UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

Dissertação de Mestrado

FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO (BDNF) NO TRANSTORNO BIPOLAR: UMA METANÁLISE

Aluna: Brisa Simões Fernandes

Orientador: Prof. Dr. Flávio Kapczinski

Porto Alegre, novembro de 2009

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO (BDNF) NO TRANSTORNO BIPOLAR: UMA METANÁLISE

Brisa Simões Fernandes

Dissertação apresentada ao Programa de Pós Graduação e Ciências Médicas: Psiquiatria da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Mestre em Psiquiatria.

Orientador: Prof. Dr. Flávio Kapczinski

Porto Alegre, 2009

F363f Fernandes, Brisa Simões

Fator neurotrófico derivado do cérebro (BDNF) no transtorno bipolar: uma metanálise / Brisa Simões Fernandes ; orient. Flávio Kapczinski. – 2009.

113 f.

Dissertação (mestrado) - Universidade Federal do Rio Grande do Sul. Faculdade de Medicina. Programa de Pós-Graduação em Ciências Médicas: Psiquiatria, Porto Alegre, BR-RS, 2009.

1. Transtorno bipolar 2. Fator neurotrófico derivado do cérebro 3. Metanálise I. Kapczinski, Flávio II. Título.

NLM: WM 207

Catalogação Biblioteca FAMED/HCPA

“The known is finite, the unknown infinite; intellectually we stand on an islet in the midst of an illimitable ocean of inexplicability. Our business in every generation is to reclaim a little more land.”

Thomas Henry Huxley, 1887
On the reception of The Origin of the Species

“Ignorance more frequently begets confidence than does knowledge: it is those who know little, and not those who know much, who so positively assert that this or that problem will never be solved by science.”

Charles Darwin, 1871
From the Introduction to The Descent of Man

William James used to preach “the will to believe”. For my part, I should wish to preach “the will to doubt”. What is wanted is not the will to believe, but the wish to find out, which is the exact opposite.

Bertrand Russell,
Source unknown

SUMÁRIO

Agradecimentos..... 6

Resumo..... 7

Abstract..... 8

Lista de Abreviaturas e Siglas..... 9

Introdução..... 11

Objetivos..... 24

Referências Bibliográficas..... 25

Artigo Submetido……. 40

Considerações Finais…….. 97

Anexo 1……..... 102

AGRADECIMENTOS

Friendship makes prosperity more shining
and lessens adversity by dividing and sharing it.

Cícero (106 BC - 43 BC), On Friendship, 44 B.C.

Ao Prof. Flávio Kapczinski, professor orientador desta dissertação, pelo exemplo incomparável de pesquisador e amor pela ciência. Muito obrigada por todo o apoio e paciência dispensados durante esta trajetória.

Às Profs. Clarissa Severino Gama e Keila Mendes Ceresér, pelo privilégio da amizade durante todos esses anos. Pela ajuda e compreensão sempre presentes nos momentos difíceis.

A todo grupo do Laboratório de Psiquiatria Molecular, por toda ajuda prestada sempre que necessário e pela convivência durante todo este período: David de Lucena, Laura Stertz, Gabriel Fries, Gabriela Colpo, Bianca Aguiar, Bianca Pfaffenseller, Júlio Walz, Fabiano Gomes, Mauricio Kunz, Leonardo Paim, Lisiane Sória, Joana Narvaez, Joana Bücker, Pedro Gói, Karine Zortéa, Miréia Zulsbach, a todos vocês um muito obrigado.

Ao CNPq, pela bolsa que viabilizou o desenvolvimento deste trabalho.

E, finalmente, à minha família, pelo carinho e incentivo: Ananda, Silvia e Ishtar.

RESUMO

Objetivos: o Fator Neurotrófico Derivado do Cérebro (BDNF) desempenha um papel central na neurogênese e plasticidade sináptica. O Transtorno Bipolar (TB) é um dos mais graves transtornos psiquiátricos e está associado a maus resultados. Alguns estudos sugerem que o BDNF está diminuído durante os episódios de humor, e normal durante a eutimia, mas esses resultados ainda são controversos. O objetivo deste estudo foi realizar uma metanálise de todos os estudos que mediram os níveis periféricos de BDNF em adultos com TB.

Métodos: foi realizada uma revisão sistemática utilizando banco de dados eletrônicos. Os critérios de inclusão foram estudos com dosagem de BDNF em plasma ou soro *in vivo* em pacientes adultos com TB. O tamanho de efeito (ES) das diferenças de BDNF entre pacientes com TB em diferentes estados de humor e controles foi calculado.

Resultados: treze estudos com 1.113 participantes foram incluídos. O BDNF se encontra diminuído tanto na mania quanto na depressão quando comparados aos controles (ES -0,81, IC 95% -1,11 a -0,52, p<0,0001 e ES -0,97, IC 95% -1,79 a -0,51, p=0,02, respectivamente). Os níveis de BDNF não foram diferentes na eutimia quando comparados com os controles (ES -0,20, IC 95% -0,61 a 0,21, p=0,33). A análise de metarregressão na eutimia mostrou que a idade (p<0,0001) e a duração da doença (p=0,04) influenciaram a variação no ES. Houve também um aumento nos níveis de BDNF após o tratamento da mania aguda (ES -0,63, IC 95% -1,11 a -0,15, p=0,01).

Conclusões: os níveis de BDNF estão consistentemente reduzidos durante os episódios maníacos e depressivos, e normalizam após o tratamento de mania aguda. Na eutimia, o BDNF diminui com a idade e o tempo de doença. Estes dados sugerem que o BDNF periférico possui potencial para se tornar um biomarcador de episódios de humor e de progressão de doença no TB.

ABSTRACT

Objectives: Brain-derived neurotrophic factor (BDNF) plays a central role in synaptic plasticity and neurogenesis. Bipolar disorder (BD) is among the most disabling of all psychiatric disorders and is associated with poor outcomes. Some studies suggest that BDNF is decreased during mood states, and normal during euthymia, but others do not. The aim of this study was to perform a meta-analysis of all studies that measured peripheral BDNF levels in adults with BD.

Methods: We conducted a systematic review using electronic database. Inclusion criteria were studies that measured BDNF in plasma or serum *in vivo* in adult patients with BD. Effect Sizes (ES) of the differences in BDNF between patients with BD in different mood states and controls were calculated.

Results: Thirteen studies with 1113 participants were included. The BDNF was decreased both in mania and depression when compared to controls (ES -0.81, 95% CI -1.11 to -0.52, $p<0.0001$ and ES -0.97, 95% CI -1.79 to -0.51, $p=0.02$, respectively). The BDNF levels were not different in euthymia when compared with controls (ES -0.20, 95% CI -0.61 to 0.21, $p=0.33$). M*eta*-regression analyses in euthymia showed that age ($p<0.0001$) and length of illness ($p=0.04$) influenced the variation in ES. There was also an increase in BDNF levels following the treatment for acute mania (ES -0.63, 95% CI -1.11 to -0.15, $p=0.01$).

Conclusions: BDNF levels are consistently reduced during manic and depressive episodes, and recover after the treatment for acute mania. In euthymia, BDNF decreases with age and length of illness. These data suggest that peripheral BDNF has the potential to be a biomarker of mood states and disease progression for BD.

LISTA DE ABREVIATURAS

APA	Associação Psiquiátrica Americana
AMPc	Monofosfato de 3',5'-Adenosina cíclico
BDNF	Fator Neurotrófíco Derivado do Cérebro
CPF	Córtex Pré-Frontal
CREB	Proteína ligada ao fator de transcrição do AMPc
d.f.	Degrees of Freedon (Graus de Liberdade)
DSM	Manual Diagnóstico e Estatístico de Trantornos Mentais
ECA-NIMH	Estudo da Área de Captação Epidemiológica
ES	Effect Size (tamanho de efeito)
GSK3	Glicogênio Sintase Quinase 3
HDRS	Escala de Avaliação de Depressão de Hamilton
IC	Intervalo de confiança
ISRS	Inibidores Seletivos de Recaptação de Serotonina
LCR	Líquido Cefalorraquidiano
NGF	Fator de Crescimento do Nervo (NGF)
NMDA	N-metil-D-Aspartato
NT-3	Neurotrofina-3
NT-4/5	Neurotrofina-4/5
NT-6	Neurotrofina-6
NT-7	Neurotrofina-7
PET	Tomografia por Emissão de Pósitrons
PKC	Proteína Quinase C
$P75^{NTR}$	Receptor Pan-Neurotrofina

SNC	Sistema Nervoso Central
TB	Transtorno Bipolar
TrkB	Proteína Tirosina Quinase B
UFRGS	Universidade Federal do Rio Grande do Sul
VPT	Valproato
YMRS	Escala de Avaliação de Mania de Young

INTRODUÇÃO

Características Clínicas do Transtorno Bipolar (TB)

O TB é um transtorno mental complexo e multifatorial, com episódios recorrentes associado com elevada morbidade clínica (Belmaker, 2004; Kilbourne *et* al., 2004). O Estudo da Área de Captação Epidemiológica (ECA-NIMH) (Weissman *et* al., 1996), conduzido nos Estados Unidos a partir de 1980, mostrou uma prevalência de 0,8% do TB tipo I. Vários estudos posteriores mostraram uma prevalência ao longo da vida de 0,5% a 7,5%, dependendo da amostra e dos critérios diagnósticos utilizados com a introdução do conceito de espectro bipolar (Akiskal *et* al., 1996; Angst, 2003). No Brasil foi encontrada a prevalência de 0,7% na população de Porto Alegre, RS (Almeida Filho *et* al., 1997).

O TB atinge igualmente homens e mulheres e a média de idade do início dos sintomas é de 20 anos (APA, 2000). A média de tempo entre o aparecimento dos primeiros sintomas e o primeiro tratamento é de aproximadamente dez anos (Leverich e Post, 2006). Segundo dados da Organização Mundial da Saúde, o TB é considerado uma das dez principais causas de incapacitação no mundo (Lopez e Murray, 1998).

A característica essencial do TB tipo I é um curso clínico caracterizado pela ocorrência de um ou mais Episódios Maníacos ou Episódios Mistos, podendo haver ou não história de Episódios Depressivos.

A Associação Psiquiátrica Americana (APA, 2000) define a presença de um episódio maníaco como um período distinto de humor anormal e persistentemente elevado, expansivo ou irritável que perdura por, pelo menos, uma semana, e com três ou mais dos seguintes sintomas (quatro se o humor for apenas irritável):

(1) autoestima inflada ou grandiosidade

(2) diminuição da necessidade de sono (por ex., sente-se descansado após apenas três horas de sono)

(3) taquilalia

(4) fuga de ideias ou experiência subjetiva de que os pensamentos estão correndo

(5) distratibilidade

(6) aumento na atividade dirigida a objetivos ou agitação psicomotora

(7) envolvimento excessivo em atividades prazerosas que têm alto potencial para consequências dolorosas (por ex., compras desenfreadas, indiscrições sexuais)

Além disso, o episódio deve ser suficientemente severo para causar prejuízo significativo no âmbito familiar, social ou ocupacional, ou necessitar de hospitalização e não ser causado por abuso de substâncias ou doença médica geral.

A APA também define critérios para Episódio Depressivo Maior, como segue:

A. No mínimo cinco dos seguintes sintomas estiveram presentes durante o período de duas semanas e representam uma alteração a partir do funcionamento anterior; pelo menos um dos sintomas é (1) humor deprimido ou (2) perda do interesse e prazer:

(1) humor deprimido na maior parte dos dias

(2) acentuada diminuição do interesse ou prazer em todas ou quase todas as atividades na maior parte do dia, quase todos os dias

(3) perda ou ganho significativo de peso sem estar em dieta (por ex. mais de 5% do peso corporal em um mês)

(4) insônia ou hipersonia quase todos os dias

(5) agitação ou retardo motor quase todos os dias

(6) fadiga ou perda de energia quase todos os dias

(7) sentimento de inutilidade ou culpa excessiva ou inadequada

(8) capacidade diminuída de pensar ou se concentrar ou indecisão

(9) pensamentos recorrentes de morte, ideação suicida, tentativa de suicídio

Além disso, os sintomas necessariamente devem causar prejuízo em todas as áreas da vida da pessoa, não podem ser causados por uso de substâncias, ou ser devido a alguma condição médica geral ou luto.

A Classificação Internacional de Doenças da Organização Mundial de Saúde (CID 10) classifica o TB como uma doença caracterizada por dois ou mais episódios nos quais o humor do paciente e seus níveis de atividade estão significativamente perturbados. Estas “perturbações do humor” consistem em elevações do humor e aumento de energia e atividades (mania e hipomania), ou em diminuição do humor e decréscimo em energia e atividades (depressão).

Mesmo com todo avanço alcançado, o TB permanece uma doença recorrente. Alguns pacientes ficam estáveis e outros experimentam episódios frequentes, estados mistos e complicações relacionadas a abuso de substâncias e prejuízo cognitivo acentuado. O prejuízo causado pela doença parece estar mais relacionado à recorrência dos episódios do que à gravidade de um dado episódio (Post *et* al., 2003).

O número médio de episódios maníacos em pacientes com TB sem tratamento ao longo da vida é de oito a nove (Goodwin e Jamison, 2007). Comumente, os pacientes apresentam períodos de exacerbação dos sintomas (episódios maníacos, mistos ou depressivos) intercalados por períodos subsindrômicos e períodos de remissão (eutimia). Antes do surgimento dos psicofármacos, os episódios duravam de quatro a 13 meses, os intervalos assintomáticos ficavam mais curtos e os episódios mais longos com a progressão da doença (Angst e Sellaro, 2000). A persistência de

sintomas subsindrômicos está associado a um maior risco de reagudização da doença (Perlis *et* al., 2006).

O diagnóstico de TB baseia-se na ocorrência de episódios de alteração do humor, onde o TB tipo I é caracterizado por um ou mais episódios maníacos ou mistos, geralmente acompanhados por episódios depressivos maiores, enquanto que no TB tipo II não ocorrem episódios maníacos, somente episódios hipomaníacos (APA, 2000).

Aspectos neurobiológicos do TB

As bases biológicas do TB incluem aspectos relacionados à genética, às vias neuro-hormonais, neurotransmissão, de transdução de sinal, de regulação da expressão gênica, estresse oxidativo, neuroplasticidade e alterações do sistema imunológico.

Há um grande número de evidências demonstrando a importância da genética no TB. O risco de um familiar em primeiro grau de um indíviduo afetado desenvolver a doença é dez vezes maior que o risco da população em geral (Craddock *et* al., 2005).

Estudos com populações gemelares demonstraram que no TB há uma concordância de 70% entre monozigóticos e de 30% em dizigóticos (Kelsoe, 2003).

Estudos neuroanatômicos utilizando imagem por ressonância magnética têm demonstrado alterações do volume de determinadas regiões cerebrais envolvidas na regulação do humor. Esses achados incluem diminuição do volume do córtex pré-frontal (CPF) subgenual e aumento do volume da amígdala e do estriado (Hajek *et* al., 2005; Strakowski *et* al., 2005). Estudos neurofuncionais com ressonância magnética funcional e tomografia por emissão de pósitrons (PET) mostram uma diminuição significativa do metabolismo do CPF durante a depressão e subsequente aumento em

algumas regiões do CPF durante a fase maníaca (Malhi *et* al., 2004a; Strakowski *et* al., 2005).

Há um número crescente de evidências de estudos de neuroimagem e post-mortem em que o TB está associado com prejuízos na neuroplasticidade e na resiliência celular (Zarate *et* al., 2006).

Estudos de imagem funcional indicam que o TB é caracterizado por excesso de atividade nas estruturas subcorticais e límbicas e atividade diminuída no CPF em resposta a estímulos emocionais salientes (Phillips *et* al., 2003).

Apesar dos inúmeros estudos avaliando a biologia do TB, pouco se sabe sobre o grau de associação entre os achados neurobiológicos e as alterações comportamentais observadas.

Os achados neuroquímicos relacionados à mania têm sido demonstrados através da avaliação de diferentes marcadores em plasma, líquor, plaquetas, soro e linfócitos. O estudo destes marcadores bioquímicos na doença visa obter informações sobre mecanismos relacionadas a alterações em funções cerebrais, como a neurotransmissão, neuroplasticidade, transdução de sinal intracelular e expressão gênica.

Com relação às alterações em sistemas de neurotransmissão no TB, estudos têm descrito modificações na regulação de sistemas de aminas biogênicas.

A dopamina é o neurotransmissor classicamente associado aos episódios maníacos. Vários estudos demonstraram a indução de mania pelo uso de agonistas dopaminérgicos. Há muito tempo se sabe do envolvimento dopaminérgico nos sintomas maníacos e depressivos (Bunney, 1975). Além disso, bloqueadores dopaminérgicos D2 são considerados efetivos no manejo da mania aguda (Yatham *et* al., 2005). Também foi demonstrado que o tratamento com divalproato de sódio reduz a

captação de L-DOPA no estriado de pacientes com TB em episódio maníaco, sugerindo uma diminuição da função dopaminérgica pré-sináptica após o uso de divalproato (Yatham *et* al., 2002). Em outros estudos, a presença de polimorfismos em genes moduladores da formação de dopamina, como o dopamina-beta-hidroxilase, também sugere a participação do metabolismo dopaminérgico no TB (Sundram *et* al., 2003; Greenwood *et* al., 2006).

Em relação aos segundos-mensageiros na mania, estudos têm descrito alterações no funcionamento de sistemas de transdução de sinais intracelulares, tais como a proteína-quinase C (PKC), o monofosfato cíclico de adenosina (AMPc) e a proteína G. Estes sistemas controlam a liberação de neurotransmissores através de diferentes mecanismos (Manji e Lenox, 1999).

Níveis elevados de glutamato, o principal neurotransmissor excitatório do SNC, foram encontrados em cérebros humanos pós-morte no CPF de pacientes com TB e Depressão Maior (Hashimoto *et* al., 2007).

O glutamato também tem papel importante na mediação das consequências comportamentais do estresse no hipocampo. De fato, glicocorticoides podem induzir a liberação de glutamato na região CA3 do hipocampo, causando aumento do fluxo de Ca++ e consequente neurotoxicidade. A excitotoxicidade pode finalmente causar atrofia hipocampal. É interessante notar que o bloqueio dos receptores NMDA parece prevenir essa atrofia. Também por isso, o sistema glutamatérgico é alvo de pesquisas sobre antidepressivos e estabilizadores do humor (Manji *et* al., 2003). Já há alguns anos, a lamotrigina e a ketamina, dois agentes antiglutamatérgicos, mostraram propriedades antidepressivas na Depressão Maior e na Depressão Bipolar (Mathew *et* al., 2005; Zarate *et* al., 2003). Fármacos estabilizadores do humor, como o Li e o VPT, exercem

efeitos neuroprotetores contra a excitotoxicidade induzida por glutamato em culturas de neurônios (Manji *et* al., 2000; Chuang, 2004).

Baseado em todos esses achados podemos inferir que a atividade glutamatérgica influencia consideravelmente na fisiopatologia do TB.

Alguns estudos demonstraram que fármacos estabilizadores do humor atuam na sinalização intracelular, sendo que o Li exerce efeitos neuroprot*et*ores em grande parte por inibição da GSK-3 (enzima pró-apoptótica) e aumento da Bcl-2 (proteína antiapoptótica) (Gould e Manji, 2005). Lítio e VPT atenuam a função da PKC, enquanto que psicoestimulantes com efeitos pró-maníacos estimulam a PKC (Bebchuk *et* al., 2000).

Neurotrofinas

Em 1953 foi identificada a primeira neurotrofina, o Fator de Crescimento do Nervo (Nerve Growth Factor – NGF). Esta descoberta ampliou o horizonte da neurobiologia para a identificação e elucidação das funções celulares.

Quase trinta anos após a identificação do NGF, o protótipo das neurotrofinas para neurônios do sistema nervoso autônomo, foi isolado em 1982, em neurônios de porcos, um homólogo do NGF, que foi chamado de Fator Neurotrófico Derivado do Cérebro (Brain-Derived Neurotrophic Factor – BDNF). A partir de então, quatro membros adicionais da família das neurotrofinas foram identificados: Neurotrofina-3 (Neurotrophin-3 – NT-3) em 1990, Neurotrofina-4/5 (Neurotrophin-4/5 – NT-4/5) em 1991, Neurotrofina-6 (Neurotrophin-6 – NT-6) em 1994 e Neurotrofina-7 (Neurotrophin-7 – NT-7) em 1998 (Lessmann *et al.,* 2003).

A descoberta dos receptores das neurotrofinas ocorreu várias décadas após a identificação do NGF, e, sem dúvida, foi um avanço gigantesco na neurobiologia,

especialmente porque forneceu ferramentas para a busca das rotas controladas pelas neurotrofinas [Ras, Rap-1, Cdc-42-Rac-Rho, como também MAPK, PI-3-kinase e phospholipase-C-C-γ (PLC-γ)]. Estas vias de sinalização intracelular moduladas pelas neurotrofinas estão envolvidas não apenas em mecanismos patológicos relacionados a eventos da doença, como também na modulação de plasticidade fisiológica. Como exemplo, cita-se a facilitação da memória em roedores e ativação de MAPK na região do CA1 pelo NGF (Walz *et* al., 2000).

A família dos receptores tirosina-quinases – Trk – é composta por três receptores que podem ser ativados por uma ou mais neurotrofinas: NGF, BDNF, NT-3 e NT-4/5. A presença de TrkA, TrkB ou TrkC confere responsividade, respectivamente, ao NGF, BDNF ou NT-4/5 e NT-3. A presença ou ausência de cadeias curtas de aminoácidos na região de cada receptor tem demonstrado regular a especificidade da resposta ao receptor Trk.

O receptor pan-neurotrofina, $p75^{NTR}$, também regula a resposta aos receptores Trk. Na presença de $p75^{NTR}$, o NT-3 é muito menos efetivo em ativar a TrkA, e o NT-3 e o NT-4/5 são muito menos efetivos em ativar a TrkB. Em outras palavras, a presença de $p75^{NTR}$ aumenta a especificidade do TrkA e do TrkB aos seus ligantes primários, NGF e BDNF, respectivamente (Huang e Reichardt, 2003).

Estudos sobre as relações entre as neurotrofinas, seus receptores e os seus efeitos ainda estão em andamento e muito precisa ser compreendido, justamente devido à grande complexidade destas relações, além das cascatas específicas que ativam. Nos estudos sobre modelos de depressão, os antidepressivos aumentam a sinalização do TrkB, sendo esta dependente da concentração de BDNF (Saarelainen *et* al., 2003). Além disto, uma das vias que sabidamente previnem contra a apoptose é a cascata de sinalização promovida pela ligação do BDNF ao seu receptor TrkB

(BDNF/TrkB) (Barde, 1994). Atualmente, também se sabe que o plexo coróide apresenta um importante papel na produção das neurotrofinas, principalmente quando o cérebro é exposto a algum tipo de insulto.

Diversos estudos têm sugerido que a indução do BDNF/TrkB é um dos mecanismos responsáveis pelos efeitos terapêuticos dos estabilizadores do humor e dos antidepressivos (Coyle e Duman, 2003; Nibuya *et al.*, 1995). Por exemplo, tem sido demonstrado que o uso do Li modula a fosforilação do receptor TrkB e do CREB (Einat *et* al., 2003; Rantamäki *et* al., 2006).

Nestas breves observações, podemos ver que as neurotrofinas promovem um jogo excepcionalmente variado de respostas que requerem, por sua vez, um mecanismo altamente regulado de transdução de sinal (Schramm *et* al., 2005), onde o antagonismo pode desempenhar um papel importante na biologia das neurotrofinas (Brodski *et al.*, 2000).

BDNF

O BDNF foi descoberto em 1982 (Barde *et* al., 1982) como a segunda de uma família de moléculas com atividade neurotrófica cuja primeira a ser identificada foi o NGF (Levi- Montalcini e Hamburger, 1951).

O BDNF é considerado a principal neurotrofina do cérebro, sendo produzido principalmente pela glia e pelos núcleos neuronais. O BDNF tem grande expressão no hipocampo, neocórtex, amígdala e cerebelo (Shimizu *et* al., 2003). O BDNF faz a modulação de diversas funções sinápticas, induzindo estímulo à maturação, nutrição, crescimento e integridade neuronal.

As neurotrofinas, em especial o BDNF, parecem estar implicadas na base fisiopatológica de diversas doenças neurodegenerativas e psiquiátricas. Evidências

clínicas e pré-clínicas indicam que o BDNF desempenha papel fundamental na plasticidade neuronal e memória. O BDNF parece mediar os principais processos dependentes de estímulo externo, isto é, aprendizado, experiências, memórias, ou seja, as suas características o tornam um potencial mediador neurobiológico dos efeitos das experiências de vida. Os antidepressivos e os estabilizadores do humor são capazes de aumentar os níveis séricos de BDNF (Frey *et* al., 2006). A administração crônica de antidepressivos aumenta a expressão de BDNF no hipocampo, bem como no CPF (Duman *et* al. 2000). Também tem sido demonstrado que o tratamento crônico com Li ou VPT aumenta a expressão do BDNF em cérebro de ratos (Fukumoto *et* al., 2001).

Os antidepressivos ISRS inibem a recaptação de serotonina em poucas horas, mas os efeitos antidepressivos só ocorrem, em geral, após duas semanas. Este fato sugere que os antidepressivos possam atuar através de mudanças adaptativas na transdução de sinal intracelular (Nestler *et* al., 2002; Gonul *et* al., 2005). A serotonina tem efeitos protetores neuronais através da ativação do AMPc e CREB, que levam à expressão do BDNF (Zuccato e Cattaneo, 2007).

Existe um crescente corpo de evidências sugerindo que a via de sinalização do BDNF/TrkB parece estar envolvida na fisiopatologia dos transtornos do humor, bem como na ação dos antidepressivos e dos estabilizadores de humor (Hashimoto *et* al., 2004).

O tratamento farmacológico do TB visa prevenir novos episódios de mania e depressão. Os estabilizadores de humor, especialmente o Li e o VPT, são tidos como fármacos de primeira linha nos tratamentos agudo e crônico do TB (Yatham LN *et* al., 2005). Estudos mostram que as características neuroprotetores do Li e VPT podem ser as responsáveis pelos seus efeitos terapêuticos e um dos mecanismos implicados seria

o da liberação de neurotrofinas (Rosa *et* al., 2006; Cunha *et* al., 2006; Laeng *et* al., 2004).

O tratamento crônico com Li ou VPT produz efeitos protetores contra excitoxidade e morte celular induzidas pelo glutamato (Shao *et* al., 2005). Em relação ao BDNF, existem muitas evidências quanto ao seu papel a longo prazo na plasticidade sináptica no hipocampo e no neocórtex. A aplicação de BDNF exógeno realça a eficácia pré-sináptica aumentando a liberação do glutamato em sinapses excitatórias (Lessmann *et al.*, 2003).

Especificamente sobre o Li, sabe-se que ele proporciona uma regulação positiva na sobrevivência celular, além de prevenir a apoptose e o retardo da neurogênese após danos agudos no cérebro (Wada *et* al., 2005).

BDNF como biomarcador no TB

O BDNF no sangue periférico pode ser avaliado no soro e no plasma de uma forma não-invasiva através de uma venopunção. O BDNF atravessa a barreira hematoencefálica e os seus níveis no soro e plasma têm uma alta correlação com BDNF no líquido cefalorraquidiano (LCR) (r = 0,8) (Karege *et* al., 2005; Pan *et* al., 1998). Portanto, é provável que os níveis de BDNF periféricos forneçam informações importantes sobre alterações do BDNF no cérebro. Utilizando esta "janela para o cérebro", vários estudos têm avaliado o papel do BDNF no TB durante os diversos estados de humor, ou seja, mania, depressão e eutimia, para ganhar alguns insights sobre a fisiopatologia desta doença, que ainda é pouco compreendida.

Há várias evidências que sugerem que os níveis de BDNF se alteram no soro e no plasma nos diferentes estados de humor (Cunha *et* al., 2006; Palomino *et* al., 2006; Machado-Vieira *et* al., 2007; Tramontina *et* al., 2006; Tramontina *et* al., 2009;

Yoshimura *et* al., 2006; Oliveira *et* al., 2009; Fernandes *et* al., 2009; Monteleone *et* al., 2008; Kauer-Sant'Anna *et* al., 2008; Mackin *et* al., 2007; Dias *et* al., 2009; Langan *et* al., 2009). No entanto, há discrepâncias entre os estudos, por exemplo, alguns estudos mostram uma diminuição do BDNF nos episódios maníacos, enquanto outros mostram ausência de diferença. Nos episódios depressivos e na eutimia a controvérsia é ainda maior: alguns estudos realizados em pacientes depressivos e eutímicos demonstraram uma diminuição dos níveis de BDNF, enquanto outros não mostraram diferença entre os pacientes com TB e os indivíduos saudáveis. As inconsistências nos resultados entre os diferentes estudos podem ser devido a diferenças nas características da população estudada ou a ausência de poder estatístico, devido a menor tamanho amostral.

Alguns estudos têm avaliado se o BDNF periférico prediz resposta ao tratamento de episódios maníacos e depressivos, mas os resultados aqui novamente são discrepantes. Assim, o papel do BDNF no tratamento de episódios de humor continua sendo um campo pouco explorado.

Uma técnica reconhecida usada para resolver discrepâncias entre estudos transversais é metanálise. Uma metanálise é um método quantitativo de combinar os resultados de estudos independentes usado para aumentar o poder estatístico e tirar conclusões. Este método aumenta o poder para se distinguir entre pequenos tamanhos de efeito e ausência de efeito. Além disso, pode ajudar a d*et*erminar se a variação de efeito entre os estudos é devida apenas à flutuação estatística esperada ou a diferenças reais na amostra utilizada. Uma análise de metarregressão, um método estatístico mais sofisticado, pode avaliar fatores de confusão responsáveis pelas discrepâncias entre os diferentes estudos.

O objetivo deste estudo foi realizar uma metanálise dos níveis de BDNF de todos os estudos transversais de soro ou plasma em adultos com TB de acordo com o estado de humor disponíveis na literatura. Foram examinados o efeito da idade, duração da doença e da gravidade do episódio de humor nos níveis de BDNF através de uma metarregressão. Também realizamos uma metanálise de todos os estudos que avaliaram os níveis de BDNF antes e após o tratamento farmacológico de um episódio de humor, a fim de analisar possíveis alterações nos níveis de BDNF com o tratamento. Isso vai ajudar a esclarecer o papel do BDNF periférico no TB.

OBJETIVOS

Objetivos Primários:

1. Avaliar os níveis periféricos de BDNF nos diferentes estados de humor do TB em relações a controles saudáveis em diferentes estudos publicados, calculando o tamanho de efeito (ES) dos pacientes em relação aos controles.
2. Avaliar possíveis mudanças nos níveis periféricos de BDNF ocorridas com o tratamento farmacológico de episódios maníacos e depressivos.

Objetivos Secundários:

1. Avaliar a influência da gravidade dos episódios maníacos através da Escala de Mania de Young (YMRS) como moderadora do ES na mania.
2. Avaliar a influência da gravidade dos episódios depressivos através da Escala de Depressão de Hamilton (HDRS) como moderadora do ES na depressão.
3. Avaliar a influência da idade e do tempo de doença em anos durante a eutimia como moderadora do ES.

REFERÊNCIAS BIBLIOGRÁFICAS

Akiskal HS. 1996. The prevalent Clinical Spectrum of Bipolar Disorders: Beyond DSM IV. *Journal of Clinical Psychopharmacology,* 16(2 Suppl 1): 4s-14s.

Almeida Filho N, Mari JJ, Coutinho E. et al. 1997. Brazilian Multicentric Study of Psychiatry Morbidity. Methodological Features and Prevalence Estimates. *British Journal of Psychiatry,* 171:524-529.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th. Ed.(DSM-IV). Washington, DC: American Psychiatric Press, 1994.

Angst J, Gamma A, Benazzi F. et al. 2003. Toward a redefinition of subthreshold bipolarity: epidemiology and proposed criteria for Bipolar II, Minor Bipolar Disorders and Hypomania. *Journal of Affective Disorders,* 73:133-146.

Angst J, Sellaro R. 2000. Historical perspectives and natural history of bipolar depression. *Biological Psychiatry*, 48(6):445-57.

Barde YA, Edgar D, Thoenen H. 1982. Purification of a new neurotrophic factor from mammalian brain. *The EMBO Journal*, 1(5):549-53.

Barde YA. 1994. Neurotrophins: a family of proteins supporting the survival of neurons. *Progress in Clinical and Biological Research,* 390:45-56.

Bebchuk JM, Arfken CL, Dolan-Manji S, Murphy J, Hasanat K, Manji HK. 2000. A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. *Archives of General Psychiatry,* 57 (1):95-7.

Belmaker RH. 2004. Medical progress: Bipolar disorder. *The New England journal of medicine*, 351(5), 476-486.

Ben-Ari Y, Cherubini E, Corradetti R, Gaiarsa JL. 1989. Giant synaptic potentials in immature rat CA3 hippocampal neurons. *Journal of Physiology,* 416:303-325.

Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, Segala M, Giacopuzzi M, et al. Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients. Eur Neuropsychopharmacol 2006; 16(8):620-624.

Brodski C, Schürch H, Dechan G. 2000. Neurotrophin-3 promotes the cholinergic differentiation of symphatic neurons*. Proceedings of the National Academy of Sciences of the USA,* 97:9683-9688.

Bunney WE Jr. 1975. The current status of research in the catecholamine theories of affective disorders. *Psychopharmacology Communications.* 1(6):599-609.

Chuang DM. 2004. Neuroprotective and neurotrophic actions of mood stabilizer lithium: can it be used to treat neurodegenerative diseases? *Critical Reviews in Neurobiology,* 16 (1-2): 83-90.

Coyle JT, Duman RS. 2003. Finding the intracellular signaling pathways affected by mood disorder treatments. *Neuron,* 38:157-160.

Craddock N, O'Donovan MC, Owen MJ. 2005. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *Journal of Medical Genetics,* 42:193-204.

Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Goncalves CA, Santin A, Kapczinski F. 2006. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neuroscience letters*, 398(3), 215-219.

Dias VV, Brissos S, Frey BN, Andreazza AC, Cardoso C, Kapczinski F. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord 2009; 11(6):663-671.

Duman RS, Malberg J, Nakagawa S, D'Sa C. 2000. Neuronal plasticity and survival in mood disorders. *Biological Psychiatry*, 48(8):732-9.

Duman RS, Monteggia LM. 2006. A neurotrophic model for stress-related mood disorders. *Biological psychiatry*, 59(12), 1116-1127.

Einat H, Yuan P, Gould TD, Li J, Du J, Manji HK, Chen G. 2003. The role of the extracellular signal-regulated kinase signaling pathway in mood regulation. *Journal of Neuroscience,* 23:7311-7316.

Fernandes BS, Gama CS, Kauer-Sant'Anna M, Lobato MI, Belmonte-de-Abreu P, Kapczinski F. Serum brain-derived neurotrophic factor in bipolar and unipolar depression: A potential adjunctive tool for differential diagnosis. J Psychiatr Res 2009; 43:1200-1204.

Frey BN, Andreazza AC, Cereser KM, Martins MR, Valvassori SS, Reus GZ, Quevedo J, Kapczinski F. 2006. Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. *Life Sciences*, 79(3), 281-286.

Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. 2001. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharmacology (Berl),* 158:100-106.

Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S. 2005. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *European Archives of Psychiatry and Clinical Neuroscience*, 255(6), 381-386.

Goodwin FK, Jamison KR. Maniac-depressive illness. New York. University Press, 2007.

Gould TD, Manji HK. 2005. Glicogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology,* 30(7): 1223-37.

Greenwood TA, Schork NJ, Eskin E, Kelsoe JR. 2006. Identification of additional variants within the human dopamine transporter gene provides further evidence for an association with bipolar disorder in two independent samples. *Molecular Psychiatry,* 11:125-133.

Hajek T, Carrey N, Alda M. 2005. Neuroanatomical abnormalities as risk factors for bipolar disorder. *Bipolar Disorders,* 7:393-403.

Hamilton M. 1960. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23: 56-62.

Hashimoto K, Sawwa A, Iyo M. 2007. Increased levels of glutamate in brain from patients with mood disorders. *Biological Psychiatry,* 62 (11): 1310-6.

Hashimoto K, Shimizu E, Iyo M. 2004. Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Research Reviews*, 45:104-114.

Huang EJ, Reichardt LF. 2003. TRK receptors : Roles in Neuronal Signal Transduction. *Annual Review of Biochemestry,* 72:609-642.

Kapczinski F, Fernandes BS, Kauer-Sant'Anna M, Gama CS, Yatham L, Berk M. The concept of staging in bipolar disorder: the role of BDNF and TNF-alpha as biomarkers. Acta Neuropsychiatrica 2009; 21(6):272-274.

Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 2005; 57(9):1068-1072.

Kauer-Sant'anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Trevor Young L, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol 2008; 4:1-12.

Kelsoe JR. 2003. Arguments for the genetic basis of the bipolar spectrum. *Journal of Affective Disorders,* 73 (1-2): 183-97.

Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Congliaro J, Haas GL. 2004. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disorder,* 6 (5): 368-73

Laeng P, Pitts RL, Lemire AL, Drabik CE, Weiner A, Tang H, Thyagarajan R, Mallon BS, Altar CA. 2004. The mood stabilizer valproic acid stimulates GABA

neurogenesis from rat forebrain stem cells. *Journal of Neurochemestry,* 91:238-251.

Langan C, Doyle K, Kelly J, Emsell L, Skinner R, McDonald C. Serum BDNF levels in euthymic bipolar disorder: preliminary results from the Galwey Bipolar Study. Bipolar Disord 2009; 11(Suppl. 1):56.

Lee HY, Kim YK. Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. Neuropsychobiology 2008; 57(4):194-199.

Lessmann V, Gottmann K, Malcangio M. 2003. Neurotrophin secretion: current facts and future prospects. *Progress in Neurobiology,* 69:341-374.

Leverich GS, Post RM. 2006. Course of bipolar illness after history of childhood trauma. *Lancet,* 367(9516), 1040-1042.

Levi-Montalcini R, Hamburger V. 1951. Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. The journal of experimental zoology. 116(2):321-61.

Lopez AD, Murray CJL. 1998. The global burden of disease, 1990-2020. *Nature Medicine,* 4:1241-1243.

Machado-Vieira R, Dietrich MO, Leke R, Cereser VH, Zanatto V, Kapczinski F, Souza DO, Portela LV, Gentil V. 2007. Decreased Plasma Brain Derived Neurotrophic Factor Levels in Unmedicated Bipolar Patients During Manic Episode. *Biological Psychiatry*, 61(2):141-143.

McEwen BS. 2006. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues in Clinical Neuroscience,* 8 (4): 367-81

Mackin P, Gallagher P, Watson S, Young AH, Ferrier IN. Changes in brain-derived neurotrophic factor following treatment with mifepristone in bipolar disorder and schizophrenia. Aust N Z J Psychiatry 2007; 41(4):321-326.

Manji H, Quiroz JA, Sporn J, Payne JL, Denicoff K, Gray N, Zarate CA, Charney DS. 2003. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult to treat depression. *Biological Psychiatry*, 53:707-742.

Manji HK, Lenox RH. 1999. Protein Kinase C signaling in the brain: molecular transduction of the mood stabilization in the treatment of manic-depressive illness. *Biological Psychiatry,* 46(10): 1328-51.

Manji HK, Moore GJ, Rajkowska G, Chen G. 2000. Neuroplasticity and cellular resilience in mood disorders. *Molecular Psychiatry,* 5 (6): 578-93.

Marano CM, Phatak P, Vemulapalli UR, Sasan A, Nalbandyan MR, Ramanujam S, et al. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. J Clin Psychiatry 2007; 68(4):512-517.

Mathew SJ, Keegan K, Smith L. 2005. Glutamate modulators as novel interventions for mood disorders. *Revista Brasileira de Psiquiatria,* 27 (3): 243-8.

Monteleone P, Serritella C, Martiadis V, Maj M. Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders. Bipolar Disord 2008; 10(1):95-100.

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. 2002. Neurobiology of depression. *Neuron,* 34:13-25.

Nibuya M, Morinobu S, Duman RS. 1995. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *Journal of Neuroscience,* 15:7539-7547.

Oliveira GS, Cereser KM, Fernandes BS, Kauer-Sant'Anna M, Fries GR, Stertz L, et al. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J Psychiatr Res 2009; 43(14):1171-1174.

Palomino A, Vallejo-Illarramendi A, Gonzalez-Pinto A, Aldama A, Gonzalez-Gomez C, Mosquera F, et al. Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients. Schizophr Res 2006; 86(1-3):321-322.

Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 1998; 37(12):1553-1561.

Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, Ketter TA, Miklowitz DJ, Otto MW, Gyulai L, Reilly-Harrington NA, Sachs GS, Thase ME. 2006. Predictors of recurrence in bipolar disorder: primary outcomes from the systematic treatment enhancement program for bipolar disorder (STEP-BD). *American Journal of Psychiatry,* 163:217-224.

Phillips ML. 2003. Understanding the neurobiology of emotion perception: Implications for psychiatry. *The British journal of psychiatry : the journal of mental science,* 182, 190-192.

Phillips ML, Drevets WC, Rauch SL, Lane R. 2003. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological psychiatry,* 54(5), 515-528.

Post RM, Denikoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE Jr, McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA. 2003. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *Journal of Clinical Psychiatry,* 64:680-690.

Rantamäki T, Knuuttila JEA, Hokkanen ME, Castrén E. 2006.The effects of acute and long-term lithium treatments on TrkB neurotrophin receptor activation in the mouse hippocampus and anterior cingulate cortex. *Neuropharmacology,* 50:421-427.

Rosa AR, Frey BN, Andreazza AC, Cereser KM, Cunha AB, Quevedo J, Santin A, Gottfried C, Gonçalves CA, Vieta E, Kapczinski F. 2006. Increased serum glial cell line-derived neurotrophic factor immunocontent during manic and depressive episodes in individuals with bipolar disorder. *Neuroscience letters,* 407(2), 146-150.

Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R, Ernfors P, Castren E. 2003. Activation of the TrkB Neurotrophin Receptor Is Induced by Antidepressant Drugs and Is Required forAntidepressant-Induced Behavioral Effects. *The Journal of Neuroscience,* 23:349 –357.

Schramm A, Schulte JH, Astrahantseff K, Apostolov O, Limpt V van,Sieverts H, Kuhfittig-Kulle S, Pfeiffer P, Versteeg R, Eggert A. 2005. Biological Effects of

TrKA and TrKB receptor signaling in neuroblastoma. *Cancer Letters,* 228:143-153.

Shao L, Young LT, Wang JF. 2005. Chronic treatment with mood stabilizers lithium and valproate prevents excitotoxicity by inhibiting oxidative stress in rat cerebral cortical cells. *Biological Psychiatry,* 58:879-884.

Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M. 2003. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biological Psychiatry*, 54(1):70-5.

Strakowski SM, DelBello MP, Adler CM. 2005. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular Psychiatry,* 10:105-116.

Sundram S, Joyce PR, Kennedy MA. 2003. Schizophrenia and bipolar affective disorder: perspectives for the development of therapeutics. *Current Molecular Medicine,* 3 (5):393-407.

Tramontina J, Frey BN, Andreazza AC, Zandona M, Santin A, Kapczinski F. Val66met polymorphism and serum brain-derived neurotrophic factor levels in bipolar disorder. Mol Psychiatry 2007; 12(3):230-231.

Tramontina JF, Andreazza AC, Kauer-Sant'anna M, Stertz L, Goi J, Chiarani F, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett 2009; 452(2):111-113.

Wada A, Yokoo H, Yanagita T, Kobayashi H. 2005. Lithium: potential therapeutics against acute brain injuries and chronic neurodegenerative diseases. *Journal of Pharmacological Sciences,* 99:307-321.

Walz JC, Andreazza AC, Frey BN, Cacilhas AA, Ceresér KM, Cunha AB, Weyne F, Stertz L, Santin A, Gonçalves CA, Kapczinski F. 2007. Serum neurotrophin-3 is increased during manic and depressive episodes in bipolar disorder. *Neuroscience letters*, 415(1):87-9.

Walz R, Lenz G, Roesler R, Vianna MMR, MArins V, Brentani R, Rodnight R, Izquierdo I. 2000. Time-dependent enhancement of inhibitory avoidance retention and MAPK activation by post-training infusion of nerve growth factor into CA1 region of hippocampus of advert rats. *European Journal of Neuroscience,* 12:2185-2189.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK. 1996. Cross-national epidemiology of major depression and bipolar disorder. *Journal of American Medical Association,* 276:293-299.

Williams RS, Cheng L, Mudge AW, Harwood AJ. 2002. A common mechanism of action for three mood-stabilizing drugs. *Nature,* 417:292-295.

Yatham LN, Liddle PF, Shiah IS, Lam RW, Ngan E, Scarrow G, Imperial M, Stoessl J, Sossi V, Ruth TJ. 2002. PET study of [^{18}F]6-fluoro-L-dopa uptake in neuroleptic- and mood-stabilizer-naive first-episode nonpsychotic mania: effects of treatment with divalproex sodium. *American Journal of Psychiatry,* 159:768-774.

Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009; 11(3):225-255.

Yoshimura R, Nakano Y, Hori H, Ikenouchi A, Ueda N, Nakamura J. Effect of risperidone on plasma catecholamine metabolites and brain-derived neurotrophic factor in patients with bipolar disorders. Hum Psychopharmacol 2006; 21(7):433-438.

Zarate CA Jr, Du J, Quiroz J, Gray NA, Denicoff KD, Singh J, Charney DS, Manji HK. 2003. Regulation of cellular plasticity cascades in the pathophysiology and

treatment of mood disorders: role of the glutamatergic system. *Annals of the New York Academy Sciences,* Nov;1003: 273-91

Zarate CA Jr, Singh J, Manji HK. 2006. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biological Psychiatry,* 59:1006-1120.

Zuccato C, Cattaneo E. 2007. Role of brain-derived neurotrophic factor in Huntington's disease. *Progress in Neurobiology,* 81(5-6):294-330.

ARTIGO SUBMETIDO À BIPOLAR DISORDERS: AN INTERNATIOAL JOURNAL OF PSYCHIATRIC AND NEUROSCIENCES EM NOVEMBRO DE 2009.

Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis

Brisa Simões Fernandes[1,2,3,4], Clarissa Severino Gama[1,2,3,4,5], Keila Maria Ceresér[1,2,3,4], Lakshmi N. Yatham[6], Gabriel Rodrigo Fries[1,2,3], Gabriela Colpo[1,2,3], David de Lucena[1,2,3,4], Mauricio Kunz[1,2,3,4], Fabiano Alves Gomes[1,2,3,4], Marcia Kauer-Sant'Anna[1,2,3,4], Flavio Kapczinski[1,2,3,4]

From:

[1] Bipolar Disorder Program, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

[2] Molecular Psychiatry Unit, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

[3] INCT for Translational Medicine, Brazil.

[4] Programa de Pós-Graduação em Medicina: Psiquiatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

[5] Schizophrenia Program, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

[6] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, Canada.

Mail address:
Flavio Kapczinski
Hospital de Clínicas de Porto Alegre.
Av Ramiro Barcelos 2350.
90035-903. Porto Alegre RS. Brazil.
Phone number: 55 51 33598845.
E-mail: kapcz@terra.com.br

Running title: BDNF in BD: a meta-analysis

Abstract

Objectives: Brain-derived neurotrophic factor (BDNF) plays a central role in synaptic plasticity and neurogenesis. Bipolar disorder (BD) is among the most disabling of all psychiatric disorders and is associated with poor outcomes. Some studies suggest that BDNF levels decrease during mood states and remain normal during euthymia, but other studies have contradicted this paradigm. Therefore, the aim of this study was to perform a meta-analysis of all studies that measured peripheral BDNF levels in adults with BD.

Methods: We conducted a systematic review using electronic databases. Inclusion criteria were studies that measured BDNF in plasma or serum *in vivo* in adult patients with BD. The resulting studies were compiled to measure the effect sizes (ESs) of the differences in BDNF levels between BD patients in different mood states and controls.

Results: Thirteen studies were included with a total of 1113 subjects. The BDNF levels were decreased in both mania and depression when compared to controls (ES -0.81, 95% CI -1.11 to -0.52, $p<0.0001$ and ES -0.97, 95% CI -1.79 to -0.51, $p=0.02$, respectively). The BDNF levels were not different in euthymia when compared to controls (ES -0.20, 95% CI -0.61 to 0.21, $p=0.33$). Meta-regression analyses in euthymia showed that age ($p<0.0001$) and length of illness ($p=0.04$) influenced the variation in ES. There was also an increase in BDNF levels following the treatment for acute mania (ES -0.63, 95% CI -1.11 to -0.15, $p=0.01$).

Conclusions: BDNF levels are consistently reduced during manic and depressive episodes and recover after treatment for acute mania. In euthymia, BDNF decreases with age and length of illness. These data suggest that peripheral BDNF could be used as a biomarker of mood states and disease progression for BD.

Key words: Bipolar disorder, BDNF, brain-derived neurotrophic factor, biomarker, systematic review, meta-analysis, mood state, mania, depression, euthymia.

Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a dimeric protein that plays a central role in synaptic plasticity and neuronal survival (1,2). This neurotrophin is found throughout the brain with particular abundance in the hippocampus and cerebral cortex, brain areas thought to be critical for the control of mood, emotion, and cognition (3).

Bipolar disorder (BD) is among the most disabling of all psychiatric disorders and is associated with high mortality rates due to suicide and other medical illnesses (4-6). The disorder has a much worse long-term outcome than previously thought. Patients frequently demonstrate sub-threshold symptoms with persistent cognitive impairment and functional decline (7,8). A morphological study has shown that protein and mRNA expression of BDNF and its receptor, tyrosine kinase B (TrkB), are significantly decreased in the prefrontal cortex (PFC) and hippocampus of suicide victims compared to control subjects (9). Further, BDNF is also decreased in the PFC and hippocampus in an animal model of mania established using d-amphetamine (10).

Peripheral BDNF in serum and plasma can be assessed non-invasively by venipuncture. BDNF crosses the blood-brain barrier, and its levels in serum and plasma are highly correlated with BDNF levels in cerebrospinal fluid (r=0.8) (11,12). Therefore, it is likely that peripheral BDNF levels provide important information about BDNF alterations in the brain. Several studies have taken advantage of this correlation to assess BDNF levels in BD patients during different mood states, namely mania, depression, and euthymia, to gain insight into the pathophysiology of this poorly understood disorder.

These studies have accumulated compelling evidence suggesting that serum and plasma BDNF levels change across the different mood states experienced in BD. However, there are discrepancies among studies, for instance, some studies show a decrease in BDNF in the manic state (13-15) while others do not (18). The controversy is even greater in the depressive (19,20)

and euthymic states (21,22): some studies conducted in depressive and euthymic patients have demonstrated decreased BDNF levels, while others have shown no difference compared to healthy subjects (13,14,18,23-26). The inconsistencies in these findings might be due to differences in the characteristics of the study populations or a lack of statistical power due to small sample sizes.

Some studies have assessed whether BDNF predicts the response to treatment in mania and depression, but the results again disagree (13,16,18,23,27). Thus, the role of BDNF in the treatment of mood episodes needs further exploration.

Meta-analysis is a recognized technique used to resolve discrepancies between cross-sectional studies. Meta-analysis is a quantitative method of combining the results of independent studies to increase statistical power and make solid conclusions. This method increases the power to distinguish between small effects and no effect. Furthermore, this approach can help to determine whether the variation in effects between studies is merely due to the expected random statistical fluctuation or instead to sample variations or trait assessment. The more sophisticated methodology of meta-regression may be used to evaluate confounders and discrepancies among different studies.

The aim of this study was to perform a meta-analysis of all available cross-sectional studies of serum or plasma BDNF levels in adults with BD according to mood state. We examined the effect of age, length of illness, and severity of mood episode on BDNF levels using a meta-regression analysis. We also performed a meta-analysis of all studies that assessed circulating BDNF levels before and after pharmacological treatment for an index mood episode to verify changes in BDNF levels with treatment. This study will help to clarify the role of peripheral BDNF in BD.

Materials and Methods

Search strategy

We conducted a systematic review of all English and non-English articles to avoid language publication bias (28) using PubMed at the National Library of Medicine, the Cochrane Library, Scielo, Lilacs, the British Library, OpenSigle, PsycInfo, and the ISI Web of Knowledge. No year or country restrictions were used. The search term used for the electronic database search was: (BDNF OR brain-derived neurotrophic factor) AND (bipolar disorder OR bipolar disorders OR manic-depressive illness). The latest search was performed in September of 2009. We then manually checked the reference sections of the publications found through our electronic search to identify additional studies that may have been missed. Abstracts from scientific meetings of the last few years were electronically searched. Study selection eligibility and exclusion criteria were prespecified.

Study selection

Inclusion criteria were: 1) adult patients with BD types I or II as defined by DSM-IV criteria (29); 2) cross-sectional studies comprised of a control group of healthy volunteers or pharmacologic studies with BDNF assessed before and after treatment; and 3) studies assessing circulating BDNF with plasma or serum samples *in vivo.* Exclusion criteria were: 1) studies assessing *BDNF* genes; 2) studies assessing biomarkers other than BDNF; 3) *in vitro* studies; and 4) morphological studies (Figure 1). The decision of whether to include studies in the meta-analysis was made based on the above criteria, and a consensus was reached among the authors on those decisions.

Data extraction and data synthesis

Two reviewers (BSF and FAG) independently extracted data [*n*, mean and standard deviation (SD)] to avoid potential mistakes. Discrepancies in data entry were double-checked by the two reviewers with the original published data and a consensus was reached. Whenever multiple reports pertained to the same groups of patients, we retained only the original report for the meta-analysis calculations to avoid duplication of information. When the necessary data were not available from the published paper, we contacted the authors and requested the necessary information, and all authors complied.

Review Manager (RevMan) version 5.0 (30) was used to calculate the standardized mean differences or effect size (ES) estimates of the differences in BDNF levels between BD patients in different mood states and healthy volunteers. Effect size estimates were calculated from the means and SDs and were derived with Hedges's adjusted *g* (30), which provides an unbiased ES adjusted for sample size. The 95% confidence interval (95% CI) of the ES was also computed.

Studies with negative results are less likely to be published than studies with positive results. To account for significant publication bias we analyzed a funnel plot graph, a scatter plot of treatment effect against a measure of study size. This was performed for all analyses, and the Egger statistic was also employed (31).

We assessed the heterogeneity across studies using the Q-statistic, a weighted sum of the squares of the deviations of individual study ES estimates from the overall estimate (32). The inconsistency across studies was quantified with the I^2 metric, which can be interpreted as the percentage of total variation across several studies due to heterogeneity (33-35).

Since the analyses showed that the studies were heterogeneous, we pooled ES results from individual studies according to the DerSimonian and Laird method of accounting for random effects, which allows population level inferences and is more stringent than fixed effect models (36). Random effect modeling assumes a genuine diversity in the results of various

studies and incorporates a between-study variance into the calculations. The direction of the ES was positive if patients with BD showed increased BDNF and negative if they showed decreased BDNF levels when compared to controls. The direction of the ES was negative if BDNF levels increased after treatment.

Unrestricted maximum likelihood random effects meta-regressions of ES were performed using the Comprehensive Meta-analysis Software (37), with mean age, length of illness, and severity of the mood episode as moderators to determine whether these covariates influenced ES. Studies were weighted such that the most precise studies had more influence in the regression analyses.

The meta-analysis consisted of three steps. First, we performed the overall analysis according to mood state. Second, sensitivity analyses were conducted to ascertain whether the results of our analyses were strongly influenced by any single study or by studies sharing some characteristic. The overall significance was recomputed after each study or group of studies with a common characteristic were deleted from the analysis. Finally, we performed the meta-regression analysis. To assess the effect of treatment on BDNF levels, we performed a meta-analysis of BDNF data before and after treatment for a current mood episode. We proceeded according to the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analysis) (38,39) and the recommendations of the Cochrane Collaboration (40). The level of significance for the ES estimates was set at $p<0.05$.

Results

The literature search yielded 181 results, of which 13 cross-sectional studies that included 1,113 participants (548 patients with BD and 565 controls) (13-24,26) were examined in the meta-analysis (Figure 1). Four studies were re-analyses of previously published data and were therefore excluded (25,41-43). Table 1 presents the characteristics of the included studies. In total, we excluded 168 articles (10,25,27,41-202,212-214). The characteristics of these articles are presented in the supplementary material. We assessed the BDNF levels in the BD patients according to their mood state. Three reports had multiple arms and were analyzed two or three times (14,18,19). All studies assessed BDNF levels using an ELISA kit. BDNF was assessed in serum except for three studies that measured plasma levels. The mean age of patients ranged from 22.40 ± 3.90 to 48.6 ± 10.80 years.

BDNF in mania

Six studies assessed the BDNF levels during manic episodes (13-16,18,19) (122 manic patients vs. 128 controls). The analysis showed that BDNF levels in manic patients were significantly lower than controls, with a large ES (ES -0.81, 95% CI -1.11 to -0.52, $p<0.0001$) (Table 2, Figure 2a). There was no publication bias according to the analysis of the funnel plot and the Egger statistic ($p=0.87$). The studies were not heterogeneous ($p=0.29$).

In order to investigate whether the choice of assessing BDNF levels in serum or plasma was responsible for the results, we conducted a sensitivity analysis, first considering only the studies performed in plasma (13,15,18), followed by only those using serum (14,16,19). The BDNF levels were still lower when the studies were analyzed in this way ($p<0.0001$ and $p=0.006$ for serum and plasma, respectively).

We performed a sensitivity analysis to determine whether an individual study was responsible for the decreased BDNF levels. Each study was individually excluded, and the

significance of the analysis was rechecked. The results remained highly significant in each of these analyses. A meta-regression analysis was performed to investigate possible moderators of BDNF. The results of the meta-regression analyses showed that the Young Mania Rating Scale (YMRS) scores significantly influenced the variation in the ES of BDNF levels of manic subjects (p=0.02), with higher YMRS scores indicating lower BDNF levels with a higher ES (Figure 3a). The BDNF levels in patients during a manic episode were not moderated by age (p=0.73) or length of illness in years (p=0.26).

BDNF in depression

Five studies measured BDNF levels in the depressive phase of BD (14,18-20,23). These studies included 107 patients and 118 healthy subjects. The studies were highly heterogeneous (p<0.001). Overall, the BDNF levels were lower during bipolar depression (ES -0.97, 95% CI -1.79 to -0.51, p=0.02) (Table 2, Figure 2b). BDNF remained at the decreased levels when analyzing the reports using serum (14,19,20,23) (p<0.04). Since only one study on bipolar depression used plasma (18), we could not compute an ES for BDNF levels measured in the plasma of BD patients during a depressive episode.

In the sensitivity analysis, the results remained significant in each of these analyses, except when the study of Oliveira *et al.* (19) was excluded (p=0.09).

The publication bias statistic of Egger *et al.* (31) was not significant (p=0.84), and the funnel plot also showed no publication bias. The meta-regression analysis showed that the Hamilton Depression Rating Scale (HDRS) scores significantly influenced the variation in the ES of BDNF levels of depressive subjects (p=0.004), with higher HDRS scores indicating lower BDNF levels with a higher ES (Figure 3b). As in the manic state, the BDNF levels in patients in a depressive episode were not moderated by age (p=0.38) or the length of illness in years (p=0.39).

BDNF in euthymia

Six studies with 638 participants (14,17,21,22,24,26) examined the BDNF levels of BD patients in euthymia, with one of those was counted twice (22) since it separately reported the results of early stage (i.e., < 3 years of disease) and late stage BD (i.e., > 10 years of disease). The studies examining BDNF levels in euthymia were highly heterogeneous (p<0.001). The test of Egger *et al.* (31) was not significant (p=0.86), and the funnel plot did not show publication bias. Two reports showed decreased BDNF in euthymic patients (21,22), while another showed increased BDNF (22). Overall, there was no difference between BDNF levels in euthymic patients and controls (ES -0.20, 95% CI -0.61 to 0.21, p=0.33). All of these studies assessed BDNF levels in serum (Figure 2c, Table 2).

The results remained non-significant in each of these sensitivity analyses, including when the early stage study of Kauer-Sant'Anna *et al.* (22) was excluded (ES -0.33, 95% CI -0.74 to -0.07, p=0.11). In this case, however, the 95% CI was large and almost significant. It is important to acknowledge that this study has some peculiar characteristics (e.g., they studied young patients that typically only had one previous manic episode).

To investigate the discrepancies among studies of BDNF levels in euthymia, we performed a meta-regression analysis to evaluate possible confounders. The results of the meta-regression analyses showed that mean age (p<0.0001) (Figure 3c) and mean length of illness (p=0.04) (Figure 3d) significantly influenced the variation in the ES of BDNF levels of euthymic subjects, with elderly subjects and a greater length of illness corresponding to lower BDNF levels with a higher ES.

BDNF changes pre- and post-pharmacological treatment

In acute mania, we found three studies with 36 participants assessing BDNF levels before and after pharmacological treatment (13,16,18) (Table 1). These studies were not heterogeneous

(p<0.36). Two reports showed an increase in BDNF levels after treatment (13,16), while the other showed no difference (18). Overall, there was an increase in BDNF levels following treatment for acute mania (ES -0.63, 95% CI -1.11 to -0.15, p=0.01) (Figure 4a). In the sensitivity analysis, the exclusion of the studies of Tramontina *et al*. (16) or Palomino *et al*. (13) made the results non-significant.

In depression, there were only two studies with 26 participants assessing BDNF levels before and after pharmacological treatment (18,23). There was no difference in BDNF levels following treatment for depression (ES 0.45, 95% CI -0.31 to 1.21, p=0.25) (Figure 4b). Nevertheless, both studies had some peculiar characteristics. The study of Yoshimura *et al*. (18) studied BDNF changes in depressive patients on risperidone, and the study of Mackin *et al.* (23) studied the effect of mifepristone, a glucocorticoid antagonist.

Discussion

This meta-analysis of the serum or plasma BDNF levels in BD during the three different phases of the disease investigated 548 patients with BD and 565 healthy subjects from 13 case-control studies.

To our knowledge, this is the first meta-analysis to be conducted on peripheral BDNF protein levels in BD patients according to mood state, although a number of studies have been performed on *BDNF* genes. This analysis showed that BDNF levels decrease during manic and depressive states, with subjects with more severe episodes presenting with lower BDNF levels. BDNF levels were found to be normal in euthymia, although the frequency of normal levels decreased with age and length of illness. In addition, pharmacological treatment for a manic episode increased BDNF levels.

Meta-analyses of observational studies present particular challenges because of inherent biases and differences in study designs (203). They may, however, provide a tool for increasing our understanding and quantifying sources of variability in results across studies (34,204). Using a meta-regression analysis, we were able to demonstrate that the sources of variability in studies conducted in euthymia depend on the mean age and length of illness.

Biomarkers are commonplace in most branches of medicine as they not only improve our understanding of the pathophysiology, but also may be a useful tool to support clinical decisions. The specific biologic features of an individual patient provide critical information about diagnosis, prognosis, or predicted response to treatment. To date, there are no clinical laboratory blood tests for psychiatric disorders, including BD. We propose that peripheral BDNF may be a blood biomarker of mood state, reflecting disease activity. This meta-analysis shows that serum and plasma BDNF levels are consistently reduced during mood episodes, making BDNF levels markers of disease state. This could be a first step in the development of a clinical laboratory test, a longstanding “Holy Grail” for psychiatry. Some preliminary results from our group

(Fernandes et al., unpublished data) found highly promising properties of serum BDNF with a sensitivity of 90% and a specificity of 85%, demonstrating that BDNF levels can accurately discriminate between patients experience, mania or depression from euthymic patients and controls. A blood exam that can assess disease activity may help with early intervention and prevention efforts and may help to monitor the response to various treatments. In conjunction with other clinical information, such tests could play an important part in personalizing treatment to increase effectiveness (205). In addition, BDNF levels are an ideal marker to assess with a laboratory exam due to the non-invasiveness of the technique, since BDNF can be assessed in the periphery via venipuncture.

One interesting use of peripheral BDNF would be as an adjunctive tool to support the proper diagnosis of BD. Clinical signs and symptoms are the central basis for establishing psychiatric diagnoses. In this setting, the lack of specificity of BDNF for psychiatric disorders has been considered a limitation. In recent work, however, we have shown that serum BDNF levels can properly discriminate bipolar from unipolar depression with a high diagnostic accuracy of 95%. Discriminating between bipolar and unipolar depression remains a diagnostic challenge because of the overlap among core clinical features and the difficulty in ascertaining past manic and hypomanic episodes. This was a cross-sectional study with a relatively small sample size and should be replicated in prospective studies. Nonetheless, the results are promising, and if replicated, serum BDNF may become an accessible blood diagnostic test to support the correct diagnosis of bipolar depression (20).

Another potentially interesting application of serum BDNF could be as a surrogate biomarker of pharmacological efficacy. Our results provide strong evidence that serum BDNF levels increase following treatment for acute mania, similar to what has been observed with BDNF expression in specific brain regions in an animal model of mania treated with lithium or valproate (10). This suggests that BDNF levels may be used to predict an individual response to

treatment for acute mania at an early time point after treatment initiation if a relationship can be established between the change in BDNF levels and clinical response. BDNF changes in relation to a mood episode could follow three different patterns. First, serum BDNF could decrease after the beginning of a mood episode, with recovery of BDNF levels after the achievement of euthymia. In this case, BDNF changes would be a consequence of mood episodes, and its assessment could be useful as a surrogate biomarker (Figure 5a). Second, serum BDNF could decrease before the beginning of a mood episode and recover before achievement of euthymia, which would make BDNF a predictor of mood episodes and response to treatment (Figure 5b). Finally, BDNF decreases could be concomitant with mood episodes, reflecting disease activity (Figure 5c). The behavior of BDNF and its temporal relationship to mood episodes in BD remains largely unknown. In Major Depressive Disorder, there are some studies showing that BDNF recovers only after achievement of euthymia (206-208) and that baseline BDNF levels can be a predictor of the response to treatment (209). There is no study regarding this topic in BD patients.

Lastly, BDNF could play a role as a biomarker of progression of disease in the staging model of BD. The construct of staging in BD is increasingly accepted as conveying meaningful information that predicts the likelihood of response, prognosis, and type of treatment (41,210,211). Currently, the staging in BD is comprised of clinical and neuropsychological features, but biomarkers remain a promising field in this setting. In this study, we showed that during euthymia, age and length of illness are important moderators of BDNF levels, and are at least partially responsible for the discrepancies in literature reports of BDNF levels during euthymia. In a study from our group, we showed that serum BDNF has promising properties for discrimination between patients with less than 3 years of disease from patients with more than 10 years, with a sensitivity of 100%, a specificity of 88%, and an accuracy of 95% (41). This

suggests that BDNF may play a role as a biomarker of the severity and prognosis of disease in the future.

Some limitations of this study must be pointed out. Our study included patients both on and off medication. This could produce a bias since some medications can increase BDNF levels. Recently, however, we showed that serum BDNF levels did not differ between BD patients on and off their medication when in an acute episode (19). The major limitation of this study remains the analysis of BDNF changes after treatment for a depressive episode. This analysis was only able to include two studies that had negative results (18,23). It must be acknowledged that the pharmacological treatments used in these studies (4), risperidone and mifepristone, are not used to treat bipolar depression, and this may have been responsible for this negative result. Studies assessing the effect of mood stabilizers and antidepressants on BDNF levels in bipolar depression are warranted to clarify this point.

In conclusion, this study resolves discrepancies found in previous studies regarding BDNF and provides evidence demonstrating that BDNF levels are reduced during mood episodes but not during euthymia. Moreover, we show that BDNF levels decrease with age and length of illness. There is also strong and consistent data suggesting that BDNF levels normalize following pharmacological treatment for a manic episode. These findings are of major importance to the field, considering the growing evidence of the involvement of neurotrophic factors in the pathophysiology of BD. Moreover, these findings support the concept of peripheral BDNF levels as a biomarker of disease activity during mood episodes and as a possible biomarker of disease progression according to the staging model. Future studies are required to determine whether the measurement of serum or plasma BDNF can be used to guide clinical decision making.

Role of funding sources

This study was supported by the Stanley Medical Research Institute, NARSAD, INCT for Translational Medicine, CNPq, CAPES, and FIPE-HCPA. These agencies had no role in the study design, in the acquisition or interpretation of the data, or in writing the report.

Financial disclosures

Dr. Flavio Kapczinski has received research grants from INCT for Translational Medicine, FIPE-HCPA, CNPq, CAPES, SMRI, NARSAD, Lilly, AstraZeneca, and Janssen. Dr. Clarissa S. Gama has received grant/research support from CNPq, FIPE–HCPA, and the Endeavour Award, and has been a paid speaker for AstraZeneca. Dr Lakshmi N. Yatham is on speaker/advisory boards for or has received research grants from AstraZeneca, Bristol–Myers Squibb, the Canadian Institutes of Health Research, the Canadian Network for Mood and Anxiety Treatments, Eli Lilly, GlaxoSmithKline, Janssen, the Michael Smith Foundation for Health Research, Pfizer, Servier, and the Stanley Foundation. Dr. Brisa Simões Fernandes, Dr. Keila Ceresér, Dr. Mauricio Kunz, Gabriel Fries, Dr. David de Lucena, Gabriela Colpo, and Dr. Fabiano Alves Gomes have declared no conflict of interest.

These agencies had no role in the study design, in the acquisition or interpretation of the data, or in writing the report.

Acknowledgements

We thank all authors of the included studies, particularly those who cooperated with us by sending necessary data for our study.

Dr. Brisa Simões Fernandes is supported by a scholarship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil.

References

1. Poo MM. Neurotrophins as synaptic modulators. Nat Rev Neurosci 2001; 2(1):24-32.
2. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001; 7(5):541-547.
3. Ernfors P, Wetmore C, Olson L, Persson H. Identification of cells in rat brain and peripheral tissues expressing mRNA for members of the nerve growth factor family. Neuron 1990; 5(4):511-526.
4. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009; 11(3):225-255.
5. Belmaker RH. Bipolar disorder. N Engl J Med 2004; 351(5):476-486.
6. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord 2002; 68(2-3):167-181.
7. Rosa AR, Andreazza AC, Kunz M, Gomes F, Santin A, Sanchez-Moreno J, et al. Predominant polarity in bipolar disorder: diagnostic implications. J Affect Disord 2008; 107(1-3):45-51.
8. Goldstein TR, Birmaher B, Axelson D, Goldstein BI, Gill MK, Esposito-Smythers C, et al. Psychosocial functioning among bipolar youth. J Affect Disord 2009; 114(1-3):174-183.
9. Pandey GN, Ren X, Rizavi HS, Conley RR, Roberts RC, Dwivedi Y. Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. Int J Neuropsychopharmacol 2008; 11(8):1047-1061.

10. Frey BN, Andreazza AC, Cereser KM, Martins MR, Valvassori SS, Reus GZ, et al. Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. Life Sci 2006; 79(3):281-286.

11. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 1998; 37(12):1553-1561.

12. Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 2005; 57(9):1068-1072.

13. Palomino A, Vallejo-Illarramendi A, Gonzalez-Pinto A, Aldama A, Gonzalez-Gomez C, Mosquera F, et al. Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients. Schizophr Res 2006; 86(1-3):321-322.

14. Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Goncalves CA, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett 2006; 398(3):215-219.

15. Machado-Vieira R, Dietrich MO, Leke R, Cereser VH, Zanatto V, Kapczinski F, et al. Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. Biol Psychiatry 2007; 61(2):142-144.

16. Tramontina JF, Andreazza AC, Kauer-Sant'anna M, Stertz L, Goi J, Chiarani F, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett 2009; 452(2):111-113.

17. Tramontina J, Frey BN, Andreazza AC, Zandona M, Santin A, Kapczinski F. Val66met polymorphism and serum brain-derived neurotrophic factor levels in bipolar disorder. Mol Psychiatry 2007; 12(3):230-231.

18. Yoshimura R, Nakano Y, Hori H, Ikenouchi A, Ueda N, Nakamura J. Effect of risperidone on plasma catecholamine metabolites and brain-derived neurotrophic factor in patients with bipolar disorders. Hum Psychopharmacol 2006; 21(7):433-438.

19. de Oliveira GS, Cereser KM, Fernandes BS, Kauer-Sant'Anna M, Fries GR, Stertz L, et al. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J Psychiatr Res 2009; 43(14):1171-1174.

20. Fernandes BS, Gama CS, Kauer-Sant'Anna M, Lobato MI, Belmonte-de-Abreu P, Kapczinski F. Serum brain-derived neurotrophic factor in bipolar and unipolar depression: A potential adjunctive tool for differential diagnosis. J Psychiatr Res 2009; 43:1200-1204.

21. Monteleone P, Serritella C, Martiadis V, Maj M. Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders. Bipolar Disord 2008; 10(1):95-100.

22. Kauer-Sant'anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Trevor Young L, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol 2008; 4:1-12.

23. Mackin P, Gallagher P, Watson S, Young AH, Ferrier IN. Changes in brain-derived neurotrophic factor following treatment with mifepristone in bipolar disorder and schizophrenia. Aust N Z J Psychiatry 2007; 41(4):321-326.

24. Dias VV, Brissos S, Frey BN, Andreazza AC, Cardoso C, Kapczinski F. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord 2009; 11(6):663-671.

25. Gama CS, Andreazza AC, Kunz M, Berk M, Belmonte-de-Abreu PS, Kapczinski F. Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder. Neurosci Lett 2007; 420(1):45-48.

26. Langan C, Doyle K, Kelly J, Emsell L, Skinner R, McDonald C. Serum BDNF levels in euthymic bipolar disorder: preliminary results from the Galwey Bipolar Study. Bipolar Disord 2009; 11(Suppl. 1):56.

27. Fernandes B, Gama CS, Massuda R, Torres M, Camargo D, Kunz M, et al. Serum brain-derived neurotrophic factor (BDNF) is not associated with response to electroconvulsive therapy (ECT): a pilot study in drug resistant depressed patients. Neurosci Lett 2009; 453(3):195-198.

28. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. Lancet 1997; 350(9074):326-329.

29. APA. Diagnostic and Statistical Manual of Mental Disorders. Washington, D.C., 2000.

30. Cooper H, Hedges LV. Cooper H; Hedges LV: The Handbook of Research Synthesis. NewYork: Russell Sage Foundation Publications, 1994.

31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109):629-634.

32. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127(9):820-826.

33. Zintzaras E, Hadjigeorgiou GM. Association of paraoxonase 1 gene polymorphisms with risk of Parkinson's disease: a meta-analysis. J Hum Genet 2004; 49(9):474-481.

34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-560.

35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11):1539-1558.

36. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3):177-188.

37. Borenstein M, Hedges LV, Higgins JPT, Rothstein H. Comprehensive Meta-analysis version 2.0, http://www.meta-analysis.com, 2006.

38. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151(4):264-269.

39. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151(4):65-94.

40. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. The Cochrane Collaboration, 2009, www.cochrane-handbook.org. .

41. Kapczinski F, Fernandes BS, Kauer-Sant'Anna M, Gama CS, Yatham L, Berk M. The concept of staging in bipolar disorder: the role of BDNF and TNF-alpha as biomarkers. Acta Neuropsychiatrica 2009; 21(6):272-274.

42. Kapczinski F, Frey BN, Andreazza AC, Kauer-Sant'Anna M, Cunha AB, Post RM. Increased oxidative stress as a mechanism for decreased BDNF levels in acute manic episodes. Rev Bras Psiquiatr 2008; 30(3):243-245.

43. Yatham LN, Kapczinski F, Andreazza AC, Trevor Young L, Lam RW, Kauer-Sant'anna M. Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder. Int J Neuropsychopharmacol 2008; 10:1-3.

44. Gallinat J, Schubert F, Bruhl R, Hellweg R, Klar AA, Kehrer C, et al. Met carriers of BDNF Val66Met genotype show increased N-acetylaspartate concentration in the anterior cingulate cortex. Neuroimage 2010; 49(1):767-771.

45. Tramontina JF, Yates D, Magalhaes PV, Trentini C, Sant'anna MK, Fries GR, et al. Brain-derived neurotrophic factor gene val66met polymorphism and executive functioning in patients with bipolar disorder. Rev Bras Psiquiatr 2009; 31(2):136-140.

46. Dutt A, McDonald C, Dempster E, Prata D, Shaikh M, Williams I, et al. The effect of COMT, BDNF, 5-HTT, NRG1 and DTNBP1 genes on hippocampal and lateral ventricular volume in psychosis. Psychol Med 2009; 39(11):1783-1797.

47. Hammonds MD, Shim SS. Effects of 4-week treatment with lithium and olanzapine on levels of brain-derived neurotrophic factor, B-cell CLL/lymphoma 2 and phosphorylated cyclic adenosine monophosphate response element-binding protein in the sub-regions of the hippocampus. Basic Clin Pharmacol Toxicol 2009; 105(2):113-119.

48. Vinberg M, Trajkovska V, Bennike B, Knorr U, Knudsen GM, Kessing LV. The BDNF Val66Met polymorphism: relation to familiar risk of affective disorder, BDNF levels and salivary cortisol. Psychoneuroendocrinology 2009; 34(9):1380-1389.

49. Szczepankiewicz A, Rybakowski JK, Skibinska M, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Wilkosc M, et al. FYN kinase gene: another glutamatergic gene associated with bipolar disorder? Neuropsychobiology 2009; 59(3):178-183.

50. Fukuchi M, Nii T, Ishimaru N, Minamino A, Hara D, Takasaki I, et al. Valproic acid induces up- or down-regulation of gene expression responsible for the neuronal excitation and inhibition in rat cortical neurons through its epigenetic actions. Neurosci Res 2009; 65(1):35-43.

51. Sumegi A. Quetiapin in bipolar disorders. Neuropsychopharmacol Hung 2008; 10(5):281-291.

52. Kawashima K, Ikeda M, Kishi T, Kitajima T, Yamanouchi Y, Kinoshita Y, et al. BDNF is not associated with schizophrenia: data from a Japanese population study and meta-analysis. Schizophr Res 2009; 112(1-3):72-79.

53. Dunham JS, Deakin JF, Miyajima F, Payton A, Toro CT. Expression of hippocampal brain-derived neurotrophic factor and its receptors in Stanley consortium brains. J Psychiatr Res 2009; 43(14):1175-1184.

54. Barnett JH, Smoller JW. The genetics of bipolar disorder. Neuroscience 2009 Apr 7.

55. Szczepankiewicz A, Skibinska M, Suwalska A, Hauser J, Rybakowski JK. The association study of three FYN polymorphisms with prophylactic lithium response in bipolar patients. Hum Psychopharmacol 2009; 24(4):287-291.

56. Matsuo K, Walss-Bass C, Nery FG, Nicoletti MA, Hatch JP, Frey BN, et al. Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder. Neuropsychopharmacology 2009; 34(8):1904-1913.

57. Kapczinski F, Dias VV, Frey BN, Kauer-Sant'Anna M. Brain-derived neurotrophic factor in bipolar disorder: beyond trait and state: comment on 'Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders'. Bipolar Disord 2009; 11(2):221-222.

58. Mick E, Faraone SV. Family and genetic association studies of bipolar disorder in children. Child Adolesc Psychiatr Clin N Am 2009; 18(2):441-453.

59. Petryshen TL, Sabeti PC, Aldinger KA, Fry B, Fan JB, Schaffner SF, et al. Population genetic study of the brain-derived neurotrophic factor (BDNF) gene. Mol Psychiatry 2009; DOI: 10.1038/mp.2009.24.

60. Gerard S. Reviewing medications for bipolar disorder: understanding the mechanisms of action. J Clin Psychiatry 2009; DOI: 10.4088/JCP.7128br6c.e02.

61. Mick E, Wozniak J, Wilens TE, Biederman J, Faraone SV. Family-based association study of the BDNF, COMT and serotonin transporter genes and DSM-IV bipolar-I disorder in children. BMC Psychiatry 2009; 4:9:2.

62. Mirakhur A, Moorhead TW, Stanfield AC, McKirdy J, Sussmann JE, Hall J, et al. Changes in gyrification over 4 years in bipolar disorder and their association with the brain-derived neurotrophic factor valine(66) methionine variant. Biol Psychiatry 2009; 66(3):293-297.

63. Le-Niculescu H, Patel SD, Bhat M, Kuczenski R, Faraone SV, Tsuang MT, et al. Convergent functional genomics of genome-wide association data for bipolar disorder: comprehensive identification of candidate genes, pathways and mechanisms. Am J Med Genet B Neuropsychiatr Genet 2009; 150(2):155-181.

64. Dmitrzak-Weglarz M, Rybakowski JK, Suwalska A, Skibinska M, Leszczynska-Rodziewicz A, Szczepankiewicz A, et al. Association studies of the BDNF and the NTRK2 gene polymorphisms with prophylactic lithium response in bipolar patients. Pharmacogenomics 2008; 9(11):1595-1603.

65. Rybakowski JK. BDNF gene: functional Val66Met polymorphism in mood disorders and schizophrenia. Pharmacogenomics 2008; 9(11):1589-1593.

66. Liu L, Foroud T, Xuei X, Berrettini W, Byerley W, Coryell W, et al. Evidence of association between brain-derived neurotrophic factor gene and bipolar disorder. Psychiatr Genet 2008; 18(6):267-274.

67. Altar CA, Hunt RA, Jurata LW, Webster MJ, Derby E, Gallagher P, et al. Insulin, IGF-1, and muscarinic agonists modulate schizophrenia-associated genes in human neuroblastoma cells. Biol Psychiatry; 64(12):1077-1087.

68. Savitz J, van der Merwe L, Ramesar R. Personality endophenotypes for bipolar affective disorder: a family-based genetic association analysis. Genes Brain Behav 2008; 7(8):869-876.

69. Berk M, Malhi GS, Hallam K, Gama CS, Dodd S, Andreazza AC, et al. Early intervention in bipolar disorders: Clinical, biochemical and neuroimaging imperatives. J Affect Disord 2009; 114:1-13.

70. Tsai SJ, Hong CJ, Liou YJ. Brain-derived neurotrophic factor and antidepressant action: another piece of evidence from pharmacogenetics. Pharmacogenomics 2008; 9(9):1353-1358.

71. Chang YC, Rapoport SI, Rao JS. Chronic administration of mood stabilizers upregulates BDNF and bcl-2 expression levels in rat frontal cortex. Neurochem Res 2009; 34(3):536-541.

72. Chepenik LG, Fredericks C, Papademetris X, Spencer L, Lacadie C, Wang F, et al. Effects of the brain-derived neurotrophic growth factor val66met variation on hippocampus morphology in bipolar disorder. Neuropsychopharmacology 2009; 34(4):944-951.

73. Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. J Am Acad Child Adolesc Psychiatry 2008; 47(9):1077-1085.

74. Vincze I, Perroud N, Buresi C, Baud P, Bellivier F, Etain B, et al. Association between brain-derived neurotrophic factor gene and a severe form of bipolar disorder, but no interaction with the serotonin transporter gene. Bipolar Disord 2008; 10(5):580-587.

75. Kapczinski F, Frey BN, Kauer-Sant'Anna M, Grassi-Oliveira R, Berk M. Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder. Expert Rev Neurother 2008; 8(7):1101-1113.

76. Castren E, Rantamaki T. Neurotrophins in depression and antidepressant effects. Novartis Found Symp 2008; 289:43-52.

77. Kloos A, Weller EB, Weller RA. Biologic basis of bipolar disorder in children and adolescents. Curr Psychiatry Rep 2008; 10(2):98-103.

78. Grassi-Oliveira R, Stein LM, Lopes RP, Teixeira AL, Bauer ME. Low plasma brain-derived neurotrophic factor and childhood physical neglect are associated with verbal

memory impairment in major depression - a preliminary report. Biol Psychiatry 2008; 64(4):281-285.

79. Abdolmaleky HM, Smith CL, Zhou JR, Thiagalingam S. Epigenetic alterations of the dopaminergic system in major psychiatric disorders. Methods Mol Biol 2008; 448:187-212.

80. Feng Y, Vetro A, Kiss E, Kapornai K, Daroczi G, Mayer L, et al. Association of the neurotrophic tyrosine kinase receptor 3 (NTRK3) gene and childhood-onset mood disorders. Am J Psychiatry 2008; 165(5):610-616.

81. Yuan TF. A broken BDNF hypothesis. Med Hypotheses 2008; 71(2):322.

82. Pillai A. Decreased expression of Sprouty2 in the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder: a correlation with BDNF expression. PLoS One 2008; 3(3):e1784.

83. Serretti A, Mandelli L. The genetics of bipolar disorder: genome 'hot regions,' genes, new potential candidates and future directions. Mol.Psychiatry 2008; 13(8):742-771.

84. Mill J, Tang T, Kaminsky Z, Khare T, Yazdanpanah S, Bouchard L, et al. Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. Am J Hum Genet 2008; 82(3):696-711.

85. Otsuki K, Uchida S, Watanuki T, Wakabayashi Y, Fujimoto M, Matsubara T, et al. Altered expression of neurotrophic factors in patients with major depression. J Psychiatr Res 2008; 42(14):1145-1153.

86. Geller B, Tillman R, Bolhofner K, Hennessy K, Cook EH. GAD1 single nucleotide polymorphism is in linkage disequilibrium with a child bipolar I disorder phenotype. J Child Adolesc Psychopharmacol 2008; 18(1):25-29.

87. Terao T. Mania is probably associated with hypoactivity of central brain-derived neurotrophic factor. Med Hypotheses 2008; 70(6):1232.

88. Tang J, Xiao L, Shu C, Wang G, Liu Z, Wang X, et al. Association of the brain-derived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. Neurosci Lett 2008; 433(2):98-102.

89. Chen L, Lawlor DA, Lewis SJ, Yuan W, Abdollahi MR, Timpson NJ, et al. Genetic association study of BDNF in depression: finding from two cohort studies and a meta-analysis. Am J Med Genet B Neuropsychiatr Genet 2008; 147(6):814-821.

90. Stahl LA, Begg DP, Weisinger RS, Sinclair AJ. The role of omega-3 fatty acids in mood disorders. Curr Opin Investig Drugs 2008; 9(1):57-64.

91. McGowan PO, Kato T. Epigenetics in mood disorders. Environ Health Prev Med 2008; 13(1):16-24.

92. Sanacora G. New understanding of mechanisms of action of bipolar medications. J Clin Psychiatry 2008; 69 Suppl 5:22-27.

93. Kauer-Sant'Anna M, Tramontina J, Andreazza AC, Cereser K, da Costa S, Santin A, et al. Traumatic life events in bipolar disorder: impact on BDNF levels and psychopathology. Bipolar Disord 2007; 9 Suppl 1:128-135.

94. Kozisek ME, Middlemas D, Bylund DB. Brain-derived neurotrophic factor and its receptor tropomyosin-related kinase B in the mechanism of action of antidepressant therapies. Pharmacol Ther 2008; 117(1):30-51.

95. Yasuda S, Liang MH, Marinova Z, Yahyavi A, Chuang DM. The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. Mol Psychiatry 2009; 14(1):51-59.

96. Trajkovska V, Vinberg M, Aznar S, Knudsen GM, Kessing LV. Whole blood BDNF levels in healthy twins discordant for affective disorder: association to life events and neuroticism. J Affect Disord 2008; 108(1-2):165-169.

97. McIntosh AM, Moorhead TW, McKirdy J, Sussmann JE, Hall J, Johnstone EC, et al. Temporal grey matter reductions in bipolar disorder are associated with the BDNF Val66Met polymorphism. Mol Psychiatry 2007; 12(10):902-903.

98. Frey BN, Walss-Bass C, Stanley JA, Nery FG, Matsuo K, Nicoletti MA, et al. Brain-derived neurotrophic factor val66met polymorphism affects prefrontal energy metabolism in bipolar disorder. Neuroreport 2007; 18(15):1567-1570.

99. Itokawa M, Yoshikawa T. Molecular biology of depressive disorders. Nippon Rinsho 2007; 65(9):1599-1606.

100. Zai G, Mundo E, Strauss J, Wong GW, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene not associated with antidepressant-induced mania. Bipolar Disord 2007; 9(5):521-525.

101. Yamasue H, Suga M, Kasai K. Investigating endophenotype of endogeneous psychotic disorders. Nihon Shinkei Seishin Yakurigaku Zasshi 2007; 27(3):85-90.

102. Kauer-Sant'Anna M, Andreazza AC, Valvassori SS, Martins MR, Barbosa LM, Schwartsmann G, et al. A gastrin-releasing peptide receptor antagonist blocks D-amphetamine-induced hyperlocomotion and increases hippocampal NGF and BDNF levels in rats. Peptides 2007; 28(7):1447-1452.

103. McQuillin A, Rizig M, Gurling HM. A microarray gene expression study of the molecular pharmacology of lithium carbonate on mouse brain mRNA to understand the neurobiology of mood stabilization and treatment of bipolar affective disorder. Pharmacogenet Genomics 2007; 17(8):605-617.

104. Savitz JB, van der Merwe L, Newman TK, Solms M, Stein DJ, Ramesar RS. The relationship between childhood abuse and dissociation. Is it influenced by catechol-O-methyltransferase (COMT) activity? Int J Neuropsychopharmacol 2008; 11(2):149-161.

105. Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. Neurosci Biobehav Rev 2007; 31(6):858-873.

106. Walz JC, Frey BN, Andreazza AC, Cereser KM, Cacilhas AA, Valvassori SS, et al. Effects of lithium and valproate on serum and hippocampal neurotrophin-3 levels in an animal model of mania. J Psychiatr Res 2008; 42(5):416-421.

107. Rybakowski JK, Suwalska A, Skibinska M, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J. Response to lithium prophylaxis: interaction between serotonin transporter and BDNF genes. Am J Med Genet B Neuropsychiatr Genet 2007; 144(6):820-823.

108. Carter CJ. eIF2B and oligodendrocyte survival: where nature and nurture meet in bipolar disorder and schizophrenia? Schizophr Bull 2007; 33(6):1343-1353.

109. Liu M, Ling SH, Li WB, Wang CY, Chen DF, Wang G. An association study between GRIN1, BDNF genes and bipolar disorder. Yi Chuan 2007; 29(1):41-46.

110. Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, et al. Greater cortical gray matter density in lithium-treated patients with bipolar disorder. Biol Psychiatry 2007; 62(1):7-16.

111. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. J Psychiatr Res 2007; 41(12):979-990.

112. Carter CJ. Multiple genes and factors associated with bipolar disorder converge on growth factor and stress activated kinase pathways controlling translation initiation: implications for oligodendrocyte viability. Neurochem Int 2007; 50(3):461-490.

113. Kato T. Molecular genetics of bipolar disorder and depression. Psychiatry Clin Neurosci 2007; 61(1):3-19.

114. Savitz J, van der Merwe L, Stein DJ, Solms M, Ramesar R. Genotype and childhood sexual trauma moderate neurocognitive performance: a possible role for brain-derived neurotrophic factor and apolipoprotein E variants. Biol Psychiatry 2007; 62(5):391-399.

115. MacKinnon DF, Zamoiski R. Panic comorbidity with bipolar disorder: what is the manic-panic connection? Bipolar Disord 2006; 8(6):648-664.

116. Shaltiel G, Chen G, Manji HK. Neurotrophic signaling cascades in the pathophysiology and treatment of bipolar disorder. Curr Opin Pharmacol 2007; 7(1):22-26.

117. Borkowska A, Wilkosc M, Tomaszewska M, Rybakowski J. Working memory: neuropsychological and neurobiological issues. Psychiatr Pol 2006; 40(3):383-399.

118. Muller DJ, de Luca V, Sicard T, King N, Strauss J, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: family-based association study. Br J Psychiatry 2006; 189:317-323.

119. Rao JS, Ertley RN, Lee HJ, DeMar JC, Arnold JT, Rapoport SI, et al. n-3 polyunsaturated fatty acid deprivation in rats decreases frontal cortex BDNF via a p38 MAPK-dependent mechanism. Mol Psychiatry 2007; 12(1):36-46.

120. Chen PS, Peng GS, Li G, Yang S, Wu X, Wang CC, et al. Valproate protects dopaminergic neurons in midbrain neuron/glia cultures by stimulating the release of neurotrophic factors from astrocytes. Mol Psychiatry 2006; 11(12):1116-1125.

121. Manji HK, Quiroz JA, Payne JL, Singh J, Lopes BP, Viegas JS, et al. The underlying neurobiology of bipolar disorder. World Psychiatry 2003; 2(3):136-146.

122. Prickaerts J, Moechars D, Cryns K, Lenaerts I, van Craenendonck H, Goris I, et al. Transgenic mice overexpressing glycogen synthase kinase 3beta: a putative model of hyperactivity and mania. J Neurosci 2006; 26(35):9022-9029.

123. Tsai SJ. The P11, tPA/plasminogen system and brain-derived neurotrophic factor: Implications for the pathogenesis of major depression and the therapeutic mechanism of antidepressants. Med Hypotheses 2007; 68(1):180-183.

124. Schule C, Zill P, Baghai TC, Eser D, Zwanzger P, Wenig N, et al. Brain-derived neurotrophic factor Val66Met polymorphism and dexamethasone/CRH test results in depressed patients. Psychoneuroendocrinology 2006; 31(8):1019-1025.

125. Michelon L, Meira-Lima I, Cordeiro Q, Miguita K, Breen G, Collier D, et al. Association study of the INPP1, 5HTT, BDNF, AP-2beta and GSK-3beta GENE variants and restrospectively scored response to lithium prophylaxis in bipolar disorder. Neurosci Lett 2006; 403(3):288-293.

126. Slopien A, Dmitrzak-Weglarz M, Rybakowski F, Rajewski A, Hauser J. Genetic background of ADHD: genes of the serotonergic system, other candidate genes, endophenotype. Psychiatr Pol 2006; 40(1):33-42.

127. Kremeyer B, Herzberg I, Garcia J, Kerr E, Duque C, Parra V, et al. Transmission distortion of BDNF variants to bipolar disorder type I patients from a South American population isolate. Am J Med Genet B Neuropsychiatr Genet 2006; 141(5):435-439.

128. Craddock N, Forty L. Genetics of affective (mood) disorders. Eur J Hum Genet. 2006; 14(6):660-668.

129. Okada T, Hashimoto R, Numakawa T, Iijima Y, Kosuga A, Tatsumi M, et al. A complex polymorphic region in the brain-derived neurotrophic factor (BDNF) gene confers susceptibility to bipolar disorder and affects transcriptional activity. Mol Psychiatry 2006; 11(7):695-703.

130. Masui T, Hashimoto R, Kusumi I, Suzuki K, Tanaka T, Nakagawa S, et al. Lithium response and Val66Met polymorphism of the brain-derived neurotrophic factor gene in Japanese patients with bipolar disorder. Psychiatr Genet 2006; 16(2):49-50.

131. Chenu F, Bourin M. Potentiation of antidepressant-like activity with lithium: mechanism involved. Curr Drug Targets 2006; 7(2):159-163.

132. Rybakowski JK, Borkowska A, Skibinska M, Szczepankiewicz A, Kapelski P, Leszczynska-Rodziewicz A, et al. Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. Psychiatry Clin Neurosci 2006; 60(1):70-76.

133. Hayden EP, Nurnberger JI. Molecular genetics of bipolar disorder. Genes Brain Behav 2006; 5(1):85-95.

134. Althoff RR, Faraone SV, Rettew DC, Morley CP, Hudziak JJ. Family, twin, adoption, and molecular genetic studies of juvenile bipolar disorder. Bipolar Disord 2005; 7(6):598-609.

135. Green EK, Raybould R, Macgregor S, Hyde S, Young AH, O'Donovan MC, et al. Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. Br J Psychiatry 2006; 188:21-25.

136. Filus JF, Rybakowski J. Neurotrophic factors and their role in the pathogenesis of affective disorders. Psychiatr Pol 2005; 39(5):883-897.

137. Wada A, Yokoo H, Yanagita T, Kobayashi H. Lithium: potential therapeutics against acute brain injuries and chronic neurodegenerative diseases. J Pharmacol Sci 2005; 99(4):307-321.

138. Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. Schizophr Bull 2006; 32(1):9-16.

139. Levinson DF. The genetics of depression: a review. Biol Psychiatry 2006; 60(2):84-92.

140. Rybakowski JK, Borkowska A, Skibinska M, Hauser J. Illness-specific association of val66met BDNF polymorphism with performance on Wisconsin Card Sorting Test in bipolar mood disorder. Mol Psychiatry 2006; 11(2):122-124.

141. Bachmann RF, Schloesser RJ, Gould TD, Manji HK. Mood stabilizers target cellular plasticity and resilience cascades: implications for the development of novel therapeutics. Mol Neurobiol 2005; 32(2):173-202.

142. Chuang DM. The antiapoptotic actions of mood stabilizers: molecular mechanisms and therapeutic potentials. Ann N Y Acad Sci 2005; 1053:195-204.

143. Lohoff FW, Sander T, Ferraro TN, Dahl JP, Gallinat J, Berrettini WH. Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. Am J Med Genet B Neuropsychiatr Genet 2005; 139(1):51-53.

144. Geller B, Tillman R. Prepubertal and early adolescent bipolar I disorder: review of diagnostic validation by Robins and Guze criteria. J Clin Psychiatry 2005; 66 Suppl 7:21-28.

145. Kato T, Kuratomi G, Kato N. Genetics of bipolar disorder. Drugs Today 2005; 41(5):335-344.

146. Rybakowski JK, Suwalska A, Skibinska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Permoda A, et al. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. Pharmacopsychiatry 2005; 38(4):166-170.

147. Tsai SJ. TrkB partial agonists: potential treatment strategy for major depression. Med Hypotheses 2007; 68(3):674-676.

148. Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, et al. Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. Biol Psychiatry 2005; 58(4):307-314.

149. Maier W, Hofgen B, Zobel A, Rietschel M. Genetic models of schizophrenia and bipolar disorder: overlapping inheritance or discrete genotypes? Eur Arch Psychiatry Clin Neurosci 2005; 255(3):159-166.

150. Gourevitch R. Neurobiological aspects of bipolar disorder. Encephale 2005; 31:S19-22.

151. Abdolmaleky HM, Thiagalingam S, Wilcox M. Genetics and epigenetics in major psychiatric disorders: dilemmas, achievements, applications, and future scope. Am J Pharmacogenomics 2005; 5(3):149-160.

152. Yatham LN. Translating knowledge of genetics and pharmacology into improving everyday practice. Bipolar Disord 2005; 7 Suppl 4:13-20.

153. Lang UE, Hellweg R, Kalus P, Bajbouj M, Lenzen KP, Sander T, et al. Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology 2005; 180(1):95-99.

154. Craddock N, O'Donovan MC, Owen MJ. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. J Med Genet 2005; 42(3):193-204.

155. Neves-Pereira M, Cheung JK, Pasdar A, Zhang F, Breen G, Yates P, et al. BDNF gene is a risk factor for schizophrenia in a Scottish population. Mol Psychiatry 2005; 10(2):208-212.

156. Skibinska M, Hauser J, Czerski PM, Leszczynska-Rodziewicz A, Kosmowska M, Kapelski P, et al. Association analysis of brain-derived neurotrophic factor (BDNF) gene Val66Met polymorphism in schizophrenia and bipolar affective disorder. World J Biol Psychiatry 2004; 5(4):215-220.

157. Rowe MK, Chuang DM. Lithium neuroprotection: molecular mechanisms and clinical implications. Expert Rev Mol Med 2004; 6(21):1-18.

158. Adams JH, Wigg KG, King N, Burcescu I, Vetro A, Kiss E, et al. Association study of neurotrophic tyrosine kinase receptor type 2 (NTRK2) and childhood-onset mood disorders. Am J Med Genet B Neuropsychiatr Genet 2005; 132(1):90-95.

159. Strauss J, Barr CL, George CJ, King N, Shaikh S, Devlin B, et al. Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. Am J Med Genet B Neuropsychiatr Genet 2004; 131(1):16-19.

160. Laeng P, Pitts RL, Lemire AL, Drabik CE, Weiner A, Tang H, et al. The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. J Neurochem 2004; 91(1):238-251.

161. Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2004; 161(9):1698-1700.

162. Kunugi H, Iijima Y, Tatsumi M, Yoshida M, Hashimoto R, Kato T, et al. No association between the Val66Met polymorphism of the brain-derived neurotrophic factor gene and bipolar disorder in a Japanese population: a multicenter study. Biol Psychiatry 2004; 56(5):376-378.

163. Payne JL. The role of estrogen in mood disorders in women. Int Rev Psychiatry 2003; 15(3):280-290.

164. Oswald P, Del-Favero J, Massat I, Souery D, Claes S, Van Broeckhoven C, et al. Non-replication of the brain-derived neurotrophic factor (BDNF) association in bipolar affective disorder: a Belgian patient-control study. Am J Med Genet B Neuropsychiatr Genet 2004; 129(1):34-35.

165. Karege F, Schwald M, Papadimitriou P, Lachausse C, Cisse M. The cAMP-dependent protein kinase A and brain-derived neurotrophic factor expression in lymphoblast cells of bipolar affective disorder. J Affect Disord 2004; 79(1-3):187-192.

166. Karege F, Schwald M, El Kouaissi R. Drug-induced decrease of protein kinase a activity reveals alteration in BDNF expression of bipolar affective disorder. Neuropsychopharmacology 2004; 29(4):805-812.

167. Tsai SJ. Is mania caused by overactivity of central brain-derived neurotrophic factor? Med Hypotheses 2004; 62(1):19-22.

168. Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF, Stanley Neuropathology Consortium. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. Mol Psychiatry 2004; 9(6):609-20, 544.

169. Maier W, Zobel A, Rietschel M. Genetics of schizophrenia and affective disorders. Pharmacopsychiatry 2003; 36 Suppl 3:S195-202.

170. Hong CJ, Huo SJ, Yen FC, Tung CL, Pan GM, Tsai SJ. Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. Neuropsychobiology 2003; 48(4):186-189.

171. Einat H, Manji HK, Gould TD, Du J, Chen G. Possible involvement of the ERK signaling cascade in bipolar disorder: behavioral leads from the study of mutant mice. Drug News Perspect 2003; 16(7):453-463.

172. Rybakowski JK, Borkowska A, Czerski PM, Skibinska M, Hauser J. Polymorphism of the brain-derived neurotrophic factor gene and performance on a cognitive prefrontal test in bipolar patients. Bipolar Disord 2003; 5(6):468-472.

173. Green E, Craddock N. Brain-derived neurotrophic factor as a potential risk locus for bipolar disorder: evidence, limitations, and implications. Curr Psychiatry Rep 2003; 5(6):469-476.

174. Schulze TG, Hardy J, McMahon FJ. Inconsistent designs of association studies: a missed opportunity. Mol Psychiatry 2003; 8(9):770-772.

175. Einat H, Yuan P, Gould TD, Li J, Du J, Zhang L, et al. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. J Neurosci 2003; 23(19):7311-7316.

176. Nakata K, Ujike H, Sakai A, Uchida N, Nomura A, Imamura T, et al. Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder. Neurosci Lett 2003; 337(1):17-20.

177. Molnar M, Potkin SG, Bunney WE, Jones EG. MRNA expression patterns and distribution of white matter neurons in dorsolateral prefrontal cortex of depressed patients differ from those in schizophrenia patients. Biol Psychiatry 2003; 53(1):39-47.

178. Manji H. Depression, III: treatments. Am J Psychiatry 2003; 160(1):24.

179. Wank R. Schizophrenia and other mental disorders require long-term adoptive immunotherapy. Med Hypotheses 2002; 59(2):154-158.

180. Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. Neuropharmacology 2002; 43(7):1173-1179.

181. Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacol Bull 2001; 35(2):5-49.

182. Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet 2002; 71(3):651-655.

183. Sklar P, Gabriel SB, McInnis MG, Bennett P, Lim YM, Tsan G, et al. Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. Mol Psychiatry 2002; 7(6):579-593.

184. Manji HK, Chen G. PKC, MAP kinases and the bcl-2 family of proteins as long-term targets for mood stabilizers. Mol Psychiatry 2002; 7 Suppl 1:S46-56.

185. Duman RS. Synaptic plasticity and mood disorders. Mol Psychiatry 2002; Suppl 1:S29-34.

186. Young LT. Postreceptor pathways for signal transduction in depression and bipolar disorder. J Psychiatry Neurosci 2001; 26 Suppl:S17-22.

187. Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry 2000; 48(8):766-777.

188. Martin A, Kaufman J, Charney D. Pharmacotherapy of early-onset depression. Update and new directions. Child Adolesc Psychiatr Clin N Am 2000; 9(1):135-157.

189. Xu J, Liu Y, Wang P, Li S, Wang Y, Li J, et al. Positive association between the brain-derived neurotrophic factor (BDNF) gene and bipolar disorder in the Han Chinese population. Am J Med Genet B Neuropsychiatr Genet 2009; DOI: 10.1002/ajmg.b.30953.

190. Krelling R, Cordeiro Q, Miracca E, Gutt EK, Petresco S, Moreno RA, et al. Molecular genetic case-control women investigation from the first Brazilian high-risk study on functional psychosis. Rev Bras Psiquiatr 2008; 30(4):341-345.

191. Krelling R, Cordeiro Q, Miracca E, Gutt EK, Petresco S, Moreno RA, et al. Molecular genetic case-control women investigation from the first Brazilian high-risk study on functional psychosis. Rev Bras Psiquiatr 2008; DOI: 10.1590/S1516-4446008005000013.

192. Altar CA, Vawter MP, Ginsberg SD. Target identification for CNS diseases by transcriptional profiling. Neuropsychopharmacology 2009; 34(1):18-54.

193. Tseng M, Alda M, Xu L, Sun X, Wang JF, Grof P, et al. BDNF protein levels are decreased in transformed lymphoblasts from lithium-responsive patients with bipolar disorder. J Psychiatry Neurosci 2008; 33(5):449-453.

194. Post RM. Promising avenues of therapeutics for bipolar illness. Dialogues Clin Neurosci 2008; 10(2):193-201.

195. De Luca V, Strauss J, Semeralul M, Huang S, Li PP, Warsh JJ, et al. Analysis of BDNF Val66Met allele-specific mRNA levels in bipolar disorder. Neurosci Lett 2008; 441(2):229-232.

196. Fan J, Sklar P. Genetics of bipolar disorder: focus on BDNF Val66Met polymorphism. Novartis Found Symp 2008; 289:60-72.

197. Kanazawa T, Glatt SJ, Kia-Keating B, Yoneda H, Tsuang MT. Meta-analysis reveals no association of the Val66Met polymorphism of brain-derived neurotrophic factor with either schizophrenia or bipolar disorder. Psychiatr Genet 2007; 17(3):165-170.

198. Farmer A, Elkin A, McGuffin P. The genetics of bipolar affective disorder. Curr Opin Psychiatry 2007; 20(1):8-12.

199. Skowronek MH, Georgi A, Jamra RA, Schumacher J, Becker T, Schmael C, et al. No association between genetic variants at the ASCT1 gene and schizophrenia or bipolar disorder in a German sample. Psychiatr Genet 2006; 16(6):233-234.

200. Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. Brain Res Brain Res Rev 2004; 45(2):104-114.

201. Hashimoto R, Fujimaki K, Jeong MR, Senatorov VV, Christ L, Leeds P, et al. Neuroprotective actions of lithium. Seishin Shinkeigaku Zasshi 2003; 105(1):81-86.

202. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 2001; 50(4):260-265.

203. Huston P, Naylor CD. Health services research: reporting on studies using secondary data sources. CMAJ 1996; 155(12):1697-1709.

204. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ 1998; 316(7125):140-144.

205. Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ, et al. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry 2009; 14(2):156-174.

206. Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, Segala M, Giacopuzzi M, et al. Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients. Eur Neuropsychopharmacol 2006; 16(8):620-624.

207. Gronli O, Stensland GO, Wynn R, Olstad R. Neurotrophic factors in serum following ECT: A pilot study. World J Biol Psychiatry 2007; 21:1-7.

208. Marano CM, Phatak P, Vemulapalli UR, Sasan A, Nalbandyan MR, Ramanujam S, et al. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. J Clin Psychiatry 2007; 68(4):512-517.

209. Lee HY, Kim YK. Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. Neuropsychobiology 2008; 57(4):194-199.

210. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord 2007; 100(1-3):279-281.

211. Berk M, Conus P, Lucas N, Hallam K, Malhi GS, Dodd S, et al. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord 2007; 9(7):671-678.

212. Kim B, Kim CY, Hong JP, Kim SY, Lee C, Joo YH. Brain-derived neurotrophic factor Val/Met polymorphism and bipolar disorder. Association of the Met allele with suicidal behavior of bipolar patients. Neuropsychobiology 2008; 58(2):97-103.

213. Tsai SJ. TrkB partial agonists: potential treatment strategy for epilepsy, mania, and autism. Med Hypotheses 2006; 66(1):173-175.

214. Knable MB. Schizophrenia and bipolar disorder: findings from studies of the Stanley Foundation Brain Collection. Schizophr Res 1999; 39(2):149-52.

Table 1. Characteristics of the studies included in the meta-analysis of serum or plasma BDNF levels in bipolar disorder.

Study	Year	Subjects	N	Gender M/F	Age*	Length of Illness*	YMRS*	HDRS*	Medication	Country
Kauer-Sant'Anna M Early-stage (22)	2009	Euthymia Control	26 26	13/13 10/16	22.40 ± 3.90 22.10 ± 3.60	2.1 ± 2.9 ---	1.53 ± 2.80 ---	3.80 ± 7.10 ---	Mood stabilizers, antipsychotics, antidepressants	Canada
Kauer-Sant'Anna M Late-stage (22)	2009	Euthymia Control	30 30	9/21 11/19	41.40 ± 8.40 43.20 ± 6.40	13.90 ± 5.12 ---	3.60 ± 4.10 ---	9.20 ± 6.00 ---	Mood stabilizers, antipsychotics, antidepressants	Brazil
Dias VV (24)	2009	Euthymia Control	65 30	24/41 14/36	37.80 ± 10.51 33.60 ± 9.66	13.30 ± 13.78 ---	1.00 ± 1.70 ---	2.50 ± 2.36 ---	Lithium, valproate, antidepressants	Spain
Machado-Vieira R (15)	2007	Mania Control	30 30	7/23 7/23	26.00 ± 4.00 26.50 ± 5.20	NA ---	36.9- ± 5.00 ---	NA ---	Drug-free	Brazil
Oliveira GS (19)	2009	Mania Depression Control	24 20 22	8/24 2/18 5/17	42.69 ±10. 46 35.75 ± 10.48 35.24 ± 8.07	14.73 ± 8.69 15.37 ± 9.32 ---	32.21 ±10.15 3.85 ± 3.90 ---	6.88 ± 6.99 21.45 ± 7.68 ---	Drug-free, mood stabilizers, typical and atypical antipsychotics, antidepressants	Brazil
Fernandes BS (20)	2009	Depression Control	40 30	13/27 12/18	41.32 ± 8.45 41.00 ± 11.99	NA ---	NA ---	23.40 ± 7.53 ---	Lithium, valproate, antidepressants, antipsychotics	Brazil

Yoshimura R (18) ‡	2006	Mania Depression Control	12 6 20	 8/10‡ 9/11	 34.00 ± 15.00‡ 30.00 ± 11.00	0.51 ± 0.32 3.02 ± 1.13 ---	22.00 ± 5.00 0.0 ---	0.0 24.00 ± 6.00 ---	Lithium, valproate	Japan
Tramontina J (17)	2006	Euthymia Control	114 137	32/82 45/92	42.54 ± 11.51 44.08 ± 13.81	18.28 ± 12.53 ---	3.92 ± 3.29 ---	9.27 ± 3.74 ---	---	Brazil
Monteleone P (21)	2008	Euthymia Control	28 22	11/17 8/14	44.42 ± 10.80 40.10 ± 16.40	15.32 ± 10.80 ---	1.10 ± 1.84 ---	1.60 ± 1.92 ---	Drug-free, lithium, valproate, carbamazepine	Italy
Cunha AC (14)	2006	Mania Depression Euthymia Control	32 21 32 32	18/14 6/15 12/20 12/20	40.13 ± 12.60 40.71 ± 9.25 40.28 ± 11.90 40.69 ± 12.12	12.78 ± 9.62 19.50 ± 14.17 17.34 ± 11.88 ---	34.47 ± 7.06 5.10 ± 3.19 3.16 ± 5.44 ---	5.16 ± 3.39 22.81 ± 4.36 4.28 ± 4.16 ---	Lithium, valproate, carbamazepine, typical and atypical antipsychotics, antidepressants	Brazil
Langan C (26)	2009	Euthymia Control	24 22	14/10 10/12	40.75 ± 9.01 40.36 ± 7.91	14.33 ± 9.39 ---	0.24 ± 0.64 ---	0.65 ± 1.06 ---	Lithium, valproate, carbamazepine	Ireland
Tramontina JF (16)	2009	Mania Control	10 10	5/5 5/5	34.90 ± 13.85 34.41 ± 3.97	11.00 ± 10.74 ---	26.20 ± 9.55 ---	2.18 ± 0.06 ---	Lithium, typical and atypical antipsychotics	Brazil
Palomino A (13)	2006	Mania Control	14 12	8/6 8/4	25.93 ± 6.88 26.27 ± 7.27	0.24 ± 0.43 ---	29.50 ±11.61 ---	17.36 ± 10.36 ---	Drug-naive and first episode	Spain
Mackin P (23)	2007	Depression Control	20 14	19/1 12/2	48.6 ± 10.80 43.7 ± 12.90	NA ---	3.6 ± 3.8 ---	18.1 ± 9.9 ---	Mood stabilizers, atypical antipsychotics, antidepressants	United Kingdom

Abbreviations: BDNF, brain-derived neurotrophic factor. YMRS, Young Mania Rating Scale. HDRS, Hamilton Depression Rating Scale. NA, not available.

* Mean ± standard deviation.

--- Control (not applicable).

‡Refers to manic and depressive patients together (no data according to the mood state available).

Table 2. Studies included that evaluated serum or plasma brain-derived neurotrophic factor (BDNF) levels in healthy subjects and in subjects with bipolar disorder according to mood state.

Studies and mood state		**Bipolar Disorder**			**Control**		
Mania *vs*. control	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Cunha AB (14)	pg/ug protein	32	0.14	0.08	32	0.20	0.07
Yoshimura R (18) *****	pg/ml	12	24.30	7.9	20	25.40	11.7
Palomino A (13) *****	ng/ml	14	3.79	1.99	12	7.92	3.95
Machado-Vieira R (15) *****	pg/ml	30	224.80	76.50	30	318.50	114.20
Tramontina JF (16)	pg/ug protein	10	0.21	0.10	10	0.31	0.05
Oliveira GS (19)	pg/ug protein	22	0.28	0.11	24	0.40	0.12
Total		**122**			**128**		
Depression *vs*. control	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Cunha AB (14)	pg/ug protein	21	0.15	0.13	32	0.20	0.07
Yoshimura R (18) *****	pg/ml	06	16.10	8.5	20	25.40	11.7
Mackin P (23)	pg/ml	20	13,755.2	7,932.2	14	13,400.4	9,107
Fernandes BS (20)	pg/ug protein	40	0.15	0.08	30	0.38	0.12
Oliveira GS (19)	pg/ug protein	20	0.22	0.17	22	0.40	0.12
Total		**107**			**118**		
Euthymia *vs*. control	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Cunha AB (14)	pg/ug protein	32	0.19	0.08	32	0.20	0.07
Tramontina J (17)	pg/ug protein	114	0.14	0.08	137	0.16	0.08
Monteleone P (21)	ng/ml	28	27.9	14.8	22	42.5	12.5
Langan C (26)	ng/ml	24	35.92	8.23	22	33.55	11.86
Dias VV (24)	pg/ug protein	65	0.28	0.21	50	0.24	0.21
Kauer-Sant'Anna M (EaS) (22)	pg/ug protein	26	0.91	0.22	26	0.77	0.20
Kauer-Sant'Anna M (LaS) (22)	pg/ug protein	30	0.33	0.16	30	0.57	0.24
Total		**319**			**319**		
Total		**548**			**565**		

*BDNF assessed in plasma. All other studies assessed BDNF in serum.

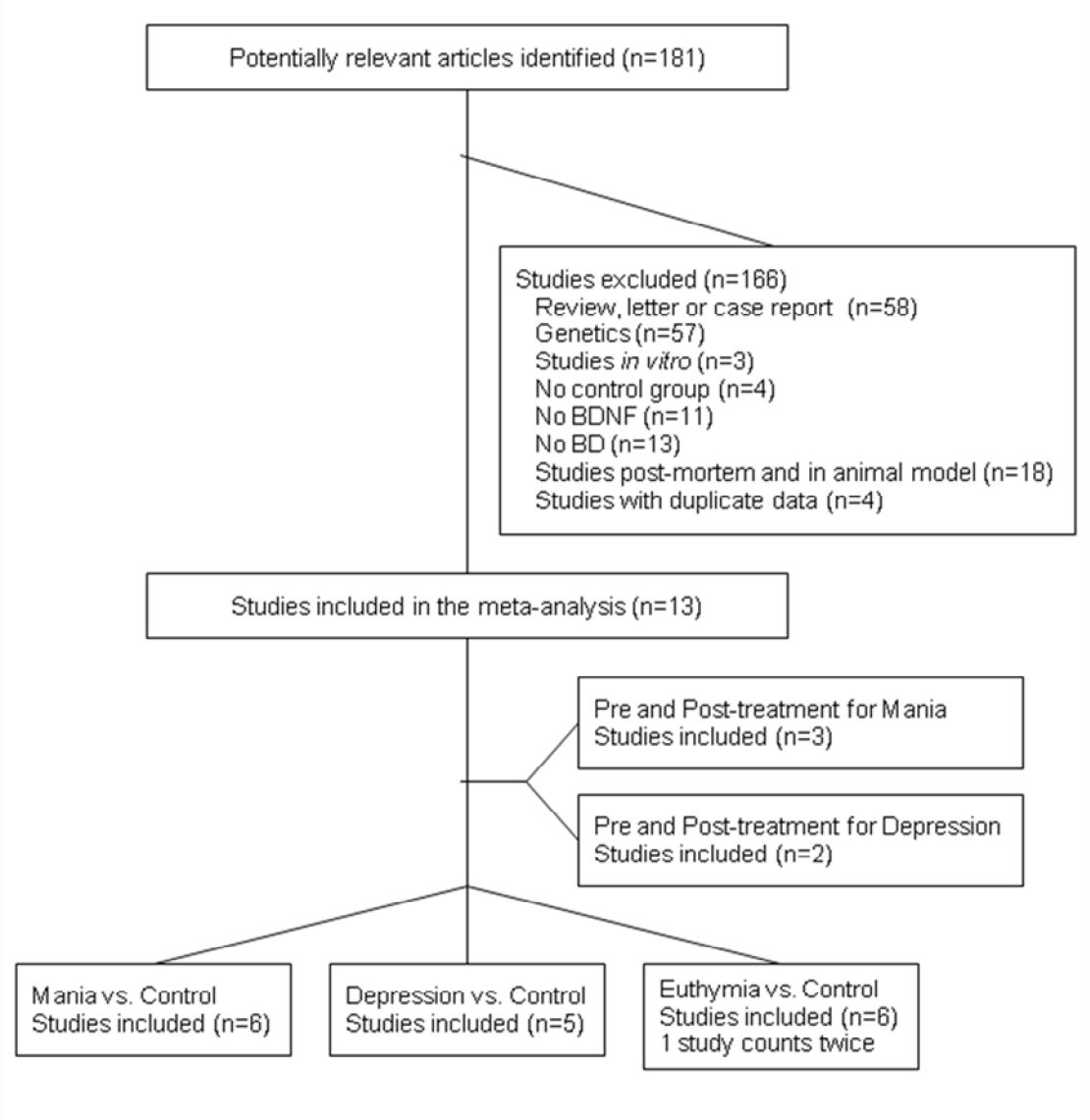

Figure 1. Flow diagram of the meta-analysis of brain-derived neurotrophic factor (BDNF) in bipolar disorder (BD).

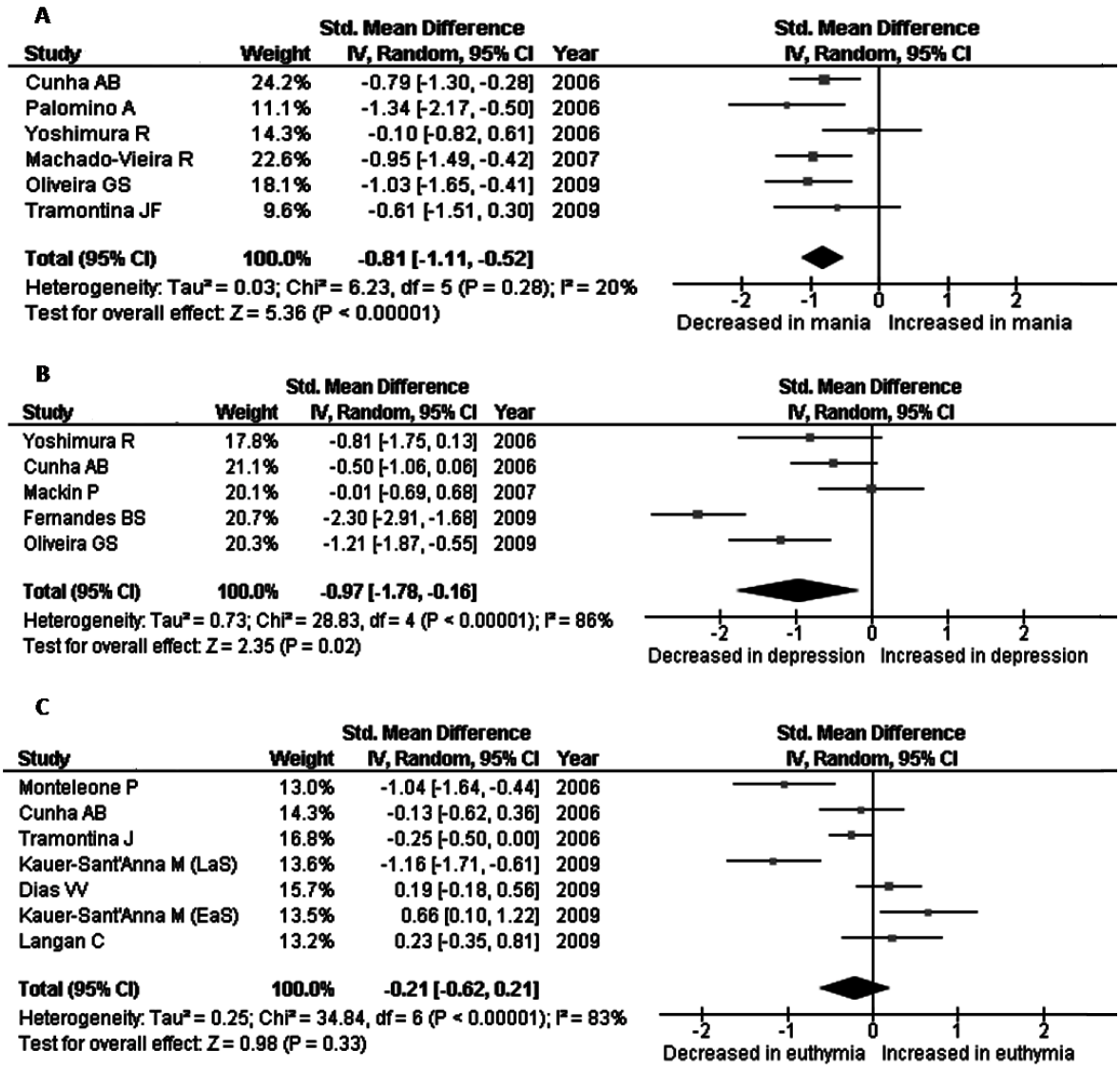

Figure 2. Forest plot graphs of the effect size (ES) estimates of serum or plasma brain-derived neurotrophic factor (BDNF) in subjects with bipolar disorder according to mood state and in healthy controls. **(A)** Patients during manic episodes *vs.* control. **(B)** Patients during depressive episodes *vs.* control. **(C)** Patients during euthymia *vs.* control. Positive ES denotes increased BDNF, and negative ES denotes decreased BDNF levels. Std. mean difference = standardized mean difference (ES). CI = Confidence Interval.

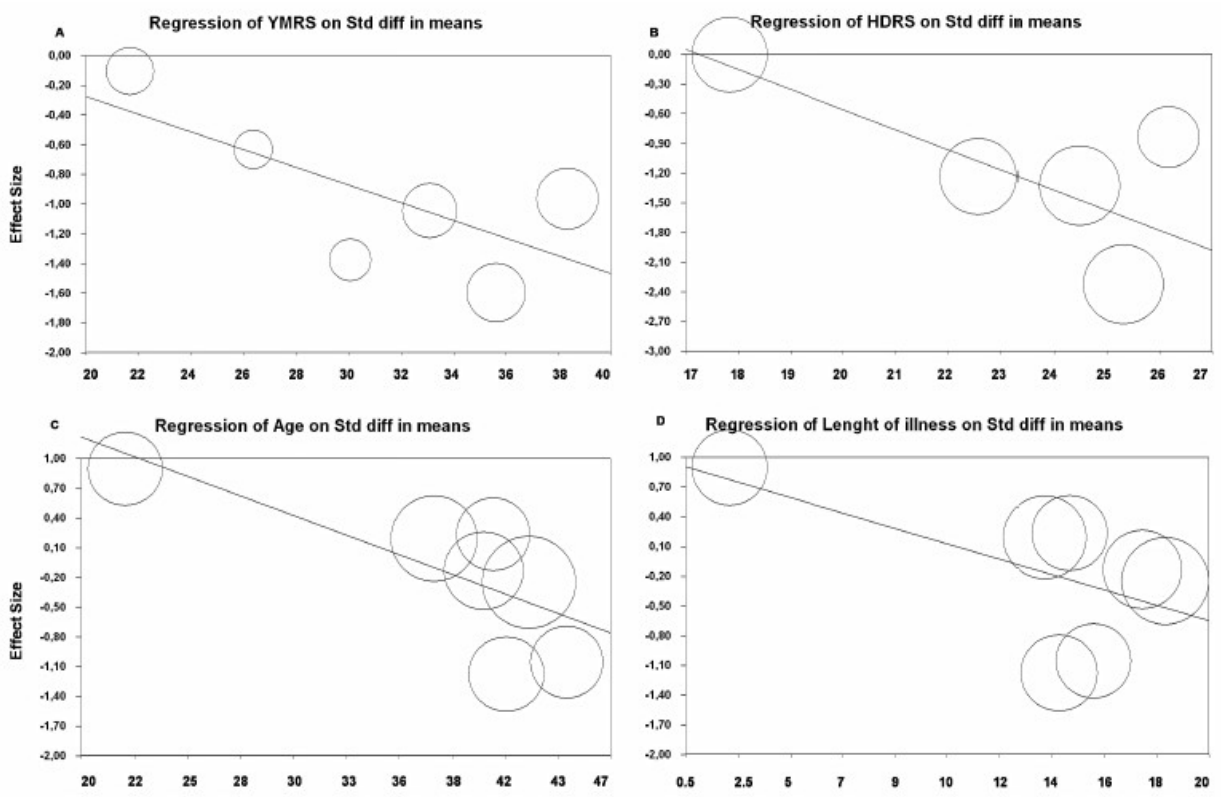

Figure 3. Meta-regression of moderators of brain-derived neurotrophic factor (BDNF). **(A)** Meta-regression on the effects of the Young Mania Rating Scale (YMRS) on the effect size (ES) for the difference between BDNF in manic bipolar disorder patients and controls. Slope = -0.0006, Q = 5.21, d.f. = 1, *p* = 0.02. **(B)** Meta-regression on the effects of the Depression Rating Scale (HDRS) on the ES for the difference between BDNF in depressive bipolar disorder patients and controls. Slope = -0.002, Q = 7.98, d.f. = 1, *p* = 0.004. **(C)** Meta-regression on the effects of age in years on the effect size (ES) for the difference between BDNF in euthymic bipolar disorder patients and controls. Slope = -0.0007, Q = 10.02, d.f. = 1, *p* = 0.001. **(D)** Meta-regression on the effects of the length of illness in years on the ES for the difference between BDNF in euthymic bipolar disorder patients and controls. Slope = -0.0007, Q = 4.06, d.f. = 1, *p* = 0.04. The circle size reflects the weight that a study obtained in the meta-regression.

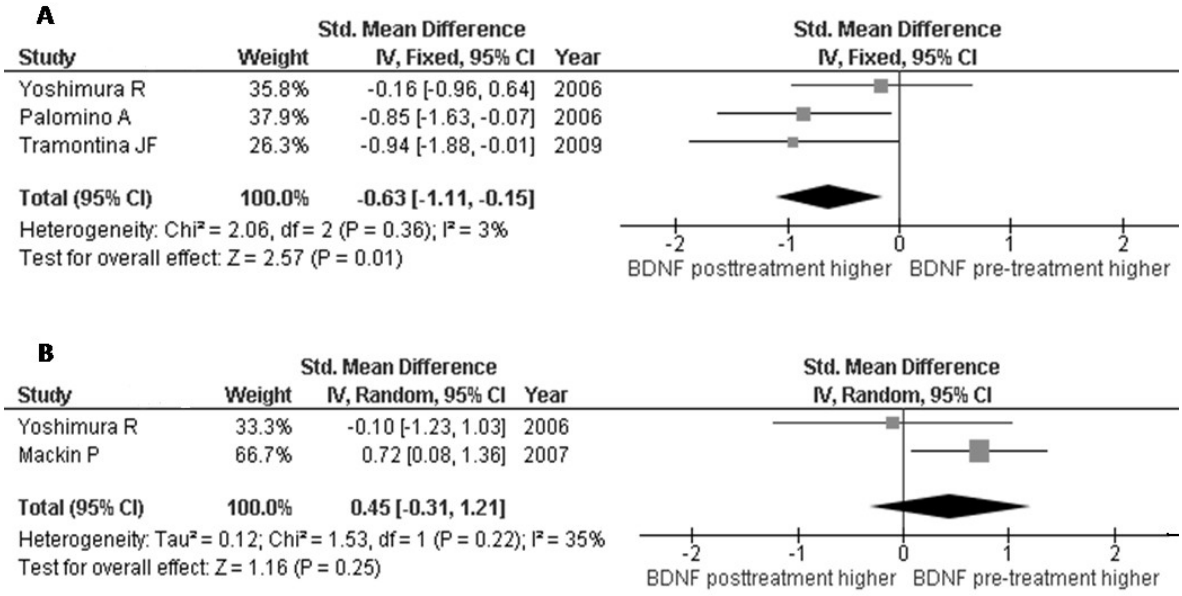

Figure 4. Forest plot graphs of the effect size (ES) estimates of serum or plasma brain-derived neurotrophic factor (BDNF) in subjects with bipolar disorders before and after pharmacological treatment for a current mood episode. **(A)** BDNF in patients in a current manic episode. **(B)** BDNF in patients in a current depressive episode. A negative ES denotes an increase in BDNF levels following pharmacological treatment, and a positive ES denotes decreased BDNF levels after pharmacological treatment. Std. mean difference = standardized mean difference (ES). CI = Confidence Interval.

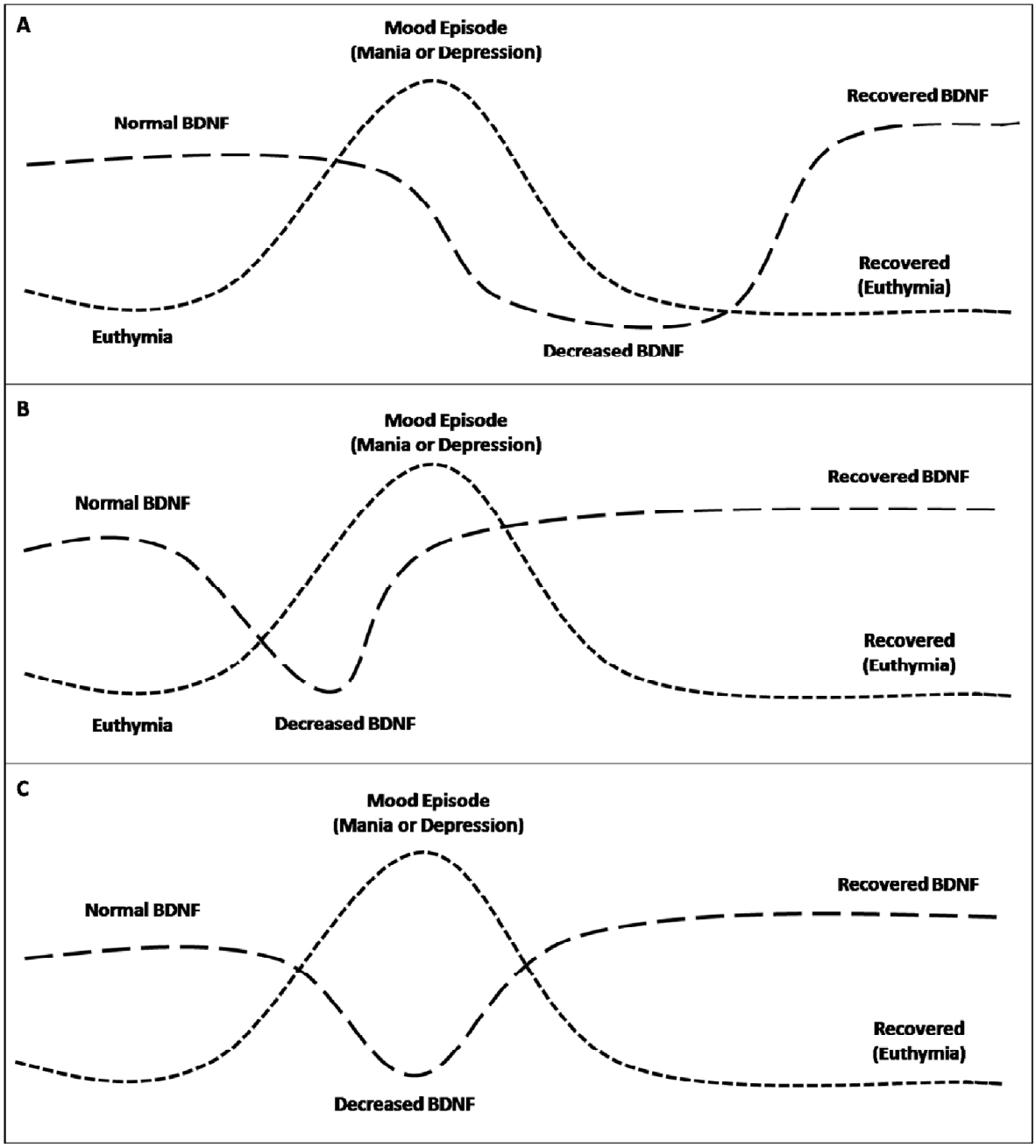

Figure 5. Serum or plasma brain-derived neurotrophic factor (BDNF) in subjects with bipolar disorder as a state-marker of manic and depressive episodes. **(A)** BDNF decreases as a consequence of a mood episode. **(B)** BDNF decreases as a predictor of a mood episode. **(C)** BDNF decreases concomitant to a mood episode.

Supplementary Material. List of studies excluded from the meta-analysis.

Study	Characteristics of excluded studies
Kapczinski F (41)	Editorial about BDNF on staging. Reanalysis data study.
Gallinat J (44)	Study is about N-acetylaspartate and not BDNF levels.
Tramontina JF (45)	Study about BDNF gene val66met polymorphism.
Dutt A (46)	COMT, BDNF, 5-HTT, NRG1 and DTNBP1 genes in psychosis.
Hammonds MD (47)	Study about levels of BDNF in hippocampus and not serum or plasma.
Vinberg M (48)	Study about BDNF Val66Met polymorphism with no control group.
Szczepankiewicz A (49)	Study about FYN kinase gene and not serum or plasma BDNF.
Fukuchi M (50)	Study is about BDNF gens in an animal model.
Fernandes B (27)	Study about serum BDNF in BD and MDD with no control group.
Sümegi A (51)	Review about quetiapin in BD.
Kawashima K (52)	Study about schizophrenia and not BD.
Dunham JS (53)	Study about BDNF in hippocampus.
Barnett JH (54)	Study about BDNF polymorphism.
Xu J (189)	Study about BDNF gene in BD.
Szczepankiewicz A (55)	Association study of FYN polymorphisms in BD.
Matsuo K (56)	Study about BDNF factor Val66Met polymorphism in BD.
Kapczinski F (57)	Comments to the article of Monteleone *et al*.
Mick E (58)	Genetic study in children with no control group.
Petryshen TL (59)	Population genetic study of BDNF.
Gerard S (60)	Review of medications for BD.
Mick E (61)	Genetic study in children with no control group.
Mirakhur A (62)	Genetic study about BDNF valine (66) methionine variant.
Krelling R (191)	Molecular genetics case-control study of Val66Met BDNF.

Krelling R (190)	Molecular genetics case-control study of Val66Met BDNF.
Le-Niculescu H (63)	Study of genome-wide association data for BD.
Dmitrzak-Weglarz M (64)	Association studies of the BDNF gene polymorphism in BD.
Rybakowski JK (65)	Review about Val66Met polymorphism in BD.
Liu L (66)	Study about BDNF factor gene and BD.
Altar CA (67)	Study with no BD patients.
Altar CA (192)	Review of target identification by transcriptional profiling.
Yatham LN (43)	Reanalysis of Kauer-Sant'Anna *et al.*
Kim B (212)	BDNF factor Val/Met polymorphism in BD.
Kapczinski F (42)	Reanalysis of Cunha *et al.*
Savitz J (68)	Family-based genetic study of endophenotypes in BD.
Berk M (69)	Review about early interventions in BD.
Tseng M (193)	BDNF measured in lymphoblasts *in vitro* and not in serum or plasma.
Tsai SJ (70)	Review of BDNF and antidepressant action.
Chang YC (71)	BDNF assessed in and bcl-2 expression levels in rat frontal cortex.
Chepenik LG (72)	BDNF val66met variation on hippocampus.
Post RM (194)	Review about new therapeutics for BD.
Pandey GN (73)	BDNF factor gene expression in children.
Vincze I (74)	BDNF genetic study in BD.
De Luca V (195)	Val66Met allele-specific mRNA levels in BD.
Kapczinski F (75)	Review about BDNF and neuroplasticity in BD.
Fan J (196)	Review of genetics of BD and BDNF.
Castrén E (76)	Review about neurotrophins in depression and antidepressants.
Kloos A (77)	Review of biological basis of BD in children and adolescents.
Grassi-Oliveira R (78)	Study of plasma BDNF in MDD.

Abdolmaleky HM (79)	Review of epigenetic in major psychiatric disorders.
Feng Y (80)	BDNF genetic study in MDD.
Yuan TF (81)	Comment.
Pillai A (82)	Study about BDNF RNAm in BD with no control group.
Serretti A (83)	Review about genetic of BD.
Mill J (84)	Genetic study in BD.
Otsuki K (85)	Study about neurotrophins others than BDNF in MDD.
Geller B (86)	Genetic study in children.
Terao T (87)	Review about BDNF and mania.
Tang J (88)	Study about BDNF gene in BD.
Chen L (89)	Genetic association study of BDNF in MDD.
Stahl LA (90)	Study about omega-3 fatty acids in mood disorders.
McGowan PO (91)	Review of epigenetics in mood disorders.
Sanacora G (92)	Review about mechanisms of action of medications for BD.
Kauer-Sant'Anna M (93)	Study of serum BDNF in BD with no control group.
Kozisek ME (94)	Review about BDNF and antidepressants mechanisms.
Yasuda S (95)	BDNF assessed in animal model.
Trajkovska V (96)	Study of whole blood BDNF with no control group.
McIntosh AM (97)	Letter of BDNF Val66Met polymorphism.
Frey BN (98)	Study about BDNF Val66Met polymorphism.
Itokawa M (99)	Review about molecular biology of depressive disorders.
Zai G (100)	Case report.
Yamasue H (101)	Genetic study in psychotic subjects.
Kauer-Sant'Anna M (102)	Study of hippocampal BDNF levels in rats.
McQuillin A (103)	Microarray study of the pharmacology of lithium on mouse brain.

Savitz JB (104)	Study about childhood abuse with no BDNF or patients with BD.
Post RM (105)	Review of kindling and sensitization as models for BD.
Walz JC (106)	Study of neurotrophin-3 in an animal model of mania.
Gama CS (25)	Overlap of the euthymic group with the study of Cunha *et al.*
Kanazawa T (197)	Meta-analysis of Val66Met polymorphism of BDNF in BD and SZ.
Rybakowski JK (107)	Study about Val66Met polymorphism in BD.
Carter CJ (108)	Review of nature and nurture in BD and SZ.
Liu M (109)	Study about BDNF genes in BD.
Bearden CE (110)	Study about cortical gray matter density in BD.
Carter CJ (112)	Review of genetic factors in BD.
Post RM (111)	Review about the role of BDNF in BD and MDD.
Kato T (113)	Review of molecular genetics of BD and MDD.
Savitz J (114)	Genetic study of BDNF gene in BD families.
MacKinnon DF (115)	Review about panic comorbidity with BD.
Farmer A (198)	Review about the genetics of BD.
Skowronek MH (199)	Study about genetic variants at the ASCT1 gene in BD and SZ.
Shaltiel G (116)	Review about neurotrophins and treatment of BD.
Borkowska A (117)	Review about working memory.
Müller DJ (118)	Family-based study about BDNF gene in BD.
Rao JS (119)	N-3 polyunsaturated fatty acid deprivation in cortex BDNF of rats.
Chen PS (120)	Study of *in vitro* neuron/glia cultures of BDNF.
Manji HK (121)	Review about the neurobiology of BD.
Prickaerts J (122)	Study of glycogen synthase kinase 3beta in rats. No BDNF.
Tsai SJ (123)	Review about BDNF and pathogenesis of MDD.
Schüle C (124)	Study of BDNF Val66Met polymorphism in MDD.

Michelon L (125)	Genetic study of BDNF in BD.
Slopien A (126)	Review of genetic background of ADHD. Not a study about BD.
Kremeyer B (127)	Genetic study of BDNF variants in BD.
Craddock N (128)	Review of genetics of mood disorders.
Okada T (129)	Genetic study of BDNF polymorphism in BD.
Masui T (130)	Study about BDNF Val66Met polymorphism BD.
Chenu F (131)	Review of potentiation of antidepressant activity with lithium.
Rybakowski JK (132)	Study of BDNF Val66Met polymorphism in BD and SZ.
Frey BN (10)	BDNF on hippocampus in an animal model of mania.
Hayden EP (133)	Review of molecular genetics of BD.
Althoff RR (134)	Review of molecular genetics of juvenile BD.
Green EK (135)	Study about genetic variation of BDNF in BD.
Filus JF (136)	Review of neurotrophins and its pathogenesis of BD.
Wada A (137)	Review of lithium in chronic neurodegenerative diseases.
Craddock N (138)	Review of genes of BD and SZ.
Levinson DF (139)	Review about genetics of MDD.
Rybakowski JK (140)	Study of val66met BDNF polymorphism in BD.
Bachmann RF (141)	Review of mood stabilizers in cellular plasticity.
Chuang DM (142)	Review about antiapoptotic actions of mood stabilizers.
Lohoff FW (143)	Study of the BDNF Val66Met polymorphism in BD.
Geller B (144)	Review of prepubertal and early adolescent BD.
Kato T (145)	Review about genetics of BD.
Rybakowski JK (146)	Study about polymorphism of the BDNF factor gene.
Tsai SJ (147)	Study about TrkB partial agonists in MDD. No BDNF assessment.
Tsai SJ (213)	Study about TrkB partial agonists. No BDNF assessment.

Schumacher J (148)	Study about BDNF polymorphism in MDD.
Maier W (149)	Review about genetic of BD and SZ.
Gourevitch R (150)	Review about neurobiological aspects of BD.
Abdolmaleky HM (151)	Review about genetics in major psychiatric disorders.
Yatham LN (152)	Review about BD.
Lang UE (153)	Study about BDNF polymorphism and anxiety.
Craddock N (154)	Review about genetics of BD and SZ.
Neves-Pereira M (155)	Study about BDNF gene in SZ.
Skibinska M (156)	Study about BDNF gene Val66Met polymorphism in BD and SZ.
Rowe MK (157)	Review about lithium neuroprotection.
Adams JH (158)	Study of neurotrophic tyrosine kinase receptor in mood disorders.
Strauss J (159)	Study of BDNF in adults with history of childhood mood disorder
Laeng P (160)	Study about valproic acid and GABA neurogenesis.
Geller B (161)	Genetic study of BDNF Val66Met in children with BD.
Kunugi H (162)	Genetic study of BDNF Val66Met polymorphism in BD.
Payne JL (163)	Review about estrogen in mood disorders in women.
Oswald P (164)	Genetic study of BDNF gene in BD.
Hashimoto K (200)	Review about BDNF in mood disorders.
Karege F (165)	Study about BDNF expression in lymphoblast cells in BD *in vitro.*
Karege F (166)	Study of BDNF *in vitro*.
Tsai SJ (167)	Review about BDNF and mania.
Knable MB (168)	*Post-mortem* study of molecular BDNF on hippocampus.
Maier W (169)	Review about genetic of BD and SZ.
Hong CJ (170)	Genetic study of BDNF polymorphism and mood disorders.
Einat H (171)	Review about the ERK signaling cascade in BD.

Rybakowski JK (172)	Study of the BDNF polymorphism in BD.
Green E (173)	Review about BDNF gene and BD.
Schulze TG (174)	Comment.
Einat H (175)	Study about mood stabilizers in the rat hippocampus.
Hashimoto R (201)	Review about the neuroprotective actions of lithium.
Nakata K (176)	Genetic study about BDNF gene and BD.
Molnar M (177)	Study about MRNA expression patterns in MDD and SZ.
Manji H (178)	Review about MDD.
Hashimoto R (180)	Study about lithium and BDNF in rodent cortical neurons.
Manji HK (181)	Review about neuroplasticity in severe mood disorders.
Wank R (179)	Review about immunotherapy in SZ.
Neves-Pereira M (182)	Genetic study of BDNF gene and BD.
Sklar P (183)	Genetic study of BDNF gene and BD.
Manji HK (184)	Review about PKC, MAP kinases and bcl-2 and mood stabilizers.
Duman RS (185)	Review about synaptic plasticity and mood disorders.
Young LT (186)	Review about postreceptor pathways in MDD and BD.
Chen B (202)	Study about BDNF on hippocampus.
Rajkowska G (187)	Postmortem studies in mood disorders. No BDNF assessment.
Martin A (188)	Review about pharmacotherapy of early-onset depression.
Knable MB (214)	Post-mortem study of BD and SZ.

BDNF: brain-derived neurotrophic factor

BD: bipolar disorder

SZ: schizophrenia

MDD: major depressive disorder

CONSIDERAÇÕES FINAIS

Nesta metanálise de BDNF sérico ou plasmático, os níveis de BDNF no BD durante as três diferentes fases da doença foram investigados em 548 pacientes com TB e em 565 indivíduos saudáveis oriundos de 13 estudos de caso-controle.

Esta é a primeira metanálise a ser realizada em BDNF periférico no TB de acordo com o estado de humor, em nível de proteínas, embora vários estudos tenham sido realizados sobre os genes do BDNF. Nós fomos capazes de demonstrar que os níveis de BDNF encontram-se diminuídos durante os episódios maníacos e depressivos. O BDNF periférico também apresenta relação com a gravidade dos episódios, ou seja, indivíduos com episódios mais graves apresentam níveis mais baixos de BDNF. Durante a eutimia, os níveis de BDNF estão normais, diminuindo com a idade e o tempo de doença. Além disso, o tratamento farmacológico aumenta os níveis de BDNF após um episódio maníaco.

Metanálises de estudos observacionais apresentam desafios particulares devido a diferenças inerentes aos diferentes estudos. No entanto, elas podem fornecer uma ferramenta para aumentar a nossa compreensão e quantificação das fontes de variabilidade nos resultados entre os estudos. Utilizando uma análise de metarregressão, fomos capazes de demonstrar que as fontes de variabilidade nos estudos conduzidos em eutimia foram diferenças na idade média e na duração da doença nos diferentes estudos.

Biomarcadores têm um lugar-comum na maioria das especialidades médicas, não só por melhorar a nossa compreensão da fisiopatologia das diversas doenças, mas também porque podem ser um instrumento útil para apoiar decisões clínicas: especificidades biológicas de um paciente individual podem fornecer informações importantes sobre o diagnóstico, prognóstico, ou predizer resposta ao tratamento. Até o

momento inexistem testes laboratoriais para transtornos psiquiátricos, incluindo o TB. Com base nos dados encontrados neste estudo, o BDNF periférico poderia ser um biomarcador dos diferentes estados de humor, refletindo atividade da doença. Esta metanálise demonstra que os níveis de BDNF no soro e plasma estão consistentemente reduzidos durante os episódios de humor, sendo discriminatórios dos estados de doença. Este poderia ser um primeiro passo para desenvolver um teste de laboratório. Alguns resultados preliminares do nosso grupo (Fernandes *et* al., dados não publicados) encontraram propriedades altamente promissoras para o BDNF sérico, com uma sensibilidade de 90% e uma especificidade de 85%, discriminando com boa acurácia mania e depressão de eutimia e controles. Um exame de sangue capaz de avaliar a atividade da doença pode ajudar na intervenção precoce e nos esforços de prevenção, bem como na monitorização da resposta aos diferentes tratamentos. Em conjunto com outras informações clínicas, tais testes poderiam desempenhar um papel importante na personalização do tratamento, aumentando sua eficácia. Além disso, há uma grande vantagem em utilizar os níveis de BDNF como um exame laboratorial, que é a não-invasividade da técnica, uma vez que o material para dosagem do BDNF pode ser acessado na periferia através de uma venopunção.

Uma aplicação interessante do BDNF periférico seria como uma ferramenta adjuvante para apoiar o diagnóstico correto do TB. Sinais e sintomas clínicos são a base central para o estabelecimento de diagnósticos psiquiátricos. Nesse contexto, a falta de especificidade do BDNF nos diversos transtornos psiquiátricos tem sido considerada uma limitação. No entanto, nós demonstramos em um trabalho recente que os níveis séricos de BDNF podem discriminar adequadamente a depressão bipolar da unipolar, com uma acurácia diagnóstica elevada de 95% (Fernandes *et* al., 2009). O diagnóstico diferencial da depressão bipolar e unipolar permanece um desafio, devido à

sobreposição das principais características clínicas e a dificuldade em determinar episódios passados de mania e hipomania. Este foi um estudo transversal com uma amostra relativamente pequena e replicações em estudos prospectivos são necessárias. No entanto, os resultados são promissores e, se replicados, o BDNF sérico pode tornar-se, no futuro, um teste acessível capaz de ajudar no diagnóstico correto da depressão bipolar.

Outra aplicação potencialmente interessante do BDNF sérico poderia ser como um biomarcador substituto de eficácia farmacológica. Nossos resultados fornecem evidências contundentes de que os níveis séricos de BDNF aumentam após o tratamento de mania aguda, semelhante ao que é visto com a expressão do BDNF em regiões específicas do cérebro em um modelo animal de mania com lítio ou valproato (Frey *et* al., 2006). Isto sugere que a medida do BDNF poderia ser usada para prever uma resposta individual ao tratamento da mania aguda logo após o início do tratamento, se uma relação puder ser estabelecida entre a mudança nos níveis de BDNF e a resposta clínica. As mudanças no BDNF em relação a um episódio de humor poderiam seguir três padrões diferentes. Primeiro, o BDNF sérico poderia diminuir após o início de um episódio de humor, com a recuperação do BDNF após o alcance da eutimia. Neste caso, as mudanças do BDNF seriam uma consequência dos episódios de humor e sua avaliação poderia ser útil como um biomarcador substituto. Em segundo lugar, o BDNF sérico poderia diminuir antes do início de um episódio de humor, recuperando-se antes do alcance da eutimia, o que tornaria o BDNF um preditor de episódios de humor e de resposta ao tratamento. Em terceiro lugar, diminuições no BDNF seriam concomitantes aos episódios de humor, refletindo a atividade da doença. O comportamento do BDNF e a sua relação temporal com os episódios de humor no TB permanecem largamente desconhecidos. No Transtorno

Depressivo Maior, existem alguns estudos mostrando que os níveis de BDNF normalizam somente após o alcance da eutimia e que o BDNF basal poderia ser um preditor de resposta ao tratamento (Bocchio-Chiavetto *et* al., 2006; Marano *et* al., 2007; Lee *et* al., 2008). No TB não há nenhum estudo sobre este tema.

Por último, o BDNF poderia desempenhar um papel como biomarcador de progressão da doença no modelo de estadiamento do TB. O modelo de estadiamento no TB é cada vez mais aceito como uma forma de transmitir informações significativas que possam predizer a probabilidade de resposta farmacológica, o prognóstico e o tipo de tratamento (Berk *et* al., 2007). Atualmente, o estadiamento no TB engloba características clínicas e neuropsicológicas, mas os biomarcadores permanecem um campo promissor nesse cenário. Mostramos neste estudo que, durante a eutimia, a idade e a duração da doença são moderadores importantes nos níveis de BDNF, sendo responsáveis, pelo menos em parte, pelas discrepâncias encontradas em estudos sobre o BDNF em eutimia na literatura. Em um estudo de nosso grupo demonstramos que o BDNF sérico tem propriedades promissoras para discriminar pacientes com menos de três anos de doença de pacientes com mais de dez anos de doença, com uma sensibilidade de 100%, especificidade de 88% e acurácia de 95% (Kapczinski *et* al., 2009). Isto sugere que o BDNF poderá desempenhar um papel como um biomarcador de gravidade e prognóstico da doença no futuro.

Algumas limitações devem ser apontadas. Nosso estudo incluiu pacientes com e sem uso de medicação. Isso poderia produzir um viés, uma vez que a medicação pode aumentar o BDNF. No entanto, recentemente, demonstramos que o BDNF no soro não diferiu entre os pacientes com TB com e sem medicação, quando em um episódio agudo (Oliveira *et* al., 2009). A principal limitação permanece na análise das mudanças BDNF após um tratamento para um episódio depressivo. Nesta análise, pudemos

incluir apenas dois estudos com resultados negativos. Deve-se reconhecer que nenhum dos tratamentos farmacológicos utilizados nestes estudos (Yatham *et* al., 2009), a risperidona e o mifepristone, são usados na depressão bipolar, e isto pode ter sido responsável por este resultado negativo. Estudos analisando mudanças nos níveis séricos de BDNF na depressão bipolar com estabilizadores de humor e antidepressivos são necessários para esclarecer este ponto.

Concluindo, este estudo resolve as discrepâncias encontradas em estudos anteriores sobre BDNF e demonstra que os níveis de BDNF estão reduzidos durante os episódios de humor, mas não durante a eutimia, e que os níveis de BDNF diminuem com a idade e com o tempo de doença. Há também dados fortes e consistentes sugerindo que os níveis de BDNF normalizam após o tratamento farmacológico para um episódio maníaco. Estes resultados são de grande importância para o campo, considerando a crescente evidência da participação do BDNF na fisiopatologia do TB. Além disso, eles apoiam a ideia da utilização dos níveis de BDNF periférico como um marcador biológico da atividade da doença durante os episódios de humor e como um possível biomarcador de progressão da doença no modelo de estadiamento. Futuros estudos são necessários para determinar se a medida de BDNF no soro ou plasma pode ser usada como um guia de tomada de decisão clínica.

ANEXO 1

PRISMA 2009 Flow Diagram