent statistical parametric tests.

For the VBM analyses, we initially conducted statistical voxel-wise group comparisons of regional GMV between BD-I patients with/without a history of CM and HC using a general linear model based on the random Gaussian field theory (Friston et al., 1994). We then conducted within-group linear correlation analyses between GMV and CTQ scores using Pearson's correlation coefficients in the overall BD-I group. Both the between-group comparisons and linear correlation analyses were conducted by covarying out the effects of total brain GMV, age, and sex. The resulting statistics were thresholded at a Z value of ≥ 3.09 (corresponding to the two-tailed $p \leq 0.001$ level, uncorrected for multiple comparisons) and displayed as statistical parametric maps in standard anatomical space, with a minimum cluster size of at least 10 voxels. Clusters were reported as significant if they survived the family-wise error (FWE) correction for multiple comparisons ($p < 0.05$) over the whole brain, on a exploratory fashion.

Finally, we used the small volume correction (SVC) approach to conduct a hypothesis-driven investigation of brain regions where abnormalities have been previously identified in neuroimaging studies of CM, namely, prefrontal cortex, amygdala, hippocampus and thalamus (Teicher and Samson, 2013; Lim et al., 2014; Hart and Rubia, 2012), which were defined using the Automated Anatomical Labeling (AAL) atlas. The findings of these hypothesis-driven, SVC analyses were reported as significant if they survived FWE correction for multiple comparisons ($p \leq 0.05$) over the specific brain regions (Ashburner, 2007).

2.5. Clinical and socio-demographic statistical analysis

We used SPSS for Windows, version 20.0 (SPSS, Chicago, IL, USA), to analyse socio-demographic and clinical data. Descriptive statistics of mean and standard deviation (SD) were conducted for continuous variables and absolute/relative frequencies (%) for categorical variables. To compare BD-I patients with HC, we performed the chi-squared test (for categorical variables) and one-way ANOVA (for continuous variables). Finally, we used the chi-squared test and independent Student's t-test to compare BD-I groups with and without CM. All statistical tests were conducted with a significance level of 5%.

3. Results

3.1. Clinical and socio-demographic data

Table 1 summarizes the clinical and demographic characteristics of participants (n=39). All patients were medicated at the time of MRI scanning. Specific details about the BD clinical profile are provided. There were no significant differences between BD-I patients with/without a history of CM and HC with regard to gender, age, and years of study. When comparing patients with CM to those without CM, there were no significant differences in suicide attempts, psychiatric hospitalizations, presence of co-morbidities, age at first mood episode, total years of disease, medication intake, parental education, or family history of BD, major depressive disorder, and suicide attempt (Table 1). Moderate to severe levels of emotional neglect was reported by 50% (n=10) of BD-I patients with CM, while 40% (n=8) reported moderate to severe levels of physical neglect. Sexual abuse rates were 45% (n=9) and physical abuse rates were 45% (n=9). The most commonly reported trauma was emotional abuse, with a prevalence of 55% (n=11). For all maltreated patients, 55% (n=11) had been exposed to more than one type of trauma (data not shown).

Detailed medication profiles in the BD-I group included the average dose (mg) for carbamazepine (mean: 600; SD, 200.00), quetiapine (mean: 392; SD, 157.76), olanzapine (mean: 11.25; SD, 2.52), risperidone (mean: 2; SD, 1.73), escitalopram (mean: 10; SD, 0.00), sertraline (mean: 112.5; SD, 25.00), clonazepam (mean: 1.66; SD, 0.52), diazepam (mean: 12.5; SD, 3.53), lamotrigine (mean: 200; SD, 0.00), topiramate (mean: 200; SD, 0.00) and zolpidem (mean: 10; SD, 0.00).

3.2. Imaging data

3.2.1. Between-group comparisons

No significant findings emerged in the whole brain comparison of GMV between BD-I patients with/without a history of CM and HC corrected for multiple comparisons.

When we used the SVC approach to conduct the hypothesis-driven investigation of specific brain regions, we found negative results when comparing the BD-I groups with/without CM and HC. We did identify a trend towards reduced GMV in the right dorsolateral prefrontal cortex in the BD-I group with CM as compared to HC [Brodmann area BA 06, peak level coordinates x,y,z=23 0 54, number of voxels (k)=105, pFWE=0.052, corrected for multiple comparisons using the SVC approach; Z-score=3.95].

3.2.2. Correlations between GMV and trauma scores within the overall BD-I group

Taking into account the CTQ total score and all childhood trauma subtypes (sexual, physical, and emotional abuse; emotional and physical neglect) separately as continuous variables, we performed a whole brain analysis within the overall BD-I group

Table 1
Demographic and clinical characteristics of the sample at the time of magnetic resonance image (MRI) scanning.

	BD-I patients with CM (n=20)	BD-I patients without CM (n=19)	HC (n=20)	F OR X^2 OR t	P-value
Gender, No. (%)					
Male	6 (30.0)	10 (52.6)	9 (45.0)	X^2 (2)=2.13	.345
Female	14 (70.0)	9 (47.4)	11 (55.0)		
Age, mean (SD)	40.35 (10.21)	43.05 (13.87)	37.40 (10.20)	F(2.58)=1.17	.316
Years of study, mean (SD)	11.00 (5.30)	12.21 (3.67)	11.75 (2.36)	F(2.58)=0.46	.631
Parental education (years), mean (SD)	12.65 (4.43)	12.79 (4.29)	13.05 (4.52)	F(2.58)=0.42	.959
Suicide attempt (SA), n (%)					
Yes	11 (55.0)	8 (42.1)	N/A	X^2 (1)=0.65	.421
No	9 (45.0)	11 (57.9)			
Psychiatric hospitalizations, n (%)					
Yes	14 (70.0)	12 (63.2)	N/A	X^2 (1)=0.21	.651
No	6 (30.0)	7 (36.8)			
Psychiatric comorbidities, n (%)					
Yes	7 (35.0)	9 (47.4)	N/A	X^2 (1)=0.62	.433
No	13 (65.0)	10 (52.6)			
Age at first mood episode, mean (SD)	25.45 (8.4)	26.63 (9.6)	N/A	t (37)=0.41	.685
Total years of disease, mean (SD)	15.10 (8.6)	16.21 (11.4)	N/A	t(37)=0.34	.733
Family history of BD, n (%)	10 (50.0)	9 (47.5)	N/A	X^2 (1)=0.27	.869
Family history of MDD, n (%)	8 (40.0)	7 (38.9)	N/A	X^2 (1)=0.01	.944
Family history of SA, n (%)	6 (30.0%)	7 (36.8%)	N/A	X^2 (1)=0.21	.651
Current medication					
Lithium, No. (%)	10 (50.0)	10 (52.6)	N/A	N/A	N/A
Lithium dose (mg), mean (SD)	855.00 (224.17)	870.00 (154.92)	N/A	t (18)=1.74	.864
Anticonvulsants, No.(%)	11 (55.0)	7 (36.8)	N/A	N/A	N/A
Divalproex dose (mg), mean (SD)	785.71 (224.93)	916.67 (129.10)	N/A	t (16)=1.39	.183
Antidepressants, No. (%)	4 (20.0)	3 (15.8)	N/A	N/A	N/A
Atypical antipsychotics, No. (%)	6 (30.0)	9 (47.4)	N/A	N/A	N/A
Benzodiazepine, No. (%)	4 (20.0)	4 (21.1)	N/A	N/A	N/A
Non benzodiazepine hypnotics No. (%)	0 (0.0)	1 (5.3)	N/A	N/A	N/A

Abbreviations: BD-I: bipolar disorder type 1; MDD: major depressive disorder; HC: healthy control; SA: suicide attempt; x^2: chi-square test; t: independent student t-test; F: frequency.

and did not find any significant associations in GMV corrected for multiple comparisons.

When using the SVC approach to guide hypothesis-driven investigations of specific brain regions, a number of significant associations between GMV and maltreatment scores were detected.

There was a significant negative correlation between CTQ total score and right dorsolateral prefrontal cortex GMV [Brodmann Area (BA) 06] and right thalamus (Table 2).

For childhood trauma subtypes, statistical maps indicated a significant negative correlation between CTQ physical neglect score and right and left thalamus GMV, CTQ emotional neglect score and right thalamus GMV, and CTQ physical abuse score and right dorsolateral prefrontal cortex GMV [BA 06; (Table 2)].

When the analysis was repeated entering age, gender and parental education (years) as confounding covariates, remained statistically significant except for left thalamus: CTQ total score

and right dorsolateral prefrontal cortex GMV [BA 06, peak level coordinates x,y,z=24 0 52, number of voxels (k)=144, pFWE=0.008, Z-score=4.49] and right thalamus [peak level coordinates x,y,z=12 −9 13, number of voxels (k)=66, pFWE=0.015, Z-score=3.65]; CTQ physical neglect score and right thalamus GMV [peak level coordinates x,y,z=12 −10 13, number of voxels (k)=152, pFWE=0.004, Z-score=4.09]; CTQ emotional neglect score and right thalamus GMV [peak level coordinates x,y,z=9 −9 12, number of voxels (k)=44, pFWE=0.029, Z-score=3.44]; and CTQ physical abuse score and right dorsolateral prefrontal cortex GMV [peak level coordinates x,y,z=21 −1 54, number of voxels (k)=39, pFWE=0.038, Z-score=4.01]. The correlation between CTQ physical neglect score was not statistically significant [peak level coordinates x,y,z=−15 −13 15, number of voxels (k)=2, pFWE=0.067, Z-score=3.14].

A figure containing brain regions of foci with significant

Table 2
Association between GMV and trauma scores within the overall BD-I group (n=39).

Trauma	Brain region	Direction of significant findings	Number of voxels[a]	Coordinate[b] x,y,z	Peak Z-score[c]	P value [d]
CTQ total	Right dorsolateral prefrontal cortex	Negative correlation	149	23 0 54	4.37	0.013
CTQ total	Right thalamus	Negative correlation	41	12 −9 13	3.54	0.021
CTQ physical neglect	Right thalamus	Negative correlation	231	12 −10 13	4.25	0.002
CTQ physical neglect	Left thalamus	Negative correlation	15	−9 −7 9	3.30	0.044
CTQ emotional neglect	Right thalamus	Negative correlation	29	11 −9 12	3.31	0.041
CTQ physical abuse	Right dorsolateral prefrontal cortex	Negative correlation	38	21 −1 54	4.04	0.043

[a] Contiguous voxels in each region that transcend the initial cutoff of Z > 3.09.
[b] MNI coordinates of the voxel of maximal statistical significance within each region.
[c] Z-scores for the voxel of maximal statistical significance in each region.
[d] Statistical significance after family-wise error correction for multiple comparisons (voxel level) within the respective volume of interest circumscribed using the small volume correction approach.

association as defined by the AAL atlas is detailed in Supplementary material 1.

4. Discussion

The main findings of this study include a number of significant negative correlations between GMV and the severity of childhood trauma scores within the overall BD-I group as follows: [1] CTQ total score and right dorsolateral PFC and right thalamus; [2] physical abuse score and right dorsolateral PFC; [3] physical neglect score and right thalamus; and [4] emotional neglect score and right thalamus.

Our results support the hypothesis that a degree and type of self-reported CM in patients with BD-I is related to greater morphological alterations in brain regions previously implicated in BD and in regulating responses to stress as well as modulating emotional behavior.

The prefrontal regions (particularly dorsolateral, ventromedial, and orbitofrontal cortex) modulate the amygdala response during social interaction, perhaps turning it down with the realization that something is not actually a threat in some cases or irrationally amplifying it in other cases (Fuster, 1980; Teicher and Samson, 2013; Turecki et al., 2012). CPF volume reduction in patients with a history of CM may be associated with fewer prefrontal, top-down projections to the thalamus and amygdala. As neuroanatomical abnormalities are interconnected, abnormalities of the thalamus, a key structure involved in the reorganization of stimuli from periphery and associative functions, would interfere in processing threatening signs and convey disturbed information to the amygdala and prefrontal regions (LeDoux and Harmondsworth, 2002). The consequence would be a negative outcome in limbic regions such as the hippocampus and hypothalamus, which would in turn trigger autonomic (e.g., heart rate) and pituitary/adrenal hormonal responses with systemic effects and neurotrophic impairments. Thus, adverse experiences during developmental stages can increase vulnerability for coping with further stressors (Turecki, 2013).

In addition, some evidence suggests that mediators of the negative effects of CM in BD may be biological sequelae, including chronic inflammation, sleep disturbances, and telomere shortening, caused by impairments in biological pathways (e.g., serotonergic transmission, neuroplasticity, immunity, calcium signaling, and circadian rhythms) (Aas et al., 2016). These issues adversely affect the nature and trajectory of normal brain development (Pechtel and Pizzagalli, 2011), particularly in late maturation of limbic–thalamic–cortical structures (Giedd and Rapoport, 2010).

Regarding our results, other studies have found reduced PFC and Thalamus GMV in individuals with CM and diagnoses of depression, anxiety disorders, substance abuse, or posttraumatic stress (Harmelen et al., 2010; Kumari et al., 2013; Lim et al., 2014; Teicher and Samson, 2013; Tomoda et al., 2009) as compared to HC. In contrast, some authors have found increased GMV (Liao et al., 2013; Richert et al., 2006). These mixed findings could be related, in part, to the timing, type, and severity of exposure together with a number of susceptibility and resilience co-factors (Teicher and Samson, 2013). More studies are needed, with different designs, neuroimaging techniques and large samples.

There is growing evidence and a consensus model that thalamus may be involved in the neurocircuitry responsible for the clinical manifestation of BD (Strakowski et al., 2012). The authors hypothesized that early developmental failure to establish healthy prefrontal–limbic networks, including amygdala, underlies the onset of mood instability. Limbic dysregulation leads to loss of emotional homeostasis and a fragile prefrontal-striatal-thalamic-amygdala network is unable to restore stability (Strakowski et al.,

2012). Moreover, some vascular injuries of the thalamus have induced behavioral changes similar to the clinical expression of BD (Carrera and Bogousslavsky, 2006; De Witte et al., 2011).

We have noted methodological limitations in this study. Our cross-sectional design limits longitudinal inferences and evaluation of developmental features. Participants were treated patients with BD having comorbidities, and certain medications may have altered the findings of VBM studies in BD (Mcintosh et al., 2004). However, the more relevant results of this study are within the overall BD group, which have similar medication profiles. Both childhood trauma exposure and brain volumes may be influenced by the socioeconomic status of the parents. We did not collect data on the economic status of the parents; this can be a confounder. But, we did collect data on the parental education and the CTQ could assess "*perceived financial sufficiency*", the subjects' perception of financial stress while they were growing up (Tomoda et al., 2009). While significant findings did not emerge in the whole brain volume analysis, they did when we used the SVC approach. However, it is well known that abnormalities identified across the entire brain have greater reliability as compared to region-of-interest approaches (Lim et al., 2014). CTQ is a retrospective self-report and has the risk of potential bias. Our findings relating to the thalamus are just below $p = 0.05$ and could be influenced by the testing of multiple areas of interest, hence replication studies are necessary. In addition, head injuries caused by CM can affect study results and should be considered as a confounding factor (Schneeberger et al., 2012). The genetic etiology of BD is still unclear and could also have an influence on study results (Schulze, 2010). Future studies with a longitudinal design and a larger sample of patients who could be monitored from disease onset are warranted. To the best of our knowledge, this study is the second to have evaluated neural correlates of CM in patients with BD-I.

In conclusion, our work is consistent with the hypothesis that self-reported CM is related to greater brain morphological abnormalities in neural networks previously related to BD and to regulating stress response and modulating emotional behavior, particularly CPF and thalamus GMV. Our findings reinforce the understanding that maltreatment as an etiological risk factor is crucial to the development of a science of preventative psychiatry, to the design of effective therapeutic regimens, and to the delineation of an accurate nosology.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at: http://dx.doi.org/10.1016/j.jad.2016.02.068.

References

Aas, M., Henry, C., Andreassen, O.A., Bellivier, F., Melle, I., Etain, B., 2016. The role of childhood trauma in bipolar disorders. Int. J. Bipolar Disord. 4, 1–10.

Anda, R.F., Dong, M., Brown, D.W., Felitti, V.J., Giles, W.H., Perry, G.S., Valerie, E.J., Dube, S.R., 2009. The relationship of adverse childhood experiences to a history of premature death of family members. BioMed Cent. Public Health 2009, 99–106.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.

Ashburner, J., 2007. A fast Diffeomorphic image registration algorithm. Neuroimage 38, 95–113.

Azevedo-Marques, P.C., Duran, F.L., Zanetti, M.V., Santos, L.C., Murray, R.M., Sca-zufca, M., Menezes, P.R., Busatto, G.F., Schaufelberger, M.S., 2011. A population-based morphometric MRI study in patients with first-episode psychotic bipolar disorder: depressive disorder subjects. Bipolar Disord. 13, 28–40.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am. J. Psychiatry 151, 1132–1136.

Bremner, J.D., 2003. Long-term effects of childhood abuse on brain and neuro-biology. Child. Adolesc. Psychiatr. Clin. 12, 271–292.

Bücker, J., Muralidharan, K., Torres, I.J., Su, W., Kozicky, J., Silveira, L.E., Bond, D.J., Honer, W.G., Kauer-Sant'anna, M., Lam, R.W., Yatham, L.N., 2014. 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). J. Psychiatr. Res. 48, 65–72.

Carrera, E., Bogousslavsky, J., 2006. The thalamus and behavior: effects of anato-mically distinct strokes. Neurology 66, 1817–1823.

Chaney, A., Carballedo, A., Amico, F., Fagan, A., Skokauskas, N., Meaney, J., Frodl, T., 2014. Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. J. Psychiatry Neurosci. 39, 50–59.

Cohen, R.A., Paul, R.H., Stroud, L., Gunstad, J., Hitsman, B.L., McCaffery, J., Sweet, L., Niaura, R., MacFarlane, A., Bryant, R.A., Gordon, E., 2006. Early life stress and adult emotional experience: an international perspective. Int. J. Psychiatry Med. 36, 35–52.

Cutajar, M.C., Mullen, P.E., Ogloff, J.R., Thomas, S.D., Wells, D.L., Spataro, J., 2010. Schizophrenia and other psychotic disorders in a cohort of sexually abused children. Arch. Gen. Psychiatry 67, 1114–1119.

Danese, A., McEwen, B.S., 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol. Behav. 106, 29–39.

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., Domschke, K., Hohoff, C., Ohrmann, P., Bauer, J., Lindner, C., Postert, C., Konrad, C., Arolt, V., Heindel, W., Suslow, T., Kugel, H., 2012. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol. Psychiatry 71, 286–293.

Daruy-Filho, L., Brietzke, E., Lafer, B., Grassi-Oliveira, R., 2011. Childhood maltreat-ment and clinical outcomes of bipolar disorder. Acta Psychiatr. Scand. 124, 427–434.

De Bellis, M.D., 2001. Developmental traumatology: the psychobiological devel-opment of maltreated children and its implications for research, treatment, and policy. Dev. Psychopathol. 13, 539–564.

De Witte, L., Brouns, R., Kavadias, D., Engelborghs, S., DeDeyn, P.P., Mariën, P., 2011. Cognitive affective and behavioral disturbances following vascular thalamic lesions: a review. Cortex 47, 273–319.

Dong, M., Anda, R.F., Felitti, V.J., Dube, S.R., Williamson, D.F., Thompson, T.J., Loo, C. M., Giles, W.M., 2004. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. Child. Abuse Neglect 28, 771–784.

Duarte, D.G.G., Maila de, C., Neves, M.C., Albuquerque, M.R., Neves, F.S., Corrêa, H.S., 2015. Sexual abuse and suicide attempt in bipolar type I patients. Rev. Bras. Psiquiatr. 37, 35–38.

Dube, S.R., Anda, R.F., Felitti, V.J., Chapman, D.P., Williamson, D.F., Giles, W.H., 2001. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the adverse childhood experiences study. J. Am. Med. Assoc. 286, 3089–3096.

Etain, B., Mathieu, F., Henry, C., Raust, A., Roy, I., Germain, A., 2010. Preferential association between childhood emotional abuse and bipolar disorder. J. Trauma Stress 23, 376–383.

Etain, B., Aas, M., Andreassen, O.A., Lorentzen, S., Dieset, I., Gard, S., Kahn, J.P., Bellivier, F., Leboyer, M., Melle, I., Henry, C., 2013. Childhood trauma is asso-ciated with severe clinical characteristics of bipolar disorders. J. Clin. Psychiatry 74, 991–998.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Valerie Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) study. Am. J. Prev. Med. 14, 245–258.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J., 1994. Statistic parametric maps in functional imaging: a general linear ap-proach. Hum. Brain Mapp. 2, 189–210.

Fuster, J.M., 1980. The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychol-ogy of the Frontal Lobe. Raven Press, New York.

Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2005. Impact of childhood abuse on the clinical course of bipolar disorder. Br. J. Psychiatry 186, 121–125.

Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2006. Course of bipolar illness after history of childhood trauma. Lancet 367, 1040–1042.

Giedd, J.N., Rapoport, J.L., 2010. Structural MRI of pediatric brain development:

what have we learned and where are we going? Neuron 67, 728–734.

Grassi-Oliveira, R., Cogo-Moreira, H., Salum, G.A., Brietzke, E., Viola, T.W., Manfro, G. G., Kristensen, C.H., Arteche, A.X., 2014. Childhood trauma questionnaire (CTQ) in Brazilian samples of different age groups: findings from confirmatory factor analysis. PLoS One 27, e87118.

Grassi-Oliveira, R., Stein, L.M., Pezzi, J.C., 2006. Translation and content validation of the childhood trauma questionnaire into Portuguese language. Rev. Saúde Pú-blica 40, 249–255.

Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., 2010. Childhood adversities and adult psychiatric disorders in the na-tional comorbidity survey replication I: associations with first onset of DSM-IV disorders. Arch. Gen. Psychiatry 67, 113–123.

Hanson, J.L., Hair, N., Shen, D.G., Shi, F., Gilmore, J.H., Wolfe, B.L., Pollak, S.D., 2013. Family poverty affects the rate of human infant brain growth. PLoS One 8, e80954.

Harmelen, A.L., Tol, M.J., Wee, N.J.A., Veltman, D.J., Aleman, A., Spinhoven, P., Bu-chem, M.A., Zitman, F.G., Penninx, W.J.H., Bernet, M., 2010. Reduced medial pré-frontal córtex volume in adults reporting childhood emotional maltreatment. Biol. Psychiatry 68, 832–838.

Hart, H., Rubia, K., 2012. Neuroimaging of child abuse: a critical review. Front. Hum. Neurosci. 6, 52–56.

Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., Wessa, M., 2011. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. J. Affect. Disord. 132, 344–355.

Kumari, V., Gudjonsson, G.H., Raghuvanshi, S., Barkataki, I., Taylor, P., Sumich, A., Das, K., Kuipers, E., Ffytche, D.H., Das, M., 2013. Reduced thalamic volume in men with antisocial personality disorder or schizophrenia and a history of serious violence and childhood abuse. Eur. Psychiatry 28, 225–234.

LeDoux, J.E., Harmondsworth, J., 2002. Synaptic Self: How our brains become who we are. Viking, New York.

Leverich, G.S., McElroy, S.L., Suppes, T., Keck, P.E., Denicoff, K.D., Nolen, W.A., 2002. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol. Psychiatry 51, 288–297.

Leverich, G.S., Post, R.M., 2006. Course of bipolar illness after history of childhood trauma. Lancet 367, 1040–1042.

Liao, M., Yang., F., Zhang., Y., He, Z., Song, M., Jiang, T., Li, Z., Lu, S., Wu, W., Su, L, Li, L, 2013. Childhood maltreatment is associated with larger left thalamic gray matter volume in adolescents with generalized anxiety disorder. PLoS One 12, 8.

Lim, L., Radua, J., Rubia, K., 2014. Gray matter abnormalities in childhood mal-treatment: a voxel-wise meta-analysis. Am. J. Psychiatry 171, 854–863.

Lutz, P.E., Turecki, G., 2014. DNA methylation and childhood maltreatment: from animal models to human studies. Neuroscience 264, 142–156.

Maguire, C., McCusker, C.G., Meenagh, C., Mulholland, C., Shannon, C., 2008. Effects of trauma on bipolar disorder: the mediational role of interpersonal difficulties and alcohol dependence. Bipolar Disord. 10, 293–302.

Matsuo, K., Nicoletti, M.A., Peluso, M.A.M., Hatch, J.P., Nemoto, K., Watanabe, Y., Nery, F.G., Monkul, E.S., Zunta-Soares, G.B., Bowden, C.L., Soares, J.C., 2009. Anterior cingulate volumes associated with trait impulsivity in individuals with bipolar disorder. Bipolar Disord. 11, 628–636.

Mcintosh, A.M., Job, D.E., Moorhead, T.W., Harrison, L.K., Forrester, K., Lawrie, S.W., Johnstone, E.C., 2004. Voxel based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. Biol. Psychiatry 56, 544–552.

Mehta, M.A., Golembo, N.I., Nosarti, C., Colvert, E., Mota, A., Williams, S.C., Rutter, M., Sonuga-Barke, E.J., 2009. Amygdala, hippocampal, and corpus callosum size following severe early institutional deprivation: the English and Romanian adoptees study pilot. J. Child Psychol. Psychiatry 50, 943–951.

Morandotti, N., Dima, D., Jogia, J., Frangou, S., Sala, M., Vidovich, G.Z., Lazzaretti., M., Gambini, F., Marraffini, E., d'Allio, G., Barale, F., Zappoli, F., Caverzasi, E., Bram-billa, P., 2013. Childhood abuse is associated with structural impairment in the ventrolateral prefrontal cortex and aggressiveness in patients with borderline personality disorder. Psychiatry Res. 213, 18–23.

Nerila, Y., Bromet, E.J., Carlson, G.A., Naz, B., 2005. Assaultive trauma and illness course in psychotic bipolar disorder: findings from the Suffolk county mental health project. Acta Psychiatr. Scand. 111, 380–383.

Nery, F.G., Gigante, A.D., Amaral, J.A., Fernandes, F.B., Berutti, M., Almeida, K.M., Carneiro, C.G., Duran, F.L., Otaduy, M.G., Leite, C.C., Busatto, G., Lafer, B., 2015. Gray matter volumes in patients with bipolar disorder and their first-degree relatives. Psychiatry Res. 234, 188–193.

Neves, M.C., Albuquerque, M.R., Malloy-Diniz, L., Nicolato, R., Neves, F.S., Souza-Duran, F.L., Busatto, G., Corrêa, H., 2015. A voxel-based morphometry study of gray matter correlates of facial emotion recognition in bipolar disorder. Psy-chiatry Res. 30, 158–164.

Nortje, G., Stein, D.J., Raduab, J., Mataix-Cols, D., Horn, N., 2013. Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. J. Affect. Disord. 15, 192–200.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Pechtel, P., Pizzagalli, D.A., 2011. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology 214, 55–70.

Radenbach, K., Flaig, V., Schneider-Axmann, T., Usher, J., Reith, W., Falkai, P., Gru-ber, O., Scherk, H., 2010. Thalamic volumes in patients with bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 260, 601–607.

Richert, K.A., Carrion, V.G., Karchemskiy, A., Reiss, A.L., 2006. Regional differences of the prefrontal cortex in pediatric PTSD: an MRI study. Depress. Anxiety 23, 17–25.

Scherk, H., Kemmer, C., Usher, J., Reith, W., Falkai, P., Gruber, O., 2008. No change to grey and white matter volumes in bipolar I disorder patients. Eur. Arch. Psychiatry Clin. Neurosci. 258, 345–349.

Schneeberger, A.R., Muenzenmaier, K.H., Battaglia, J., Castille, D., Link, B.G., 2012. Childhood abuse, head injuries, and use of medical emergency services in people with severe mental illness. J. Aggress. Maltreat. Trauma 21, 570–582.

Schulze, T.G., 2010. Genetic research into bipolar disorder: the need for a research framework that integrates sophisticated molecular biology and clinically informed phenotype characterization. Psychiatr. Clin. N. Am. 33, 67–82.

Scott, K.M., Smith, D.R., Ellis, P.M., 2010. Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. Arch. Gen. Psychiatry 67, 712–719.

Selvaraj, S., Arnone, D., Job, D., Stanfield, A., Farrow, T.F.D., Nugent, A.C., Scherk, H., Gruber, O., Chen, X., Sachdev, P.S., Dickstein, D.P., Malhi, G.S., Ha, T.H., Ha, K., Phillips, M.L., McIntosh, A.M., 2012. Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. Bipolar Disord. 14, 135–145.

Sheffield, J.M., Williams, L.E., Woodward, N.D., Heckers, S., 2013. Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. Schizophr. Res. 143, 185–191.

Strakowski, S.M., Adler, C.M., Almeida, J., Altshuler, L.L., Blumberg, H.P., Chang, D.C., DelBello, M.P., Frangou, S., McIntosh, A., Phillips, M.L., Sussman, J.E., Townsend, J.D., 2012. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord. 14, 313–325.

Sugaya, L., Hasin, D.S., Olfson, M., Lin, K.H., Grant, B.F., Blanco, C.J., 2012. Child physical abuse and adult mental health: a national study. J. Trauma Stress 25, 384–392.

Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am. J. Psychiatry 170, 1114–1133.

Tohen, M., Frank, E., Bowden, C.L., Colom, F., Ghaemi, S.N., Yatham, L.N., Malhi, G.S., Calabrese, J.R., Nolen, W.A., Vieta, E., Kapczinski, F., Goodwin, G.M., Suppes, T., Sachs, G.S., Chengappa, K.N.R., Grunze, H., Mitchell, P.B., Kanba, S., Berk, M., 2009. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 11, 453–473.

Tomoda, A., Navalta, C.P., Polcari, A., Sadato, N., Teicher, M.H., 2009. Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. Biol. Psychiatry 66, 642–648.

Tomoda, A., Sheu, Y., Rabi, K., Suzuki, H., Navalta, C.P., Polcari, A., Teicher, M.H., 2011. Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. NeuroImage 54, S280–S286.

Tomoda, A., Polcari, A., Anderson, C.M., Teicher, M.H., 2012. Reduced visual cortex gray matter volume and thickness in young adults who witnessed domestic violence during childhood. PLoS One 7, e52528.

Tottenham, N., Hare, T.A., Quinn, B.T., McCarry, T.W., Nurse, M., Gilhooly, T., Millner, A., Galvan, A., Davidson, M.C., Eigsti, I.M., Thomas, K.M., Freed, P.J., Booma, E.S., Gunnar, M.R., Altemus, M., Aronson, J., Casey, B.J., 2010. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev. Sci. 13, 46–61.

Turecki, G., Ernst, C., Jollant, F., Labonté, B., Mechawar, N., 2012. The neurodevelopmental origins of suicidal behavior. Trends Neurosci. 35, 14–23.

Turecki, G., 2013. The epigenetic basis of behavioral phenotypes: is there reason for continued optimism. Depress. Anxiety 30, 1147–1150.

Turecki, G., Ernst, C., Jollant, F., Labonté, B., Mechawar, N., 2012. The neurodevelopmental origins of suicidal behavior. Trends Neurosci. 35, 14–23.

Turecki, G., Ota, V.K., Belangero, S.I., Jackowski, A., Kaufman, A., 2014. Early life adversity, genomic plasticity, and psychopathology. Lancet Psychiatry 2, 461–466.

Van Harmelen, A.L., Tol, M.J., Wee, N.J.A., Veltman, D.J., Aleman, A., Spinhoven, P., Buchem, M.A., Zitman, F.G., Penninx, W.J.H., Bernet, M., 2010. Reduced medial pré-frontal córtex volume in adults reporting childhood emotional maltreatment. Biol. Psychiatry 68, 832–838.

Vilela, J.A.A., Crippa, J.A.S., Del-Ben, C.M., Loureiro, S.R., 2005. Reliability and validity of a Portuguese version of the young mania rating scale. Braz. J. Med. Biol. Res. 38, 1429–1439.

Watts-English, T., Fortson, B.L., Gibler, N., Hooper, S.R., DeBellis, M.D., 2006. The psychobiology of maltreatment in childhood. J. Soc. Issues 62, 717–736.

Widom, C.S., DuMont, K., Czaja, S.J., 2007. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch. Gen. Psychiatry 64, 49–56.

Williams, J.B., 1988. A structured interview guide for the Hamilton Depression Rating Scale. Arch. Gen. Psychiatry 45, 742–747.

Yang, B.Z., Zhang, H., Ge, W., Douglas-Palumberi, H., Perepletchikova, F., Gelernter, J., Kaufman, J., 2013. Child abuse and epigenetic mechanisms of disease risk. Am. J. Prev. Med. 44, 101–107.

4.3 Artigo 4: Structural brain abnormalities in patientes with type I bipolar disorder and suicidal behaviour

Structural brain abnormalities in patients with type I bipolar disorder and suicidal behavior

Dante G. G. Duarte[a][3], Maila de Castro L. Neves[a], Maicon R. Albuquerque[b], Gustavo Turecki[c], Yang Ding[c], Fabio Luis de Souza-Duran[d], Geraldo Busatto[d], Humberto Correa[a]

[a]Mental Health Department, Universidade Federal de Minas Gerais (UFMG), Brazil
[b]Federal University of Viçosa, Brazil
[c]McGill Group for Suicide Studies, Department of Psychiatry, McGill University, Montreal, Canada
[d]Laboratory of Neuroimaging in Psychiatry (LIM-21), Research in Applied Neuroscience, Support Care of the University of São Paulo (NAPNA-USP), Brazil

Abstract

Some studies have identified brain morphological changes in the frontolimbic network (FLN) in bipolar subjects who attempt suicide (SA). However, neuroimaging findings are scant and heterogeneous. The present study investigated neuroanatomical abnormalities in FLN aiming to find a possible neural signature for suicide behavior in patients with bipolar disorder type I (BD-I). We used voxel-based morphometry to compare euthymic patients with BD-I who had attempted suicide (n=20), euthymic patients with BD-I who had not attempted suicide (n=19) and healthy controls (HCs) (n=20). We divided the patients who had attempted suicide into two groups based on the highest medical lethality of their previous SA. Compared to the participants who had not attempted suicide, the patients with BD-I who had attempted suicide

exhibited significantly increased gray matter volume (GMV) in the right rostral anterior cingulate cortex (ACC), which was more pronounced and extended further to the left ACC in the high-lethality subgroup. GMV was also related to suicide lethality in the insula and orbitofrontal cortex. The current findings suggest that morphological changes in the FLN may be a marker of suicidality and it severity in BD patients and could help clinicians to identify and prevent further suicidal acts.

Keywords: bipolar disorder; suicide behavior; voxel-based morphometry; gray matter brain volume; frontolimbic network

1. Introduction

Suicide, a serious public health problem, accounts for almost one million deaths worldwide per year (http://who.int/mental_health/suicideprevent). The impact is even larger regarding suicide attempts (SAs) because they occur approximately 10 to 20 times more frequently than completed suicide (Goodwin and Jamison, 2007). Suicide predominantly affects individuals with mental disorders, such as patients with bipolar disorder (BD), who have an absolute risk for SAs over their lifetime ranging between 20% and 30%, the highest documented SA risk for any individual group (Leverich, et al., 2003; Valtonen, et al., 2005; Nordentoft et al., 2011).

BD is a highly heritable mental illness known to have polygenetic variants, however, there is a wide array of complex interactions involved in the etiology; most are poorly clarified (Schulze, 2010). The dissection of BD into more homogeneous subphenotypes may improve the identification of neurobiological markers (Schulze, 2010). From this perspective, the investigation of brain changes associated with subphenotypic features such as suicidal behavior and medical lethality, circadian rhythm disruption, neuropsychological deficits and psychotic symptoms may contribute to more consistent findings in neuroimaging studies of BD.

Our group and others have documented the presence of subtle GMV abnormalities in patients with BD relative to HCs, as well as in patients with BD who have a lifetime history of childhood-maltreatment, lifetime history of psychotic symptoms and in patients with BD who have attempted suicide compared to those who have not. These abnormalities were identified via voxel-based morphometry (VBM) investigations into several brain regions,

including the frontal lobe (OFC, prefrontal cortex-PFC), ACC, insula, corpus callosum, thalamus, amygdala, and hippocampus (Sublette et al., 2006; Benedetti et al., 2011; de Azevedo-Marques Périco et al., 2011; Houenou et al., 2011; Selvaraj et al., 2012; van Heerigen et al., 2014; Nery et al., 2015; Neves et al., 2015; Duarte et al., 2016; Neves et al., 2016).

Despite the growing evidence in this field, the findings have not been consistently replicated and none of then have evaluated neural correlates of suicide medical lethality. Some authors have argued that a dysfunctional frontolimbic network (FLN) is a useful theoretical framework for understanding SAs and it lethality in BD (Giakoumatos et al., 2013; Malhi et al., 2013). The FLN consists of frontal components, the ACC and subcortical brain structures, such as the amygdala, hippocampus, insula and thalamus (Phillips et al., 2003; Phillips et al., 2008). Over time, aberrant frontal modulation of the limbic system produces significant FLN disturbances that manifest clinically as extreme mood fluctuations, increased impulsivity and disrupted decision-making with more vulnerability to SAs (Strakowski et al., 2012). Additionally, further studies are needed to disentangle the neurobiological pathways underneath suicide behavior in BD diagnoses.

In the present structural MRI study, we assessed a homogeneous sample of 39 euthymic patients with type I BD who were stratified according to their SA history in addition to 20 HCs. The aim of the study was to determine whether engagement in a SA and it severity (i.e., medical lethality) are associated with specific regional brain volume abnormalities in patients with BD. We had two main hypotheses: 1.) patients with type I BD who have attempted suicide (BD-SA group) have morphological alterations in brain regions that integrate the FLN relative to patients with BD who have not attempted suicide (BD-NSA group), and 2.) high-lethality SAs are related to more severe brain abnormalities.

2. Materials and Methods

2.1. Subjects

Forty-seven patients with BD-I and twenty HCs, aged between 18 and 65 years, were screened. We recruited patients with BD-I from the *Núcleo de Transtornos Afetivos* (a tertiary service specialized in affective disorders) in the Federal University of Minas Gerais, Belo Horizonte, Brazil. None of the participants received any financial incentives. All participants were right-handed, interviewed by a psychiatrist who used the Mini International

Neuropsychiatry Interview Plus (MINI-Plus) (Sheehan et al., 1998) and were required to score >40 on the Edinburgh Inventory (Oldfield, 1971). The healthy subjects were selected from the same community of the BD-I patients. They were evaluated by a psychiatrist using the MINI-PLUS, and those who had current or past Axis I DSM-IV- TR psychiatric disorders, first-degree relatives with any Axis I DSM-IV-TR psychiatric disorder and with history of suicidal behavior were excluded (more details are presented in Table 1). To study BD-I separate from the effects of any current mood episode, we only included patients with BD-I who were in remission, which was defined as not meeting any criteria for a mood episode within the last 2 months (Tohen et al., 2009) and scores below 8 on the Young Mania Rating Scale (Vilela et al., 2005) and the 21-item version of the Hamilton Depression Rating Scale (Williams, 1988). Childhood maltreatment and household dysfunction were categorically assessed using a childhood trauma questionnaire (CTQ) as previously described (Etain et al., 2013; Duarte et al., 2016).

The following exclusion criteria were applied: [1] presence of active tobacco, alcohol, and drug use disorders in the last 12 months, [2] serious medical condition that adversely affects the central nervous system, [3] current neurological disorders, and [4] lifetime history of head injuries. Of the 47 patients initially evaluated, one was excluded for use of a pacemaker; three for not being right-handed; one for alcohol abuse; and one for absence on exam day and our inability to contact him/her. Afterward, two of the remaining patients were excluded because of image acquisition artifacts, thereby leaving a total of 39 eligible patients.

The Research and Ethics Committee of UFMG approved the study in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from all participants after a complete study description was provided.

2.2. Suicide assessment

The patients were classified as having a positive suicidal history if they reported one or more self-directed injurious acts with a variable degree of intent to end one's own life (Mann, 2003). A psychiatrist assessed lifetime suicide history using a semi-structured interview and by performing a review of medical records. Furthermore, a supplementary interview with at least one close family member was performed to confirm patient information. Suicidal patients were also administered the Suicide Intent Scale (Beck et al., 1975) to measure intent at the time of the most lethal attempt, and current suicidal ideation was assessed with the Beck Scale for Suicidal Ideation (Beck et al., 1979). The SA methods

were classified as non-violent (drug overdose) or violent (cuts beyond superficial scratch, jumping from a height, shooting, hanging) (Neves et al., 2009).

The medical lethality of SAs was assessed with Beck's Medical Lethality Scale (BLS) (Beck et al., 1975). The patients were classified according to BLS score based on the degree of medical damage caused by the most lethal attempt. The BLS scores medical damage from 0 (no injury) to 8 (fatal), with anchor points depending on the medical lethality of an attempt. Low-lethality attempters (n=10) scored 3 or less (i.e., the subjects were conscious but sleepy after having used sedative drugs, cut themselves with minimal bleeding, or sustained minor bruises after having jumped). High-lethality attempters (n=10) scored 4 or more, that is, they required hospitalization for medical treatment of the sequelae of the attempt (i.e., coma resulting from the use of sedative drugs, cutting of major veins that required surgical intervention, or sustaining fractures after having jumped). The mean interval between the most recent suicide attempt and the time of the study was more than 4 years (mean ± SD, 52.3 ± 72.9 months) to avoid the medical effects of the attempt affecting the study results. The BLS has demonstrated good inter-rater reliability (intra-class correlation coefficient = 0.80) (Lester and Beck, 1975).

2.3. Image acquisition

Brain imaging data were acquired with a 1.5-T Phillips MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands) using a T1-3D SPGR sequence. Contiguous axial images across the entire brain were acquired with the following parameters: TE = 6 ms, TR = 35 ms, flip angle = 45º, acquisition matrix = 288 x 288, and voxel size = 0.85 mm × 0.85 mm × 1 mm (190 slices).

2.4. Image processing and statistical analysis

Data were processed using Statistical Parametric Mapping software (SPM8) (Welcome Department of Imaging Neuroscience, London), running in MATLAB R2009b (MathWorks, Sherborn, MA). The processing details have been described elsewhere (Duarte et al., 2016). Briefly, we first manually oriented all MRI datasets to place the anterior commissure at the origin of the three-dimensional Montreal Neurological Institute (MNI) coordinate system. The images were then segmented into GM and white matter using the unified segmentation procedure described by Ashburner and Friston (2005). The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007) was then used to spatially normalize the segmented images; this

procedure maximizes localization sensitivity and accuracy by registering individual structural images to an asymmetric custom T1-weighted template derived from the participants' structural images rather than to a standard T1-weighted template based on a different sample (Ashburner, 2007). These fully normalized images were resliced with trilinear interpolation to a final voxel size of $1.5 \times 1.5 \times 1.5$ mm³. An additional "modulation" step was applied, consisting of multiplying each spatially normalized gray matter (GM) image by its relative volume before and after normalization; this ensured that the total amount of GM in each voxel was preserved. Finally, the resulting GM images were smoothed using an 8-mm isotropic kernel at full-width half-maximum to ensure a normal distribution of the data, as required by subsequent statistical parametric tests.

We used Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (SPSS, Chicago, IL, USA) to analyze sociodemographic and clinical data. Descriptive statistics, such as the mean and standard deviation (SD), were calculated for continuous variables, and absolute and relative frequencies (%) were calculated for categorical variables. To compare the patients with BD-I to the HCs, we used the chi-square test for categorical variables and one-way ANOVA for continuous variables. Finally, we used the chi-square test and the independent Student's t-test to compare the BD-SA and BD-NSA groups and to assess SA lethality. All statistical tests had a significance level of 5%.

For the VBM analysis, between-group statistical comparisons of the mean GMV were performed using a general linear model based on random Gaussian field theory (Friston et al., 1995). Only voxels with values above an absolute threshold of p = 0.05 were included in the analyses. The ANOVA test was performed within groups and the Post-Hoc test in between-group comparison two by two. First, we conducted exploratory between-group GMV whole-brain comparisons between the following groups: a) patients with BD-I vs. HCs, b) subgroups of patients with BD-I defined by attempter status against HCs, c) patients with BD-I and a lifetime history of SAs of different levels of lethality. For the patients with BD-I and a lifetime history of SA, the following 2-group comparisons were performed: GM volume in high-lethality attempters vs. low-lethality attempters, high-lethality attempters vs. patients with BD who had not attempted suicide, and low-lethality attempters vs. patients with BD who had not attempted suicide. The between-group comparisons were conducted by co-varying out the effects of total brain GMV, age, sex and education (years). The resulting statistics were thresholded at a Z value of ≥ 3.09 (corresponding to the two-tailed $p \leq 0.001$ level, uncorrected for multiple comparisons) and displayed as statistical parametric maps in standard anatomical space, with a minimum cluster size of at least 25 voxels. Clusters were

reported as significant if they survived family-wise error (FWE) correction for multiple comparisons ($p < 0.05$) over the whole brain in an exploratory fashion.

Finally, we performed small volume correction (SVC) to conduct a hypothesis-driven investigation of FLN brain regions where abnormalities have been identified in neuroimaging studies of suicidal behavior and lethality in BD, namely, the PFC, OFC, ACC, amygdala, hippocampus, insula and thalamus which were defined using the Automated Anatomical Labeling atlas in SPM toolbox. The findings of these hypothesis-driven SVC analyses were reported as significant if they survived FWE correction for multiple comparisons (pFWE < 0.05) over the specific brain region being evaluated (Ashburner, 2007; Friston et al., 1995).

3. Results

3.1. Clinical and sociodemographic data

Table 1 summarizes the clinical and demographic characteristics of the participants. All the patients were medicated at the time of MRI scanning. Specific details about the BD clinical profile are provided. There were no significant differences between the patients with BD-I with/without a lifetime history of SA and the HCs with regard to gender, age, and years of study. When comparing the patients who had attempted suicide to those who had not, there were no significant differences in the variables (see table 1). Notably, similar use of lithium and anticonvulsants were found between the groups.

Table 1

Demographic and clinical characteristics of the sample at the time of magnetic resonance image (MRI) scanning.

	BD-I with SA (n=20)	BD-I without SA (n=19)	HC (n=20)	F or X² or t	P-Value
Gender, No.(%)					
Male	8 (40.0)	8 (42.1)	9 (45.0)	X² (2) = 0.10	.950
Female	12 (60.0)	11 (57.9)	11 (55.0)		
Age, mean (SD)	41.10 (12.64)	42.26 (11.70)	37.40 (10.20)	F (2,58)= 0.95	.393
Years of study, mean (SD)	11.90 (5.23)	11.26 (3.86)	11.75 (2.36)	F (2,58)= 0.13	.874
Parental education (years), mean (SD)	12.60 (4.67)	12.84 (4.00)	13.05 (4.52)	F (2,58)= 0.04	.949
Psychiatric hospitalizations, n (%)					
Yes	14 (70.0)	12 (63.2)	N/A	X² (1) = 0.21	.651
No	6 (30.0)	7 (36.8)			
Psychiatric comorbidities, n (%)					
Yes	7 (35.0)	9 (47.3)	N/A	X² (1) = 0.27	.605
No	12 (60.0)	11 (57.8)			
Age at first mood episode, mean (SD)	24.60 (9.3)	27.5 (8.5)	N/A	t (37) = 1.02	.313
Total years of disease, mean (SD)	16.65 (10.82)	14.58 (9.15)	N/A	t (37) = -0.64	.524
Family history of BD, n (%)	11 (55.0)	8 (42.1)	N/A	X² (1) = 0.65	.421
Family history of MDD, n (%)	9 (45.0)	6 (31.6)	N/A	X² (1) = 0.99	.319
Family history of SA, n (%)	9 (45.0)	4 (21.1)	N/A	X² (1) = 2.51	.113
Childhood maltreatment, n(%)	11 (55.0)	9 (47.3)	N/A	X² (1) = 1.25	.264
Lifetime history of psychotic symptoms, n(%)	10 (50.0)	8 (42.1)	N/A	X² (1) = 0.54	.387
Current medication					
Lithium, No.(%)	9 (45.0)	11 (57.8)	N/A	N/A	N/A
Lithium dose (mg), mean (SD)	878.57 (182.25)	853.85 (197.34)	N/A	t (18) = -0.27	.787
Anticonvulsants, No.(%)	10 (50.0)	8 (42.1)	N/A	N/A	N/A
Anticonvulsants dose (mg), mean (SD)	928.57 (121.99)	775.00 (223.61)	N/A	t (11) = -1.83	.102
Antidepressants, No.(%)	4 (20.0)	3 (15.8)	N/A	N/A	N/A
Atypical antipsychotics, No.(%)	7 (35.0)	8 (42.1)	N/A	N/A	N/A
Benzodiazepine, No.(%)	4 (20.0)	4 (21.1)	N/A	N/A	N/A
Non benzodiazepine hypnotics No.(%)	1 (5.0)	0 (0.0)	N/A	N/A	N/A

Abbreviations: BD-I: bipolar disorder type 1; MDD: major depressive disorder; HC: healthy control; SA: suicide attempt; x²: chi-square test; t: independent student t-test; F: frequency.

Table 2 describes the clinical features, sociodemographic characteristics and suicide profiles within the BD-SA group. There were no significant differences between the high- and low-lethality attempters with regard to the variables (see table 2). The number of lifetime SAs differed greatly between the high- and low-lethality attempters. Moreover, the high-lethality attempters had greater suicide intent at the time of their most lethal attempt compared to the low-lethality attempters.

However, the groups did not significantly differ in the violence of suicide methodology. Lithium intake based on dose (mg) did not differ between the high- and low-lethality groups, with 5 (55%) and a mean (SD) of 863.42 (151.12) in the high-lethality group and 4 (45%) with a mean (SD) of 845 (196.17) in the low-lethality group.

Table 2.
Suicide Profile of Low-Lethality and High-Lethality Bipolar Suicide Attempters.

	Low Lethality (n=10)	High Lethality (n=10)	Without SA	F or X² or t	P-Value
Gender, No.(%)					
Male	5 (50.0)	7 (70.0)	11 (57.9)	X² (2) = 0.84	.656
Female	5 (50.0)	3 (30.0)	8 (42.1)		
Age, mean (SD)	41.40 (12.91)	38.20 (12.49)	42.26 (11.70)	F (2,38) = 0.37	.693
Years of study, mean (SD)	11.70 (4.60)	12.10 (6.04)	11.26 (3.86)	F (2,38) = 0.11	.897
Age at first mood episode, mean (SD)	23.10 (8.65)	26.19 (10.15)	27.53 (8.50)	F (2,38) = 0.80	.458
Total years of disease, mean (SD)	18.50 (11.87)	14.80 (9.93)	14.58 (9.15)	F (2,38) = 0.54	.587
Childhood maltreatment, No.(%)	5 (50.0)	6 (60.0)	N/A	X² (1) = 0.43	.702
Suicidal ideation score at admission, mean (SD)	3.55 (4.21)	4.60 (2.80)	N/A	t (18) = -0.72	.497
Number of SA, mean (SD)	1.10 (0.31)	2.20 (1.03)	N/A	t (18) = -3.22	**.005***
Suicide intent scale score at time of most lethal attempt, mean (SD)	19.60 (6.00)	29.50 (9.45)	N/A	t (18) = -2.79	**.012***
Violent method of SA, No.(%)	2 (20.0)	3 (30.0)	N/A	N/A	N/A

Abbreviations: BD-I: bipolar disorder type 1; SA: suicide attempt; x²: chi-square test; t: independent student t-test; F: frequency. **p< 0.05***

3.2 Imaging data

3.2.1 GMV differences in between-group comparisons

No statistical significance was attained with the use of FWE-correction for multiple comparisons over the whole brain (p<0.05) in the ANOVA and the T test. The negative results are presented in supplement 1.

When SVC analysis was guided by a priori selection of brain regions, the BD-SA group presented increased GMV in the right rostral ACC compared with the BD-NSA group [Brodmann area (BA), 24; peak level coordinates, x, y, z = 5, 17, 25; number of voxels (k), 163; pFWE, 0.016, corrected for multiple comparisons using the SVC approach; Z-score, 3.71]. Furthermore, this increased GMV was more pronounced and extended further toward the left ACC in the high-lethality attempters compared to those who had not attempted suicide (Figure 1). There were no differences in any of the other *a priori* selected brain regions between the groups.
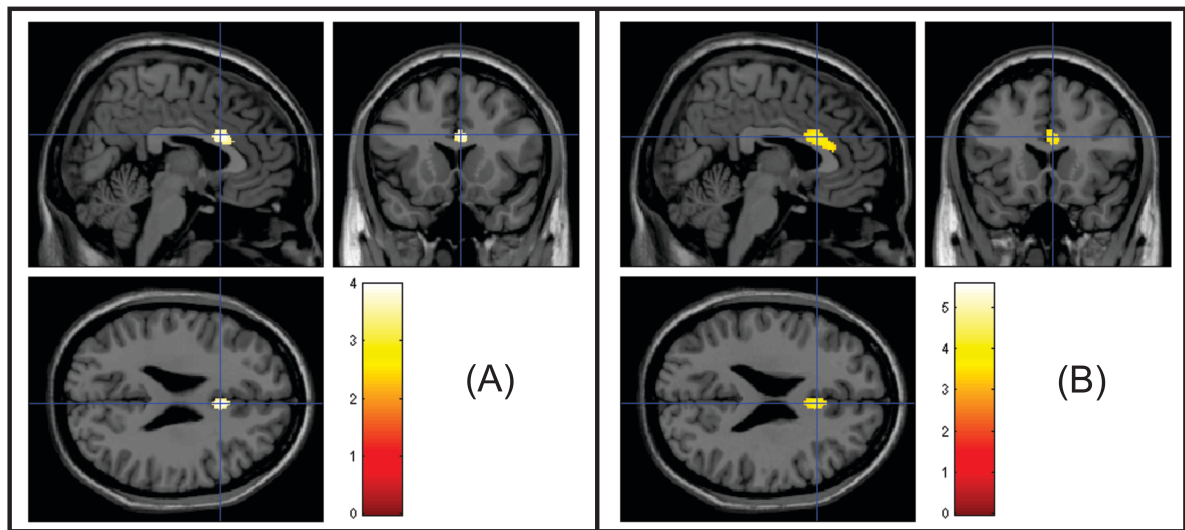
Figure 1. Brain region of significant (A) increased right rostral ACC GMV between BD-I suicide attempters compared to non-attempters; (B) more pronounced increased right rostral ACC GMV and extended further toward left portion between high-lethality attempters compared to non-attempters (filtered at the Z > 3.09 threshold). Voxel clusters shown are those that retained significance after family-wise error correction for multiple comparisons, as performed using the SVC tool in SPM (*p*FWE < 0.05) with an extent threshold of 25 voxels. Each intersection shows the peak of greatest significance within the cluster (highlighted in yellow). The colored bars of the Y-axis represent the T-value. Abbreviations: ACC: anterior cingulate cortex GMV: gray matter volume; SA: suicide attempt; SVC: small volume correction; SPM: statistical parametric mapping.

Among the BD-SA group, those who had made high-lethality attempts had significantly increased GMV in the left insula (BA 13) compared with the low-lethality attempters. Finally, the low-lethality attempters had increased GMV in the left OFC (BA 47) compared with the BD-NSA group. There were no differences in any of the other a priori selected brain regions between the groups. The results are presented in Table 3.

Table 3
Comparison between GMV and medical suicide lethality within the overall BD-I group (n = 39)

Brain Regions	Number of Voxels [a]	Coordinate[b] x,y,z	Peak Z-score[c]	P value[d]
High-Lethality < Low-Lethality: NONE				
High-Lethality > Low-Lethality				
Left Insula	52	-42 -12 3	3.54	0.041
High-Lethality < Non-Attempters: NONE				
High-Lethality > Non-Attempters				
Right Anterior Cingulate Cortex	388	5 20 24	3.93	0.014
Low-Lethality < Non-Attempters: NONE				
Low-Lethality > Non-Attempters				
Left Inferior Orbitofrontal Cortex	26	-38 31 -18	3.49	0.039

[a] Contiguous voxels in each region that transcend the initial cutoff of Z >3.09 with p <0.05
[b] MNI coordinates of the voxel of maximal statistical significance within each region.
[c] Z-scores for the voxel of maximal statistical significance in each region.
[d] Statistical significance after family-wise error correction for multiple comparisons (voxel level) within the respective volume of interest circumscribed using the small volume correction approach.

4. Discussion

In the current study, we found significant differences in GMV between the BD-SA and BD-NSA groups and between high- and low-lethality attempters, suggesting that specific neural circuits are related to suicidal behavior. The affected areas included the OFC, ACC and insula. Our findings support the hypotheses that suicidal patients with BD-I have brain morphological alterations in regions that integrate the FLN compared to non-suicidal patients with BD-I and that high-lethality attempts are related to more severe brain abnormalities.

Increased volume in specific brain regions in subjects with BD is not a rare finding, as described by an international collaborative mega-analysis of patient data from adults with BD (Hallahan et al., 2011). We consider our most robust finding the enlargement of right rostral ACC GMV in patients with BD who had attempted suicide compared to those who had not. Furthermore, this increased GMV was more pronounced and extended further toward the left ACC in the high-lethality attempters compared to those who had not attempted suicide. Notably, there were no significant differences in this region between the low-lethality attempters and those who had not attempted suicide, reinforcing the association between volume alterations in this region and the medical lethality of SAs.

The ACC is part of the limbic system and is located in the medial part of the frontal lobe. The rostral subdivision of the ACC plays a role in affective regulation, while the dorsal subdivision is involved in cognitive control (Bush et al., 2000), with connections to the frontal cortex, amygdala, hypothalamus, insula, and hippocampus. Furthermore, this region is part of the FLN and involved in assessing the importance of motivational information as well as in regulating emotional responses, decision-making and impulsivity (Bush et al., 2000).

There is scant literature regarding volumetric abnormalities in the ACC and their association with SAs in patients with BD. Rather, most of the currently available articles on suicide are primarily based on functional neuroimaging in patients diagnosed with depression. To date, volumetric neuroimaging studies in patients with BD have found a negative correlation between SA history and the volume of the bilateral dorsal ACC (Benedetti et al., 2011). However, in conjunction analysis, lithium-treated patients have shown higher GM volumes in the same cortical region (Benedetti et al., 2011). Volumetric reduction in the left dorsal-caudal ACC was found in high-lethality attempters compared with low-lethality attempters in a sample of BD patients (Giakoumatos et al., 2013). Matsuo and colleagues did not find any differences in ACC volume, but they did find that degree of impulsivity was negatively correlated with left rostral ACC GMV (Matsuo, Nicoletti, Peluso, et al., 2009) in patients with BD who have attempted suicide, and with left dorsal ACC volume in healthy subjects (Matsuo, Nicoletti, Nemoto, et al., 2009). The above-mentioned results demonstrate that different studies have identified abnormalities in different sub-regions of the ACC. Furthermore, no previous studies have shown alterations in the ACC sub-region that was identified to contain alterations in the present work.

Methodological differences between the above-referenced studies and the current study may explain, at least in part, the differences in the results obtained. For instance, previous VBM studies (Matsuo, Nicoletti, Peluso, et al., 2009; Matsuo, Nicoletti, Nemoto, et al., 2009; Benedetti et al., 2011) have used previous versions of SPM software, whereas the current study used SPM8 with the DARTEL Toolbox. Some authors have demonstrated that the use of the DARTEL Toolbox provides superior results when compared to previous versions of the program (Ashburner, 2009; Klein et al., 2009; Tahmasebi et al., 2009). Additionally, Giakoumatos et al., (2013) used Freesurfer to analyze their results. The use of these different methods might account for the discrepancies in the results. Second, the samples of previous studies have included patients with type I and II BD (Matsuo, Nicoletti, Peluso, et al., 2009), bipolar patients with psychotic symptoms (Giakoumatos et al., 2013) and patients on depressive episode of BD (Benedetti et al., 2011). Third, increased GMV in the

whole brain (Watson et al., 1997; Brierley et al., 2002; Sassi et al., 2002; Bearden et al., 2007) and in the ACC (Atmaca et al., 2007; Yatham et al., 2007) in patients with BD can be related to lithium treatment, specifically because of the effects of lithium on neuronal plasticity (Chen et al., 2000) and neuroprotection (Licht et al., 1994). Neither the present study nor those mentioned above had information about lithium treatment duration, and we cannot discount the possibility that lithium played a role in the differences between our and others' findings; nonetheless, there were no significant differences in lithium intake between our BD groups. Fourth, intensive interventions and medical care may have caused more pronounced increases in brain volume in the most severely affected patients, as shown in the high-lethality sub-group. This hypothesis has also been proposed by other researchers (Javadapour et al., 2007; Lijffijt et al., 2014; Lisy et al., 2011).

A growing body of evidence suggests that ACC abnormalities are linked to suicidality across different diagnostic categories of psychiatric disorders, including major depressive disorder (Monkul et al., 2007; Wagner et al., 2011), schizophrenia (van Heeringen et al., 2011), and borderline personality disorder (Soloff et al., 2012). Further studies are needed to clarify if abnormalities in the ACC are a suicide-related transnosographic phenomenon, i.e., whether they are present across different psychiatric diagnoses.

Augmented GMV in the insula was found in the high-lethality attempters compared to the low-lethality attempters. The insular cortex is involved in emotional processing and has critical participation in mood regulation (New et al., 2008). Our group recently published that there is a GMV reduction in the left insula in patients with BD-I compared to HCs (Neves et al., 2016) and in patients with BD-I and a lifetime history of hallucinations compared to subjects with the same diagnosis but no history of hallucinations (Neves et al., 2015). The same brain region was identified in both investigations, thus reinforcing the view that abnormalities in the insular cortex may be relevant to the pathophysiology of BD.

Collectively, one possible explanation could be that hyperactivity of FLN structures such as OFC, ACC and insula potentially lead to changes in brain plasticity and hypertrophy as compensatory mechanisms (Fears et al., 2015; Javadapour et al., 2007; Lisy et al., 2011) to regulate emotional states (Sublette et al., 2006) and to mitigate the failures in frontal "top-down" modulation found in BD (Strakowski et al., 2012). In addition to this, the epigenetic dysregulation of the glucocorticoid receptor (hypothalamic–pituitary–adrenal dysregulation) (Turecki, 2014), and serotonin receptor binding (Underwood et al., 2012) play important role in this process. Differences in the activation of these regions have been demonstrated in several studies using a variety of imaging modalities, such as positron emission tomography

(Oquendo et al., 2003; Sublette et al., 2013) and functional MRI (Jollant et al., 2008, 2010; Reisch et al., 2010; Pan et al., 2011; Fan et al., 2013; Pan, Segreti, et al., 2013; Pan, Hassel, et al., 2013).

Our sample consisted of well-characterized and homogenous euthymic outpatients with BD-I without any other comorbid medical conditions. However, our results must be interpreted in view of several methodological limitations. The use of a retrospective and cross-sectional study design has the risk of potential recall bias and limits longitudinal and neurodevelopmental inferences. Future studies with a longitudinal design with a larger number of patients who are followed up from the onset of disease are warranted. The brain imaging data acquired for the present study were acquired after SA, and it remains a possibility that the observed differences resulted from such attempts rather than from pre-existing brain abnormalities. However, because low-lethality attempts were less likely to cause brain abnormalities, it is noteworthy that a comparison of low-lethality attempters to non-attempters identified significant structural brain differences even when high- lethality attempters were excluded. Moreover, we co-varied our between-group comparisons for several factors, such as sex, age, education, and total intracranial volume and thereby addressed the potential confounding effects of these variables.

In summary, the current work identified a set of brain structural abnormalities that may be a marker of previous etiopathogenic processes affecting regions that have been implicated in SAs and lethality, as well as in emotional and behavioral regulation, decision-making and adaptive responses to stress. Such results can help psychiatrists and clinicians to define high-risk groups for suicidal behavior, and highlights the need to address this hidden epidemic burden.

Disclosure of interest

Role of the funding source

References

Adler, C.M., Levine, A.D., DelBello, M.P., Strakowski, S.M., 2005. Changes in gray matter volume in patients with bipolar disorder. Biol. Psychiatry 58, 151–157.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95-113.

Ashburner, J., 2009. Computational anatomy with the SPM software. Magn. Re- sonan. Imaging 27, 1163–1174.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839- 851.

Atmaca, M., Ozdemir, H., Cetinkaya, S., Parmaksiz, S., Belli, H., Poyraz, A.K., Tezcan, E., Ogur, E., 2007. Cingulate gyrus volumetry in drug free bipolar patients and patients treated with valproate or valproate and quetiapine. J. Psychiatr. Res. 41, 821–827.

Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Brain Res. Rev. 22, 229–244.

Bearden, C.E., Thompson, P.M., Dalwani, M., Hayashi, K.M., Lee, A.D., Nicoletti, M., Trakhtenbroit, M., Glahn, D.C., Brambilla, P., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D.J., Soares, J.C., 2007. Greater cortical gray matter density in lithium-treated patients with bipolar disorder. Biol. Psychiatry 62, 7–16.

Beck, A.T., Beck, R., Kovacs, M., 1975. Classification of suicidal behaviors: I. Quantifying intent and medical lethality. Am. J. Psychiatry 132, 285-287.

Beck, A.T., Kovacs, M., Weissman, A., 1979. Assessment of suicidal intention: the scale for suicide ideation. J. Consult. Clin. Psychol. 47, 343-352.

Benedetti, F., Radaelli, D., Poletti, S., Locatelli, C., Falini, A., Colombo, C., Smeraldi, E., 2011. Opposite effects of suicidality and lithium on gray matter Volumes in bipolar depression. J. Affect. Disord. 135, 139 – 147.

Brierley, B., Shaw, P., David, A.S., 2002. The human amygdala: a systematic review and meta-analysis of volumetric magnetic resonance imaging. Brain Res. Brain Res. Rev. 39, 84-105.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.

Chen, G., Rajkowska, G., Du, F., Seraji-Bozorgzad, N., Manji, H.K., 2000. Enhancement of hippocampal neurogenesis by lithium. J. Neurochem. 75, 1729–1734.

de Azevedo-Marques Périco, C., Duran, F.L., Zanetti, M.V., Santos, L.C., Murray, R.M., Scazufca, M., Menezes, P.R., Busatto, G.F.,Schaufelberger, M.S., 2011.A population-based morphometric MRI study in patients with first-episode psychotic bipolar disorder: comparison with geographically matched healthy controls and major depressive disorder subjects. Bipolar Disord. 13, 28-40.

Desmyter, S., van Heeringen, C., Audenaert, K., 2011. Structural and functional neuroimaging studies of the suicidal brain. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 796–808. doi:10.1016/j.pnpbp.2010.12.026.

Duarte, D.G.. Neves, Mde C, Albuquerque, M.R., Neves, F.S., Corrêa, H., 2015. Sexual abuse and suicide attempt in bipolar type I patients. Rev. Bras. Psiquiatr. 37, 180–182.

Duarte, D.G.. Neves, Mde C., Albuquerque, M.R., de Souza-Duran, F.L., Busatto, G., Corrêa, H., 2016. Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: a voxel-based morphometric study. J. Affect. Disord. 197, 74–80.

Dwivedi, Y. (Ed.), 2012. The Neurobiological Basis of Suicide, first ed.. CRC Press, New York.

Etain, B., Aas, M., Andreassen, O.A., Lorentzen, S., Dieset, I., Gard, S., Kahn, J.P., Bellivier, F., Leboyer, M., Melle, I., Henry, C., 2013. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. J. Clin. Psychiatry 74, 991- 998.

Fan, T. T., Wu, X., Yao, L., and Dong, J. (2013). Abnormal baseline brain activity in suicidal and non-suicidal patients with major depressive disorder. Neurosci. Lett. 534, 35–40. doi: 10.1016/j.neulet.2012.11.032

Fears, S.C., Schür, R., Sjouwerman, R., Service, S.K., Araya, C., Araya, X., Bejarano, J., Knowles, E., Gomez-Makhinson, J., Lopez, M.C., Aldana, I., Teshiba, T.M., Abaryan, Z., Al-Sharif, N.B., Navarro, L., Tishler, T.A., Altshuler, L., Bartzokis, G., Escobar,

J.I., Glahn, D.C., Thompson, P.M., Lopez-Jaramillo, C., Macaya, G., Molina, J., Reus, V.I., Sabatti, C., Cantor, R.M., Freimer, N.B., Bearden, C.E., 2015. Brain structure-function associations in multi-generational families genetically enriched for bipolar disorder. Brain 138, 2087–2102.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J., 1995. Statistic parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Giakoumatos, C.I., Tandon, N., Shah, J., Mathew, I.T., Brady, R.O., Clementz, B.A., Pearlson, G.D., Thaker, G.K., Tamminga, C.A., Sweeney, J.A., Keshavan, M.S., 2013. Are structural brain abnormalities associated with suicidal behavior in patients with psychotic disorders? J. Psychiatr. Res. 47, 1389–1395.

Goodwin, F., Jamison, K., 2007. Manic-Depressive Illness. Oxford University Press, New York, pp. 223–245.

Hallahan, B., Newell, J., Soares, J.C., Brambilla, P., Strakowski, S.M., Fleck, D.E., Kieseppä, T., Altshuler, L.L., Fornito, A., Malhi, G.S., McIntosh, A.M., Yurgelun-Todd, D.A., Labar, K.S., Sharma, V., MacQueen, G.M., Murray, R.M., McDonald, C., 2011. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol. Psychiatry 69, 326-335.

Houenou, J., Frommberger, J., Carde, S., Glasbrenner, M., Diener, C., Leboyer, M., Wessa, M., 2011. Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. J. Affect. Disord. 132, 344–355.

Hozer, F., Houenou, J., 2016. Can neuroimaging disentangle bipolar disorder? J. Affect. Disord. 195 , 199 – 214.

Javadapour, A., Malhi, G.S., Ivanovski, B., Chen, X., Wen, W., Sachdev, P., 2007. Increased anterior cingulate cortex volume in bipolar I disorder. Aust N Z J. Psychiatry 41, 910-916.

Jollant, F., Lawrence, N.L., Olié, E., Guillaume, S., Courtet, P., 2011. The suicidal mind and brain: a review of neuropsychological and neuroimaging studies. World J. Biol. Psychiatry 12, 319–339.

Jollant, F., Lawrence, N.S., Giampietro, V., Brammer, M.J., Fullana, M.A., Drapier, D., Courtet, P., Phillips, M.L., 2008. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. Am. J. Psychiatry 165, 740–748.

Klein, A., Andersson, J., Ardekani, B.A., Ashburner, J., Avants, B., Chiang, M.-C., Christensen, G.E., Collins, D.L., Gee, J., Hellier, P., Song, J.H., Jenkinson, M., Lepage, C., Rueckert, D., Thompson, P., Vercauteren, T., Woods, R.P., Mann, J.J., Parsey, R.V., 2009. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage 46, 786–802.

Lester, D., Beck, A.T., 1975. Suicidal intent, medical lethality of the suicide attempt, and components of depression. J. Clin. Psychol. 31, 11–12.

Leverich, G.S., Altshuler, L.L., Frye, M.A., 2003. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. J Clin Psychiatry. 64, 506–515.

Licht, R.W., Larsen, J.O., Smith, D., Braendgaard, H., 1994. Effect of chronic lithium treatment with or without haloperidol on number and sizes of neurons in rat neocortex. Pharmacology 115, 371–374 .

Lijffijt, M., Rourke, E.D., Swann, A.C., Zunta-Soares, G.B., Soares, J.C., 2014. Illness-course modulates suicidality-related prefrontal gray matter reduction in women with bipolar disorder. Acta Psychiatr. Scand. 130, 374-387.

Lisy, M.E., Jarvis, K.B., DelBello, M.P., Mills, N.P., Weber, W.A., Fleck, D., Strakowski, S.M., Adler, C.M., 2011. Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. Bipolar Disord. 13, 396–405.

Lyoo, I.K., Dager, S.R., Kim, J.E., Yoon, S.J., Friedman, S.D., Dunner, D.L., Renshaw, P.F., 2010. Lithium-induced gray matter volume increase as a neural correlate of treatment response in bipolar disorder: a longitudinal brain imaging study. Neuropsychopharmacology 35, 1743–1750.

Malhi, G.S., Bargh, D.M., Kuiper, S., Coulston, C.M. , Das, P., 2013. Modeling bipolar disorder suicidality. Bipolar Disord. 15, 559-574.

Maller, J.J., Thaveenthiran, P., Thomson, R.H., McQueen, S., Fitzgerald, P.B., 2014. Volumetric, cortical thickness and white matter integrity alterations in bipolar disorder type I and II. J. Affect. Disord. 169, 118–127.

Manji, H.K., Moore, G.J., Chen, G., 2000. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biol. Psychiatry 48, 740–754.

Mann, J.J., 2003. Neurobiology of suicidal behaviour. Nat. Rev. Neurosci. 4, 819–828.

Maris, R.W., Berman, A.L., Silverman, M.M., 2000, Comprehensive Textbook of Suicidology. The Guilford Press, New York, p. 19.

Matsuo, K., Kopecek, M., Nicoletti, M.A., Hatch, J.P., Watanabe, Y., Nery, F.G., Zunta-Soares, G., Soares, J.C., 2012. New structural brain imaging endophenotype in bipolar disorder. Mol. Psychiatry 17, 412–420.

Matsuo, K., Nicoletti, M., Nemoto, K., Hatch, J.P., Peluso, M.A., Nery, F.G., Soares, J.C., 2009b. A voxel-based morphometry study of frontal gray matter correlates of impulsivity. Hum. Brain Mapp. 30, 1188–1195.

Matsuo, K., Nicoletti, M.A., Peluso, M.A., Hatch, J.P., Nemoto, K., Watanabe, Y., Nery, F.G., Monkul, E.S., Zunta-Soares, G.B., Bowden, C.L., Soares, J.C., 2009a. Anterior cingulate Volumes associated with trait impulsivity in individuals with bipolar disorder. Bipolar Disord. 11, 628–636.

Monkul, E.S., Hatch, J.P., Nicoletti, M.A., Spence, S., Brambilla, P., Lacerda, A.L., Sassi, R.B., Mallinger, A.G., Keshavan, M.S., Soares, J.C., 2007. Fronto-limbic brain structures in suicidal and non- suicidal female patients with major depressive disorder. Mol. Psychiatry 12, 360–366.

Nery, F.G., Gigante, A.D., Amaral, J.A., Fernandes, F.B., Berutti, M., Almeida, K.M., Carneiro, Cde G., Duran, F.L., Otaduy M.G., Leite, C.C., Busatto, G., Lafter, B., 2015. Gray matter volumes in patients with bipolar disorder and their first-degree relatives. Psychiatry Res. 234, 188-193.

Neves, F.S., Malloy-Diniz, L.F., Barbosa, I.G., Brasil, P.M., Corrêa, H., 2009. Bipolar disorder first episode and suicidal behavior: are there differences according to type of suicide attempt? Rev. Bras. Psiquiatr. 31, 114-118.

Neves, Mde C., Albuquerque, M.R., Malloy-Diniz, L., Nicolato, R., Silva Neves, F., de Souza-Duran, F.L., Busatto, G., Corrêa, H., (2015). A voxel-based morphometry study of gray matter correlates of facial emotion recognition in bipolar disorder. Psychiatry Res. 233, 158-164.

Neves, M.de C., Duarte, D.G., Albuquerque, M.R., Nicolato, R., Neves, F.S., Souza-Duran, F.L., Busatto, G., Corrêa, H., 2016. Neural correlates of hallucinations in bipolar disorder. Rev. Bras. Psiquiatr. 38, 1–5.

New, A.S., Goodman, M., Triebwasser, J., Siever, L.J., 2008. Recent advances in the biological study of personality disorders. Psychiatr. Clin. North Am. 31, 441–461. PubMed: 18638645.

Nordentoft, M., Mortensen, P.B., Pedersen, C.B., 2011. Absolute risk of suicide after first Hospital contact in mental disorder. Arch. Gen. Psychiatry 68, 1058-1064.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Oquendo, M.A., Placidi, G.P., Malone, K.M., Campbell, C., Keilp, J., Brodsky, B., Kegeles, L.S., Cooper, T.B., Parsey, R.V., van Heertum, R.L., Mann, J.J., 2003. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Arch. Gen. Psychiatry 60, 14–22.

Pan, L., Segreti, A., Almeida, J., Jollant, F., Lawrence, N., Brent, D., Phillips, M., 2013b. Preserved hippocampal function during learning in the context of risk in adolescent suicide attempt. Psychiatry Res. 211, 112–118.

Pan, L.A., Batezati-Alves, S.C., Almeida, J.R., Segreti, A., Akkal, D., Hassel, S., Lakdawala, S., Brent, D.A., Phillips, M.L., 2011. Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. J. Am. Acad. Child Adolesc. Psychiatry 50, 602–611.

Pan, L.A., Hassel, S., Segreti, A.M., Nau, S.A., Brent, D.A., Phillips, M.L., 2013a. Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in adolescents with and without suicide attempt. Psychol. Med. 43, 2129–2142.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003b. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol. Psychiatry 54, 515–528.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry 13, 829, 833–857.

Reisch, T., Seifritz, E., Esposito, F., Wiest, R., Valach, L., Michel, K., 2010. An fMRI study on mental pain and suicidal behavior. J. Affect. Disord. 126, 321–325. PubMed: 20434779.

Sassi, R.B., Nicoletti, M., Brambilla, P., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S., Soares, J.C., 2002. Increased gray matter volume in lithium-treated bipolar disorder patients. Neurosci. Lett. 329, 243–245.

Schulze, T.G., 2010. Genetic research into bipolar disorder: the need for a research framework that integrates sophisticated molecular biology and clinically informed phenotype characterization. Psychiatr. Clin. North Am. 33, 67 – 82.

Selvaraj, S., Arnone, D., Job, D., Stanfield, A., Farrow, T.F., Nugent, A.C., Scherk, H., Gruber, O., Chen, X., Sachdev, P.S., Dickstein, D.P., Malhi, G.S., Ha, T.H., Ha, K., Phillips, M.L., McIntosh, A.M., 2012. Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. Bipolar Disord. 14, 135–145.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20) , 22-33.

Soloff, P., White, R., Diwadkar, V.A., 2014. Impulsivity, aggression and brain structure in high and low lethality suicide attempters with borderline personality disorder. Psychiatryres. 222, 131–139.

Soloff, P.H., Chiappetta, L., 2012b. Prospective predictors of suicidal behavior in BPD at 6 year follow-up. Am. J. Psychiatry 169, 484–490. doi:10.1176/appi.ajp.2011.11091378.

Soloff, P.H., Pruitt, P., Sharma, M., Radwan, J., White, R., Diwadkar, V.A., 2012a. Structural brain abnormalities and suicidal behavior in borderline personality disorder. J. Psychiatr. Res. 46, 516–525.

Strakowski, S.M., Adler, C.M., Almeida, J., Altshuler, L.L., Blumberg, H.P., Chang, K.D., DelBello, M.P., Frangou, S., McIntosh, A., Phillips, M.L., Sussman, J.E., Townsend, J.D., 2012. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord. 14, 313–325.

Sublette, M.E., Oquendo, M.A., Mann, J.J., 2006. Rational approaches to the neurobiologic study of youth at risk for bipolar disorder and suicide. Bipolar Disord. 8, 526–542.

Sublette, M.E., Milak, M.S., Galfalvy, H.C., Oquendo, M.A., Malone, K.M., J. John Mann, J.J., 2013. Regional Brain Glucose Uptake Distinguishes Suicide Attempters from Non-Attempters in Major Depression. Arch Suicide Res. 17, 1-14.

Tahmasebi, A.M., Abolmaesumi, P., Zheng, Z.Z., Munhall, K.G., Johnsrude, I.S., 2009. Reducing inter-subject anatomical variation: effect of normalization method on sensitivity of functional magnetic resonance imaging data analysis in auditory cortex and the superior temporal region. Neuroimage 47, 1522–1531.

Tohen, M., Frank, E., Bowden, C.L., Colom, F., Ghaemi, S.N., Yatham, L.N., Malhi, G.S., Calabrese, J.R., Nolen, W.A., Vieta, E., Kapczinski, F., Goodwin, G.M., Suppes, T., Sachs, G.S., Chengappa, K.R., Grunze, H., Mitchell, P.B., Kanba, S., Berk, M., 2009. The International Society for Bipolar Disorders (ISBD) Task Force report on the

nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 11, 453-473.

Turecki, G., 2014. The molecular bases of the suicidal brain. Nat. Rev. Neurosci. 15, 802–816.

Turecki, G., Brent, D.A., 2016. Suicide and suicidal behaviour. Lancet 387, 1227–1239.

Turecki, G., Ernst, C., Jollant, F., Labonté, B., Mechawar, N., 2012.The neurodevelopmental origins of suicidal behavior. Trends Neurosci. 35, 14–23.

Underwood, M.D., Kassir, S.A., Bakalian, M.J., Galfalvy, H., Mann, J.J., Arango, V., 2012. Neuron density and serotonin receptor binding in prefrontal cortex in suicide. Int. J. Neuropsychopharmacol. 15, 435-447.

Valtonen, H., Suominen K., Mantere, O., Leppamaki, S., Arvilommi, P., Isometsa, E.I., 2005. Suicidal ideation and attempts in bipolar I and II disorders. J Clin Psychiatry. 66, 1456–1462.

van Heeringen, C., Bijttebier, S., Godfrin, K., 2011. Suicidal brains: a review of functional and structural brain studies in association with suicidal behaviour. Neurosci. Biobehav. Rev. 35, 688–698.

van Heeringen, K., Bijttebier, S., Desmyter, S., Vervaet, M., Baeken, C., 2014. Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. Front. Hum. Neurosci. 8, 824.

van Heeringen, K., Mann, J.J., 2014. The neurobiology of suicide. Lancet Psychiatry 1, 63 – 72.

Vilela, J.A., Crippa, J.A., Del-Ben, C.M., Loureiro, S.R., 2005. Reliability and validity of a Portuguese version of the Young Mania Rating Scale. Braz. J. Med. Biol. Res. 38, 1429-1439.

Wagner, G., Koch, K., Schachtzabel, C., Schultz, C.C., Sauer, H., Schlösser, R.G., 2011. Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? Neuroimage 54, 1607-1614.

Watson, C., Jack, C.R., Cendes, F., 1997. Volumetric magnetic resonance imaging. Clinical applications and contributions to the understanding of temporal lobe epilepsy. Arch. Neurol. 54, 1521 -1531.

Webster, M.J., O'Grady, J., Kleinman, J.E., Weickert, C.S., 2005. Glial fibrillary acidic protein mRNA levels in the cingulate cortex of individuals with depression, bipolar disorder and schizophrenia. Neuroscience 133, 453–461.

Williams, J.B., 1988. A structured interview guide for the Hamilton Depression Rating Scale. Arch. Gen. Psychiatry 45, 742–747.

Yatham, L.N., Lyoo, I.K., Liddle, P., Renshaw, P.F., Wan, D., Lam, R.W., Hwang, J., 2007. A magnetic resonance imaging study of mood stabilizer- and neuroleptic-naïve first-episode mania. Bipolar Disord. 9, 693–697.

Zhang, H., Chen, Z., Jia, Z., Gong, Q., 2014. Dysfunction of neural circuitry in depressive patients with suicidal behaviors: a review of structural and functional neuroimaging studies. Prog. Neuropsychopharmacol. Biol. Psychiatry 53, 61–66.

5 DISCUSSÃO

Ao abordar o trauma infantil e o comportamento suicida em pacientes portadores de transtorno afetivo bipolar, deparamo-nos com um tema complexo e que exige uma aproximação multidimensional. O conjunto dos artigos visou a responder aos objetivos propostos no presente trabalho. Iniciamos com uma revisão da literatura e meta-análise sobre a população de bipolares que demonstrou existir uma forte associação entre TI com seus subtipos e CS (Artigo 1). O Artigo 2, por sua vez, mostrou essa associação com abuso sexual na nossa amostra de bipolares. Em seguida, demonstramos, por meio do Artigo 3, que os tipos de TI e sua gravidade foram relacionados a anormalidades do VSC em componentes de circuitos neurais do sistema fronto-límbico, e através do Artigo 4, verificamos que alterações neuroanatômicas em regiões desse sistema estariam associadas ao CS.

O Artigo 1 foi além de mostrar a associação entre TI e CS em indivíduos bipolares. Teve como ponto central discutir a heterogeneidade na definição e na forma de avaliar o TI, o que dificulta o entendimento e a consolidação de um construto confiável. Para isso, o estudo por completo, foi baseado em trabalhos que utilizaram o Questionário de Trauma na Infância (*Childhood Trauma Questionnaire* – CTQ), que apesar de não haver superioridade comprovada sobre as outras escalas, têm grande validade no cenário internacional. O argumento predominante foi trazer dados homogêneos que permitam realizar comparações fidedignas entre as variáveis e servir como base para futuros trabalhos dessa temática.

Ao investigar os pacientes da nossa amostra, o Artigo 2 mostrou diferença significativa entre abuso sexual no grupo suicida *versus* não suicida e replicou achados de outros trabalhos em pacientes bipolares (LEBOYER *et al*., 2007; DARUY-FILHO *et al.,* 2011), incluindo estudos longitudinais (DEVRIES, 2014). Segundo Leboyer *et al.* (2007), ter sofrido abuso sexual e abuso emocional em uma amostra de 201 pacientes com TAB foi associado a risco dobrado de tentativa de suicídio [OR=2.71, (1.07-6.86, p=0.04)]. Contudo, a influência dos subtipos de TI no CS ainda permanece desconhecida e pouco replicada (ETAIN *et al.,* 2008). Vale salientar que, quando o número de sujeitos foi reduzido para atender aos nossos critérios dos estudos de neuroimagem, não existiu diferença estatística em nenhum subtipo de TI. Esse fato indica que o abuso sexual estaria circunscrito àquela população de bipolares excluída.

É relevante apontar que os Artigos 2, 3 e 4 não acharam diferenças com significância estatística em variáveis sociodemográficas e clínicas entre os grupos de comparação. Esse fato, por um lado reduz possíveis fatores de confusão, por outro, não replica os achados de

alguns estudos atuais (ALLOY *et al.,* 2006; FISHER; HOSANG, 2010; DARUY-FILHO *et al.,* 2011; AAS *et al.,* 2016). Todavia, no Artigo 4, achamos um maior número de tentativas de suicídio ao longo da vida e de intencionalidade suicida no grupo com alta letalidade comparado ao de baixa letalidade suicida. Esses dados corroboram o que a maioria dos estudos têm argumentado, a importância de subdividir o CS quanto à letalidade, pois parece tratar-se de uma população com maior gravidade, com características mais homogêneas e similaridades neurobiológicas àqueles que faleceram por suicídio (VAN HERIGEEEN; MANN, 2014; TURECKI; BRENT, 2016).

Artigo 3, por sua vez, demonstrou que a gravidade do TI estava relacionada à redução do PFC dorsolateral (DLPFC) e do tálamo. Outra contribuição desse trabalho foi demonstrar que o subtipo de trauma, abuso físico, teve correlação com o DLPFC e que as negligências física e emocional tiveram correlação com o tálamo. Essas informações são de grande valia para buscarmos um substrato neural de maior vulnerabilidade a determinados tipos de TI. Os argumentos propostos basearam-se nos diversos mediadores possíveis entre o TI e essas sequelas biológicas, passando pelo aumento da carga alostática, tais como: inflamação crônica, distúrbio do ritmo circadiano e encurtamento do telômero, associados, por outro lado, aos fatores individuais de resiliência. Outra explicação detalhou as consequências dessas estruturas afetadas nas manifestações clínicas do TAB.

Aprofundando o estudo de neuroimagem, verificamos no Artigo 4 anormalidades do VSC em indivíduos com história de CS. O achado de maior relevância foi o aumento do cíngulo anterior no grupo que tentou suicídio, e sua extensão ainda maior naqueles com alta letalidade suicida. Outras áreas que formam o FLN também foram estatisticamente significativas, tais como OFC e ínsula. O artigo aprofundou a discussão desses achados e propôs que essas anormalidades são assinaturas neurais de processos etiopatogênicos pregressos e que poderiam servir de marcadores biológicos para CS e letalidade em pacientes bipolares.

Integrando os resultados do Artigo 3 e 4, podemos inferir que a redução do VSC no PFC e no tálamo precoce no neurodesenvolvimento desses indivíduos bipolares pode ter prejudicado a conectividade e a modulação com as demais regiões e ter levado à perda da homeostase cerebral e a um aumento da carga alostática em sistemas envolvidos na resposta ao estresse. Com isso, cíngulo anterior, OFC e ínsula podem ter entrado em hiperatividade e hiperfunção como mecanismos compensatórios para restabelecer o equilíbrio e a estabilidade emocional, levando à alteração da plasticidade e à hipertrofia dessas estruturas (FEARS *et al.,*

2015; JAVADAPOUR *et al.,* 2007; LISY *et al.,* 2011). Ressaltamos também, a importância de não inferir causalidade nesses tipos de estudos transversais.

O modelo proposto para explicar os nossos achados de neuroimagem será detalhadamente descrito a seguir e na Figura 3. O esquema distribui as regiões dentro de um contexto, mostrando que muitas anormalidades neuroanatômicas estão interconectadas e integram componentes de um circuito responsável por regular a resposta a ameaças e ao estresse, assim como, regular o humor e o comportamento emocional.

Figura 3 - Modelo hipotético representando regiões cerebrais envolvidas na regulação da resposta emocional e ao estresse[4]
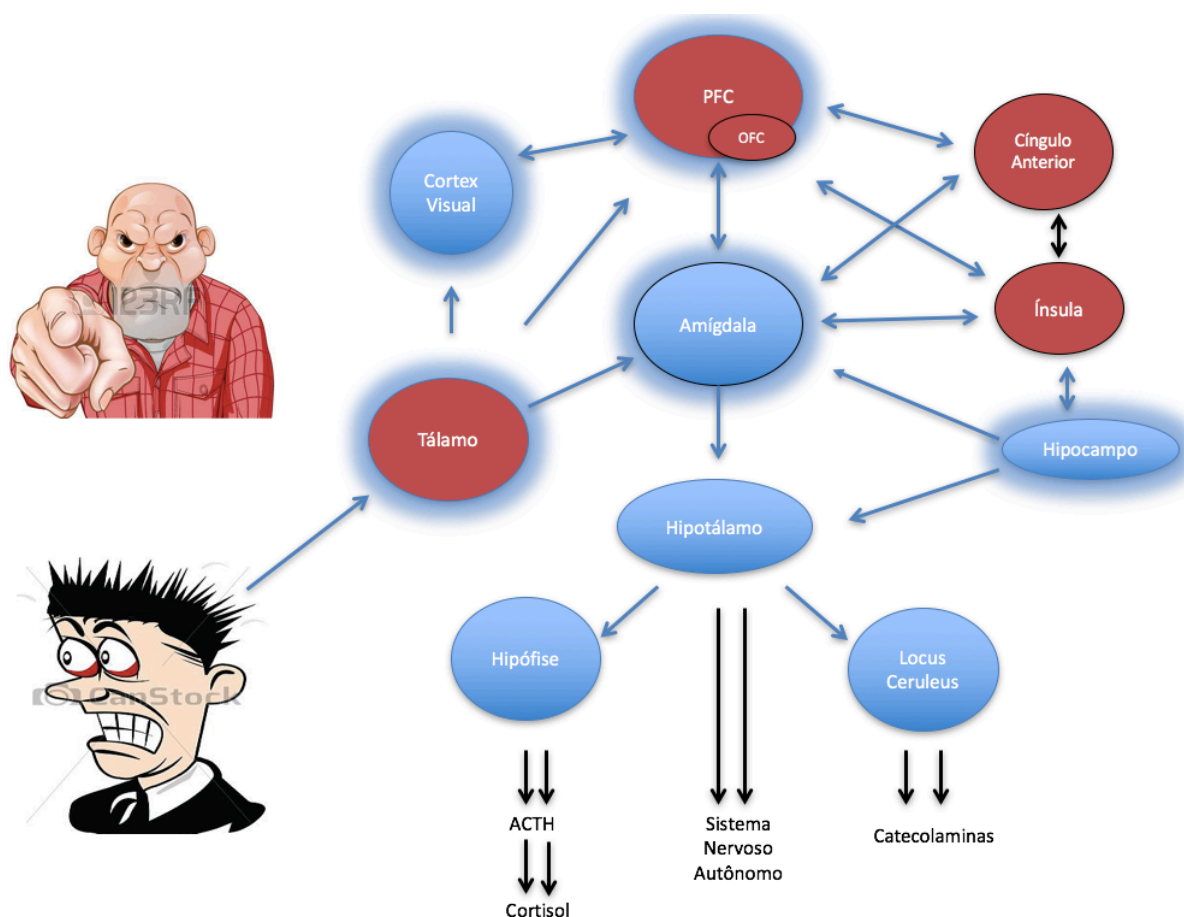
Nota: Em vermelho, resultados desse estudo, em azul, regiões a partir de dados da literatura (TEICHER, SAMSON, 2013; LIM; RADUA; RUBIA, 2014), em preto, aumento da função. Algumas estruturas presentes em artigos dessa temática não foram inseridas nessa figura: corpo caloso (BUCKER *et al.,* 2014) e córtex temporal (LIM; RADUA; RUBIA, 2014).
Adaptado e modificado com autorização de Teicher e Samson (2013).

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[4] O TI alteraria o desenvolvimento de algumas áreas e redes neurais desse circuito, que serve para reprogramar a reação a adversidades subsequentes. Essas alterações levariam a um maior risco de CS.

Resumidamente, o tálamo e o córtex sensorial processam sinais e sons de ameaça e transmitem a informação para amígdala e para o PFC, anormalidades dessas estruturas podem interferir no processamento de sinais e na transmissão deturpada do estímulo. As regiões pré-frontais são consideradas o local de controle cognitivo superior, a sede das representações dos alvos e metas do indivíduo e do planejamento de como alcançá-las (DAVIDSON, 2003). Essas estruturas modulam a resposta da amígdala e das estruturas límbicas em situações sociais, reduzindo a sua atividade frente a estímulos que não são ameaçadores, ou quando alteradas, ativando-as de forma desproporcional.

O comprometimento dessas regiões está relacionado com redução das projeções *top-down* e um fraco controle das estruturas límbicas e subcorticais. O hipocampo também processa essa informação proveniente do tálamo e tem papel importante para recuperar memórias explícitas relevantes. A amígdala integra essa informação e transmite para o hipotálamo, que por sua vez regula o sistema nervoso autônomo, as respostas hormonais da hipófise (cortisol) e do *locus ceruleus* (catecolaminas). Como as regiões neuroanatômicas são interconectadas, a amígdala sofre influências de outras estruturas: o cíngulo anterior realiza uma ligação entre os processos emocionais e atencionais e exerce um papel importante na monitoração do próprio desempenho e impulsividade, podendo representar um moderador de conflitos (DAVIDSON *et al.,* 2003).

A ínsula com múltiplas conexões recíprocas com o PFC e o córtex anterior do cíngulo está relacionada à integração multissensorial, à geração de afetos e às discrepâncias entre expectativas e acontecimentos reais, sendo essencial para flexibilizar ações, diante da mudança de contingências dando uma sensação de autovaloração e capacitação (PALANIYAPPAN; LIDDLE, 2012) (Figura 3).

As regiões acima, principalmente o PFC (incluindo o OFC), o cíngulo, a ínsula, a amígdala e o tálamo, são envolvidas nos atuais modelos neurobiológicos do TAB (STRAKOWSKI *et al.,* 2012). Os autores defendem que anormalidades nessas estruturas podem levar à deterioração da conectividade neuronal e à perda do equilíbrio emocional resultando na instabilidade do humor. Na ausência de integridade do circuito pré-frontal-cíngulo-estriado-talâmico-límbico que poderia restaurar esse equilíbrio, os indivíduos bipolares estão em risco para desenvolver extremos de humor, desregulação afetiva, *déficits* cognitivos progressivos e CS (STRAKOWSKY, 2012).

Nos bipolares, é possível que a inabilidade do PFC de projetar desfechos futuros positivos pode ser a base para os sentimentos de desesperança, aprisionamento e sensação de derrota/fracasso, que no contexto de um episódio depressivo pode deflagrar ideação suicida.

Adicionando-se a isso, com o comprometimento da ínsula, temos uma redução da autovaloração quanto às próprias habilidades. Em contrapartida, a suicidabilidade na (hipo)mania é caracterizada por impulsividade e envolvimento em situações de alto risco, ambos comportamentos podem estar associados à disfunção do OFC e do cíngulo anterior. Todavia, tais alterações não são limitadas aos episódios de humor e podem manifestar também na eutimia (MALHI *et al.*, 2013).

As anormalidades presentes na figura 3 podem aumentar o risco de CS (YANG; CLUM, 2000; SINCLAIR *et al.,* 2007). Estudos recentes apontam que indivíduos expostos a TI e com história de CS formam um grupo com características em comum (TURECKI *et al.,* 2012). Apresentam aumento da sensibilidade para sinais emocionais específicos (CHA *et al.,* 2010) e dificuldades para tomada de decisão (JOLLANT *et al.*, 2005) – associados à disfunção do OFC e ínsula (JOLLANT *et al.,* 2008); redução nas habilidades de resolução de problemas e impulsividade (SPECKENS; HAWTON, 2005), atenção comprometida e fluência verbal reduzida (KEILP *et al.,* 2001) – associados ao PFC e cíngulo anterior (OQUENDO *et al.,* 2003).

Estudos de neuroimagem estrutural em suicidas revelaram alterações em diversas regiões cerebrais contíguas com as relatadas em indivíduos com TI, incluindo PFC (RUSCH *et al.*, 2008), OFC (MONKUL *et al.,* 2007; AGUILAR *et al.,* 2008), cíngulo anterior (WAGNER *et al.*, 2011), amígdala (MONKUL *et al.,* 2007) e tálamo (AGUILAR *et al.,* 2008). Os *déficits* cognitivos e a resposta desadaptativa ao estresse provavelmente mediam a relação entre TI e CS (YANG; CLUM, 2000; SINCLAIR *et al.,* 2007). Dando consistência a esse raciocínio, indivíduos sadios com alta produção de cortisol frente a teste de estresse social mostraram maiores alterações em tomada de decisão do que aqueles com baixa produção de cortisol (VAN DEN BOS; HARTEVELD; STOOP, 2009). O comprometimento da capacidade de resolução de problemas foi demonstrado em indivíduos com CS seguidos por evento estressante (WILLIAMS *et al.,* 2005) e em parentes de primeiro grau de sujeitos que morreram por suicídio (GROVER *et al.,* 2009).

5.1 Limitações

O presente trabalho possui algumas limitações que devem ser devidamente explicadas. Trata-se de um estudo transversal, portanto não podemos inferir causalidade, nem evolução temporal. Além disso, o CTQ é um questionário retrospectivo, o qual tem risco de viés de memória.

Os pacientes tinham comorbidades e estavam em tratamento, sabe-se que certas medicações podem alterar os resultados de estudos de VBM em TAB (MCINTOSH *et al.,* 2004). Todavia, não houve diferenças estatísticas nessas variáveis entre os grupos, os quais tinham o mesmo perfil de medicamentos em uso.

Tanto a exposição ao TI quanto o VSC podem ser influenciados pelo *status* socioeconômico dos pais. Nós não coletamos dados sobre a situação econômica dos pais, por outro lado, mostramos dados relevantes sobre a escolaridade parental e o CTQ avalia a percepção do paciente sobre as condições financeiras familiares na infância (TOMODA *et al.,* 2009a; 2009b; TOMODA *et al.,* 2011).

Nossos principais resultados foram obtidos em regiões de interesse com hipóteses a priori por meio da ferramenta *small volume correction* - SVC, e não da análise de cérebro inteiro. Sabemos que essa última técnica é superior, contudo as evidências mostram que abordagens por regiões de interesse também têm grande validade e confiabilidade (LIM; RADUA; RUBIA, 2014).

A fisiopatologia do TAB é complexa e pouco conhecida e pode ter influenciado os achados do estudo (SCHULTZE, 2010).

Não está claro se as alterações morfológicas em pacientes com TAB são estáticas ou progressivas, se os achados são parte da fisiopatologia (neurodesenvolvimento) ou consequência de um epifenômeno da doença (neurodegeneração) (YATHAM *et al.,* 2007). Futuros estudos com desenhos longitudinais e amostras maiores são necessários.

6 CONCLUSÕES

O presente trabalho sugere que TI e CS estão relacionados a anormalidades morfológicas em redes neurais que compõem o sistema fronto-límbico em pacientes bipolares do tipo I. Ressaltamos a necessidade pela busca de neuromarcadores, ou assinaturas cerebrais de processos etiopatogênicos pregressos que poderiam estar associadas a um pior desfecho clínico do TAB e à suicidabilidade (STRAKOWSKI *et al.,* 2012). Como um terço dessa população morre na primeira tentativa de suicídio, eleva-se a importância da detecção dos pacientes susceptíveis antes que qualquer tentativa seja feita, permitindo aos profissionais de saúde planejar melhor a prevenção e a terapêutica (VAN HEERINGEN; MANN 2014). O maior desafio é entender como o TI pode interagir com a expressão de genes e afetar a morfologia e o funcionamento cerebral por longo período de tempo, e em tal magnitude

detectável nos exames de neuroimagem (DANNLOWSKI *et al.,* 2012; LUTZ; TURECKI, 2014).

7 PERSPECTIVAS FUTURAS

O TI está entre os mais promissores fatores ambientais relacionados à gravidade do CS no TAB e em outras doenças psiquiátricas. Sendo assim, merece futuras investigações para aprimorar nosso entendimento sobre a complexa interação entre susceptibilidade genética e fatores ambientais.

Para isso, alguns pontos deveriam ser exaustivamente debatidos: a influência de cada tipo de trauma e a idade crítica que o organismo é mais susceptível; se as especificidades da associação entre TI e CS no TAB são comuns a outros diagnósticos psiquiátricos; o papel do gênero como fator moderador da associação entre as variáveis; aprofundar o entendimento sobre os sistemas biológicos envolvidos na neurogênese e neuroplasticidade; e por fim, se as alterações neurocognitivas relacionadas ao CS são similares nos indivíduos bipolares com e sem TI.

Como os preditores clínicos da relação entre TI e CS não têm grande eficácia, a neuroimagem fornece novas direções para detecção de pacientes em alto risco para suicídio. Novos estudos deveriam subclassificar o CS em termos de intenção e letalidade para desvendar redes neurais específicas correspondentes. Finalmente, esses estudos deveriam integrar alterações em determinados circuitos cerebrais e seus correlatos genéticos.

Concluindo, novas abordagens terapêuticas deveriam visar à prevenção, à identificação e ao manejo do TI. Técnicas de psicoterapias e de dessensibilização têm sido extensivamente estudadas para atenuar o impacto desse estressor. Em adultos já acometidos, novos tratamentos têm sido pesquisados, tais como: estimulação magnética transcraniana e medicamentos que atuam no eixo HPA, em neurotrofinas, análogos da ketamina e inibidores de acetilação de histonas.

REFERÊNCIAS

AAS, M. *et al.* The role of childhood trauma in bipolar disorders. **Int. J Bipolar Disorder**, v. 4, p. 1-10, 2016.

AGNEW-BLAIS, J.; DANESE, A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. **Lancet Psychiatry,** v. 3, p. 342-349, 2016.

AGUILAR, E. J. *et al.* Left orbitofrontal and superior temporal gyrus structural changes associated to suicidal behavior in patients with schizophrenia. **Prog. Neuropsychopharmacol. Biol. Psychiatry,** v. 32, p. 1673–1676, 2008.

ALLOY, L.B. *et al. Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: mediation* by cognitive vulnerability to depression. **Clinical Child and Family Psychology Review**, v. 9, p. 23–64, 2006.

ALLOY, L. B., *et al.* The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. **Clinical Psychology Review**, v. 25, p. 1043–1075, 2005.

ALT, S. R., *et al.* Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. **Psychoneuroendocrinology,** v. 35, p. 544–556, 2010.

ANDERSEN, S. L, *et al.*. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. **J Neuropsychiatry Clin Neurosci**., v. 20, n. 3, p. 292–301, 2008.

BAUMEISTER D, *et al.* Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. **Mol Psychiatry,** v. 21, p. 642–649, 2015.

BENEDETTI, F., *et al.* Opposite effects of suicidality and lithium on grey matter volumes in bipolar depression. **J. Affect Disord.,** v. 135, 139–147, 2011.

BERNSTEIN, D. P, *et al.*. Initial reliability and validity of a new retrospective measure of child abuse and neglect. **Am J Psychiatry,** v. 151, p. 1132–6, 1994.

BOLDRINI, M. *et al.* Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides. **J Psychiatr Res**, v. 42, p. 433–42, 2008

BREZO, J. *et al.* Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. **Acta Psychiatr. Scand.,** v. 113, p. 180–206, 2006.

BREZO, J. *et al.*. Natural history of suicidal behaviors in a population-based sample of young adults. **Psychol. Med.**, v. 37, p. 1563–1574, 2007.

BREZO ,J. *et al.* Predicting suicide attempts in young adults with histories of childhood abuse. **British Journal of Psychiatry**, v. 193, p. 134–139, 2008a.

BREZO, J. *et al.*. Childhood trajectories of anxiousness and disruptiveness as predictors of suicide attempts. **Arch. Pediatr. Adolesc. Med.,** v. 162, p. 1015–1021, 2008b.

BRIETZKE, E. *et al.* Impact of childhood stress on psychopathology. **Revista Brasileira de Psiquiatria**, v. 34, p. 480-488, 2012.

BÜCKER, J. *et al.* 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). **J Psychiatr Res**, v. 48, n. 1, p. 65-72, jan. 2014.

CASPI, A.; MOFFITT, T. E. Gene-environment interactions in psychiatry: joining forces with neuroscience. **Nat Rev Neuroscience,** v. 7, p. 583–590, 2006.

CASPI, A. *et al.* Role of genotype in the cycle of violence in maltreated children. **Science,** v. 297, p. 851–854, 2002.

CHA, C., *et al.* Attentional bias toward suicide-related stimuli predicts suicidal behavior. **J. Abnorm. Psychol.**, v. 119, p. 616–622, 2010.

CHANEY, A. *et al.* Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. **Journal of Psychiatry Neuroscience**, v. 39, p. 50–59, 2014.

COELHO R, *et al.* R. Childhood maltreatment and inflammatory markers: a systematic review. **Acta Psychiatr Scand.**, v. 129, p. 180–92, 2014.

COHEN, R. A. *et al.* Early life stress and adult emotional experience: an international perspective. **International Journal of Psychiatry Medicine,** v. 36, p. 35–52, 2006.

DARUY-FILHO, L. *et al.* Childhood maltreatment and clinical outcomes of bipolar disorder. **Acta Psychiatrica Scandinavica**, v. 124, p. 427–434, 2011.

DAVIDSON, R. J. Seven Sins in the study of emotion: correctives from affective neuroscience. **Brain and Cognition,** v. 52, p. 129-132, 2003.

DEVRIES, K. M., Childhood sexual abuse and suicidal behavior: a meta-analysis. **Pediatrics,** v. 133, p. 1331–44, 2014.

ENNS, M. W. *et al.* Childhood adversities and risk for suicidal ideation and attempts: a longitudinal population-based study. **Psychol Med.,** v. 36, n. 12, p. 1769-78, dez. 2006.

ERNST, C. *et al.* Alternative splicing, methylation state, and expression profile of tropomyosin-related kinase B in the frontal cortex of suicide completers. **Arch. Gen. Psychiatry,** v. 66, p. 22–32, 2009a.

ERNST, C. *et al.* Histone methylation and decreased expression of TrkB.T1 in orbital frontal cortex of suicide completers. **Mol. Psychiatry**, v. 14, p. 830–832, 2009b.
ETAIN, B. *et al.* Beyond genetics: Childhood affective trauma in bipolar disorder. **Bipolar Disorders,** v. 10, p. 867–876, 2008.

FEARS, S. C. *et al.* Brain structure-function associations in multi-generational families genetically enriched for bipolar disorder. **Brain,** v. 138, p. 2087–2102, 2015.

FELITTI V. *et al*. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. **American Journal Preventive Medicine,** v. 14, p. 245-258 1998.

FERGUSSON, D.M.; WOODWARD, L. J.; HORWOOD, L. J. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. **Psychol. Med.,** v. 30, p. 23–39, 2000.

FISHER, H. L.; HOSANG, G. M. Childhood maltreatment and bipolar disorder: A critical review of the evidence. **Mind & Brain - The Journal of Psychiatry,** v. 1, p. 750–785, 2010.

FRANK. O. *et al.* Human endogenous retrovirus expression profiles in samples from brains of patients with schizo- phrenia and bipolar disorders. **J Virol,** v. 79, p. 10890–10901, 2005.

GARNO, J. L. *et al.* Bipolar disorder with comorbid cluster B personality disorder features: impact on suicidality. **J Clin Psychiatry,** v. 66, p. 339–345, 2005a.

GARNO, J. L. *et al.* Impact of childhood abuse on the clinical course of bipolar disorder. **Br J. Psychiatry,** v.1, n. 86, p. 121–125, 2005b.

GIAKOUMATOS, C. I. *et al*. Are structural brain abnormalities associated with suicidal behavior in patients with psychotic disorders? **J. Psychiatr. Res.,** v. 47, p. 1389–1395, 2013.

GILMORE, J. H, *et al.* MC: Genetic and environmental contributions to neonatal brain structure: a twin study. **Hum Brain Mapp.,** v.31, p. 1174–1182, 2010.

GOODWIN, F. K.; JAMISON, K. R. **Doença maníaco-depressiva:** transtorno bipolar e depressão recorrente. 2. ed. Porto Alegre: ArtMed, 2010.

GRAAF-PETERS, V. B.; HADDERS-ALGRA, M. Ontogeny of the human central nervous system: what is happening when? **Early Hum Dev.,** v.82, p. 257–266, 2006.

GRASSI-OLIVEIRA, R.; STEIN, L. M.; PEZZI, J. C. Translation and content validation of the Childhood Trauma Questionnaire into Portuguese language. **Revista de Saúde Pública**, v. 40, p. 249–255, 2006.

GROVER, K. *et al.* Problem solving moderates the effects of life event stress and chronic stress on suicidal behaviors in adolescence. **J. Clin. Psychol.,** v. 65, p. 1281–1290, 2009.

HAMMERSLEY, P. *et al.* Childhood trauma and hallucinations in bipolar affective disorder: preliminary investigation. **Br J Psychiatry,** v. 182, p. 543–547, 2003.
HART, H.; RUBIA, K. Neuroimaging of child abuse: a critical review. **Frontiers in Human Neuroscience,** v. 6, p. 1-24, 2012.

HASHIMOTO, K. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. **Psychiatry and Clinical Neuroscience**, v. 64, p. 341–357, 2010.

HOZER, F.; HOUENOU, J. Can neuroimaging disentangle bipolar disorder. Journal **of Affective Disorders**, v. 195 , p. 199–214, 2016.

HYUN, M.; FRIEDMAN, S. D.; DUNNER, D. L. Relationship of childhood physical and sexual abuse to adult bipolar disorder. **Bipolar Disord**, v. 2, p. 131–135, 2000.

JAVADAPOUR, A. *et al.* Increased anterior cingulate cortex volume in bipolar I disorder. **Aust N Z J Psychiatry,** v. 41, p. 910–916, 2007.

JOLLANT, F. *et al.* Impaired decision making in suicide attempters. **Am. J. Psychiatry**, v. 162, p. 304–310, 2005.

JOLLANT, F. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. **Am. J. Psychiatry**, v. 165, p. 740–748, 2008

JOLLANT, F. *et al.* The suicidal mind and brain: a review of neuropsychological and neuroimaging studies. **World J Biol Psychiatry,** v. 12, n. 5, p. 319-39, ago. 2011.

KAPCZINSKI, F. *et al.* Allostatic load in bipolar disorder: Implications for pathophysiology and treatment. **Neuroscience and Biobehavioral Reviews,** v. 32, p. 675–692, 2008.

KEILP, J. G. *et al.* Neuropsychological dysfunction in depressed suicide attempters. **Am. J. Psychiatry,** v. 158, p. 735–741, 2001.

KINNEY, D. K. *et al.* Pre- and perinatal complications and risk for bipolar disorder: a retrospective study. **J Affect Disord**, v. 50, p. 117–124, 1998.

KITAYAMA N.; QUINN, S.; BREMNER, J.D. Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. **Journal of Affective Disorder,** v. 90, p. 171–174, 2006.

KRAEPELIN E. **Manic depressive insanity and paranoia**. Edinburgh: E. and S. Livingstone, 1921.

LEBOYER M. *et al.* Childhood affective trauma in bipolar affective disorder. **Bipolar Disord**, v. 9 (Suppl. 1), p. 1-9, 2007.

LEVERICH, G. S. *et al.* Early physical and sexual abuse associated with an adverse course of bipolar illness. **Biol Psychiatry,** v. 51, p. 288–297, 2002.

LEVERICH, G. S, POST, R. M. Course of bipolar illness after history of childhood trauma. **Lancet,** v. 367, p. 1040– 1042, 2006.

LIJFFIJT, M. *et al.* Illness- course modulates suicidality-related prefrontal grey matter reduction in women with bipolar disorder. **Acta Psychiatr. Scand.,** v. 130, p. 374–387, 2014.

LIM, L.; RADUA, J.; RUBIA, K. Gray Matter Abnormalities in Childhood Maltreatment:A Voxel-Wise Meta-Analysis. **American Journal Psychiatry,** v. 171, p. 854-863, 2014.

LIMA, I.V.M.; SOUGEY, E.B.; VALLADA FILHO, H.P. Genética dos transtornos afetivos. **Rev. Psiq. Clín**, v. 31, p. 34-39, 2004.

LISY, M. E. *et al.* Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. **Bipolar Disord.,** v. 13, p. 396–405, 2011.

LUTZ, P.E.; TURECKI, G. DNA methylation and childhood maltreatment: from animal models to human studies. **Neuroscience,** v. 264, p. 142-56, 2014.

MAHON, K. *et al.* Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study. **Bipolar Disord**., v. 14, p. 80–89, 2012.

MALHI, G. S. *et al.* Modeling bipolar disorder suicidality. **Bipolar Disord.,** v. 15, p. 559-574, 2013.

MANN, J. J. *et al*. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. **Arch. Gen. Psychiatry.,** v. 60, p. 14–22, 2003.

MATSUO, K. *et al.* Anterior cingulate volumes associated with trait impulsivity in individuals with bipolar disorder. **Bipolar Disord.,** v. 11, p. 628–636, 2009.

MATSUO, K. *et al.* Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. **Neurosci. Lett.,** v. 469, p. 75–80, 2010.

MCGOWAN, P.O. *et al*. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. **Nature Neuroscience,** v. 12, 342–348, 2009.

MCINTOSH, A. M. *et al.* Voxel based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. **Biological Psychiatry,** v. 56, p. 544–552, 2004.

MEHTA, M. A. *et al.* Amygdala, hippocampal, and corpus callosum size following severe early institutional deprivation: the English and Romanian adoptees study pilot. **Journal of Child Psychology and Psychiatry,** v. 50, p. 943–951, 2009.

MERALI, Z. *et al.* Corticotropin-releasing hormone, arginine vasopressin, gastrin-releasing peptide, and neuromedin B alterations in stress-relevant brain regions of suicides and control subjects. **Biol. Psychiatry,** v. 59, p. 594–602, 2006.

MONKUL, E. S. *et al.* Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. **Mol. Psychiatry**, v. 12, p. 360–366, 2007.

MORANDOTTI, N. *et al*. Childhood abuse is associated with structural impairment in the ventrolateral prefrontal cortex and aggressiveness in patients with borderline personality disorder. **Psychiatry Research**, v. 213, p. 18–23, 2013.

MUEHLENKAMP, J. J. *et al*. Abuse subtypes and nonsuicidal self-injury: preliminary evidence of complex emotion regulation patterns. **J Nerv Ment D**is., v. 198, p. 58–263, 2010.

MUNKHOLM, K. *et al.* Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. **J Psychiatr Res.,** v. 47, p. 1119–33, 2013.

NEVES, M.C. *et al.* Neural correlates of hallucinations in bipolar disorder. **Revista Brasileira de Psiquiatria,** v. 28, p. 1-5, 2016.

NORDENTOFT, M.; MORTENSEN, P. B.; PEDERSEN, C. B. Absolute risk of suicide after first hospital contact in mental disorder. **Arch Gen Psychiatry,** v. 68, p. 1058–1064, 2011.

OQUENDO, M.A. *et al.* Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. **Arch. Gen. Psychiatry**, v. 60, p. 14–22, 2003.

PALANIYAPPAN L.; LIDDLE P. F. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. **Journal of Psychiatry and Neuroscience**, v.37, n.1, p. 17-27, 2012.

PARSEY, R. V. *et al.* Altered serotonin 1A binding in major depression: a [carbonyl-C-11] WAY100635 positron emission tomography study. **Biol Psychiatry,** v. 59, p. 106–13, 2006.

PHILLIPS, M. L.; LADOUCEUR, C. D.; DREVETS, W.C. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. **Mol. Psychiatry**, v. 13, p. 829, 833–857, 2008.

REILLY-HARRINGTON, N. A. *et al.* Cognitive styles and life events interact to predict bipolar and unipolar symptomatology**. J Abnorm Psychol.**, v. 108, p. 567–578, 1999.

RUSCH, N. *et al..* Inferior frontal white matter volume and suicidality in schizophrenia. **Psychiatry Res.,** v. 164, p. 206–214, 2008.

SADOCK B.; SADOCK V. **Compêndio de Psiquiatria**: ciências do comportamento e psiquiatria clínica. 9. ed. Porto Alegre: Artmed, 2007.

SALVATORE, M. *et al.* Borna disease virus in brains of North American and European people with schizophrenia and bipolar disorder. Bornavirus Study Group. **Lancet,** v. 349, p. 1813–1814, 1997.

SCHULZE, T. G. Genetic research into bipolar disorder: the need for a research framework that integrates sophisticated molecular biology and clinically informed phenotype characterization. **Psychiatr. Clin. North Am.** v. 33, p. 67 – 82, 2010.

SHEFFIELD, J. M., *et al.* Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. **Schizophrenia Research**, v. 143, p. 185–191, 2013.

SINCLAIR, J. M. *et al.* The role of autobiographical memory specificity in deliberate self-harm: correlates and consequences. **J. Affect. Disord**, v. 102, p. 11–18, 2007.

SPECKENS, A. E.; HAWTON, K. Social problem solving in adolescents with suicidal behavior: a systematic review. **Suicide Life Threat. Behav.,** v. 35, p. 365–387, 2005

SOLOFF, P.H. *et al.* Structural brain abnormalities and suicidal behavior in borderline personality disorder. **J. Psychiatr. Res.,** v. 46, p. 516–525, 2012.

STRAKOWSKI, S. M., *et al.* The functional neuroanatomy of bipolar disorder: a consensus model. **Bipolar Disord**. v. 14, p. 313–325, 2012.

TEICHER, M. H. *et al.* Childhood neglect is associated with reduced corpus callosum area. **Biological Psychiatry,** v. 56, p. 80–85, 2004.

TEICHER, M. H.; TOMODA, A.; ANDERSEN, S. L. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? **Ann N Y Acad Sci,** v. 1071, p. 313–323, 2006.

TEICHER, M. H.; SAMSON, J. A. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. **American Journal of Psychiatry,** v. 170, p. 1114–1133, 2013.

TOMODA, A. *et al.* Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. **Neuroimage**, v. 47 (Suppl. 2), p. T66–T71, 2009a.

TOMODA, A. *et al.* Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. **Biological Psychiatry**, v. 66, p. 642–648, 2009b.

TOMODA, A. *et al*. Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. **Neuroimage,** v. 54, p. 280–286, 2011.

TOMODA, A. *et al.* Reduced Visual Cortex Gray Matter Volume and Thickness in Young Adults Who Witnessed Domestic Violence during Childhood. **PloS one,** v. 7, n. 12, p. e52528, 2012.

TORRES, I. J.; BOUDREAU, V. G.; YATHAM, L. N. Neuropsychological functioning in euthymic bipolar disorder: a meta- analysis. **Acta Psychiatr Scand.,** v. 116, p. 17–26, 2007.

TOTTENHAM, N. *et al.* Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. **Developmental Scienc**e, v. 13, p. 46–61, 2010.

TOWNSEND, J.; ALTSHULER, L. L. Emotion processing and regulation in bipolar disorder: a review. **Bipolar Disord.,** v. 14, p. 326–33, 2012.

TSUCHIYA, K.J.; BYRNE, M.; MORTENSEN, P.B. Risk factors in relation to an emergence of bipolar disorder: a systematic review. **Bipolar Disord,** v. 5, p. 231–242, 2003.

TURECKI, G. *et al.* The neurodeve- lopmental origins of suicidal behavior. **Trends in Neurosciences,** v. 35, p. 14-23, 2012.

TURECKI, G. The molecular bases of the suicidal brain. **Nat. Rev. Neurosci**., v. 15, p. 802–816, 2014.

TURECKI, G.; BRENT, D. A., Suicide and suicidal behaviour. **Lancet,** v. 387, p. 1227–1239, 2016.

TURSICH M. *et al.* Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. **Transl Psychiatry**., v. 4, p. e413, 2014.

VAN DEN BOS, R.; HARTEVELD M.; STOOP H. Stress and decision-making in humans: performance is related to cortisol reactivity, albeit differently in men and women. **Psychoneuroendocrinology,** v. 34, p. 1449–1458, 2009.

VAN HARMELEN, A. L. *et al*. Reduced medial pré-frontal córtex volume in adults reporting childhood emotional maltreatment. **Biological Psychiatry**, v., 68, p. 832– 838, 2010.

VAN HEERINGEN, *et al.* Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. **Front. Hum. Neurosci, v.** 8, n. 824, 2014.

VAN HEERINGEN, K.; MANN, J. J. The neurobiology of suicide. **Lancet Psychiatry**, v. 1, p. 63 – 72, 2014.

VAN LAAR, M. *et al.* Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? **Addiction,** v.102, p. 1251–1260, 2007.

VYTHILINGAM M. *et al.* Childhood trauma associated with smaller hippocampal volume in women with major depression. **American Journal of Psychiatry**, v. 159, p. 2072–2080, 2002.

WAGNER, G. *et al.* Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? **Neuroimage,** v. 54, p. 1607–1614, 2011.

WATTS-ENGLISH., T., *et al.* The psychobiology of maltreatment in childhood. **Journal of Social Issues**, v. 62, p. 717–736, 2006.

WELLCOME TRUST CONSORTIUM. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. **Nature,** v. 447, p. 661–678, 2007.

WENIGER G. *et al.* Amygdala and hippocampal volumes and cognition in adult survivors of childhood abuse with dissociative disorders. **Acta Psychiatr. Scand**., v. 118, p. 281–290, 2008.

WILLIAMS, J. M. *et al.* Problem solving deteriorates following mood challenge in formerly depressed patients with a history of suicidal ideation. **J. Abnorm. Psychol.,** v. 114, p. 421–431, 2005.

YANG, B.; CLUM, G. A. Childhood stress leads to later suicidality via its effect on cognitive functioning. Suicide Life **Threat. Behav.,** v. 30, p. 183–198, 2000.

YATES, T. M.; CARLSON, E. A.; EGELAND, B. A prospective study of child maltreatment and self-injurious behavior in a com- munity sample. **Dev Psychopathol.,** v. 20, p. 651–671, 2008.

YATHAM L.N. *et al.* The International Society for Bipolar Disorders–Battery for Assessment of Neurocognition (ISBD-BANC). **Bipolar Disorders**, v. 12, p. 351–363, 2010.

ANEXOS

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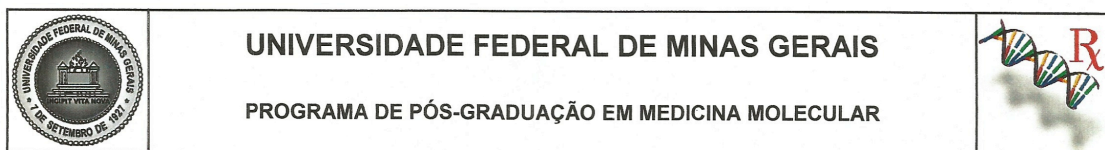
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CORRELATOS NEURAIS DO TRAUMA INFANTIL E COMPORTAMENTO SUICIDA EM PACIENTES ADULTOS COM TRANSTORNO BIPOLAR: UM ESTUDO DE MORFOMETRIA BASEADA NO VOXEL
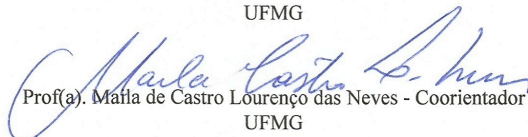
DANTE GALILEU GUEDES DUARTE

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em MEDICINA MOLECULAR, como requisito para obtenção do grau de Doutor em MEDICINA MOLECULAR, área de concentração MEDICINA MOLECULAR.

Aprovada em 29 de novembro de 2016, pela banca constituída pelos membros:

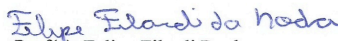Prof(a). Humberto Correa da Silva Filho - Orientador
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UFMG

Prof(a). Maicon Rodrigues de Albuquerque
UFMG

Prof(a). Alexandre Aguiar Ferreira
FCMMG

Prof(a). Felipe Filardi Rocha
HSOCOR

Belo Horizonte, 29 de novembro de 2016.

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA MOLECULAR

ATA DA DEFESA DE TESE DO ALUNO
DANTE GALILEU GUEDES DUARTE

Realizou-se, no dia 29 de novembro de 2016, às 09:00 horas, sala 526, 5º andar da Faculdade de Medicina, da Universidade Federal de Minas Gerais, a defesa de tese, intitulada *CORRELATOS NEURAIS DO TRAUMA INFANTIL E COMPORTAMENTO SUICIDA EM PACIENTES ADULTOS COM TRANSTORNO BIPOLAR: UM ESTUDO DE MORFOMETRIA BASEADA NO VOXEL*, apresentada por DANTE GALILEU GUEDES DUARTE, número de registro **2014709968**, graduado no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em MEDICINA MOLECULAR, à seguinte Comissão Examinadora: Prof(a). Humberto Correa da Silva Filho - Orientador (UFMG), Prof(a). Maila de Castro Lourenço das Neves – Coorientador (UFMG), Prof(a). Maicon Rodrigues de Albuquerque (UFMG), Prof(a). Alexandre Aguiar Ferreira (FCMMG), Prof(a). Felipe Filardi Rocha (HSOCOR).

A Comissão considerou a tese:

(X) Aprovada

( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.

Belo Horizonte, 29 de novembro de 2016.

Prof(a). Humberto Correa da Silva Filho (Doutor)

Prof(a). Maila de Castro Lourenco das Neves (Doutora)

Prof(a). Maicon Rodrigues de Albuquerque (Doutor)

Prof(a). Alexandre Aguiar Ferreira (Doutor)

Prof(a). Felipe Filardi Rocha (Doutor)

30/11/16
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Declaração

Declaramos, para os devidos fins, que **DANTE GALILEU GUEDES DUARTE**, número de registro **2014709968**, cumpriu os requisitos regulamentares para obtenção do grau de doutor no Programa de Pós-Graduação em MEDICINA MOLECULAR da Universidade Federal de Minas Gerais, Brasil, tendo defendido sua tese intitulada *CORRELATOS NEURAIS DO TRAUMA INFANTIL E COMPORTAMENTO SUICIDA EM PACIENTES ADULTOS COM TRANSTORNO BIPOLAR: UM ESTUDO DE MORFOMETRIA BASEADA NO VOXEL*, no dia 29/11/2016.

Belo Horizonte, 30 de novembro de 2016.

Prof(a). Luiz Armando Cunha de Marco
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Kind regards,

Monte S. Buchsbaum, M.D.
Editor for North America Office
Psychiatry Research: Neuroimaging

Comments from the editor and reviewers:

PARECER DE APROVAÇÃO DA PESQUISA NO COMITÊ DE ÉTICA DA UFMG

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

Parecer nº. ETIC 0431.0.203.000-10

Interessado(a): Prof. Fernando Silva Neves
Departamento de Saúde Mental
Faculdade de Medicina - UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 12 de novembro de 2010, após atendidas as solicitações de diligência, o projeto de pesquisa intitulado **"Investigação da capacidade de reconhecimento de emoções faciais em pacientes com transtorno afetivo bipolar e controles saudáveis e seus possíveis determinantes genéticos e morfológicos"** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Maria Teresa Marques Amaral
Coordenadora do COEP-UFMG

Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II - 2º andar – Sala 2005 – Cep:31270-901 – BH-MG
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