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

O FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO (BDNF) COMO BIOMARCADOR NOS TRANSTORNOS PSIQUIÁTRICOS MAIORES

Brisa Simões Fernandes

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Brisa Simões Fernandes

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Tese apresentada ao Programa de Pós-Graduação em Ciências Biológicas: Bioquímica, como requisito parcial para obtenção do título de doutor em Ciências Biológicas: Bioquímica

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"A scientific man ought to have no wishes, no affections

- a mere heart of stone."

Charles Darwin

"This world is not something in which certainty is possible ...

and therefore you must learn to act on things which

you still very much doubt."

Bertrand Russell

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À CAPES, pela bolsa que viabilizou o desenvolvimento deste trabalho.

APRESENTAÇÃO

Os resultados desta tese estão apresentados sob a forma de artigos científicos, em dois capítulos (Parte II). As seções Métodos, Resultados, Discussão e Referências Bibliográficas encontram-se nos próprios artigos.

Os itens Introdução (Parte I), Discussão e Conclusão (Parte III), encontrados nesta tese apresentam interpretação e comentários gerais sobre os capítulos contidos neste trabalho. As referências contidas no final da tese referem-se somente às citações que aparecem nos itens Introdução e Discussão.

SUMÁRIO

PARTE I

RESUMO

Tem sido postulado que os distúrbios psiquiátricos, incluindo a esquizofrenia, estão relacionados com uma redução da expressão do fator neurotrófico derivado do cérebro (BDNF). Nos últimos anos um número crescente de estudos clínicos que avaliaram BDNF no sangue (soro ou plasma obtido do sangue, nesta tese também designado como “periférico”) de indivíduos com esquizofrenia, transtorno bipolar e transtorno depressivo maior foram publicados. Nossos objetivos nesta tese foram verificar se o BDNF periférico está diminuído na esquizofrenia em conjunto com as sintomatologias positiva e negativa, e se aumenta posteriormente no decurso de um tratamento com antipsicóticos. Para isso, realizamos duas metanálises distintas de BDNF periférico em esquizofrenia, incluindo um total de 41 estudos e mais de 7.000 participantes. Níveis periféricos de BDNF no soro e no plasma estão moderadamente reduzidos em pessoas com esquizofrenia quando comparados com controles saudáveis a partir do primeiro episódio psicótico, e esta diminuição é acentuada com a progressão da doença. Além disso, a diminuição do BDNF periférico não se correlaciona com a gravidade dos sintomas positivos e negativos. No plasma, mas não no soro, os níveis periféricos de BDNF são sempre aumentados após o tratamento com antipsicóticos, independentemente da resposta do paciente ao medicamento. Depois, queríamos verificar a especificidade dos níveis de BDNF no soro e plasma nos transtornos psiquiátricos maiores. Para isso, foi realizada uma metanálise comparativa de 99 estudos de BDNF no soro e plasma na esquizofrenia, transtorno bipolar e transtorno depressivo maior, e verificamos que os níveis periféricos de BDNF estão igualmente reduzidos em todas

essas condições, mas que ele retorna ao normal durante a fase de remissão de transtorno bipolar e transtorno depressivo maior. Em conclusão, há evidências de que a esquizofrenia está relacionada com níveis alterados de BDNF periférico. Se estes níveis de BDNF estão causalmente relacionados com o desenvolvimento da esquizofrenia ou se eles são apenas um epifenômeno nesta patologia ainda precisa ser determinado. Além disso, os níveis de BDNF no soro e plasma são inespecíficos para a esquizofrenia, transtorno bipolar e transtorno depressivo maior, mas podem ser considerados um biomarcador de atividade de doença nessas condições.

ABSTRACT

It has been postulated that psychiatric disorders, including schizophrenia, are related with a lower expression of brain-derived neurotrophic factor (BDNF). In the last few years an increasing number of clinical studies assessing BDNF in serum and plasma of subjects with schizophrenia, bipolar disorder, and major depressive disorder have been published. The aims in this thesis were to verify if peripheral BDNF is decreased in SZ in tandem with positive and negative symptomatology, and if it increases subsequently in the course of antipsychotic treatment. For this, we conducted two distinct meta-analyses of peripheral BDNF in SZ including a total of 41 studies and more than 7,000 participants. Peripheral BDNF levels in serum and plasma are moderately reduced in persons with SZ when compared to controls following the first episode of psychosis, and this decrease is accentuated with the progression of the disorder. Mostly notably, the extent peripheral BDNF level decrease does not correlate with the severity of positive and negative symptoms. In plasma, but not serum, peripheral BDNF levels are always increased after antipsychotic treatment irrespective of the patient's response to the medication. After, we wanted to verify the specificity of serum and plasma BDNF levels in major psychiatric disorders. For this, we conducted a comparative meta-analysis of 99 studies of serum and plasma BDNF in schizophrenia, bipolar disorder, and major depressive disorder, and verified that peripheral BDNF levels are equally reduced in all these conditions, but that it returns to normal during the remission phase of bipolar disorder and major depressive disorder. In conclusion, there is compelling evidence that SZ is related to altered levels of peripheral BDNF. Whether these BDNF

levels are causally related to the development of SZ or if they are merely a pathology epiphenomenon remains to be seen. In addition, serum and plasma BDNF levels are unspecific for schizophrenia, bipolar disorder and major depressive disorder, but can be considered a biomarker of disease activity in these conditions.

LISTA DE ABREVIATURAS

APA	Associação Psiquiátrica Americana
AMPc	Monofosfato de 3', 5' –Adenosina cíclico
BDNF	Fator Neurotrófico Derivado do Cérebro
BPRS	Brief Psychiatric Rating Scale
CPF	Córtex Pré-Frontal
CREB	Proteína ligada ao fator de transcrição do AMPc
d.f.	Degrees of Freedom (Graus de Liberdade)
DM	Depressão Maior
DSM	Manual Diagnóstico e Estatístico de Transtornos 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
PANSS	Positive and Negative Symptoms Scale
P75 ^{NTR}	Receptor Pan – Neurotrofina
SNC	Sistema Nervoso Central

TB	Transtorno Bipolar
TB tipo I	Transtorno Bipolar do Tipo I
TrkB	Proteína Tirosina Quinase B
UFRGS	Universidade Federal do Rio Grande do Sul
VPT	Valproato
YMRS	Escala de Avaliação de Mania de Young

INTRODUÇÃO

Em Psiquiatria, a esquizofrenia, o Transtorno Bipolar (TB) e a Depressão Maior (DM) estão entre as patologias mais graves, possuindo um importante componente biológico, sendo por vezes chamadas de transtornos psiquiátricos maiores. No DSM-5 (APA, 2013), o capítulo referente ao TB foi colocado entre os referentes à esquizofrenia e DM, em reconhecimento de um contínuo entre as três patologias em termos de diagnóstico, sintomas, história familiar e genética.

Primeiramente, serão descritas brevemente cada uma dessas três patologias.

Epidemiologia e características clínicas

Esquizofrenia

Apesar de ser uma entidade nosológica há mais de um século, a esquizofrenia permanece a mais grave enfermidade mental, na qual o tratamento muitas vezes se mostra apenas uma medida paliativa. Desde a introdução dos primeiros antipsicóticos, pouca mudança houve em termos efetivos para resolução desta patologia. A esquizofrenia é uma doença mental crônica, caracterizada por distorções do pensamento, delírios bizarros, alterações na sensopercepção, déficits cognitivos e respostas emocionais inadequadas, que podem levar o paciente a variados graus de deterioração demencial e a uma significativa mudança na qualidade de vida destes indivíduos. Critérios diagnósticos claros são baseados em características fenomenológicas no DSM-5 (APA, 2013). É uma doença que atinge de 1% até 4% da população (Sartorius et al., 1986), considerando

todo seu espectro de sintomas (CID-10), e caracteriza-se por ser grave e produzir, inexoravelmente, comprometimento funcional cognitivo do individuo. Costuma ocorrer no final da adolescência e inicio da vida adulta, afetando ambos os sexos. A patologia tende a interferir no desempenho escolar e profissional destes pacientes, que terão dificuldade de ingressar na universidade, e de assumir posições de trabalho que exijam maior responsabilidade. Como resultado, o status social e econômico estes pacientes é reduzido. O individuo, na maioria das vezes, torna-se incapaz de gerenciar sua vida e constitui, então, um ônus para sua rede social e o Estado (Ustun, 1999). As estimativas de gestos no Brasil ainda são incipientes, porém o último levantamento realizado somente no estado de São Paulo mostra que os gastos anuais em despesas hospitalares, farmacológicas e sociais são de aproximadamente 192 milhões de dólares com a esquizofrenia (Leitão et al, 1998).

Os sintomas da esquizofrenia envolvem uma série de disfunções cognitivas e emocionais que acometem a percepção, o raciocínio lógico, a linguagem, o controle comportamental, o afeto, a fluência do pensamento, a prosódia do discurso, a capacidade hedônica, os impulsos, a memória e a atenção. Nenhum sintoma isolado é patognomônico de esquizofrenia: o diagnóstico envolve o reconhecimento de uma constelação de sinais e sintomas associados com prejuízo no funcionamento ocupacional ou social. Estes sintomas podem ser divididos em positivos (delírios, alucinações, discurso desorganizado, comportamento amplamente desorganizado) e negativos (embotamento afetivo, alogia e abulia) Os sintomas tem uma duração mínima de seis meses e incluem, no primeiro mês, sintomas da fase

ativa, ditos positivos, como: delírios, alucinações, discurso desorganizado, comportamento amplamente desorganizado ou catatônico, crises agressivas, agitação extrema e desagregação do pensamento; os sintomas negativos também podem ocorrer, sendo estes: embotamento afetivo, dificuldade de julgamento, depressão e falta de motivação (APA, 2013).

No momento, não é possível prevenir a esquizofrenia. Dessa forma, o foco comum é o tratamento e a reabilitação do paciente. A farmacoterapia tem provado ser o ponto-chave na terapêutica. Embora não curativas, as drogas antipsicóticas se estabeleceram como o tratamento primário para todos os estágios da doença, pois possibilitam uma redução no tempo de hospitalização e a possibilidade de manutenção dos pacientes por mais tempo em seus lares (Marder at al, 1991).

Entre 25% e 35% de todos os pacientes se mantêm refratários ao tratamento com antipsicóticos clássicos e cerca de 80% de todos os pacientes permanecem com sintomas negativos e cognitivos residuais (Davis, 1980; Haring et al, 1990).

Transtorno bipolar

O TB é um transtorno mental complexo e multifatorial, com episódios recorrentes associados com elevada morbidade clínica (Belmaker, 2004; Kilbourne at al, 2004), sendo dividido basicamente em tipos I e II, o primeiro apresentando episódios maníacos e o segundo hipomaníacos. 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 do 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 inicio dos sintomas é de 20 anos. 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, 2013) define a presença de um episódio maníaco como um período distinto de humor anormal e persistentemente elevado, expansivo ou irritável acompanhados por autoestima inflada ou grandiosidade, diminuição da necessidade de sono (por exemplo, sente-se descansado após apenas três horas de sono), taquilalia, fuga de idéias ou experiência subjetiva de que os pensamentos estão correndo, distratibilidade, aumento na atividade dirigida a objetivos ou agitação psicomotora, e envolvimento excessivo em atividades prazerosas que têm alto potencial para conseqüências dolorosas (por exemplo, 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 Episódio Depressivo Maior como humor deprimido ou perda do interesse e prazer acompanhados por humor deprimido na maior parte dos dias, acentuada diminuição do interesse ou prazer em todas ou quase todas as atividades na maior parte do dia, quase todos os dias, perda ou ganho significativo de peso sem estar em dieta (por exemplo, mais de 5% do peso corporal em um mês), insônia ou hipersonia quase todos os dias, agitação ou retardo motor quase todos os dias, fadiga ou perda de energia quase todos os dias, sentimento de inutilidade ou culpa excessiva ou inadequada, capacidade diminuída de pensar ou se concentrar ou indecisão, e 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.

Mesmo com todo avanço alcançado, o TB permanece uma doença recorrente. Alguns pacientes ficam estáveis e outros experimentam episódios freqüentes, 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 episódio (Post et al., 2003).

O número médio de episódios maníacos em pacientes com TB sem tratamento ao longo da vida é de 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 at 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, geralmente acompanhados por episódios depressivos maiores, enquanto que no TB tipo II não ocorrem episódios maníacos (APA, 2013).

Depressão Maior

A depressão é uma condição comum, de curso crônico e recorrente. Está frequentemente associada com incapacitação funcional e comprometimento da saúde física. Os pacientes deprimidos apresentam limitação da sua atividade e bem estar, além de uma maior utilização de serviços de saúde. O somatório do seu impacto e da sua grande prevalência na população geral faz a depressão ser considerada hoje um importante problema de saúde pública (Andrews, 2001). Há evidencias suficientes da eficácia das medicações antidepressivas no tratamento da depressão com efeito significativamente superior ao placebo, seja reduzindo os sintomas (resposta) ou eliminando-os (remissão), ao menos nos casos moderados e graves (Anderson et al., 2000) e na depressão psicótica (Spiker et al., 1985).

A evolução nas pesquisas sobre etiologia, fisiopatogenia e marcadores biológicos da depressão também é, de certa forma, frustrante. Os estudos que buscaram fatores biológicos associados à etiologia e

fisiopatogenia da depressão mostram resultados conflitantes, raramente replicados por diferentes grupos de pesquisa (Parker 2005).

Neurotrofinas nos transtornos psiquiátricos maiores

As bases biológicas do TB, DM e esquizofrenia incluem aspectos relacionados, entre outros, às vias neuro-hormonais, neurotransmissão, de transdução de sinal, de regulação da expressão gênica, estresse oxidativo, neuroplasticidade e alterações do sistema imunológico. Nesta tese nos ateremos às neurotrofinas, em particular o fator neurotrófico derivado do cérebro.

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

Os achados neuroquímicos relacionados nestas patologias 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 relacionados a alterações em funções cerebrais, incluindo neurotransmissão, neuroplasticidade, transdução de sinal intracelular e expressão gênica.

Em 1951 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 – 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-42Rac-Rho, como também MAPK, PL-3-kinase e phospholipase-C-C-y (PLC-y)). Estas vias de sinalização intracelular moduladas pela 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 demostrado 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 o 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). A Figura 1 abaixo ilustra os receptores do BDNF.

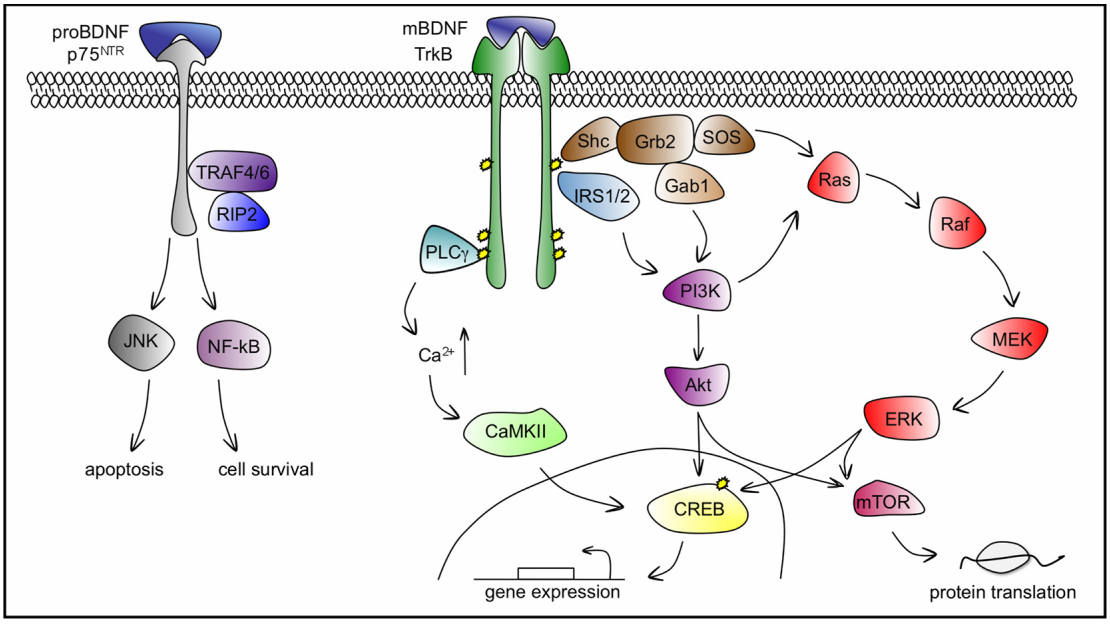

Figura 1. As vias de sinalização celular ativados pelos receptores TrkB e p75^{NTR} (Cunha et al., 2010).

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 especificas que ativam. Nos estudos sobre modelos de depressão,

os antidepressivos aumentam a sinalização do TrkB, sendo esta dependente da concentração de BDNF (Saarelain et al., 2003). Além disto, uma das vias que sabidamente previnem contra a apoptose é a cascata de sinalização promovida pela ligação de BDNF ao seu receptor TrkB (BDNF/TrkB) (Barde, 1994).

Diversos estudos têm sugerido que a indução do BDNF/TrkB é um dos mecanismos responsáveis pelos efeitos terapêuticos dos antipsicóticos, dos estabilizadores do humor e dos antidepressivos (Coyle e Duman, 2003; Ninuya et al., 1995). Por exemplo, tem sido demostrado que o uso do Li modula a fosforilação do receptor TrkB e do CREB (Einat et al., 2003; Rantemaki 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 at al., 2000).

BDNF

O BDNF foi descoberto em 1982 (Barde et al., 1982) como o segundo 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 estímulos 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). Abaixo, na Figura 2, podemos visualizar a liberação de BDNF produzido por antidepressivos ISRS.

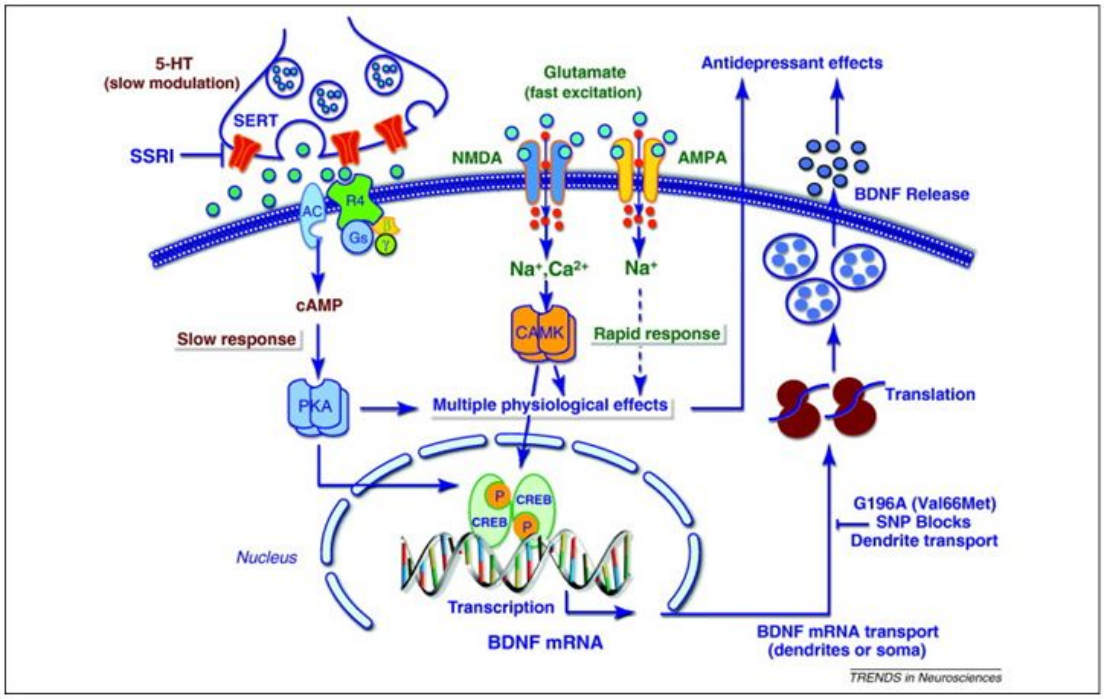

Figura 2. Aumento de BDNF na fenda sináptica pelo uso de antidepressivos do tipo Inibidores Seletivos da Recaptação da Serotonina (ISRS) (Duman e Voleti, 2012).

Existe um crescente corpo de evidências sugerindo que a via de sinalização do BDNF/TrkB parece estar envolvida na fisiopatologia dos transtornos do humor e da esquizofrenia, bem como na ação dos antidepressivos, estabilizadores de humor e antipsicóticos (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 neuroprotetoras 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; 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 platicidade 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 (Wadee et al., 2005).

BDNF como biomarcador nos transtornos psiquiátricos maiores

O BDNF no sangue periférico pode ser avaliado no soro e no plasma de uma forma praticamente 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 o 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, DM e esquizofrenia para ganhar alguns insights sobre a fisiopatologia destas doenças, que ainda são pouco compreendidas.

Há várias evidências que sugerem que os níveis de BDNF se alteram no soro e no plasma nos diferentes estados de humor, diminuindo nos episódios maníacos e depressivos, e normalizando na eutimia (Cunha et al., 2006; Palomino et al., 2006; Machado- Vieira et al., 2007; Tramontina et al., 2009; Yoshimura et al., 2006; Oliveira et al., 2009; Fernades et al., 2009 Monteleone et al., 2008; Mackin et al., 2007; Dias et al., 2009; Langan et al., 2009; Fernandes et al., 2011), como podemos ver a seguir na Figura 3, referentes a uma metanálise sobre BDNF sérico e plasmático no TB durante episódios maníacos, depressivos e eutimia (Fernandes et al., 2011).

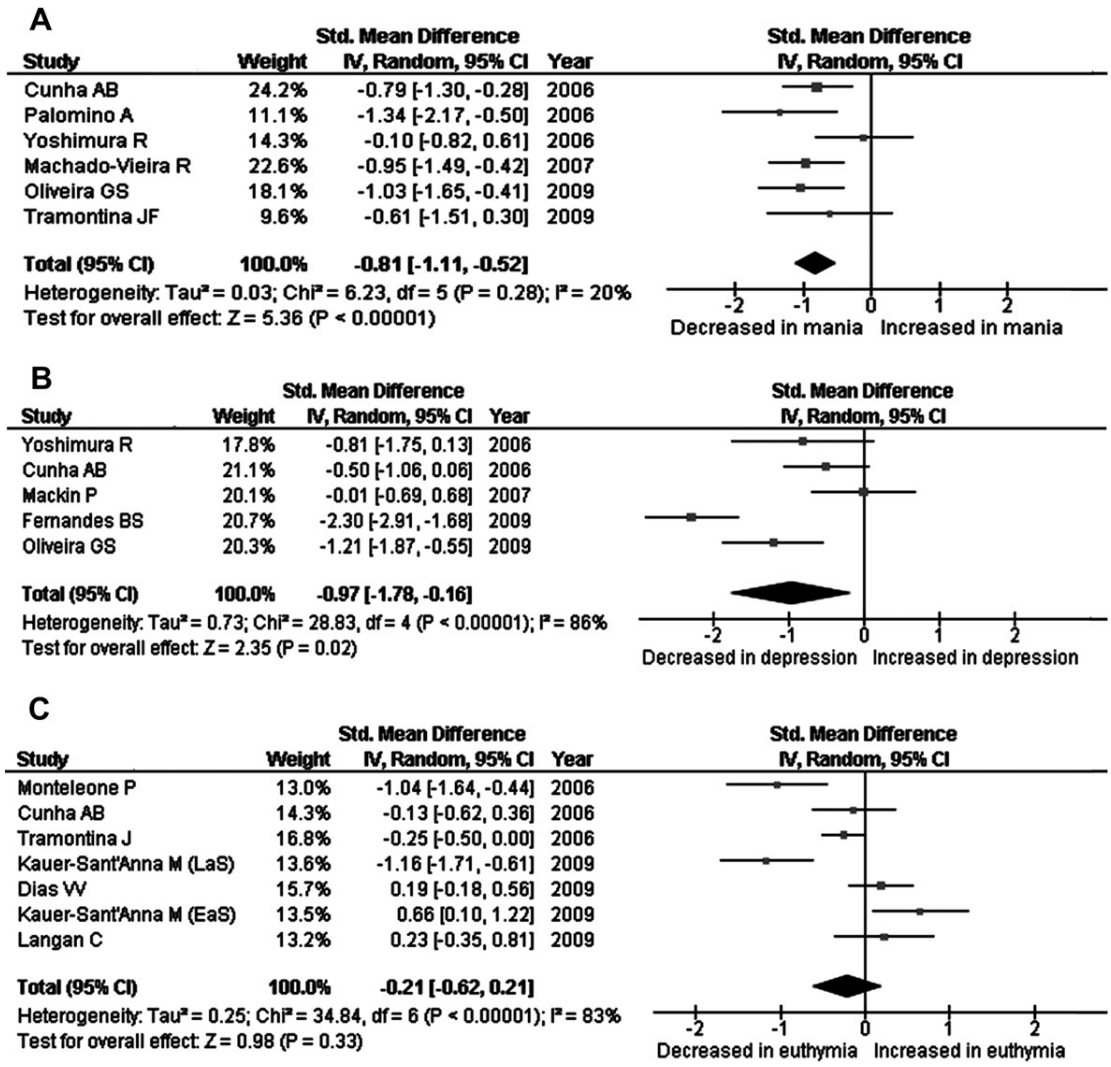

Figura 3. Forest Plot do BDNF sérico e plasmático no Transtorno Bipolar. O mesmo se encontra diminuído nos episódios agudos (mania e depressão) e normal na eutimia comparados com controles normais (Fernandes et al., 2011).

Além disso, há fortes evidências de que o BDNF se encontra diminuído nos episódios agudos de DM, porém se estes seguem reduzidos ou normalizam durante a remissão dos episódios depressivos é menos claro (Sen et al., 2008). Em 2013, foi publicada uma metanálise sobre BDNF sérico na DM, que mostrou níveis diminuídos de BDNF em sujeitos com DM

independente da presença de antidepressivos (Molendijk et al., 2013) (Figura 4) e que os níveis séricos de BDNF não se correlacionam com a gravidade dos sintomas depressivos em pacientes com e sem medicação.

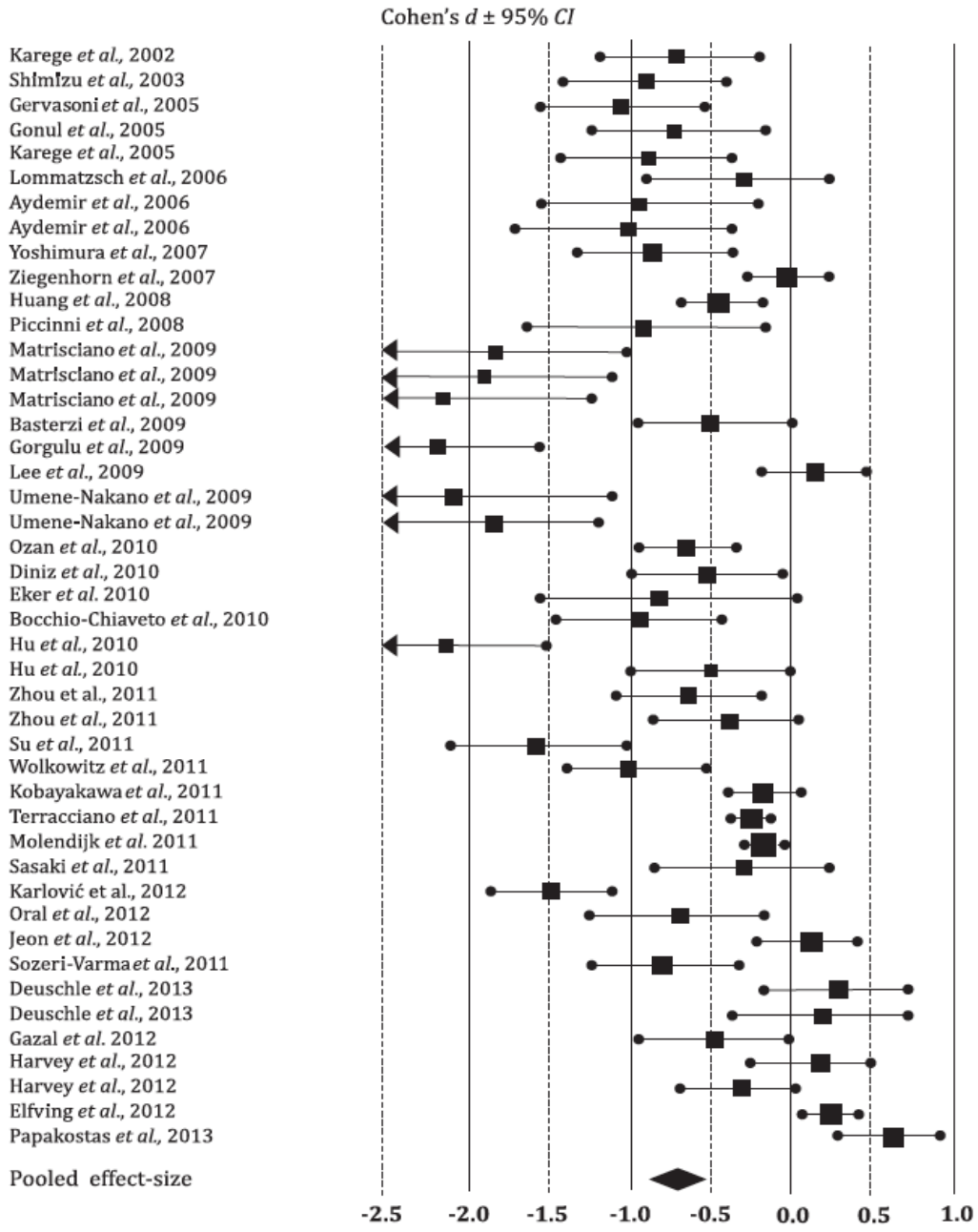

Figura 4. Forest Plot do BDNF sérico na Depressão Maior. O mesmo se encontra diminuído nos episódios agudos de depressão independente do uso de medicação (Molendijk et al., 2013).

Na esquizofrenia, uma metanálise publicada em 2010 envolvendo 16 artigos mostrou níveis diminuídos de BDNF em soro e plasma de indivíduos com esquizofrenia quando comparados com controles saudáveis (Green et al., 2010), a qual produziu, de acordo com os autores, evidência de moderada qualidade da diminuição dos níveis de BDNF, porém os resultados obtidos foram altamente heterogêneos, evidenciando grande discrepância entre os estudos (Figura 5).

Patient type		Hedges's g	Lower limit	Upper limit	p-Value	Patient mean	Control mean
Drug naive	Huang 2006^	-0.406	-1.055	0.243	0.220	10	96
Drug naive	Jindal 2010	-0.527	-1.033	-0.021	0.041	24	41
Drug naive	Jocker-Scherub 2006	-0.018	-0.333	0.298	0.913	102	61
Drug naive	Lee 2009^	0.378	-0.136	0.892	0.150	24	36
Drug naive	Palomino 2006^	-0.958	-1.586	-0.330	0.003	21	21
Drug naive	Rizos 2008	-1.299	-1.941	-0.658	0.000	37	15
Drug naive	Shimizu 2003^	-0.524	-1.117	0.069	0.084	15	40
Drug naive		-0.446	-0.850	-0.043	0.030		
Scz medicated	Grillo 2006	-1.349	-1.884	-0.814	0.000	44	25
Scz medicated	Huang 2006*	0.038	-0.232	0.307	0.784	116	96
Scz medicated	Ikeda 2008	-0.651	-0.968	-0.334	0.000	74	87
Scz medicated	Lee 2009*	0.351	-0.109	0.812	0.135	36	36
Scz medicated	Mackin 2007	-0.042	-0.709	0.625	0.902	20	14
Scz medicated	Palomino 2006*	-0.714	-1.327	-0.101	0.022	21	21
Scz medicated	Pirildar 2004	-1.748	-2.433	-1.062	0.000	22	22
Scz medicated	Reis 2008	1.776	1.158	2.394	0.000	40	20
Scz medicated	Shimizu 2003*	-0.057	-0.551	0.437	0.822	25	40
Scz medicated	Toyooka 2002	-0.843	-1.330	-0.356	0.001	34	35
Scz medicated	Vinogradov 2009	-0.593	-1.151	-0.035	0.037	56	16
Scz medicated	Xiu 2009	-0.931	-1.088	-0.773	0.000	364	323
Scz medicated	Yoshimura 2007	-0.415	-0.700	-0.130	0.004	89	104
Scz medicated		-0.401	-0.765	-0.036	0.031		

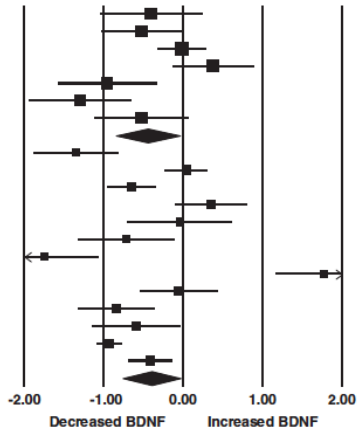

Figura 5. Forest Plot do BDNF sérico e plasmático na esquizofrenia. O mesmo se encontra diminuído independente do uso de medicação (Green et al., 2010).

Ainda quanto à esquizofrenia, há discrepâncias entre os estudos, por exemplo, alguns estudos mostram uma diminuição do BDNF, enquanto outros mostram ausência de diferença ou até aumento (Gama et al., 2007). No que se refere à relação entre os níveis de BDNF e a gravidade dos sintomas negativos e positivos, a controvérsia é ainda maior: alguns estudos

mostram uma correlação negativa entre os sintomas positivos e os níveis de BDNF sérico ou plasmático, outros mostram presença de correlação somente com os sintomas negativos, enquanto a maioria das publicações não evidenciam correlação entre os níveis de BDNF e a gravidade dos sintomas (Ajami et al., 2014; Gonzalez-Pinto et al., 2010; Jindal et al., 2010).

As inconsistências nos resultados entre os diferentes estudos podem ser devido a diferenças nas características da população estudadas ou a ausência de poder estatístico, devido a menor tamanho amostral.

Alguns estudos têm avaliado se o BDNF periférico se altera após o uso de antipsicóticos, mas os resultados aqui novamente são discrepantes. Assim, o papel do BDNF no tratamento da esquizofrenia continua sendo um campo pouco explorado.

Um outro ponto importante, porém praticamente inexplorado, é o do comportamento do BDNF periférico ao longo do espectro esquizoafetivo. Embora se saiba que o BDNF se encontra diminuído no TB, na DM e na esquizofrenia, se desconhece se a extensão da diminuição é equivalente nestas três patologias.

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 determinar 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 desta tese foi realizar uma metanálise dos níveis de BDNF de todos os estudos transversais e longitudinais de soro ou plasma em esquizofrenia disponíveis na literatura. Foram examinados o efeito de moderadores através de uma metarregressão. Também realizamos uma metanálise de todos os estudos que avaliaram os níveis de BDNF antes e após o tratamento farmacológico com antipsicóticos na esquizofrenia, a fim de analisar possíveis alterações nos níveis de BDNF com o tratamento. Após, realizamos uma metanálise comparativa dos níveis periféricos de BDNF na esquizofrenia, TB e DM, a fim de investigar se há diferenças entre os níveis de BDNF ao longo do espectro esquizoafetivo.

OBJETIVOS

1. Realizar uma metanálise dos níveis séricos e plasmáticos de BDNF na esquizofrenia em relação a controles saudáveis, avaliando o efeito de moderadores como gravidade dos sintomas positivos e negativos, tempo de doença, idade, dose de antipsicóticos, e índice de massa corporal, bem como uso de medicação e fonte do BDNF (soro ou plasma).
2. Realizar uma metanálise dos níveis séricos e plasmáticos de BDNF na esquizofrenia antes e depois do uso de antipsicóticos, avaliando o efeito de moderadores como gravidade dos sintomas positivos e negativos, tempo de doença, idade, dose de antipsicóticos, e tempo de tratamento, bem como uso de medicação e fonte do BDNF (soro ou plasma).
3. Realizar uma metanálise comparativa entre os níveis de BDNF na esquizofrenia, TB e DM, para avaliar a extensão da diminuição dos níveis de BDNF ao longo do espectro esquizoafetivo.

PARTE II

CAPÍTULO 1:

PERIPHERAL BRAIN-DERIVED NEUROTROPHIC FACTOR IN SCHIZOPHRENIA AND THE ROLE OF ANTIPSYCHOTICS: A SYSTEMATIC REVIEW AND META-ANALYSIS

ARTIGO PUBLICADO NA REVISTA *MOLECULAR PSYCHIATRY*

Molecular Psychiatry (2014), 1–12

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ORIGINAL ARTICLE

Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications

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It has been postulated that schizophrenia (SZ) is related to a lower expression of brain-derived neurotrophic factor (BDNF). In the past few years, an increasing number of divergent clinical studies assessing BDNF in serum and plasma have been published. It is now possible to verify the relationship between BDNF levels and severity of symptoms in SZ as well as the effects of antipsychotic drugs on BDNF using meta-analysis. The aims of this study were to verify if peripheral BDNF is decreased in SZ, whether its levels are correlated with positive and negative symptomatology and if BDNF levels change after antipsychotic treatment. This report consists of two distinct meta-analyses of peripheral BDNF in SZ including a total of 41 studies and more than 7000 participants: (1) peripheral BDNF levels in serum and plasma were moderately reduced in SZ compared with controls. Notably, this decrease was accentuated with the disease duration. However, the extent of peripheral BDNF level decrease did not correlate with the severity of positive and negative symptoms. (2) In plasma, but not serum, peripheral BDNF levels are consistently increased after antipsychotic treatment irrespective of the patient's response to medication. In conclusion, there is compelling evidence that there are decreased levels of peripheral BDNF in SZ, in parallel to previously described reduced cerebral BDNF expression. It remains unclear whether these systemic changes are causally related to the development of SZ or if they are merely a pathologic epiphenomenon.

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INTRODUCTION

In the past decade, it has been postulated that schizophrenia (SZ), a disorder associated with perturbations in synaptogenesis and neuroplasticity and with altered connectivity of neural networks,[1,2] is associated with altered neurotrophin levels in the brain, particularly a lowered expression of brain-derived neurotrophic factor (BDNF).[2–8] Mounting preclinical and clinical evidence has corroborated that BDNF levels are decreased in the prefrontal cortex and hippocampus in SZ, and that this decrease might be partly reversed by antipsychotics.[9–15]

BDNF, the most abundant neurotrophin in the central nervous system, crosses the blood–brain barrier (BBB),[16] and its levels in serum and plasma are highly correlated with BDNF levels in cerebrospinal fluid ($r = 0.8$)[17,18] and with cortical integrity,[19] although levels are ~10 and 500 times higher in plasma and serum, respectively, than in cerebrospinal fluid.[20] It is tempting to assume that peripheral BDNF levels mirror and as a result provide direct information about the protein's levels in the brain. The 'periphery as a window to the brain' concept has led to an ever-increasing number of clinical studies assessing BDNF in serum and plasma. Most of these studies[3–8,20–32] have shown a decrease in BDNF levels in SZ, which is why the protein is being considered both as an SZ biomarker and as a potential player in the process of neuroprogression in SZ and other neuropsychiatric disorders.[33] In extension of the neurotrophin hypothesis, the idea has arisen that BDNF and the severity of positive and negative symptoms in SZ behave in an orchestrated manner, with lower levels of the protein correlating with higher symptom intensity: indeed, some but not all studies demonstrated an inverse correlation between peripheral BDNF levels and positive and negative symptoms.[4,27,34–36] The neurotrophin hypothesis also assumes that one possible contributory mechanism of action of antipsychotic drugs, in relieving SZ symptoms, is by increasing BDNF levels in the brain. However, among some positive findings, most studies have failed to demonstrate an increase in peripheral BDNF levels following antipsychotic treatment.[4,8,28,37–39]

These inconsistent findings might be caused by heterogeneous patient populations or by small sample sizes lacking statistical power.[40] Meta-analysis is a recognized technique used to resolve discrepancies between studies. It is a quantitative method that combines results from independent studies to increase statistical power to derive more solid conclusions. This allows to distinguish small effects from no effect. It also helps to determine whether the variation in effects between studies is merely because of the expected random statistical fluctuation or instead to sample variations or trait assessment.[40,41] In addition, meta-regression may be used to evaluate confounders and discrepancies among different studies.[42,43] In 2010, a meta-analysis of 16 cross-sectional studies of persons with SZ in comparison with healthy subjects was published, showing a moderate decrease of peripheral BDNF levels in SZ.[44] Since then, a considerably greater number of studies has been published, particularly longitudinal studies, investigating

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changes in BDNF levels before and after the use of antipsychotics. Thus, the possibility to more definitively analyze the relationship between BDNF levels, severity of SZ symptoms and treatment response now emerges.

The aims of this study were to verify if peripheral BDNF levels are decreased in SZ, and whether its levels are correlated with positive and negative symptomatology. In addition, we wanted to find out whether BDNF levels change following antipsychotic therapy. With this in mind, we performed a meta-analysis of all cross-sectional studies of serum and plasma BDNF levels in SZ compared with healthy subjects. In addition, we evaluated longitudinal studies on BDNF levels before and after antipsychotic use, exploring its relations with positive and negative symptoms and response to treatment. This is now possible because of the large amount of data currently available and will help to clarify the role of peripheral BDNF as a biomarker in SZ and as a potential mechanism of action of antipsychotics.

MATERIALS AND METHODS

This study is comprised of two major meta-analyses: (1) a between-group meta-analysis comparing serum and plasma BDNF levels in persons with SZ and in healthy controls, and (2) a within-group meta-analysis comparing changes in BDNF levels before and after antipsychotic treatment. We adhered to the guidelines that are recommended by the preferred reporting items for systematic reviews and Meta-analyses of Observational Studies Statement (MOOSE)[41] and by the Cochrane Collaboration.[40] The literature search, decisions on inclusion, data extraction and quality control were all performed independently by two of the authors (BSF and PN).

Search strategy

We conducted a systematic search for all possibly eligible-English and non-English peer-reviewed articles to avoid language publication bias[45,46] using Medline, Embase, the Cochrane Library, Scielo, PsycInfo, Scopus and 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 (SZ OR schizoaffective OR schizophreniform OR schizophrenic OR psychosis). The latest search was performed in March of 2014. We then manually checked the reference sections of the publications found through our electronic search to identify additional studies that may have been missed. Study selection eligibility and exclusion criteria were prespecified.

Study selection

The inclusion criteria were: (1) adult subjects with SZ, schizoaffective or schizophreniform disorder as defined by American Psychiatric Association,[47] which for now on will be referred as SZ for purposes of simplicity; (2) pairwise comparison with a control group of healthy volunteers for the first meta-analysis, or longitudinal studies before and after use of antipsychotics for the second meta-analysis and (3) studies assessing circulating serum or plasma BDNF in human blood samples *in vivo*. An exclusion criterion was: (1) *post-mortem* studies (Supplementary Figure 1S). 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

Two reviewers (BSF and PN) independently extracted data (*n*, mean and s.d.) to avoid potential errors. We extracted data, by diagnostic status, regarding BDNF levels, sex, age, length of illness, body-mass index (BMI), daily dose of antipsychotics in chlorpromazine equivalents and the Positive and Negative Symptoms Scale (PANSS) total score, as well as its positive and negative subscores.[48] When studies reported other scales closely related to PANSS, such as the Brief Psychiatric Rating Scale,[49] the Scale for the Assessment of Positive Symptoms or the Scale for the Assessment of Negative Symptoms,[50] we converted their values into a PANSS score as suggested by the Cochrane Collaboration when performing meta-regressions with different but closely related scales.[40] This was carried out for seven studies.[6,26,30,36,51–53] According to information available in the studies, we performed a subgroup analysis considering subjects with SZ as first episode psychosis (less than one year of disease) or as non-first episode psychosis (more than 1 year of disease). Subjects with SZ were considered drug-naive when they had no lifetime exposition to any psychiatric medication and drug-free if they were off psychiatric medication for at least 1 week before the blood withdrawl. For the within-group meta-analysis, we further performed a subgroup analysis regarding the response to antipsychotic medication, which we defined as a reduction of at least 40% in the PANSS total score, or in PANSS positive scores if the former was not available.[54]

Discrepancies in data entry were double-checked by the reviewers with the original published data and consensus was reached. When the necessary data were not available from the published paper, we contacted the authors and requested for the necessary information. If the results were graphically presented and the authors could not provide the data, we used a method for data extraction from the graphs explained by Sistrom *et al.*[55] Whenever multiple reports pertained to the same groups of patients, we retained only the most comprehensive report for the meta-analyses calculations to avoid duplication of information; in the case of longitudinal pharmacologic studies, we included only the baseline information for the between-group meta-analysis, and used the follow-up information only for the within-group meta-analysis. When the longitudinal studies presented data on more than one-point follow-up, we considered only the longer one.

Quality assessment

We used the Newcastle–Ottawa Scale (NOS)[56] as recommended by the Cochrane Collaboration[40] to assess the quality of the eligible observational studies. For the between- and within-group meta-analyses, we used the NOS for case–control and for cohort studies, respectively. Overall quality score was defined as the frequency of criteria that were met by the particular study. The NOS scale contains eight items in the case–control and nine items in the cohort section, categorized into the three domains of selection, comparability, exposure and outcome (the last only for the cohort scale). A series of response options is provided for each item. A star system is used to enable semiquantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item, with the exception of the comparability domain, which allows the assignment of two stars. As such, the NOS ranges between zero and nine stars.[57] Item'non-response rate' from Exposure in the case–control scale was not applicable; therefore, a maximum of eight stars was considered. For the cohort scale, we considered the maximum as nine stars. Supplementary Table 1S (Supplementary Material) shows an evaluation of the included studies for possible bias. The quality score of the included studies ranged from one to six. All studies were included in the posterior analyses.

Publication bias

Studies with negative results are less likely to be published than studies with positive results.[40] To account for significant publication bias, we analyzed a funnel plot graph, a scatter plot of treatment effect against a measure of study size and the Egger test.[3,19–22] The trim-and-fill procedure,[58] a validated manner to estimate an effect size (ES) after bias has been taken into account, was performed in case of publication bias. Finally, the Fail-safe N test (file drawer statistic)[59] was used to quantify the number of possible negative omitted studies that would be required to make our results nonsignificant ($P > 0.05$).

Statistical analysis

Comprehensive meta-analysis Software version 2.0 (Borenstein, NH, USA) was used in all analyses. Because studies used different measurement methods, standardized mean difference estimates of the differences in BDNF levels between subjects with SZ and healthy controls were used as the ES,[40] using Hedges's adjusted *g*, which provides an unbiased ES adjusted for sample size, using the formula ((mean BDNF levels SZ – mean BDNF levels controls)/pooled s.d. of the mean) for the between-group meta-analysis and ((mean BDNF levels posttreatment – mean BDNF levels pre-treatment)/pooled s.d. of the mean) for the within-group meta-analysis. The 95% confidence interval (95% CI) of the ES was also computed. An ES of 0.2 is considered as indicating a low effect, meaning a small difference in BDNF levels between subjects with SZ and controls, an ES of 0.5 a moderate effect and an ES of 0.8 a large effect.[40]

We assessed the heterogeneity across studies using the Cochran *Q* test,[60] a weighted sum of the squares of the deviations of individual study ES estimates from the overall estimate and a *P*-value of < 0.10 was considered significant (i.e., showing heterogeneity). The inconsistency

across studies was then quantified with the I^2 metric,[43,61] which can be interpreted as the percentage of total variation across several studies because of heterogeneity, and it is considered substantial when $>50\%$. Since the analyses showed that the studies were heterogeneous, we pooled ES results from individual studies according to the unrestricted maximum-likelihood method of accounting for random effects, which allows population-level inferences and is more stringent than fixed-effect models.[42] Random-effect modeling assumes a genuine diversity in the results of various studies and incorporates a between-study variance into the calculations.[40]

Thereafter, we performed a cumulative meta-analysis, which addresses the impact of new studies on prior pooled results.[62,63] For this analysis, data were sorted in chronological order. The earliest available study was entered into the analysis first. At each step of the cumulative meta-analysis, one more study was added to the analysis and the mean ES and 95% CI were recalculated. The formulas for calculation of cumulative mean ES are the same as in the traditional meta-analysis; the only difference is that the mean is not calculated for the whole group of studies at once but is instead recalculated each time a new study is added to the analysis. This allows estimation of the contribution of individual studies, and the evolution of the magnitude and direction of research findings can be followed in more detail.

The direction of the ES was positive if subjects with SZ showed increased BDNF and negative if they showed decreased BDNF levels when compared with controls for the between-group meta-analysis. In the within-group meta-analysis, the ES was positive if persons with SZ presented increases in BDNF levels in the follow-up, and negative if BDNF levels decreased with treatment.

Unrestricted maximum-likelihood random-effects meta-regressions[42] of ES were performed with mean age, length of illness, BMI, NOS score and severity of disease as assessed by PANSS as moderators to determine whether these covariates influenced the ES. To verify possible effects of medication on BDNF levels, when possible we extracted data regarding daily dose of antipsychotics in chlorpromazine equivalents. Studies were weighted such that the most precise studies, quantified by the sample size and 95% CI, had more influence in the regression analyses.

The meta-analyses consisted of four steps. First, we performed the overall analysis for the between- and within-group meta-analyses. Second, sensitivity analyses for both meta-analysis 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. Third, we performed meta-regression analysis to investigate possible sources of heterogeneity to our results. Finally, we performed the cumulative meta-analysis. The level of significance for the ES estimates was set at $P<0.05$.

RESULTS

We identified 568 studies through electronic searches, all of which had the abstract written in English. Of these, 491 were excluded on the basis of title and abstract, leaving 77 studies for further evaluation. Thirty-five studies[3,5–8,20–32,34,36,37,39,51–53,64–73] fulfilled our inclusion criteria for the between-group meta-analyses, providing data on 5247 participants, of whom 2667 were subjects with SZ and 2580 healthy controls. Twelve studies[4,8,28,32,37–39,72,74–77] were included in the within-group meta-analysis, comprising data on 463 persons before and after treatment with antipsychotics. Some studies provided more than one pairwise comparison.

Supplementary Tables 1S to 7S summarize the included studies. The studies were published from 2002 to 2014 and varied in sample size (from 7 to 657). The mean age varied from 21.00 ± 8.8 to 49.6 ± 9.0 years. For the between-group meta-analysis, 17 studies presented data on first episode psychosis[6–8,20–23,27,28,30,31,37,64,65,68,69,72] and 22 on non-first episode psychosis.[3,5,6,21,24–26,28,29,32,34,36,37,39,51–53,66,67,70,71,73] Twenty-five studies assessed BDNF levels in serum[5–8,21,24–27,29–32,34,36,37,39,51–53,65,67,69,71,73] and 10 in plasma.[3,20,22,23,28,64,66,68,70,72]

Of the 17 between-subjects associations regarding first episode psychosis, 14 referred to drug-naive,[6,7,20–23,27,28,30,31,37,64,68,69] two to drug-free[8,72] and one to already medicated subjects with SZ;[65] of the 22 between-subjects associations regarding non-first episode psychosis SZ, 4 referred to drug-free subjects,[28,32,37,39] one to drug-naive[66] and 17 to medicated participants.[3,5,6,21,24–26,29,34,36,51–53,67,70,71,73] The mean antipsychotic daily dose in chlorpromazine equivalents ranged from 306 to 975 mg. In most of the studies, the control group was matched by gender and age to the case group.

The general demographic characteristics of the within-group meta-analysis were similar to the above mentioned. The follow-up ranged from 4 to 52 weeks. All studies except one[38] included persons who were drug-naive or psychiatric medication-free at baseline. The antipsychotic used in the follow-up differed: risperidone and olanzapine were the most common, the former was used as treatment in nine studies[8,28,32,37,39,72,74–76] and the later in six studies.[4,8,32,38,39,76] Aripiprazole,[76,77] haloperidol,[32,39] clozapine,[37,74] quetiapine[39]and amisulpride[32,39] were also used as treatment. Some studies used a combination of different antipsychotics. The antipsychotic dose varied from 150 to 492 chlorpromazine equivalents per day. All studies presented improvement of symptoms, although not necessarily response to antipsychotics, as assessed by the PANSS in the follow-up.

All 41 studies measured BDNF levels using an ELISA Kit (refer to Supplementary Table S5 for the names of the ELISA Kits).

Meta-analyses

Overall, random-effects between-group meta-analysis showed that serum and plasma BDNF levels were moderately decreased in subjects with SZ when compared with healthy controls ($g=-0.70$, 95% CI: −0.94 to −0.45, $P<0.0001$, 39 between-group comparisons, $n=5247$). When we carried out a subgroup analysis, we verified that BDNF levels were decreased in first episode psychosis ($g=-0.87$, 95% CI: −1.23 to −0.51, $P<0.0001$, 17 between-group comparisons, $n=1560$) with a large ES, and also in non-first episode psychosis SZ ($g=-0.56$, 95% CI: −0.90 to −0.22, $P=0.0002$, 22 between-group comparisons, $n=3687$), this time with a moderate effect (Figure 1). Hereafter, we conducted a subgroup analysis in the subjects with SZ according to use of medication; once more, BDNF levels were decreased in both drug-naïve/free subjects ($g=-0.84$, 95% CI: −1.17 to −0.51, $P<0.0001$, 21 between-group comparisons, $n=1881$) with a large effect, and in medicated individuals ($g=-0.53$, 95% CI: −0.92 to −0.15, $P=0.0007$, 18 between-group comparisons, $n=3366$) with a moderate effect (Figure 2). Finally, a subgroup analysis according to the source of BDNF (i.e., serum or plasma) was executed. These analyses showed decreased BDNF levels in SZ relative to controls regardless of the source (Supplementary Figure 4S). In all subgroup analyses, the heterogeneity remained considerable (Table 1).

Subsequently, we conducted the within-group meta-analysis to test the hypothesis that treatment with antipsychotics would increase BDNF levels in the periphery. Altogether, the longitudinal studies showed that the use of antipsychotics was associated with a small but significant increase in serum and plasma BDNF levels ($g=0.26$, 95% CI: 0.12–0.44, $P<0.0001$, 14 within-group comparisons, $n=463$). When we grouped the studies according to response to antipsychotic treatment (i.e., at least 40% reduction in the PANSS scores), we found that BDNF increased after treatment in both responders ($g=0.23$, 95% CI: 0.04–0.41, $P=0.015$, 6 within-group comparisons, $n=145$) and non-responders ($g=0.31$, 95% CI: 0.08–0.55, $P=0.008$, 8 within-group comparisons, $n=318$) (Figure 3). Conducting a subgroup analysis according to the source of peripheral BDNF, we verified that antipsychotic treatment increased BDNF levels in plasma ($g=0.37$, 95% CI: 0.15–0.59, $P=0.001$, 8 within-group comparisons, $n=283$) but not in serum ($g=0.15$, 95% CI: −0.04 to 0.34, $P=0.19$, 6 within-group comparisons, $n=170$) (Figure 4). In all subgroup analyses, the heterogeneity remained high, except for the subgroup of responders and serum, where it was considerably decreased (I^2 17.19 and 34.10, respectively) (Table 1).

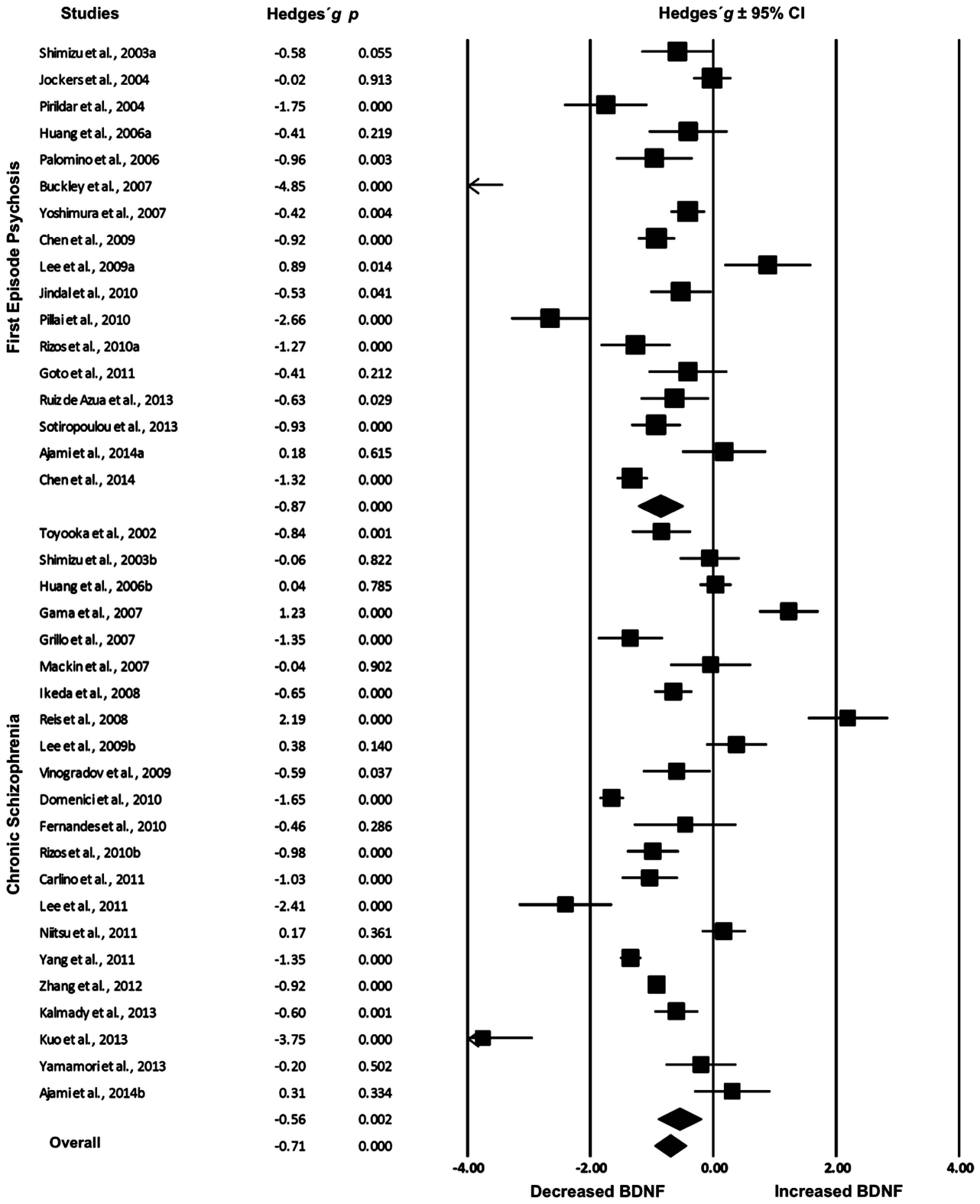

Figure 1. First episode psychosis and non-first episode psychosis SZ. Forest plot for random-effects between-group meta-analysis on serum and plasma BDNF levels in persons with SZ and healthy controls. The sizes of the squares are proportional to sample size. A total of 35 studies were included, comprising 2667 persons with SZ and 2580 healthy controls.

Sensitivity analyses

We re-ran both meta-analyses excluding studies one at a time to determine the robustness of the analyses and to verify if a particular study was responsible for the high heterogeneity. No single study fully explained the heterogeneity, and the results remained significant in all cases. In the between-group meta-analysis, two studies[23,67] presented a particularly high ES. When we re-ran the analysis excluding these studies, there was a

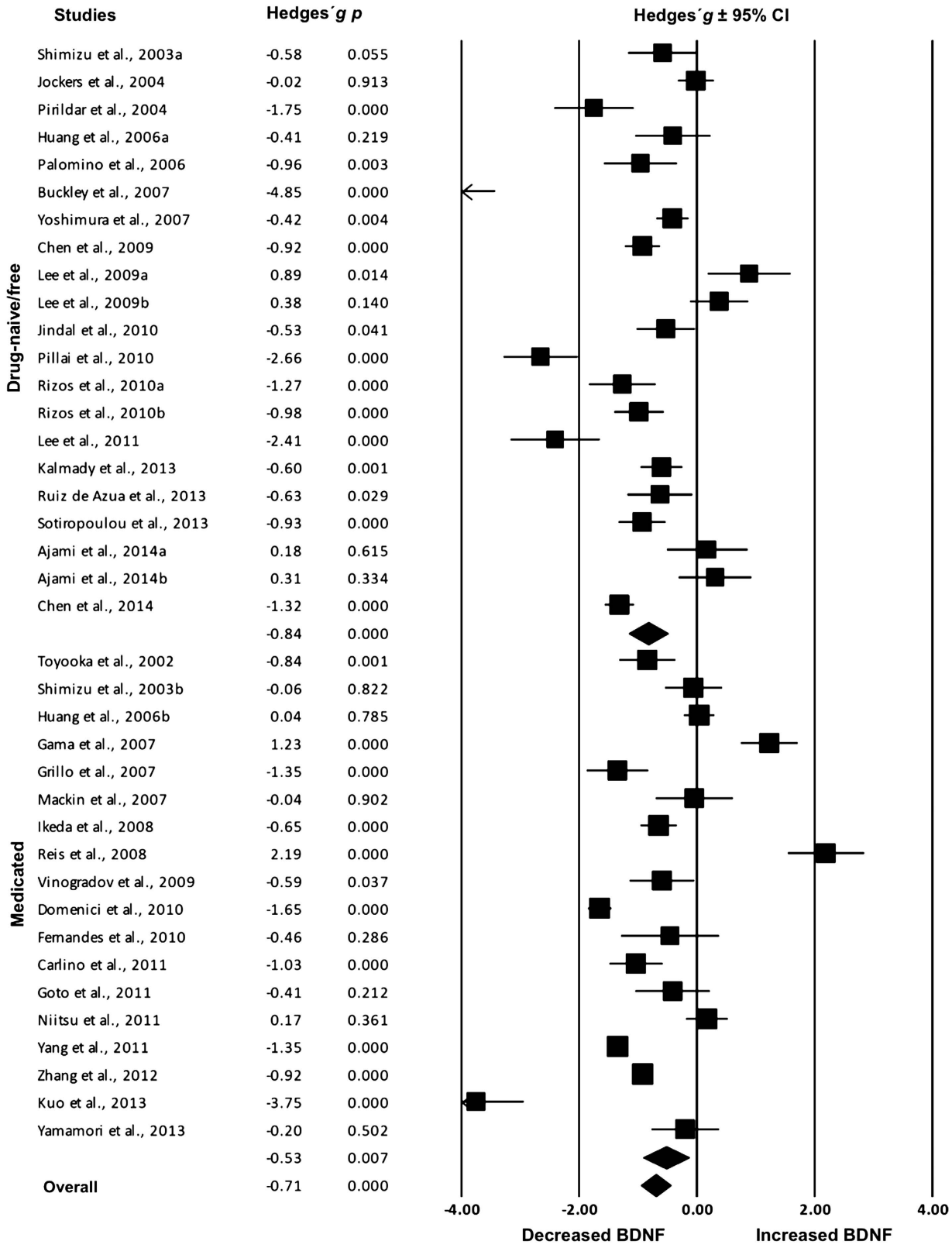

Figure 2. Drug-naive-free and medicated SZ. Forest plot for random-effects between-group meta-analysis on serum and plasma BDNF levels in persons with SZ and healthy controls. The sizes of the squares are proportional to sample size. A total of 35 studies were included, comprising 2667 persons with SZ and 2580 healthy controls.

Table 1. Statistics on between- and within-group meta-analyses regarding serum and plasma BDNF levels in schizophrenia

Groupwise	*No. of pairwise*	*No. of subjects*		*Meta-analysis*				*Heterogeneity*		
		SZ	*HC*	*Hedges' g*	*95% CI*		*P-value*	I^2	Q	*P-value*
Between-group										
SZ vs HC	39	2667	2580	−0.71	−0.96	−0.46	**0.0001**	93.59	593.59	**0.0001**
SZ vs HC except Buckley and Kuo	37	2619	2536	−0.56	−0.80	−0.33	**0.0001**	92.98	512.60	**0.0001**
FEP vs HC	17	714	846	−0.87	−1.23	−0.51	**0.0001**	89.59	153.73	**0.0001**
Chronic SZ vs HC	22	1953	1734	−0.56	−0.90	−0.22	**0.0002**	95.22	439.48	**0.0001**
FEP drug-naive/free vs HC	16	696	828	−0.90	−1.28	−0.53	**0.0001**	90.16	152.47	**0.0001**
Chronic drug-naive/free vs HC	5	169	188	−0.63	−1.40	−0.10	**0.0400**	91.43	46.68	**0.0001**
Chronic medicated vs HC	17	1784	1546	−0.54	−0.94	−0.14	**0.0080**	95.86	386.33	**0.0001**
Drug-free/naive vs HC	21	865	1016	−0.84	−1.17	−0.51	**0.0001**	90.14	202.77	**0.0001**
Medicated vs HC	18	1802	1564	−0.53	−0.92	−0.15	**0.0007**	95.62	388.07	**0.0001**
SZ vs HC—plasma	11	673	753	−0.97	−1.50	−0.44	**0.0001**	94.52	182.55	**0.0001**
SZ vs HC—serum	28	1994	1827	−0.60	−0.88	−0.31	**0.0001**	93.07	389.63	**0.0001**
Within-group										
SZ before vs after antipsychotics	14	463	—	0.26	0.12	0.44	**0.0001**	62.33	34.51	**0.0010**
Responders[a]	6	145	—	0.23	0.04	0.41	**0.0150**	17.19	6.04	0.3030
Non-responders[a]	8	318	—	0.31	0.08	0.55	**0.0080**	75.04	28.05	**0.0001**
SZ—Plasma	8	283	—	0.37	0.15	0.59	**0.0010**	69.15	22.69	**0.0020**
SZ—Serum	6	170	—	0.15	−0.04	0.34	0.1190	34.10	7.59	0.1800

Moderator	*No. of pairwise*	*No. of subjects*		*Meta-regression*				*Meta-regression*		
		SZ	*HC*	*Slope*	*95% CI*		*P-value*	*Intercept*	Z	*P-value*
Between-group										
PANSS total—all	26	1857	1777	−0.007	−0.002	0.006	0.290	0.02	−0.04	0.960
PANSS total—drug-naive/free	14	571	679	−0.003	−0.011	0.003	0.320	−0.44	−1.18	0.240
PANSS-P—all	24	1642	1618	−0.014	−0.074	0.046	0.630	−0.175	−0.24	0.810
PANSS-P—drug-naive/free	15	506	637	−0.035	−0.107	0.036	0.330	0.163	0.186	0.850
PANSS-N—all	24	1642	1618	−0.014	−0.074	0.046	0.640	−0.175	−0.24	0.810
PANSS-N—drug-naive/free	15	506	637	−0.020	−0.044	0.004	0.100	−0.203	−0.68	0.490
Chlorpromazine equivalents—all	14	1634	1611	0.001	−0.003	0.003	0.580	−0.805	−1.22	0.220
Age—all	39	2667	2580	−0.010	−0.150	0.079	0.130	−0.193	−2.35	**0.010**
Age—drug-naive/free	21	865	1016	0.037	−0.047	0.121	0.388	−2.005	−1.49	0.135
BMI—all	14	1634	1611	−0.010	−0.150	0.079	0.130	−0.193	−2.35	**0.001**
Length of illness—all	32	2060	2002	−0.013	−0.019	−0.007	**0.001**	−0.498	−8.06	**0.001**
Length of illness—drug-naive/free	12	369	550	0.008	−0.219	0.236	0.941	−0.798	−4.95	**0.001**
Sample size—all	39	2667	2580	−0.001	−0.003	0.016	0.514	−0.635	−2.96	**0.030**
NOS—all	39	2667	2580	−0.130	−0.360	0.100	0.290	−0.320	−0.80	0.420
Within-group										
Reduction PANSS total—all	10	280	—	0.002	−0.005	0.010	0.552	0.295	1.73	0.082
%Reduction PANSS total—all	11	339	—	−0.001	−0.002	0.009	0.926	0.196	0.95	0.337
Reduction PANSS-P—all	12	388	—	0.022	−0.020	0.064	0.309	0.470	2.10	**0.035**
%Reduction PANSS-P—all	12	388	—	0.004	−0.008	0.017	0.492	0.423	1.70	0.083
Reduction PANSS-N—all	12	388	—	0.020	−0.026	0.067	0.389	0.348	2.26	**0.023**
%Reduction PANSS-N—all	12	388	—	0.002	−0.010	0.016	0.672	0.326	1.88	0.058
Chlorpromazine equivalents—all	11	415	—	−0.001	−0.002	0.001	0.180	0.625	2.37	**0.017**
Age—all	14	463	—	−0.020	−0.048	0.007	0.147	0.960	2.04	**0.041**
Length of illness—all	12	396	—	−0.008	−0.019	0.003	0.182	0.267	3.48	**0.005**
Length of follow-up—all	14	463	—	0.093	0.047	0.140	**0.001**	−0.320	−2.06	**0.038**
Length of follow-up—plasma	8	293	—	0.117	0.064	0.169	**0.001**	−0.476	−2.41	**0.015**
Length of follow-up—serum	6	170	—	−0.124	−0.275	0.025	0.104	0.790	1.95	0.051
Sample size—all	14	463	—	0.001	−0.001	0.009	0.882	0.263	1.38	0.166
NOS—all	14	463	—	0.004	−0.002	0.007	0.281	−0.184	−0.74	0.672

Abbreviations: BMI, body-mass index in $kg\,m^{-2}$; CI, confidence interval; FEP, first episode psychosis; HC, healthy controls; PANSS-N, Positive and Negative Symptoms Scale negative symptoms subscore; PANSS-P, Positive and Negative Symptoms Scale positive symptoms subscore; PANSS total, Positive and Negative Symptoms Scale total score; NOS, Newcastle-Ottawa Scale; SZ, schizophrenia. [a]Response to antipsychotics: an improvement of at least 40% at PANSS total scores, or at PANSS positive scores if the former was unavailable. Bold values indicate significant *P*-values < 0.05.

decrease in the pooled ES from −0.70 (95% CI: −0.45 to −0.94, $P < 0.001$) to −0.56 (95% CI: −0.33 to −0.80, $P < 0.001$), although the results remained highly significant. As there was no major change in the heterogeneity (I^2 decreased from 93.59 to 92.98), we kept both studies in the main analysis.

Meta-regressions

We performed a meta-regression analysis in an exploratory attempt to identify the sources of heterogeneity between studies. In univariate meta-regression models, the covariates of age, BMI, sample size and NOS study quality did not explain the high

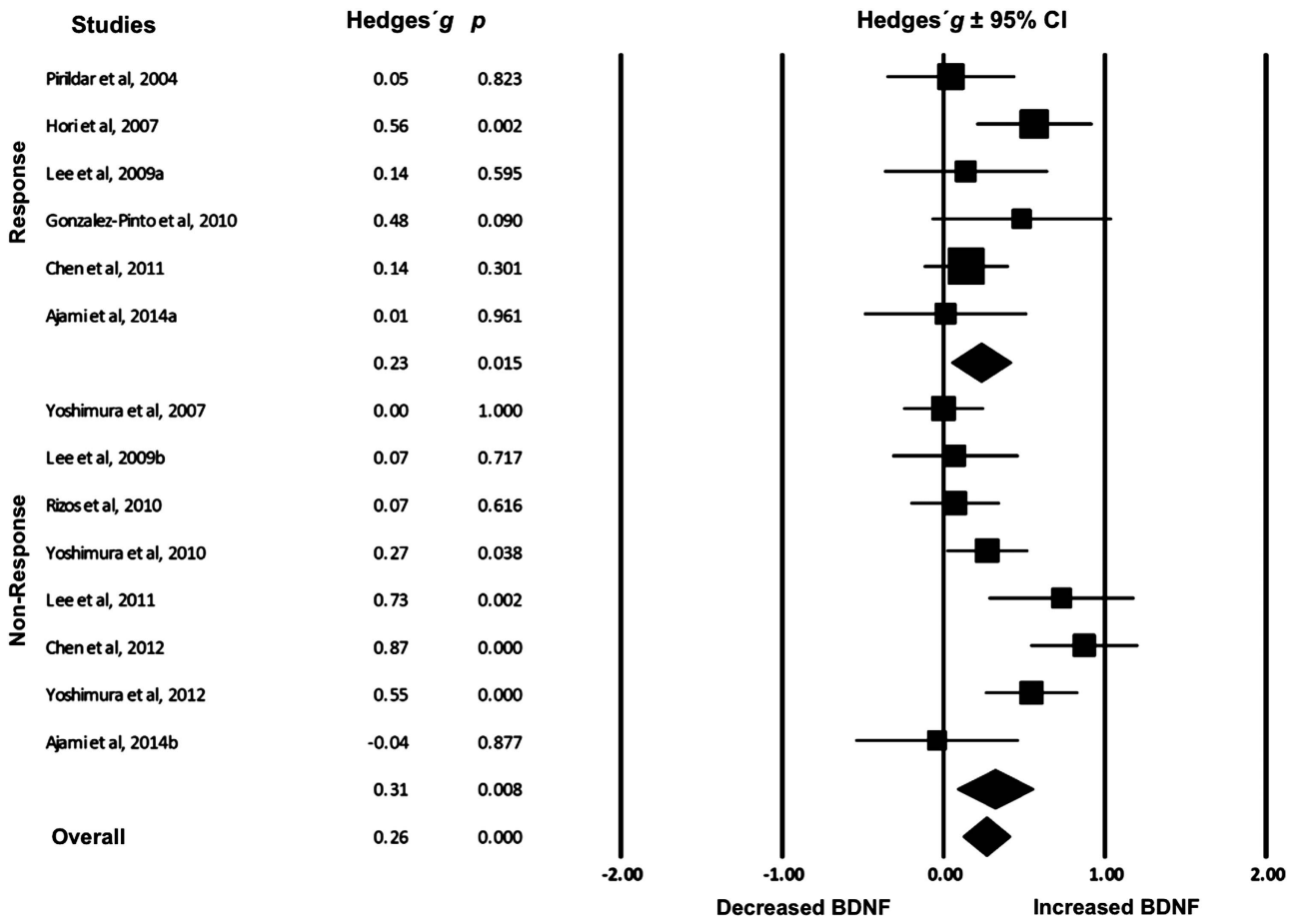

Figure 3. Forest plot for random-effects within-group meta-analysis on serum and plasma BDNF levels in persons with SZ before and after antipsychotic treatment according to response (at least 40% reduction in PANSS scores). The sizes of the squares are proportional to sample size. A total of 12 studies were included, comprising 463 persons with SZ.

heterogeneity in the between-group meta-analysis. Notably, neither the severity of positive or negative symptoms as assessed by PANSS, or the daily dose of antipsychotics in chlorpromazine equivalents were related to the magnitude of the ES. When we considered only the studies that used originally PANSS scores and not all available studies, the results were the same. In contrast, we did find an inverse association between the ES on between-group differences in BDNF levels and the mean length of illness of the patients who were included in a particular study (slope = –0.013, 95% CI: –0.019 to –0.007, $P < 0.0001$). This association indicated that the greater the length of illness, the greater the decrease in BDNF levels in SZ (see Table 1 for details).

When we executed the meta-regression for the within-group meta-analysis, only length of follow-up in weeks was related to increase in BDNF levels during the course of treatment with antipsychotics. This association was such that increased BDNF levels during the course of treatment were observed to a larger extent in persons who were treated for a longer period of time (slope = 0.093, 95% CI: 0.047–0.140, $P < 0.0001$). After that, we split the analysis according the source of BDNF, and found that BDNF levels only increased over time in plasma but not in serum. Once more, neither severity nor decreases in positive or negative symptoms (as assessed by PANSS) were related to the increase in BDNF levels over the course of treatment. In addition, the antipsychotic dose in chlorpromazine equivalents was not related to the improvement in BDNF levels (Table 1).

Publication bias and power

We found no evidence of publication bias in any of the funnel plots, and the Egger's test was not significant ($P = 0.22$ and $P = 0.26$, respectively) (Supplementary Figures 2S and 3S). As most studies composing the within-group meta-analysis yielded a negative result, we calculated the necessary sample size to detect a difference in BDNF levels following treatment with antipsychotics. In these calculations, we considered a power of 80% and a *P*-value of 0.05 (two-sided, paired *t*-test). For this, we used the pooled ES of 0.26, found as a result of our within-group meta-analysis, as the true real magnitude of the effect. These calculations estimated that 119 persons would be required to reliably detect differences in serum and plasma BDNF levels in a follow-up study. The sample sizes of the studies included in this particular meta-analysis ranged from 12 to 59 and thus were individually largely underpowered to detect differences in BDNF levels reliably.

Cumulative meta-analyses

Finally, we performed a cumulative analysis to verify the stability of the ES over time. For the between-group analysis, there was a large variation on the ES from 2002 to 2010; after 2010, the ES remained steady over time (Supplementary Figure 5S). For the within-group meta-analysis, the ES remained stable after 2012 (Supplementary Figure 6S).

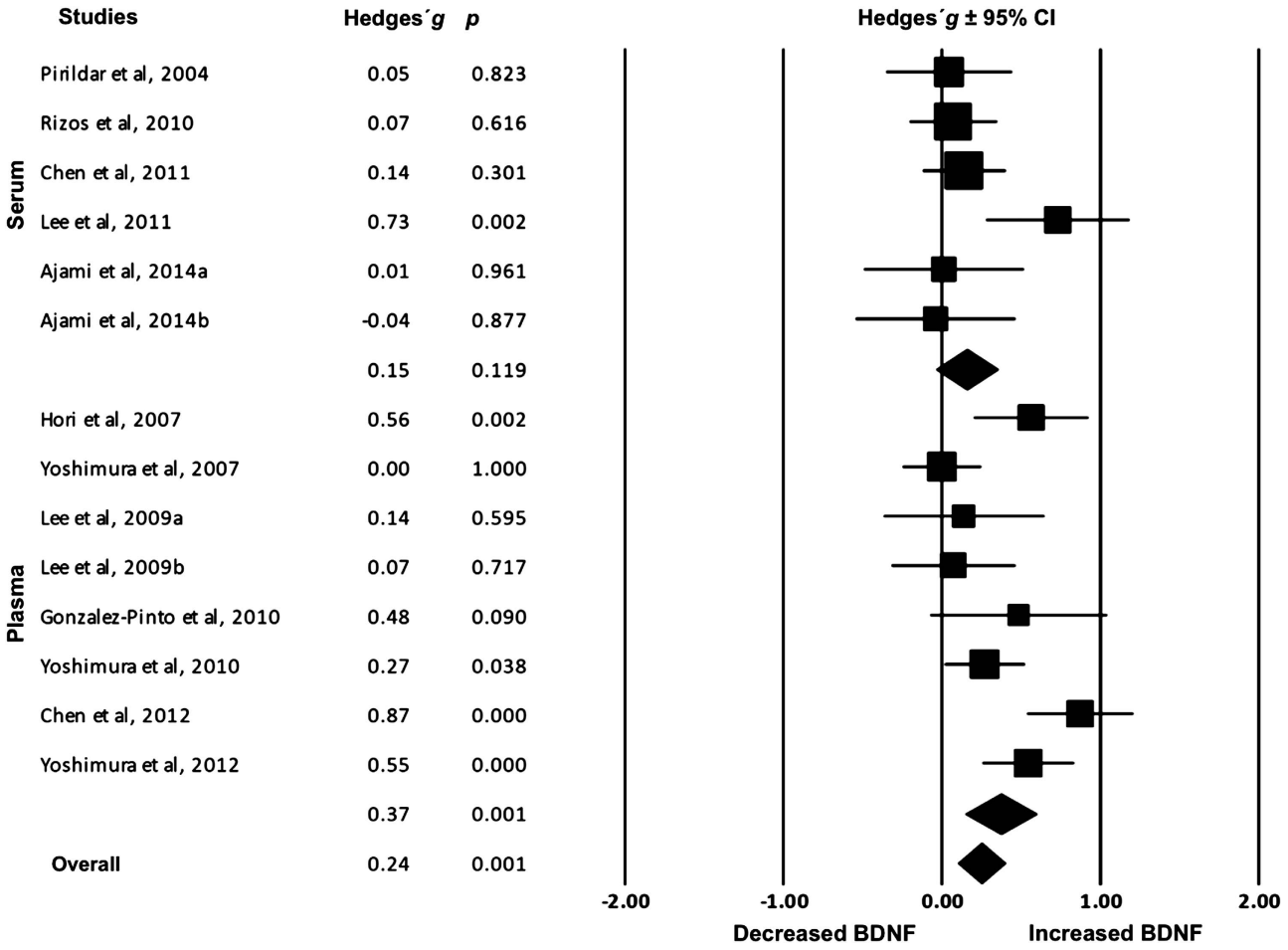

Figure 4. Forest plot for random-effects within-group meta-analysis on serum and plasma BDNF levels in persons with SZ before and after antipsychotic treatment according to source (serum or plasma). The sizes of the squares are proportional to sample size. A total of 12 studies were included, comprising 463 persons with SZ.

DISCUSSION

This meta-analysis of peripheral BDNF in SZ included a total of 41 cross-sectional and longitudinal studies with more than 7000 participants. We were able to show that peripheral BDNF levels in both serum and plasma are moderately reduced in persons with SZ when compared with healthy controls. This decrease was already evident in first episode SZ, but is more accentuated with the progression of the disorder as assessed by the length of illness. BDNF levels in SZ are lower regardless of the exposure to psychiatric medication, and BDNF levels have no relationship to the amount of antipsychotic medication used. Mostly notably, refuting our previous hypothesis and the common notion in the literature, the extent of the decrease in peripheral BDNF levels does not parallel the severity of positive and negative symptoms, which together constitute the core phenotype of SZ. When analyzing the influence of antipsychotics on BDNF, we could demonstrate that peripheral BDNF levels increase with treatment, irrespective of dose and of the presence or absence of response to antipsychotic medication in plasma but not in serum in a time-dependent manner.

Lower levels of BDNF in plasma and serum in SZ in comparison with controls were demonstrated in an early meta-analysis on this subject.[44] However, after including more than two times the number of studies included in the previous paper, we found a pooled result of –0.70 (95% CI: –0.94 to –0.45) versus the original result of –0.45 (95% CI: –0.77 to –0.14), almost out of the 95% CI obtained in the previous meta-analysis. This strongly suggests that peripheral BDNF levels in SZ are even more reduced than previously thought. Also, we did not find any association between age and the decrease in BDNF, but uncovered that the decrease in BDNF becomes more accentuated with the temporal course of the disease. This speaks for a role of BDNF in neuroprogression, a phenomenon that also occurs in bipolar disorder (BD) and depression,[33,78–81] which postulates that the central nervous system (CNS) pathologically reorganizes during the course of severe mental illness.[82] The lack of association between BDNF and age in our data may be due to the fact that most studies regarding first episode psychosis and unmedicated subjects included younger samples. However, age and length of illness are two variables highly correlated, but length of illness appears to be more relevant to BDNF levels than age itself.

Peripheral BDNF as a biomarker in SZ

The role of BDNF in serum and plasma as a biomarker in psychiatric conditions, including SZ, has been latterly debated.[83–88] We found no association between serum and plasma BDNF levels and severity of positive and negative symptoms. Recently, we showed in our meta-analysis focusing on peripheral BDNF levels in mood disorders that, although peripheral BDNF is of little value as a diagnostic biomarker in psychiatric disorders because of

its lack of specificity, it might be a biomarker of disease activity, since it was decreased in bipolar disorder and major depressive disorder during acute episodes, but returned to normal after remission.[84] In the same line, a recent meta-analysis in major depressive disorder showed the absence of association between serum BDNF and severity of mood symptoms.[89] It appears that in major psychiatric disorders (meaning SZ, BD and major depressive disorder), lower peripheral BDNF levels represent a phenomenon that is associated qualitatively but not quantitatively with these conditions. It should also be noted that the daily dose of antipsychotics was not related to BDNF levels. Taken together, these results might indicate that although the neurotrophin pathway is altered, this phenomenon is the result of an already existent pathology that gets perpetuated by itself and not the other way around. Either way, it cannot be considered as a SZ-specific diagnostic marker, or as a parameter mirroring disease severity.

One relevant issue regarding the pathophysiologic role of peripheral BDNF levels in SZ is the effect of administration of antipsychotics on BDNF levels. This has the potential to clarify the neurotrophin hypothesis as well as the mechanisms of antipsychotic agents. BDNF is believed to have a pivotal role in synaptic plasticity at dopaminergic and glutamatergic synapses,[2] systems of paramount importance for the occurrence of positive and negative symptoms. Almost all studies published analyzing antipsychotic-induced changes in BDNF levels produced negative results.[28,37,39,72] We showed that plasma but not serum BDNF levels increase to a small extent after antipsychotic treatment in both responders and non-responders regardless of the level of improvement in symptomatology. According to our *post hoc* sample size calculations, most studies regarding this point were seriously underpowered. This may explain why a positive result was only produced as a result of a pooled analysis, which achieved a greater power.

Whether an increase in BDNF or an improvement of symptoms occurs first has been a matter of much debate, with conflicting data.[4,28,39,53,90] This is a pivotal point and needs further studies in order to clarify both the role of neurotrophins in the mechanism of action of antipsychotics and the role of peripheral BDNF as a biomarker of response to treatment. To provide a definitive answer to these questions a longitudinal study with frequent blood draws would be necessary. Our results of an increase in BDNF levels even in non-responders may suggest that changes in BDNF precede changes in phenotype, albeit not in a mediating or quantitative manner, or that BDNF changes are unrelated to antipsychotic response, representing an epiphenomenon in this situation. This limits the use of serum and plasma BDNF as a surrogate biomarker of response to antipsychotics. It should also be noted that the increase in BDNF levels after antipsychotic treatment was small, and not significant enough to result in the disappearance of the difference between subjects with SZ and controls.

The 'periphery as a window to the brain' conception

To determine what a decreased serum and plasma BDNF level means for the pathophysiology of SZ, and to discuss how useful peripheral BDNF levels can be as a surrogate biomarker of CNS physiology (the 'window to the brain notion'), we have to consider the plasma and serum BDNF sources. The brain contributes to a large amount of circulating BDNF in blood and is considered its major source.[91,92] Nevertheless, it is crucial to note that, although BDNF levels in serum and plasma are commonly referred to as proxies of BDNF levels in the CNS, serum and plasma represent in fact two different compartments. This is obvious by the fact that BDNF concentrations in serum are 20 to 50 times higher than in plasma.[93,94] Peripheral BDNF is largely stored in platelets, which actively absorb it from the circulation,[95] and is released from activated platelets to serum during the clotting process.[96] Although complementary DNA of BDNF has been detected in platelets,[94] serum BDNF levels largely reflect the pool of BDNF stored and released from platelets during coagulation. It has been demonstrated that the amount of BDNF in serum is nearly identical to the amount of BDNF found in washed platelet lysates.[92,95] Apart from platelets, major non-neuronal peripheral cells contributing to BDNF levels in serum and plasma include vascular smooth cells, endothelial cells, lymphocytes and monocytes.[97,98] The fact that most BDNF found in serum, although originally secreted by neuronal cells, is released from platelets after storage may suggest that serum BDNF levels may be a less accurate marker of acute changes in CNS than plasma BDNF.[51,90,99–101] In our analyses, the magnitude of the ES of the decreased BDNF levels in SZ in comparison with controls was high for plasma but only moderate for serum. This may be because of the fact that the still ongoing release of BDNF from platelets obscures serum BDNF levels. Our data show that after antipsychotic treatment peripheral BDNF levels increase in plasma but not in serum, suggesting that not all 'periphery' is the same in mirroring the brain, and that BDNF levels in plasma may be more accurately reflecting the situation in the CNS.

Strengths and limitations

Our study relied on a large sample size (41 studies including more than 7000 subjects), which permitted us to draw accurate results through meta-analysis and meta-regression techniques. Our results are unlikely to be caused by publication bias, as the funnel plots for both meta-analyses were symmetrical and a large amount of negative unpublished studies would be necessary to turn our positive results into nonsignificant ones. In addition, through a series of sensitivity and subgroup analyses, we were able to rule out the possibility that the results were biased because of a unique outlier. The above-mentioned approach also allowed us to try to investigate and rule out any single study as the sole source of the high heterogeneity found in virtually all analyses.

Notwithstanding its significant strengths, our paper has some inherent limitations because of its design and statistical methods used. First, the subgroup analysis of changes in serum of BDNF pre- and posttreatment and some of the meta-regressions may have failed to achieve statistical significance owing to a lack of power in these specific analyses, giving us a false-negative result. Second, the meta-analysis on BDNF levels in persons with SZ compared with controls provides us with a pooled result originating from cross-sectional studies. Therefore, we cannot draw any causal associations, meaning that we do not know if a decrease in BDNF levels is a cause and prerequisite for SZ development or an epiphenomenon such as a counterbalance consequence of SZ development. Similarly, although we showed that peripheral BDNF levels increase after antipsychotic treatment, we cannot know if this increase is a prerequisite for its function or merely an epiphenomenon unrelated to its mechanism of action. Third, the extent of changes in the periphery to mirror changes in the brain, reasons for decreased BDNF levels in SZ and increased levels after antipsychotic treatment remain to be elucidated. Thus, the extrapolation of these findings in serum and plasma to the CNS needs to be carried out with caution. Finally, we cannot discriminate the pro-BDNF (an active precursor of mature BDNF), which is thought to have proapoptotic affects, from the mature BDNF in our data. Most of the studies used kits not sensitive enough to make that distinction, apart from some notable exceptions with conflicting results.[34,36,70]

Final conclusions

Our meta-analysis of 41 studies comprising more than 7000 persons with SZ and healthy controls provide strong evidence that peripheral BDNF levels in serum and plasma are decreased in SZ, providing evidence of a systemic nature in this condition. This

decrease in BDNF levels is evident since the first episode of psychosis, and is accentuated further with prolonged illness in a manner unrelated to the severity of disease. Furthermore, antipsychotic treatment improves BDNF levels independent of symptom improvement. In summary, our results support the notion of SZ as a systemic disorder with peripheral and cerebral manifestations, reinforcing the idea of peripheral BDNF as a putative trait biomarker in SZ, although not mirroring disease severity, and give added validity to the concept that schizophrenia can be investigated through studies of blood-based biomarkers. Future studies need to clarify if these alterations in BDNF levels have a causal relationship to the development of SZ or if they are merely an epiphenomenon of the pathology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Brain-derived Neurotrophic Factor in Schizophrenia: A Meta-Analysis

Supplementary Material - Tables

Note: All reference numbers refer to the reference list in the main manuscript text.

Table 1S. Newcastle-Ottawa quality assessment scale for case-control (between group) and cohort (within-group) studies.

Between-Group Studies	Selection	Comparability	Exposure	Total
Ajami *et al.,* 2014 (37)	*	*	---	2
Buckley *et al.,* 2007 (23)	**	*	*	4
Carlino *et al.,* 2011 (34)	*	*	*	4
Chen *et al.,* 2009 (27)	**	*	*	4
Chen *et al.,* 2014 (64)	*	*	---	2
Domenici *et al.,* 2010 (3)	*	*	---	2
Fernandes *et al.,* 2010 (51)	**	*	*	4
Gama *et al.,* 2007(24)	*	---	---	1
Goto *et al.,* 2011 (65)	---	*	---	1
Grillo *et al.,* 2007 (25)	*	**	*	4
Huang *et al.,* 2006 (21)	---	**	---	2
Ikeda *et al.,* 2008 (52)	***	*	---	4
Jindal *et al.,* 2010 (30)	*	*	*	3
Jockers *et al.,* 2004 (7)	**	*	---	3
Kalmady *et al.,* 2013 (66)	**	*	*	4
Kuo *et al.,* 2013 (67)	**	*	*	4
Lee *et al.,* 2011 (39)	---	*	---	1
Lee *et al.,* 2009 (28)	*	*	**	4

Mackin *et al.,* 2007 (53)	***	*	**	6
Niitsu *et al.,* 2011 (36)	***	*	*	5
Palomino *et al.,* 2006 (22)	---	---	*	1
Pillai *et al.,* 2010 (20)	***	---	**	5
Pirildar *et al.,* 2004 (8)	**	*	*	4
Reis *et al.,* 2008 (26)	*	*	---	2
Rizos *et al.,* 2010 (31)	---	*	*	2
Rizos *et al.,* 2010 (32)	*	*	*	3
Ruiz de Azua *et al.,* 2013 (68)	***	**	*	6
Shimizu *et al.,* 2003 (6)	*	---	---	1
Sotiropoulou *et al.,* 2013 (69)	---	*	---	1
Toyooka *et al.,* 2002 (5)	*	*	---	2
Vinogradov *et al.,* 2009 (29)	***	**	*	6
Yamamori *et al.,* 2013 (70)	*	*	*	3
Yang *et al.,* 2011 (71)	**	**	---	4
Yoshimura *et al.,* 2007 (72)	**	*	---	3
Zhang *et al.,* 2012 (73)	***	*	---	4

Within-Group Studies	**Selection**	**Comparability**	**Outcome**	**Total**
Ajami *et al.,* 2014 (37)	**	*	*	4
Chen *et al.,* 2011 (74)	***	---	*	4
Chen *et al.,* 2012 (75)	**	*	**	5
Gonzalez-Pinto *et al.,* 2010 (4)	**	*	*	4
Hori *et al.,* 2007 (38)	**	*	**	5
Lee *et al.,* 2009 (28)	**	*	*	4
Lee et al., 2011 (39)	**	*	*	4
Pirildar *et al.,* 2004 (8)	*	*	**	4
Rizos *et al.,* 2010 (31)	*	---	*	2
Yoshimura *et al.*, 2010 (76)	*	*	*	3
Yoshimura *et al*., 2012 (77)	***	*	---	4
Yoshimura *et al*., 2007 (72)	***	*	*	5

Scale ranges between zero and nine stars. Highest quality studies awarded maximum of one star for each item, with exception of comparability, which can have two stars. Item “non-response rate” from Exposure was not applicable, and then a maximum of eight stars was considered for the case-control scale. The cohort scale considered the maximum of nine stars.

Table 2S. Demographic characteristics of studies included in the between-group meta-analysis of serum or plasma BDNF levels in schizophrenia.

Study	Year	Subjects	Gender M/F	PANSS-T*	PANSS-PS*	PANSS-NS*	BMI*	Length of * illness (years)	Age (years)*	Chlorpromazine equivalents (mg/day)*	Medication
Ajami A (37)	2014	First episode Chronic Control	20/6& 20/6& 20/6	77.55 ± 21.45 95.00 ± 21.85	18.63 ± 8.57 23.53 ± 7.99	22.09 ± 7.31 27.93 ± 7.36	NA	0.56 ± 0.22 5.47 ± 1.76	33.18 ± 9.00 33.93 ± 10.13 33.92 ± 8.86	–––	Drug-naïve (FEP) and Drug-free (Chronic)
Buckley P (23)	2007	First episode Control	8/7 9/5	NA	15.00 ± 5.12	NA	NA	1.20 ± 1.05	21.00 ± 8.83 25.00 ± 5.72	–––	Drug-naïve
Carlino D (34)	2011	Chronic Control	20/20 20/20	73.60 ± 13.00	17.25 ± 7.81	25.27 ± 9.51	23.55 ± 6.40 23.95 ± 6.70	23.05 ± 10.00	48.00± 10.00 44.00± 10.00	424.60 ± 270.40	Typical and atypical antipsychotics
Chen C (27)	2009	First episode Control	47/41 49/41	83.40 ± 18.90	25.60 ± 6.30	18.30 ± 7.20	22.40 ± 3.80 22.90 ± 3.80	1.90 ± 1.50	30.75± 10.52 34.00± 4.70	–––	Drug-naïve
Chen S (64)	2014	First episode Control	84/67 77/49	87.50 ± 13.90	NA	NA	NA	NA	30.80± 8.30 33.40± 7.50	–––	Drug-naïve
Domenici E (3)	2010	Chronic Control	115/114 81/173	NA	NA	NA	26.60 ± 4.90 24.20 ± 3.40	NA	37.80 ± 10.70 48.90 ± 14.20	NA	Typical and atypical antipsychotics
Fernandes BS (51)	2010	Chronic Control	2/5 6/15	79.15 ± 19.59#	31.90 ± 8.70#	24.80 ± 8.90#	25.24 ± 2.50 23.52 ± 2.20	16.49 ± 3.72	35.79 ± 10.34 35.27 ± 10.20	597.00 ± 339.40	Typical and atypical antipsychotics
Gama C (24)	2007	Chronic Control	18/42 15/11	NA	NA	NA	NA	15.52 ± 8.74	35.35 ± 10.36 40.68 ± 12.12	561.00 ± 322.90	Typical and atypical antipsychotics, clozapine
Goto N (65)	2011	First episode Control	9/9 9/9	68.10 ± 17.00	15.90 ± 4.20	17.20 ± 5.30	NA	0.75 ± 0.52	29.00 ± 11.00 30.00 ± 11.00	625.00 ± 92.00	Atypical antipsychotics
Grillo R (25)	2007	Chronic Control	19/25 12/13	NA	NA	NA	NA	13.50 ± 8.70	35.50 ± 12.50 34.11 ± 13.00	330.36 ± 175.72	Clozapine, typical antipsychotics
Huang T (21)	2006	First episode Chronic Control	72/54& 72/54& 36/60	NA	NA	NA	23.00 ± 3.00 25.20 ± 4.70 22.10 ± 3.50	1.00 ± 0.50 6.40 ± 4.60	27.10 ± 9.70 34.60 ± 10.20 29.10 ± 5.30	___ NA	Drug-naïve (FEP), typical and atypical antipsychotics (Chronic)
Ikeda Y (52)	2008	Chronic Control	39/35 47/40	85.00 ± 37.83#	NA	NA	23.60 ± 4.70 23.10 ± 2.10	19.60 ± 11.20	41.90 ± 11.10 39.80 ± 10.70	936.60 ± 588.80	Typical and atypical antipsychotics
Jindal R (30)	2010	First episode Control	17/7 25/16	NA	14.00 ± 10.04$	22.71 ± 10.92$	25.24 ± 2.50 23.52 ± 2.20	NA	22.40 ± 5.47 22.31 ± 5.67	–––	Drug-naïve
Jockers M (7)	2004	First episode Control	50/52 28/33	NA	NA	NA	NA	NA	31.80 ± 9.00 32.30 ± 9.50	–––	Drug-naïve
Kalmady S (66)	2013	Chronic Control	31/28 29/31	NA	NA	NA	NA	NA	31.10 ± 7.20 26.40 ± 4.70	–––	Drug-naïve
Kuo F (67)	2013	Chronic Control	19/14 12/18	NA	NA	NA	29.50 ± 3.64 28.30 ± 2.50	3.90 ± 3.30	32.18 ± 8.78 38.29 ± 10.29	640.00 ± 275.00	Typical and atypical antipsychotics

Lee A (39)	2011	Chronic Control	13/9 13/9	93.00 ± 26.00	NA	NA	NA	NA	39.14± 14.00 39.20± 14.00	___	Drug-free
Lee B (28)	2009	First episode Chronic Control	7/03 8/18 15/21	88.20 ± 23.30 99.70 ± 24.90	26.00 ± 7.70 26.60 ± 6.90	18.80 ± 8.40 24.20 ± 9.40	21.10 ± 2.80 22.20 ± 4.10 22.37 ± 2.75	0.34 ± 0.24 6.40 ± 4.83	30.10 ± 7.40 31.80 ± 8.10 31.30 ± 7.90	___	Drug-naïve (FEP), drug-naïve or drug-free for at lest 4 weeks (Chronic)
Mackin (53)	2007	Chronic Control	18/2 12/2	61.50 ± 28.33#	NA	NA	NA	NA	42.1 ± 10.30 43.7 ± 12.90	NA	Typical and atypical antipsychotics
Niitsu T (36)	2011	Chronic Control	26/37 25/27	54.50 ± 24.50#	NA	33.54 ± 9.82$	NA	9.10 ± 7.30	35.90 ± 8.20 34.90 ± 7.30	306.00 ± 204.00	Atypical antipsychotics
Palomino A (22)	2006	First episode Control	NA NA	66.80 ± 20.79	24.13 ± 6.77	25.20 ± 5.17	NA	0.25 ± 0.20	23.70 ± 5.72 25.50 ± 5.40	___	Drug-naïve
Pillai A (20)	2010	First episode Control	15/19 13/23	104.13 ± 20.59	29.86 ± 6.08	23.68 ± 6.83	NA	0.30 ± 0.23	32.18 ± 8.78 38.29 ± 10.29	___	Drug-naïve
Pirildar S (8)	2004	First episode Control	7/15 7/15	145.81 ± 9.65	30.81 ± 7.99	30.27 ± 7.31	NA	1.20 ± 1.09	27.81 ± 9.54 25.70 ± 7.80	___	Drug-free for at least 2 weeks
Reis H (26)	2008	Chronic Control	40/0 20/0	83.33 ± 28.33#	17.10 ± 7.5	24.10 ± 4.40	NA	32.40 ± 9.20	52.30 ± 9.80 52.30 ± 9.80	NA	Typical antipsychotics
Rizos E (31)	2010	First episode Control	16/21 13/22	NA	34.32 ± 7.26	31.02 ± 9.04	NA	0.52 ± 0.47	26.81 ± 9.22 26.59 ± 4.47	___	Drug-naïve
Rizos E (32)	2010	Chronic Control	32/15 29/15	NA	24.75 ± 7.22	23.86 ± 10.72	NA	23.84 ± 7.82	43.63 ± 10.91 46.50 ± 14.90	___	Drug-free for at least 12 weeks
Ruiz de Azua S (68)	2013	First episode Control	10/7 26/19	88.71 ± 26.63	25.12 ± 5.41	18.41 ± 9.05	NA	0.30 ± 0.25	24.65 ± 7.52 24.00 ± 8.71	___	Drug-naïve
Shimizu E (6)	2003	First episode Chronic Control	7/8 13/12 20/20	56.84 ± 21.34# 44.00 ± 32.60#	31.50 ± 17.85# 16.59 ± 6.15#	8.05 ± 9.20# 9.17 ± 5.95#	NA	1.09 ± 1.06 14.10 ± 9.87	34.70 ± 16.00 36.00 ± 13.20 35.60 ± 14.60	___ 727.00 ± 412.00	Drug-naïve (FEP), typical and atypical antipsychotics (Chronic)
Sotiropoulou M (69)	2013	First episode Control	34/16 34/16	98.69 ± 21.55	24.75 ± 6.38	30.04 ± 6.47	NA	1.150 ± 1.20	29.84 ± 8.20 31.36 ± 7.96	___	Drug-naïve
Toyooka K (5)	2002	Chronic Control	17/17 14/21	NA	NA	NA	NA	25.00 ± 12.30	48.60 ± 14.00 45.60 ± 11.30	975.00 ± 520.00	Typical and atypical antipsychotics
Vinogradov F (29)	2009	Chronic Control	42/14 10/6	2.35 ± 0.65	NA	NA	29.24 ± 5.01 26.87 ± 4.30	23.04 ± 9.12	43.95 ± 9.30 44.50 ± 11.69	477.00 ± 482.00	Typical and atypical antipsychotics
Yamamori H (70)	2013	Chronic Control	12/10 12/10	52.90 ± 9.60	23.00 ± 4.60	25.50 ± 5.50	NA	17.20 ± 11.10	38.10 ± 13.20 38.10 ± 12.90	597.00 ± 173.00	Clozapine
Yang Y (71)	2011	Chronic Control	281/83 228/95	60.15 ± 15.78	12.80 ± 5.60	21.00 ± 7.50	24.20 ± 4.90 24.90 ± 5.00	27.00 ± 10.10	49.90 ± 9.90 50.90 ± 9.10	490.82 ± 500.71	Typical and atypical antipsychotics
Yoshimura R (73)	2007	First episode Control	52/37 48/55	107.10 ± 24.40	31.30 ± 5.60	24.20 ± 6.40	NA	1.50 ± 0.55	37.00 ± 13.00 40.00 ± 23.00	___	Drug-free for at least 1 week
Zhang X (73)	2012	Chronic Control	578/79 263/182	60.90 ± 14.10	12.60 ± 5.40	21.80 ± 7.00	24.70 ± 4.00 25.10 ± 4.20	27.30 ± 9.30	48.40 ± 13.70 44.90 ± 13.60	462.00 ± 396.00	Typical and atypical antipsychotics

Abbreviations: BDNF, brain-derived neurotrophic factor; PANSS-T, Positive and Negative Symptoms Scale total score; PANSS-PS, Positive and Negative Symptoms Scale positive symptoms sub-score; PANSS-NS, Positive and Negative Symptoms Scale negative symptoms sub-score; BMI, body-mass index in kg/m^2; FEP, first episode psychosis; NA, not available.

* Mean ± standard deviation.

BPRS scores converted to PANSS scores.

$ SAPS and SANS scores converted to PANSS-PS and PANSS-NS scores, respectively.

& Values not shown separately for each group.

Table 3S. Demographic characteristics of studies included in the within-group meta-analysis of serum or plasma BDNF levels in schizophrenia.

Study	Subjects	Treatment Medication	Chlorpromazine equivalents (mg/day)*	Time Point	PANSS-T*	PANSS-PS*	PANSS-NS*	Length of treatment (weeks)*	Length of illness (years)*	Age (years)*	Baseline Medication
Ajami A (37)	FEP and Chronic	Clozapine or risperidone	NA	Before After	87.61 ± 22.99 52.93 ± 12.63	21.64 ± 8.44 11.46 ± 4.07	25.46 ± 7.77 15.92 ± 6.79	06	3.10	33.18	Drug-naïve/free
Chen C (74)	Chronic	Clozapine or risperidone	282.00	Before After	134.90 ± 11.2 61.18 ± 28.73	NA	NA	04	8.00	35.40	Drug-free
Chen S (75)	Chronic	Risperidone	150.00	Before After	84.62 ± 12.83 NA	20.43 ± 8.74 15.99 ± 9.82	21.47 ± 9.64 18.25 ± 9.39	11	NA	28.60	NA
Gonzalez-Pinto A (4)	FEP	Olanzapine	300.00	Before After	79.95 ± 15.27 45.05 ± 10.57	24.78 ± 4.21 12.02 ± 5.95	13.99 ± 6.27 12.73 ± 13.91	52	0.25	24.01	Drug-naïve
Hori H (38)	Chronic	Olanzapine	320.00	Before After	NA	25.50 ± 5.00 14.80 ± 6.10	25.40 ± 5.10 18.60 ± 4.20	08	3.90	35.00	Typical and atypical antipsychotics
Lee B (28)	FEP and Chronic	Risperidone	280.00	Before After	97.80 ± 24.40 57.80 ± 24.90	25.40 ± 5.00 14.27 ± 5.10	22.70 ± 9.30 15.70 ± 8.40	06	4.71	31.30	Drug-naïve/free
Lee A (39)	Chronic	Olanzapine, risperidone, haloperidol, quetiapine or amisulpride	NA	Before After	93.00 ± 26.00 69.00 ± 26.00	NA	NA	04	NA	32.90	Drug-naïve/free
Pirildar S (8)	FEP	Clozapine, olanzapine or risperidone	385.00	Before After	119.12 ± 9.93 67.65 ± 11.40	30.81 ± 7.99 16.45 ± 8.96	30.27 ± 7.31 17.63 ± 11.32	06	1.20	27.81	Drug-free for at least 2 weeks
Rizos E (31)	Chronic	Olanzapine, risperidone, haloperidol or amisulpride	492.08	Before After	NA	24.75 ± 7.22 16.73 ± 5.07	23.86 ± 10.72 20.64 ± 8.50	06	23.84	43.63	Drug-free for at least 12 weeks
Yoshimura R (76)	FEP	Olanzapine, risperidone, or aripripazole	270.00	Before After	NA	NA	NA	08	1.18	25.00	Drug-naïve
Yoshimura R (77)	FEP	Aripripazole	268.00	Before After	75.00 ± 8.10 54.00 ± 9.60	21.80 ± 3.10 15.20 ± 3.20	22.70 ± 2.70 16.60 ± 3.30	08	0.90	30.80	Drug-naïve
Yoshimura R (73)	FEP	Risperidone	180.00	Before After	107.10 ± 24.4 84.80 ± 22.30	31.30 ± 5.60 22.20 ± 14.50	24.20 ± 6.40 19.20 ± 6.40	04	1.70	37.00	Drug-free for at least 1 week

Abbreviations: BDNF, brain-derived neurotrophic factor; PANSS-T, Positive and Negative Symptoms Scale total score; PANSS-PS, Positive and Negative Symptoms Scale positive symptoms sub-score; PANSS-NS, Positive and Negative Symptoms Scale negative symptoms sub-score; FEP, first episode psychosis; NA, not available.

* Mean ± standard deviation.

Table 4S. Changes in PANSS scores with antipsychotic treatment.

Study	Response*	Year	Change in PANSS-T (%)	Change in PANSS-P (%)	Change in PANSS-N (%)
Ajami A (37)	Yes	2014	-49.39 (-49.77)	-15.16 (-57.79)	-13.46 (-48.35)
	No		-20.00 (-26.31)	-4.85 (-29.06)	-5.61 (-24.31)
Chen C (74)	Yes	2011	-73.72 (-55.01)	NA	NA
Chen S (75)	No	2012	NA	-4.44 (-21.73)	-3.23 (-14.99)
Gonzalez-Pinto A (4)	Yes	2010	-34.90 (-43.65)	-12.76 (-51.50)	-1.26 (-9.00)
Hori (38)	Yes	2007	NA	-10.70 (-41.96)	-6.90 (-27.17)
Lee B (28)	Yes	2009	-52.80 (-57.90)	-17.80 (-66.91)	-10.20 (-5.23)
	No		-17.20 (-18.43)	-5.10 (-21.16)	-0.70 (-3.18)
Lee A (39)	No	2011	-29.00 (-25.80)	NA	NA
Pirildar S (8)	Yes	2004	-51.47 (-43.25)	-14.36 (-46.61)	-12.64 (-41.76)
Rizos E (31)	No	2010	NA	-8.02 (-32.43)	-3.02 (-13.21)
Yoshimura R (76)	No	2010	NA (-29.94)	NA (-30.01)	NA (-26.07)
Yoshimura R (77)	No	2012	-21.00 (-38.89)	-6.60 (-30.80)	-6.10 (-26.70)
Yoshimura R (73)	No	2007	-22.30 (-20.82)	-9.10 (-29.07)	-5.00 (-20.40)

Abbreviations: PANSS-T, Positive and Negative Symptoms Scale total score; PANSS-PS, Positive and Negative Symptoms Scale positive symptoms sub-score; PANSS-NS, Positive and Negative Symptoms Scale negative symptoms sub-score; NA, not available.

* Defined as a 40% decrease in PANSS-T scores; when PANSS-T unavailable, we used the PANSS-P.

Table 5S. Demographic characteristics of studies included in the meta-analysis of serum or plasma BDNF levels in schizophrenia.

Between-Group Studies	Year	Subjects	Kit (all ELISA method)	Subtype of BDNF assessed	Source	Country
Ajami A (37)	2014	First episode and Chronic	Glory Science, USA	Total BDNF	Serum	Iran
Buckley P (23)	2007	First episode	R&D Systems	Total BDNF	Plasma	United States
Carlino D (34)	2011	Chronic	Promega, WI, USA	Total BDNF	Serum	Italy
Chen C (27)	2009	First episode	BanDing Biomedical, Inc., Beijing, China	Total BDNF	Serum	China
Chen S (64)	2014	First episode	Quantikine Human Cytokine Kit, R&D	Total BDNF	Plasma	Taiwan
Domenici E (3)	2010	Chronic	Not available		Plasma	Germany
Fernandes BS (51)	2010	Chronic	Chemicon, USA	Total BDNF	Serum	Brazil
Gama C (24)	2007	Chronic	CYT 306, Chemicon International USA	Total BDNF	Serum	Brazil
Goto N (65)	2011	First episode	ELISA kit (Chemikine, Chemicon, CA, USA)	Total BDNF	Serum	Japan
Grillo R (25)	2007	Chronic	Promega, Co, USA	Total BDNF	Serum	Brazil
Huang T (21)	2006	First episode and Chronic	Not available		Serum	Taiwan
Ikeda Y (52)	2008	Chronic	Promega, WI, USA	Total BDNF	Serum	Japan
Jindal R (30)	2010	First episode	Not available		Serum	United States
Jockers M (7)	2004	First episode	R&D Systems, MN, USA	Total BDNF	Serum	Germany
Kalmady S (66)	2013	Chronic	DuoSet, R&D Systems, MN, USA	Total BDNF	Plasma	India
Kuo F (67)	2013	Chronic	Promega Inc., Mannheim, Germany	Total BDNF	Serum	Taiwan
Lee A (39)	2011	Chronic	R&D Systems, MN, USA	Total BDNF	Serum	Germany
Lee B (28)	2009	Chronic	Promega, Southampton, UK	Total BDNF	Plasma	Korea
Mackin (53)	2007	Chronic	Promega, WI, USA	Total BDNF	Serum	United Kingdom
Niitsu T (36)	2011	Chronic	CYT306, Chemicon	Total BDNF	Serum	Japan
Palomino A (22)	2006	First episode	Promega, USA	Total BDNF	Plasma	Spain
Pillai A (20)	2010	First episode	Promega, WI, USA	Total BDNF	Plasma	United States
Pirildar S (8)	2004	First episode	DuoSet, R&D Systems, MN, USA	Total BDNF	Serum	Turkey
Reis H (26)	2008	Chronic	R&D Systems, MN, USA	Total BDNF	Serum	Brazil
Rizos E (31)	2010	First episode	R&D Systems, MN, USA	Total BDNF	Serum	Greece
Rizos E (32)	2010	Chronic	CYT306, Millipore, USA	Total BDNF	Serum	Greece
Ruiz de Azua S (68)	2013	First episode	Promega, WI, USA	Total BDNF	Plasma	Spain
Shimizu E (6)	2003	First episode and Chronic	Promega, USA	Total BDNF	Serum	Japan
Sotiropoulou M (69)	2013	First episode	R&D Systems, MN, USA	Total BDNF	Serum	Greece
Toyooka K (5)	2002	Chronic	Not available		Serum	Japan

Vinogradov F (29)	2009	Chronic	R&D Systems, MN, USA	Total BDNF	Serum	United States
Yamamori H (70)	2013	Chronic	Adipo Bioscience, Santa Clara, CA, USA	Mature BDNF	Plasma	Japan
Yang Y (71)	2011	Chronic	BanDing Biomedical, Inc., Beijing, China	Total BDNF	Serum	China
Yoshimura R (73)	2007	First episode	Promega, WI, USA	Total BDNF	Plasma	Japan
Zhang X (73)	2012	Chronic	BanDing Biomedical, Inc., Beijing, China	Total BDNF	Serum	China
Within-Group Studies	**Year**	**Subjects**	**Kit (all ELISA method)**		**Source**	**Country**
Ajami A (37)	2014	First episode and Chronic	Glory Science, USA	Total BDNF	Serum	Iran
Chen C (74)	2011	Chronic	Promega, USA	Total BDNF	Serum	Taiwan
Chen S (75)	2012	Chronic	R&D Systems, Minneapolis	Total BDNF	Plasma	Taiwan
Gonzalez-Pinto A (4)	2010	First episode	Promega, USA	Total BDNF	Plasma	Spain
Hori H (38)	2007	First episode and Chronic	Promega, USA	Total BDNF	Plasma	Japan
Lee B (28)	2009	Chronic	Promega, Southampton, UK	Total BDNF	Plasma	Korea
Lee A (39)	2011	Chronic	R&D Systems, MN, USA	Total BDNF	Serum	Germany
Pirildar S (8)	2004	First episode	DuoSet, R&D Systems, MN, USA	Total BDNF	Serum	Turkey
Rizos E (31)	2010	Chronic	CYT306, Millipore, USA	Total BDNF	Serum	Greece
Yoshimura R (22)	2010	First episode	Promega, WI, USA	Total BDNF	Plasma	Japan
Yoshimura R (77)	2012	First episode	Promega, WI, USA	Total BDNF	Plasma	Japan
Yoshimura R (76)	2007	First episode	Promega, WI, USA	Total BDNF	Plasma	Japan

Table 6S. Between-group studies that evaluated serum or plasma brain-derived neurotrophic factor (BDNF) levels in healthy subjects and subjects with schizophrenia.

Studies		**Schizophrenia**			**Control**		
Between-Group	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Ajami A (37) - FEP	pg/ml	11	3.78	3.30	26	3.18	3.32
Ajami A (37) – C	pg/ml	15	4.38	4.56	26	3.18	3.32
Buckley P (23)	pg/ml	15	135.00	21.77	14	290.50	38.81
Carlino D (34)	ng/ml	40	25.60	2.00	40	28.90	4.00
Chen C (27)	ng/ml	88	9.00	4.20	90	12.10	2.20
Chen S (64)	ng/ml	151	6.70	7.00	126	17.30	9.10
Domenici E (3)	ng/ml	229	4.30	1.20	254	6.20	1.10
Fernandes B (51)	pg/ug protein	7	0.14	0.05	21	0.16	0.04
Gama C (24)	pg/ug protein	60	1.21	0.98	26	0.19	0.08
Goto N (65)	ng/ml	18	15.00	4.50	18	17.00	5.00
Grillo R (25)	pg/ml	44	112.20	47.90	25	168.80	26.30
Huang T (21) - FEP	ng/ml	10	11.39	6.12	96	14.18	6.86
Huang T (21) – C	ng/ml	116	14.44	6.96	96	14.18	6.86
Ikeda Y (52)	ng/ml	74	37.08	20.42	87	52.24	25.28
Jindal R (30)	pg/ml	24	97.58	31.41	41	116.78	38.42
Jockers M (7)	pg/ml	102	13.10	5.90	61	13.20	5.20
Kalmady S (66)	ng/ml	59	28.80	11.70	60	34.90	8.20
Kuo F (67)	ng/ml	33	4.45	3.65	30	21.47	5.25
Lee A (39)	ng/ml	22	4.38	2.10	22	15.39	6.00
Lee B (28) – FEP	pg/ml	10	1227.93	699.31	36	880.61	244.57
Lee B (28) – C	pg/ml	26	1000.47	389.38	36	880.61	244.57
Mackin (53)	pg/ml	20	13436.00	7979.00	14	13800	9107.00
Niitsu T (36)	ng/ml	63	15.30	3.8	52	14.60	4.40
Palomino A (22)	ng/ml	21	4.19	2.26	21	7.55	4.31
Pillai A (20)	pg/ml	34	750.00	80.80	36	980.00	90.00
Pirildar S (8)	ng/ml	22	14.53	2.93	22	26.80	9.30
Reis H (26)	pg/ml	40	7751.00	1847.00	20	3500.00	2048
Rizos E (31)	ng/ml	37	18.87	8.23	21	29.20	7.73
Rizos E (32)	ng/ml	47	19.19	8.58	44	27.50	8.17

Ruiz de Azua (68)	ng/ml	17	6.53	4.14	45	9.19	4.21
Shimizu E (6) - FEP	ng/ml	15	23.80	3.10	40	28.50	9.10
Shimizu E (6) - C	ng/ml	25	27.90	12.30	40	28.50	9.10
Sotiropoulou M (69)	ng/ml	50	12.62	1.86	50	14.52	2.18
Toyooka K (5)	ng/ml	34	6.30	3.40	35	11.40	7.70
Vinogradov F (29)	ng/ml	56	25.27	10.34	16	31.30	8.95
Yamamori H (70)	pg/ml	22	559.50	370.20	22	647.50	489.10
Yang Y (71)	ng/ml	264	8.80	2.30	323	11.90	2.30
Yoshimura R (73)	ng/ml	89	1.40	0.63	103	1.85	1.35
Zhang X (73)	ng/ml	657	9.50	2.90	445	11.90	2.10
Total		**2667**			**2580**		

Table 7S. Within-group studies that evaluated serum or plasma brain-derived neurotrophic factor (BDNF) levels in subjects with schizophrenia.

Studies		**Before Treatment**			**After Treatment**		
Within-Group	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Ajami A (37) – Responders	pg/ml	13	4.22	3.64	13	4.27	3.67
Ajami A (35) – Non-Responders	pg/ml	13	4.04	4.51	13	3.86	3.76
Chen C (74) – Responders	ng/ml	53	5.00	3.90	53	5.58	4.20
Chen S (75) – Non-Responders	ng/ml	45	4.88	3.20	45	8.06	3.87
Gonzalez-Pinto A (4) – Responders	ng/ml	12	4.01	2.09	12	5.32	2.79
Hori H (38) – Responders	pg/ml	32	1.70	1.00	32	2.20	0.50
Lee B (28) – Responders	pg/ml	13	1,079.64	484.60	13	1,165.66	643.92
Lee B (28) – Non-Responders	pg/ml	23	923.17	379.63	23	954.70	446.74
Lee A (39) – Non-Responders	ng/ml	22	4.38	2.00	22	7.01	4.00
Pirildar S (8) – Responders	ng/ml	22	14.19	8.12	22	14.53	2.93
Rizos E (31) – Non-Responders	ng/ml	47	19.19	8.58	47	19.91	10.73
Yoshimura R (76) – Non-Responders	ng/ml	59	0.90	0.39	59	1.01	0.41
Yoshimura R (77) – Non-Responders	ng/ml	50	0.70	0.40	50	0.90	0.30
Yoshimura R (73) – Non-Responders	ng/ml	59	1.60	1.10	59	1.60	1.40
Total		**463**			**463**		

BDNF Meta-analysis: Checklist summarising compliance with MOOSE guidelines

Reporting background should include	
Problem definition	Yes
Hypothesis statement	Yes
Description	Yes
Type of exposure or intervention used	Yes
Type of study designs used	Yes
Study population	Yes
Reporting of search strategy should include	
Qualifications of searches (e.g. librarians and investigators)	Yes
Search strategy, including time period included in the synthesis and keywords	Yes
Effort to include all available studies, including contact with authors	Yes
Databases and registries searched	Yes
Search software used, name and version, including special features	Yes
Use of hand searching (e.g. reference lists of obtained articles)	No
List of citations located and those excluded including justification	Available on request
Method of addressing articles published in languages other than English	Yes
Method of handling abstracts and unpublished studies	No
Description of any contact with authors	No
Reporting methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	Yes
Documentation of how data were classified and coded (e.g., multiple raters, blinding, and inter-rater reliability)	Yes
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	Yes
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes
Assessment of heterogeneity	Yes
Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes

Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Yes
Table giving descriptive information for each study included	Yes
Results of sensitivity testing (e.g., subgroup analysis)	Yes
Indication of statistical uncertainty of findings	Yes
Reporting of discussion should include	
Quantitative assessment of bias (e.g., publication bias)	Yes
Justification for exclusion (e.g., exclusion of non–English-language citations)	Yes
Assessment of quality of included studies	Yes
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Yes
Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	Yes
Guidelines for future research	Yes
Disclosure of funding source	Yes

Brain-derived Neurotrophic Factor in Schizophrenia: A Meta-Analysis

Supplementary Material - Figures

Figure 1S. Flow diagram. Some studies were included in more than one category.

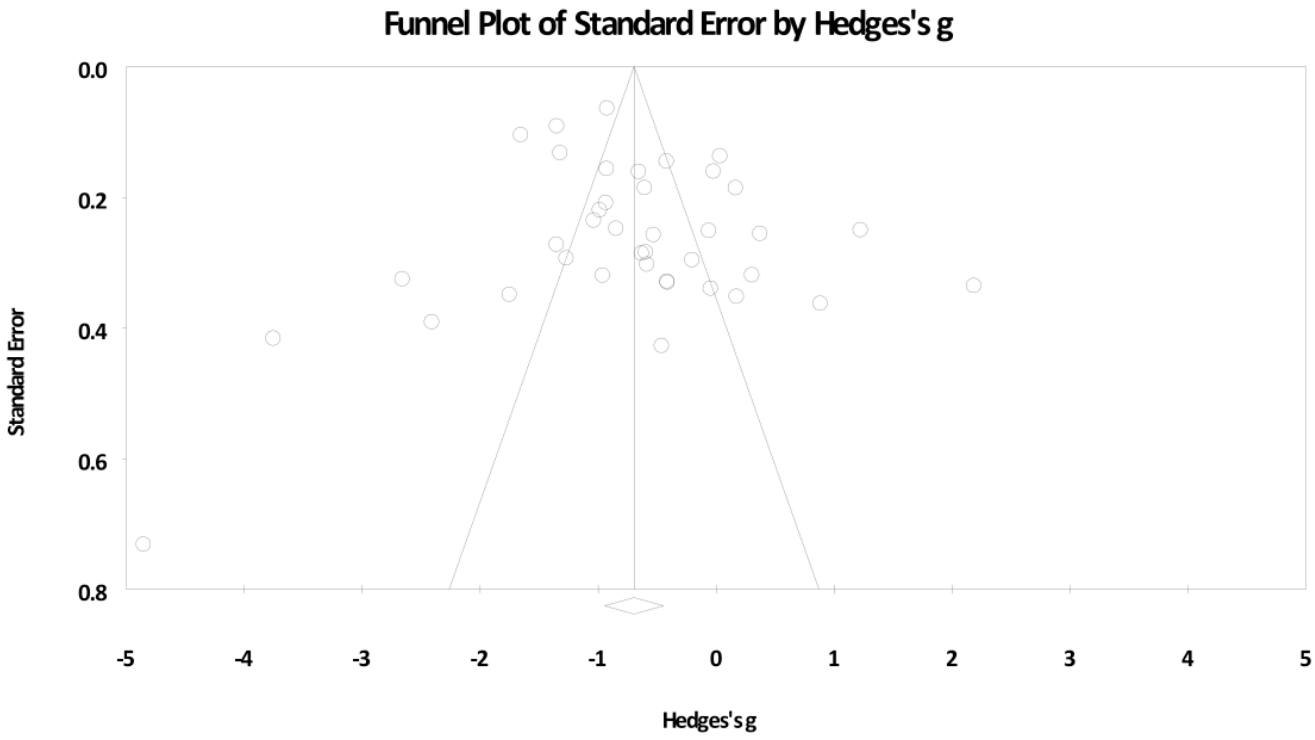

Figure 2S. Funnel plot and trim-and-fill estimation of serum and plasma BDNF levels in schizophrenia (SZ) when compared to controls (between-group comparison). White circles depict observed associations. The trim-and-fill estimation suggests that there were no negative studies missing due to publication bias (right region of the mean), with the Egger's test being not significant (p=0.22), confirming the symmetry of the funnel plot. The white diamond depicts the aggregated point estimate. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 4313 negative omitted studies would be required to make $p > 0.05$, also supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias.

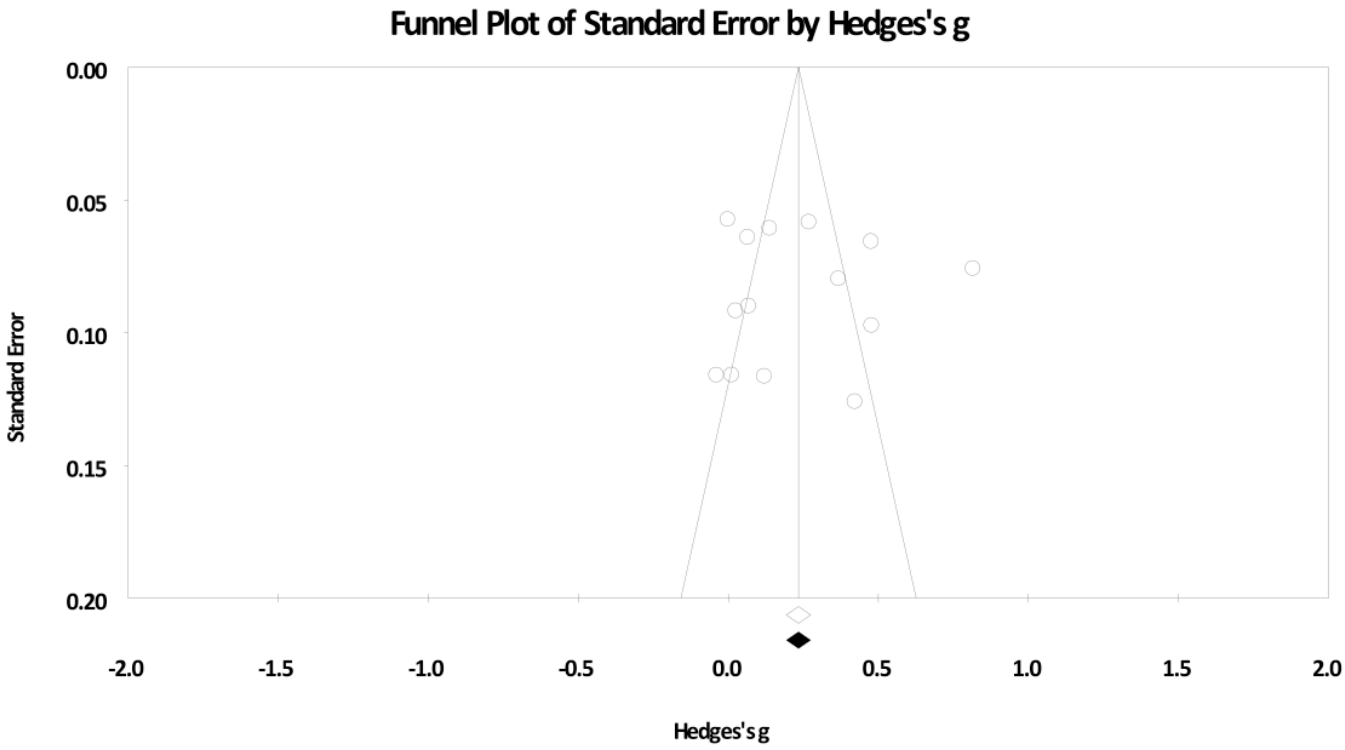

Figure 3S. Funnel plot and trim-and-fill estimation of serum and plasma BDNF levels in schizophrenia (SZ) before and after treatment with antipsychotics (within-group comparison). White circles depict observed associations. The trim-and-fill estimation suggests that there were no negative studies missing due to publication bias (right region of the mean), with the Egger's test being not significant (p=0.26), confirming the symmetry of the funnel plot. The white diamond depicts the aggregated point estimate. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 103 negative omitted studies would be required to make $p > 0.05$, also supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias.

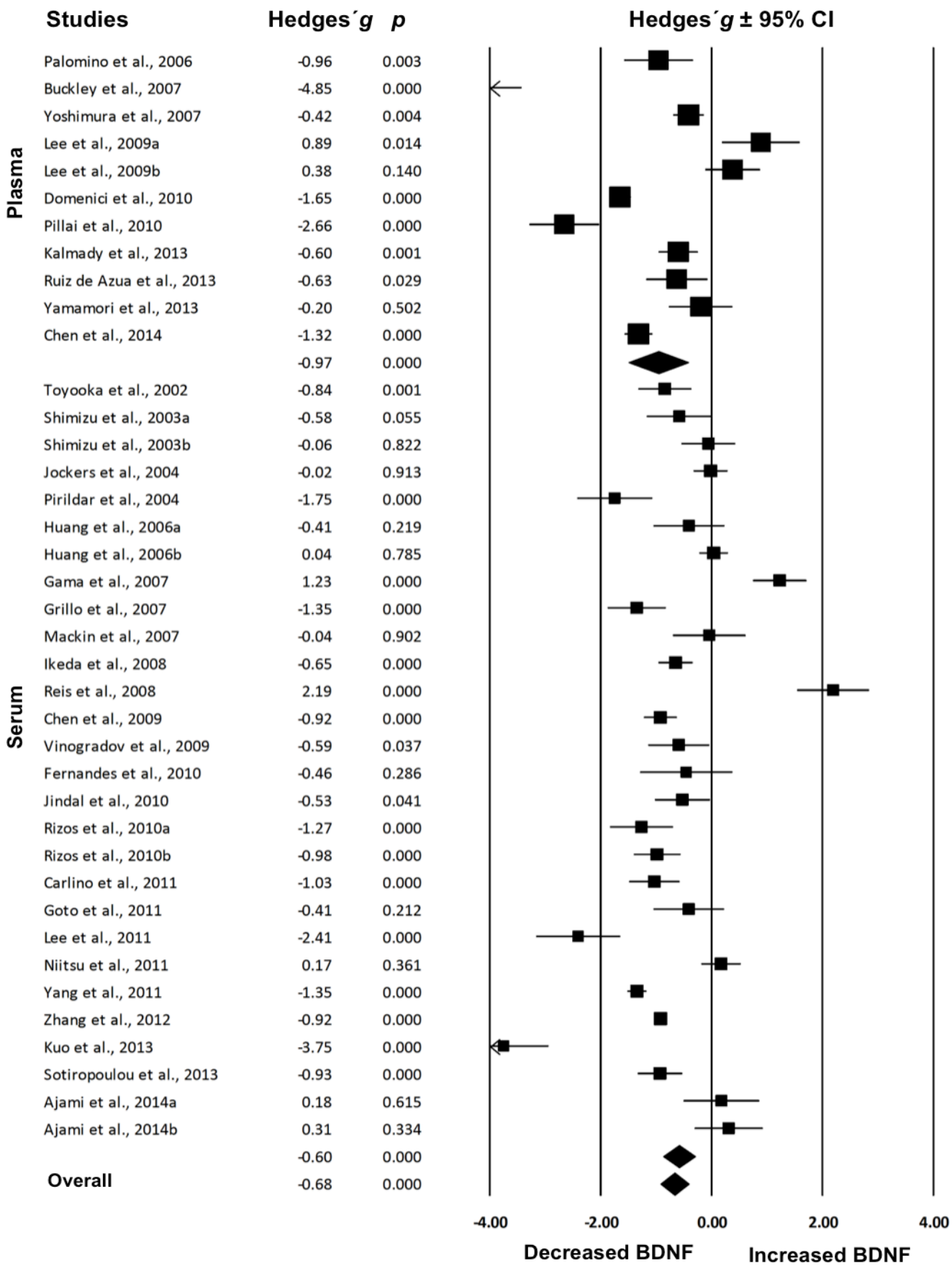

Figure 4S. Forest plot for random effects between-group meta-analysis on serum and plasma BDNF levels in persons with SZ and healthy controls according BDNF source (serum vs. plasma). The sizes of the squares are proportional to sample size. A total of 35 studies were included, comprising 2,667 persons with SZ and 2,580 healthy controls.

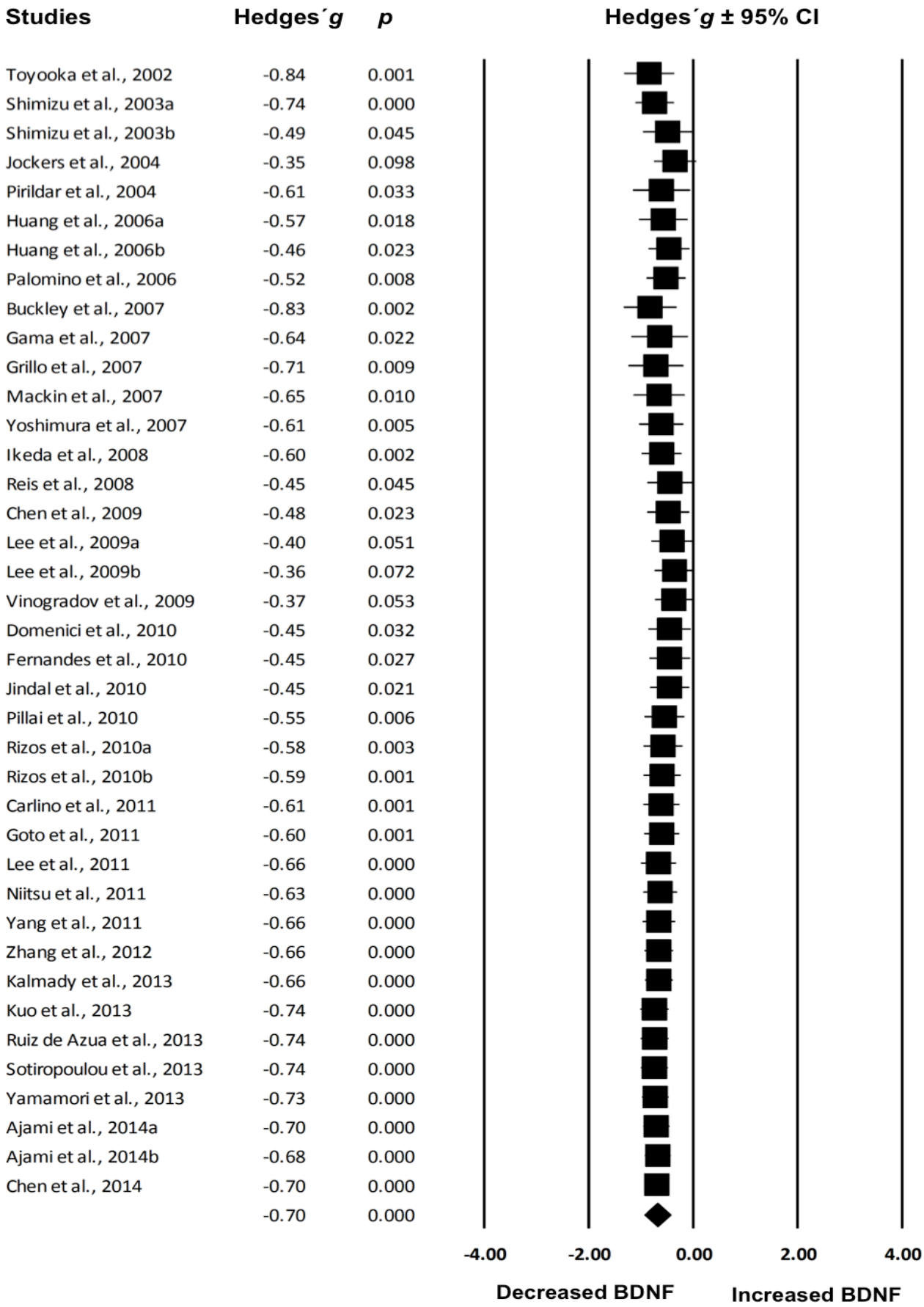

Figure 5S. Cumulative between-group meta-analysis on serum and plasma BDNF levels in persons with SZ and in healthy controls.

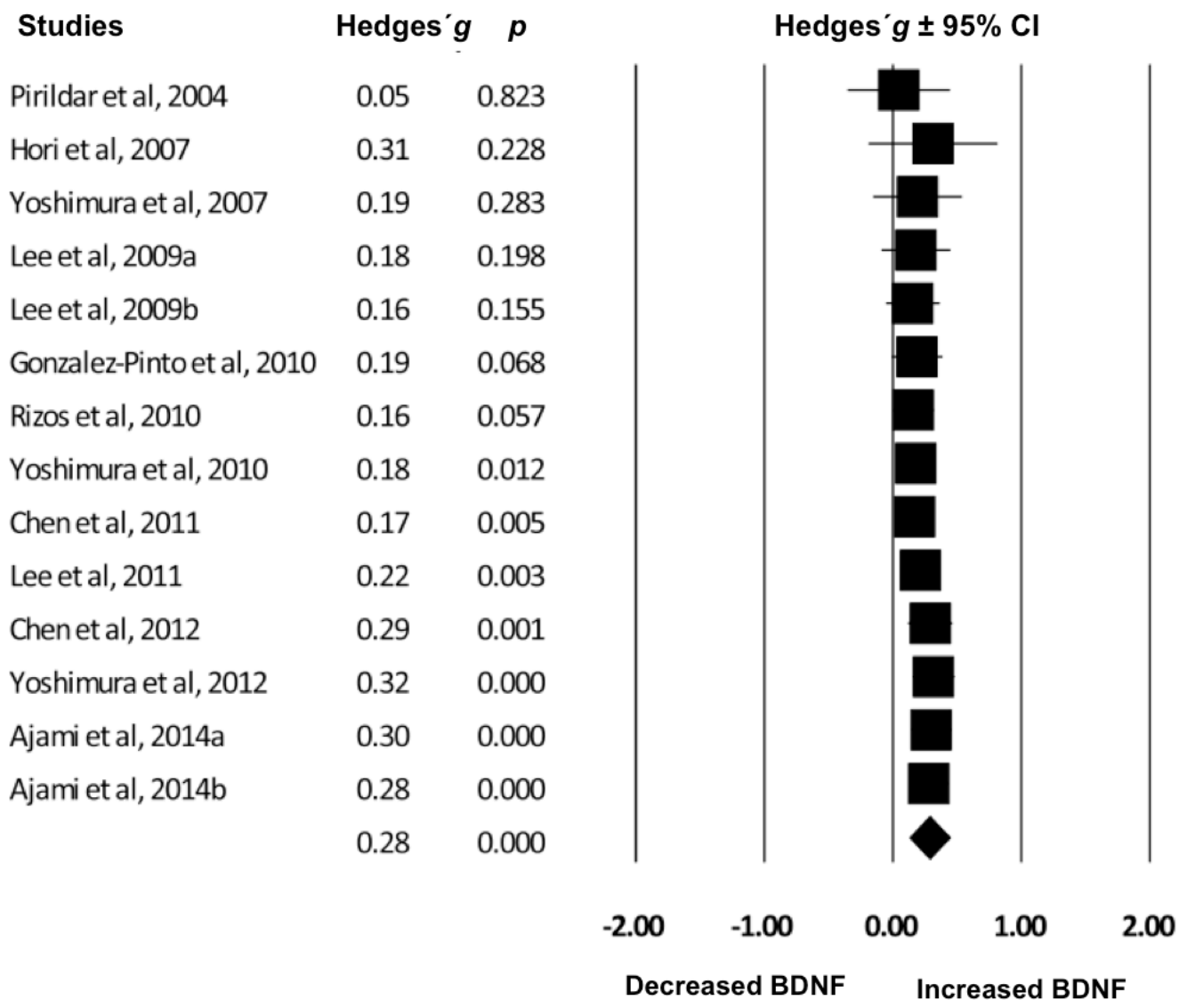

Figure 6S. Cumulative within-group meta-analysis on serum and plasma BDNF levels in persons with SZ before and after antipsychotic treatment.

CAPITULO 2:

DECREASED PERIPHERAL BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS ARE A BIOMARKER OF DISEASE ACTIVITY IN MAJOR PSYCHIATRIC DISORDERS: A COMPARATIVE META-ANALYSIS

ARTIGO PUBLICADO NA REVISTA *MOLECULAR PSYCHIATRY*

Molecular Psychiatry (2013), 1–2

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LETTER TO THE EDITOR

Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: a comparative meta-analysis

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Brain-derived neurotrophic factor (BDNF) is a dimeric protein that has a central role in neurogenesis and neuroplasticity. This neurotrophin is found throughout the brain and is particularly abundant in the hippocampus and cerebral cortex, brain areas critical for the control of mood, emotion and cognition.[1] The secretion and uptake of BDNF in neurons occur at both axons and dendrites, either constitutively or in response to neural activity, and it is also synthesized and released by astrocytes.[2] It appears to be involved in the pathophysiology of mood disorders (MD) and schizophrenia (SZ), evidenced by reports of decreased serum and cerebrospinal fluid (CSF) levels in SZ, bipolar disorder (BD) and major depressive disorder (MDD).[3–5] Furthermore, BDNF levels are influenced by psychiatric medications such as antidepressants, mood stabilizers and antipsychotics.[3–5] On these grounds, BDNF levels as measured in serum and plasma have been promoted as a potential biomarker of diagnosis in these psychiatric disorders.[6]

BDNF crosses the blood–brain barrier, and its levels in serum and plasma are highly correlated with BDNF levels in CSF ($r = 0.8$).[7,8] Several studies have taken advantage of this 'window to the brain', with the great majority showing decreased BDNF levels in acutely ill subjects. However, the specificity, extent and relationship of peripheral BDNF levels to disease activity are not fully known; clarifying these issues was the aim of this meta-analysis. The hypothesis of this comparative meta-analysis was that peripheral BDNF levels would be lower in SZ and MD during acute episodes, and that serum or plasma BDNF could serve as a biomarker of disease activity, whereas not as a biomarker for diagnosis in these conditions.

To quantify and validate the specificity of serum and plasma BDNF levels in this study, we combined and compared results from a systematic and quantitative meta-analysis of electronic databases for MD and SZ. Inclusion criteria were studies that measured BDNF in plasma or serum *in vivo* in adult subjects with BD, MDD or SZ. Results from these studies were compiled to measure the effect size (ES) of BDNF level differences between patients and controls. To adjust for systematic measurement effects, we calculated the ES of each study according to Hedges' *g* from their means and s.d., which produces an unbiased ES adjusted for sample size. The direction of the ES was positive if patients showed increased BDNF, and negative if they showed decreased BDNF levels when compared with controls. As the data were highly skewed, we used non-parametric methods. Kruskal–Wallis test and Conover–Inman *post hoc* test were used for statistical analysis. All tests were two-tailed, and we considered statistically significant *P*-values < 0.05. Results are shown as median and interquartile range of the ES. Studies with negative results are less likely to be published than studies with positive results. We took this into account in our statistical analyses and, although we found some evidence for publication bias, it was insufficient to affect our main results (Supplementary Material).

Our comparative meta-analysis included 99 studies involving 907 subjects with BD, 3762 with MDD, 2436 with SZ and 8795 healthy controls. Of those, 45 studies included only subjects free of use of psychiatric medication for at least 7 days (Supplementary Material). Serum and plasma BDNF levels reached highly negative ES in BD during depressive episodes (−0.98, −1.91 to −0.50), in BD during manic episodes (−0.78, −0.99 to −0.20), in MDD in acute episodes (−0.84, −1.32 to −0.30) and in SZ (−0.70, −1.30 to −0.21). There were no differences in the decreased peripheral BDNF levels among the groups ($P = 0.49$). As hypothesized, the ESs in BD during euthymia and in MDD in remission were near zero (−0.02, −0.25 to 0.64 and −0.07, −0.38 to 0.31, respectively, $P = 0.84$), suggesting no difference or small difference in BDNF levels between euthymic subjects with BD, with remitted MDD, and healthy controls. The decrease in BDNF levels was more marked in the subjects with SZ and MD in acute episodes when compared with subjects with BD in euthymia and with MDD in remission (−0.70, −1.30 to −0.21, −0.82, −1.23 to −0.23, and −0.02, −0.30 to 0.35, respectively, $P = 0.0001$). Notwithstanding the differences in peripheral BDNF levels among groups were significant, the values presented a large amplitude with noteworthy overlap, not allowing us to properly discriminate subjects in acute psychiatric states from those on remission solely on its levels (Figure 1).

The present data do not allow us to distinguish whether peripheral sources produce or release less BDNF or if decreased brain protein's synthesis or release is responsible for lower plasma and serum levels. Concentrations of BDNF are much higher in serum (>1000×) or plasma (~10×) than in CSF.[8] Therefore, it appears likely that blood BDNF is lower in acute episodes of MD and in SZ because of reduced peripheral than reduced cerebral synthesis/release. Much BDNF is derived from other tissues than the brain, including smooth muscle, liver and endothelial cells. However, it may still have important effects on brain and mediate the effects for instance of exercise on mood.[4,9] Nonetheless, for a better understanding of the underlying dynamic processes, future studies should determine the ratios of BDNF concentrations in CSF in serum and plasma in both patients (acutely ill and remitted) and controls. Changes in BDNF may represent a counter-regulatory response to other etiological factors of the illness, such as metabolic and redox factors.[10]

Our results support the hypothesis that BDNF is involved in the pathophysiology of both MD and SZ. These findings are in line

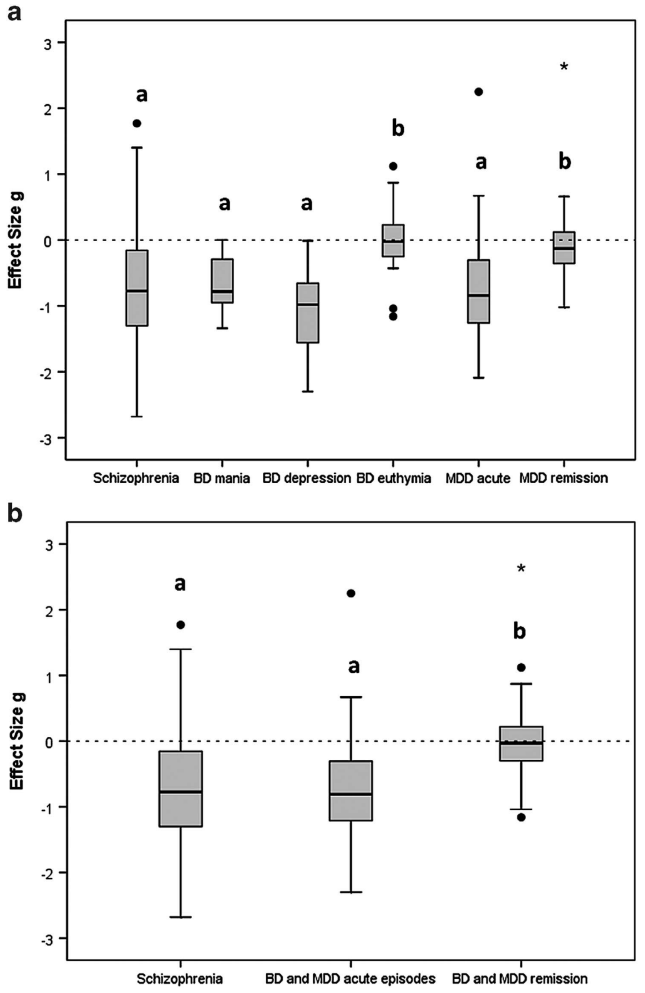

Figure 1. Box-plots of the effect sizes (ES) of serum and plasma brain-derived neurotrophic factor (BDNF) levels in schizophrenia (SZ), bipolar disorder (BD) in acute mania, depression and euthymia, and major depressive disorder (MDD) in acute episode and remission from individual studies as identified by the systematic review and meta-analysis. (**a**) There were no differences in BDNF levels among SZ, BD in acute episodes and MDD in acute episode (Kruskal–Wallis test, $P = 0.49$). The decrease in BDNF levels was more marked in subjects with SZ or BD and MDD during acute episodes when compared with subjects with BD in euthymia and MDD in remission (Kruskal–Wallis test with Conover–Inman post test; $P = 0.0001$). (**b**) BDNF levels according to disease activity. Decreased BDNF levels were observed in subjects with SZ, BD and MDD during acute episodes when compared with subjects with BD in euthymia and with MDD in remission (Kruskal–Wallis test with Conover–Inman *post hoc* test; $P = 0.0001$). A total of 99 studies were included, comprising 907 subjects with BD, 3762 subjects with MDD, 2436 subjects with SZ and 8795 controls (21, 31 and 54 studies, respectively; some studies contributed to more than one diagnostic group). The presence of statistical significance is identified by the letters *a* and *b*. Identical letters denote absence of significance, and different letters denote presence of significance.

with previous studies showing that alterations of BDNF expression are a mechanism shared by BD, MDD and SZ.[3–6] BDNF does not appear to be a diagnostic biomarker across the schizoaffective spectrum of psychiatric disorders, but may reflect underlying disease activity. However, notably, the severity of depressive symptoms in MDD seems to be unrelated to BDNF serum levels.[4] Furthermore, decreased BDNF levels may be related to the suppressive effects elicited by stress of an acute psychiatric disease episode.[9,10] Stress may also have an important causal role in the initiation or exacerbation of psychiatric disorders that can be detected by peripheral biomarkers. Although as a trait marker, BDNF might not properly differentiate SZ, BD and MDD, it differentiates euthymia from mania and bipolar depression in BD, and the remitted from the acute state in MDD, suggesting that BDNF levels assessed peripherally in serum or plasma are a state biomarker of disease activity reflecting common pathophysiology. Yet a biomarker of disease activity, due to the large amplitude variation in BDNF serum and plasma values, it is unlikely that it will translate as an useful biomarker in clinical practice.

'The search strategy for the systematic review, study selection, data extraction and data synthesis, tables and flow diagram are described in the Supplementary Information, available on the *Molecular Psychiatry* website.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Methods:

Search strategy for the systematic review

We conducted a systematic review of all English and non-English articles to avoid language publication bias 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 OR mania OR manic OR depressive OR depression) OR (major depression disorder OR major depressive episode OR depression OR depressive OR depressive disorder) OR (schizophrenia OR schizophrenic OR schizoaffective disorder OR psychotic disorder OR positive symptoms). The final search was performed in July of 2013. 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 pre-specified.

Study selection

Inclusion criteria were: 1) adult patients (18 years old or more) with BD types I or II, SZ, or MDD as defined by DSM-IV criteria; 2) cross-sectional studies comprised of a control group of healthy volunteers; 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; 4) morphological studies; and 5) comorbidity with neurodegenerative disorders such as dementia, and cancer, or studies assessing women during pregnancy or immediately after delivery. For the remitted state of MDD and BD in euthymia we accepted data of subjects after the beginning of medication since the subjects achieved remission (defined by a HDRS and YMRS < 8) and the samples were collected at least 7 days after achieving remission provided that control group was included (Figure 1, Flow diagram).

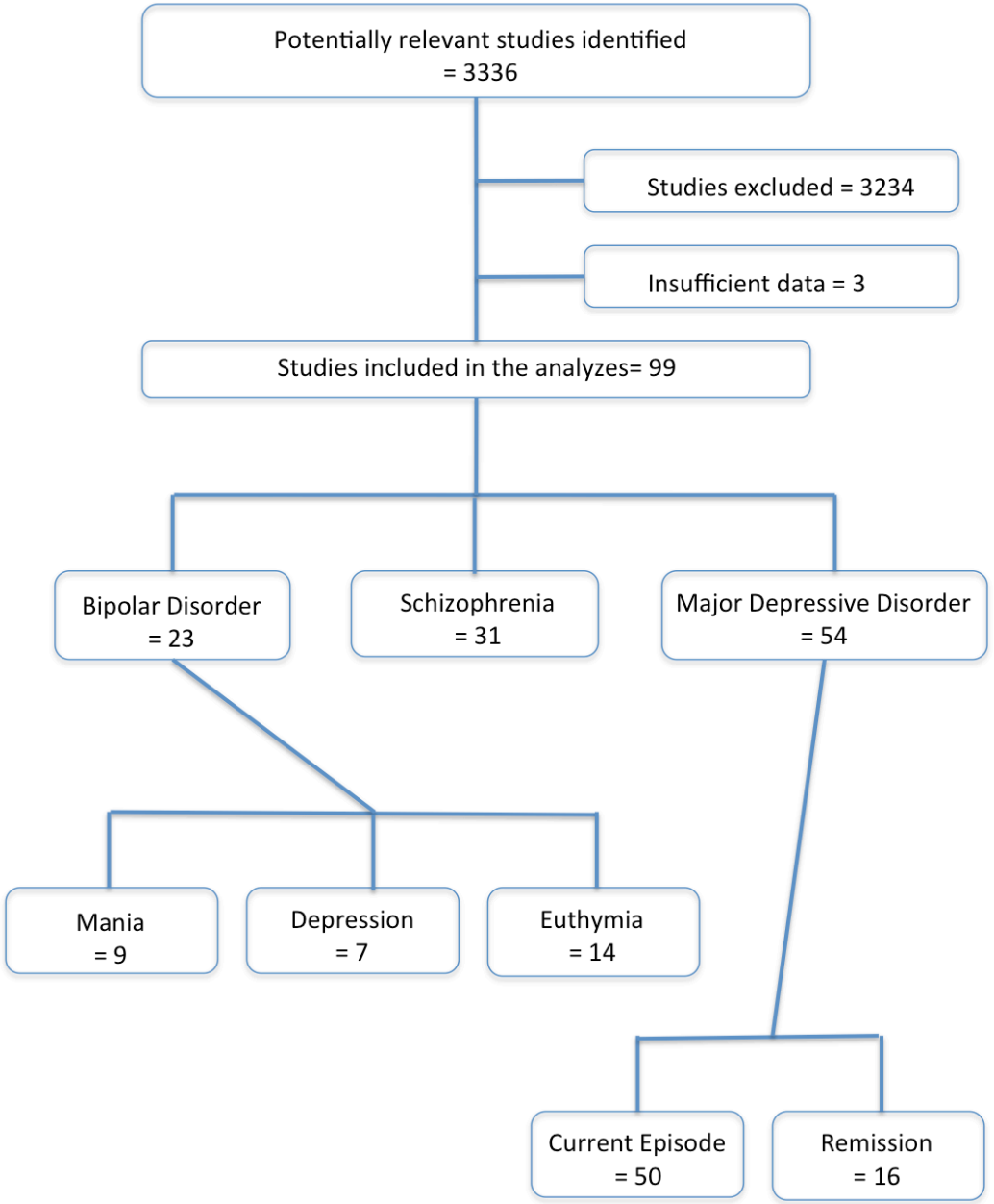

Figure 1. Flow diagram. Some studies were included in more than one diagnostic group.

Data extraction and data synthesis

Dr. Brisa S Fernandes extracted data [*n*, mean and standard deviation (SD)]. 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 (Tables 1 and 2).

ReviewManager (RevMan) version 5.0 was used to calculate the standardized mean differences or effect size (ES) estimate BDNF level differences between patients in distinct mood states and healthy volunteers. Effect size estimates were calculated from the means and SDs and were derived with Hedges's adjusted *g*, which provides an unbiased ES adjusted for sample size (Table 3).

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 (Figure 2), a scatter plot of treatment effect against a measure of study size. Publication bias was assessed by inspection of funnel plots and the Egger test, which assesses the degree of funnel plot asymmetry. The trim-and-fill procedure, a validated method to estimate an effect-size after bias has been taken into account, was performed in case of publication bias. Publication bias was also investigated by Classic fail-safe N, which is ananalysis of the number of missing (unpublished) studies that would bring the observed *p value* to > 0.05. This was performed for all analyses. We also assessed presence of heterogeneity in the studies by the *I2* metric.

The direction of the ES was positive if patients showed increased BDNF levels and negative if they showed decreased BDNF levels when compared to controls.

We proceeded according to the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analysis) and the recommendations of the Cochrane Collaboration. The level of significance for the ES estimates was set to $p<0.05$.

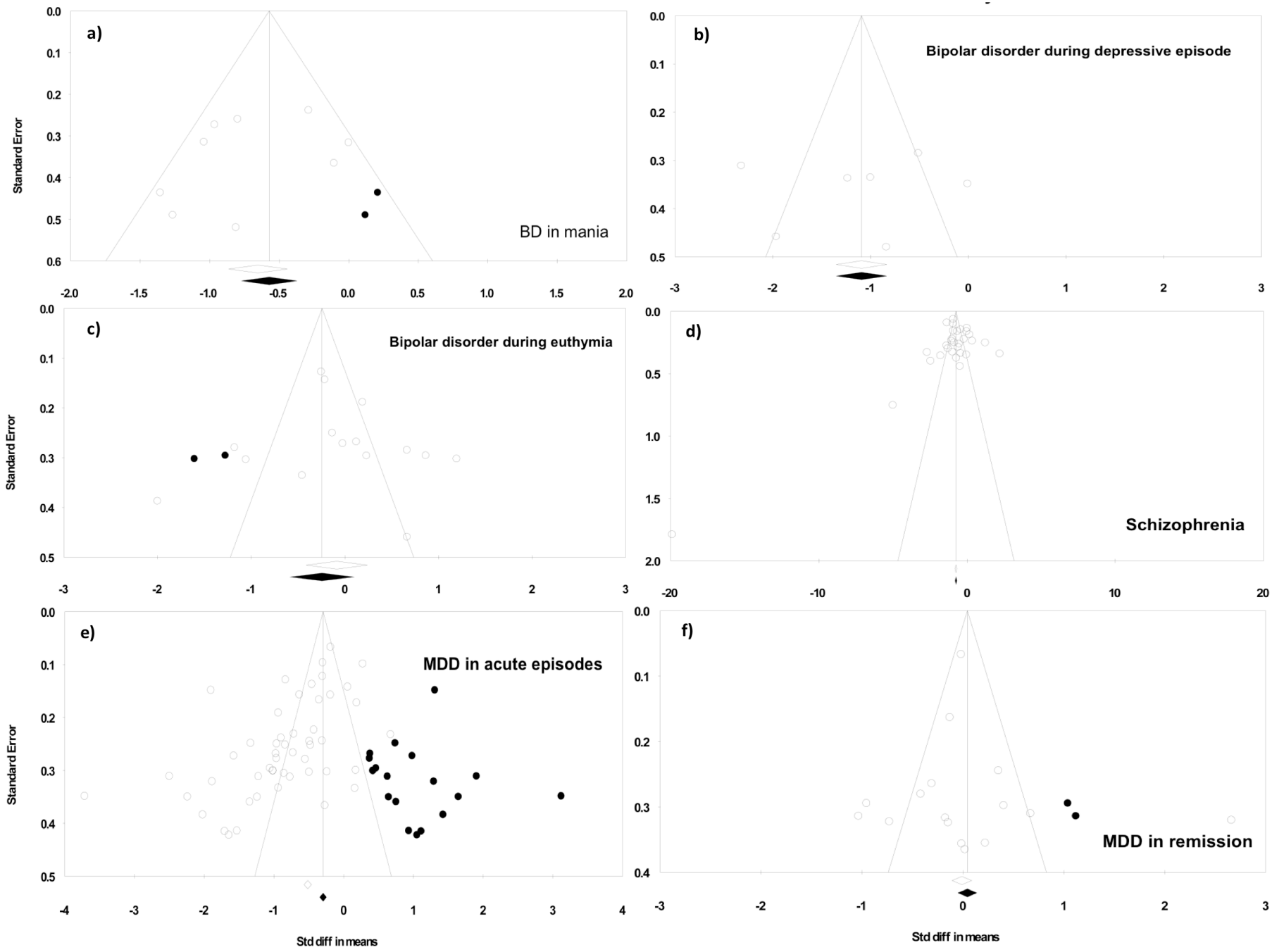
a)
BD in mania
b)
Bipolar disorder during depressive episode
c)
Bipolar disorder during euthymia
d)
Schizophrenia
e)
MDD in acute episodes
f)
MDD in remission
Standard Error
Std diff in means

Figure 2. Funnel plots and trim-and-fill estimation of all analyses of serum and plasma BDNF levels when compared to controls. Open circles depict observed associations and filled circles imputed values.

a) **Bipolar disorder in manic episodes.** The trim-and-fill estimation suggests that possibly 2 negative studies were missing due to publication bias. However,the Egger's test was not significant (p=0.38), confirming the symmetry of the funnel plot. The open diamonds depict the aggregated point estimate (h = -0.78, 95% CI = -0.99 – -0.40) and the filleddiamonds the aggregated point estimate after the imputation of 2 studies (h = -0.68), resulting in a symmetrical funnel-plot. The aggregated point estimate value after the imputation of the missing studies were close to the original point estimate and are still significant. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 82 unincluded studies would be required to make P > 0.05, supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias.

b) **Bipolar disorder in depressive episodes.** The trim-and-fill estimation suggests that there were no negative studies missing due to publication bias, with the Egger's test not significant (p=0.82), confirming the symmetry of the funnel plot. The open diamond depicts the aggregated point estimate and the filled diamond the aggregated point estimate as the same. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 119 unincluded studies would be required to make P > 0.05, supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias.

c) **Bipolar disorder in euthymia.** The trim-and-fill estimation suggests that there were no negative studies missing due to publication bias, with the Egger's test not significant (p=0.83), confirming the symmetry of the funnel plot. Possibly, there were 2 positive studies missing. The open diamond depicts the aggregated point estimate (h = -0.02, 95% CI = -0.22 – 0.38) and the filled diamond the aggregated point estimate after the imputation of 2 studies (h = -0.01), resulting in a symmetrical funnel-plot. The aggregated point estimate value after the imputation of the missing studies were close to the original point estimate and are still significant. Assessment of publication bias using the Fail-safe N (file drawer statistic) were not conducted in this analysis, since the pooled ES were not significant.

d) **Schizophrenia.** The trim-and-fill estimation suggests that there were no negative studies missing due to publication bias, with the Egger's test not significant (p=0.85), confirming the symmetry of the funnel plot. The open diamond depicts the aggregated point estimate and the filled diamond the aggregated point estimate as the same. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 3025 unincluded studies would be required to make P > 0.05, supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias.

e) **Major depressive disorder in acute episodes.** The trim-and-fill estimation suggests that possibly 19 negative studies were missing due to publication bias, and this was supported by a significant Egger's test (p=0.004), confirming the asymmetry of the funnel plot. The open diamond depicts the aggregated point estimate (h = -0.84, 95% CI = -1.09 – -0.40) and the filled diamond the aggregated point estimate after the imputation of 19 studies (h = -0.49), resulting in a symmetrical funnel plot. The aggregated point estimate value after the imputation of the missing studies were still significant. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 6565 unincluded studies would be required to make P > 0.05, supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias.

f) **Major depressive disorder in remission.** The trim-and-fill estimation suggests that there were 2 negative studies missing due to publication bias.However, the Egger's test was not significant (p=0.85), confirming the symmetry of the funnel plot. The open diamond depicts the aggregated point estimate and the filled diamond the aggregated point estimate as the same. Assessment of publication bias using the Fail-safe N (file drawer statistic) revealed that 119 unincluded studies would be required to make P > 0.05, supporting the view that the positive results of our meta-analysis are not likely to be a result of publication bias. Assessment of publication bias using the Fail-safe N (file drawer statistic) were not conducted in this analysis, since the pooled ES were not significant.

Table 1: Demographic characteristics of studies included in the meta-analysis of serum or plasma BDNF levels in bipolar disorder, major depressive disorder, and schizophrenia.

Study	Year	Subjects	N	Gender M/F	Age*	Medication	Source	Country
Bipolar Disorder								
Barbosa I (3) #	2010	Euthymia Control	19 38	6/15 12/20	40.71 ± 9.25 40.28 ± 11.90	Lithium, antidepressants, valproate, carbamazepine, and antipsychotics	Plasma	Brazil
Barbosa I (4)	2012	Euthymia Control	25 25	8/17 11/14	50.88 ± 9.11 48.04 ± 7.08	Lithium, valproate, and antipsychotics	Plasma	Brazil
Chou Y (10)	2012	Euthymia Control	23 33	6/17 12/21	36.50 ± 8.90 37.60 ± 7.80	Valproate, antipsychotics	Plasma	Taiwan
Cunha AC (12)	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	Lithium, valproate, carbamazepine, typical and atypical antipsychotics, antidepressants	Serum	Brazil
Dias VV (17)	2009	Euthymia Control	65 30	24/41 14/36	37.80 ± 10.51 33.60 ± 9.66	Lithium, valproate, antidepressants	Serum	Spain
Fernandes BS (21)	2009	Depression Control	40 30	13/27 12/18	41.32 ± 8.45 41.00 ± 11.99	Lithium, valproate, antidepressants, antipsychotics	Serum	Brazil
Gama C (23)	2007	Euthymia Control	30 26	18/12 15/11	40.28 ± 11.90 40.68 ± 12.12	Lithium, valproate	Serum	Brazil
Huang T (33)	2012	Mania Control	26 56	12/14 20/36	33.20 ± 11.70 32.50 ± 5.70	Lithium, valproate, and antipsychotics	Serum	Taiwan
Kapczinski F (40)	2011	Mania Depression Euthymia Control	20 20 20 80	12/20 14/20 12/20 60/80	37.90 ± 12.10 46.10 ± 9.30 46.60 ± 12.7 40.70 ± 12.5	Lithium, antidepressants, valproate, carbamazepine	Serum	Brazil
Kauer-Sant'Anna M Early-stage (45)	2009	Euthymia Control	26 26	13/13 10/16	22.40 ± 3.90 22.10 ± 3.60	Mood stabilizers, antipsychotics, antidepressants	Serum	Canada
Kauer-Sant'Anna M Late-stage (45)	2009	Euthymia Control	30 30	9/21 11/19	41.40 ± 8.40 43.20 ± 6.40	Mood stabilizers, antipsychotics, antidepressants	Serum	Brazil
Langan C (49)	2009	Euthymia Control	24 22	14/10 10/12	40.75 ± 9.01 40.36 ± 7.91	Lithium, valproate, carbamazepine	Serum	Ireland

Machado-Vieira R (54)	2007	Mania Control	30 30	7/23 7/23	26.00 ± 4.00 26.50 ± 5.20	Drug-free	Plasma	Brazil
Mackin P (55)	2007	Depression Control	20 14	19/1 12/2	48.6 ± 10.80 43.7 ± 12.90	Mood stabilizers, atypical antipsychotics, antidepressants	Serum	United Kingdom
Monteleone P (58)	2008	Euthymia Control	28 22	11/17 8/14	44.42 ± 10.80 40.10 ± 16.40	Drug-free, lithium, valproate, carbamazepine	Serum	Italy
Palomino A (63)	2006	Mania Control	14 12	8/6 8/4	25.93 ± 6.88 26.27 ± 7.27	Drug-naive and first episode	Plasma	Spain
Rybakowski J (72)	2010	Euthymia Control	13 60	7/6 25/35	51.30 ± 12.10 52.10 ± 13.60	Lithium	Plasma	Poland
Su S (79)	2011	Depression Control	10 21	NA NA	22.70 ± 2.90 25.00 ± 3.00	Drug-free	Serum	Taiwan
Suwalska A (80)	2010	Euthymia Control	141 75	90/51 52/23	53.70 ± 12.70 55.70 ± 11.70	Lithium	Serum	Poland
Tramontina J (83)	2006	Euthymia Control	114 137	32/82 45/92	42.54 ± 11.51 44.08 ± 13.81	NA	Serum	Brazil
Tramontina JF (84)	2009	Euthymia Mania Control	10 10 10	5/5 5/5 5/5	34.90 ± 13.85 34.90 ± 13.85 34.41 ± 3.97	Lithium, typical and atypical antipsychotics	Serum	Brazil
Yoshimura R (93)	2006	Mania Depression Control	12 6 20	8/10‡ 9/11	34.00 ± 15.00‡ 30.00 ± 11.00	Lithium, valproate	Plasma	Japan
Major Depressive Disorder								
Aydemir C (1)	2006	Depressed Control	20 20	0/20 0/20	35.55 ± 7.58 34.60 ± 7.86	Drug-free	Serum	Turkey
Aydemir O (2)	2007	Depressed Control	24 26	7/17 6/20	33.90 ± 15.70 31.40 ± 5.90	Drug-free	Serum	Turkey
Basterzi A (5)	2009	Depressed Control	43 15	15/33 6/9	32.00 ± 11.00 36.00 ± 10.00	Antidepressants	Serum	Turkey
Bocchio-Chiavetto (6)	2010	Depressed Control	25 59	5/20 11/48	43.36 ± 9.97 42.59 ± 10.07	Drug-free	Serum	Italy
Chu C (11)	2012	Depressed Control	12 122	NA NA	82.40 ± 4.40 81.80 ± 5.00	Antidepressants	Plasma	China
Dalby R (13)	2013	Depressed Control	22 22	7/15 7/15	57.40 ± 4.60 59.20 ± 7.30	Antidepressants, antipsychotics	Plasma	Denmark
Deuschle M (15)	2013	Depressed Control	55 14	14/41 1/13	53.20 ± 17.20 56.70 ± 11.60	Drug-free	Serum	Germany
Deveci A (16)	2007	Depressed	24	7/17	33.90 ± 15.70	NA	Serum	Turkey

		Control	26	6/20	31.40 ± 5.90			
Diniz B (18)	2010	Depressed Control	29 42	6/23 6/36	NA NA	Drug-free	Serum	Brazil
Eker C (19)	2010	Depressed Control	25 22	7/18 5/17	32.10 ± 9.30 29.70 ± 6.40	Drug-free	Serum	Turkey
Elfving B (20)	2012	Depressed Control	162 289	27/135 58/231	46.50 ± 9.60 45.70 ± 10.40	Antidepressants	Serum	Denmark
Fernandes BS (21)	2009	Depressed Control	10 30	4/6 12/18	44.80 ± 17.97 41.00 ± 11.99	Lithium, valproate, antidepressants, antipsychotics	Serum	Brazil
Gervasoni N (24)	2005	Depressed Control	26 26	11/15 13/13	40.50 ± 10.70 39.60 ± 12.20	Drug-free, antidepressants	Serum	Switzer Land
Gonul A (25)	2005	Depressed Control	28 18	7/21 6/12	35.50 ± 8.10 35.70 ± 5.80	Drug-free	Serum	Turkey
Gorgulo Y (27)	2009	Depressed Control	41 33	11/20 11/30	33.27 ± 11.18 35.00 ± 12.24	Drug-free, antidepressants	Serum	Turkey
Gustafsson G (30)	2009	Depressed Control	18 18	9/9 9/9	NA NA	Drug-free	Plasma	Sweden
Harvey B (31)	2013	Depressed Control	89 111	41/48 60/51	44.60 ± 7.60 43.53 ± 7.98	Drug-free	Serum	South Africa
Hu Y (32)	2010	Depressed Control	28 28	5/23 10/18	41.00 ± 14.80 44.70 ± 4.40	Drug-free	Serum	China
Huang T (34)	2007	Depressed Control	111 107	91/20 65/42	36.00 ± 10.10 28.90 ± 5.10	Drug-free	Serum	Taiwan
Jeon H (37)	2012	Depressed Control	105 50	27/78 18/32	46.30 ± 12.70 40.30 ± 12.70	NA	Serum	Korea
Karege F (42)	2005	Depressed Control	43 35	27/16 18/17	36.00 ± 10.00 31.00 ± 11.00	Drug-free	Serum	Switzer Land
Karege F (43)	2002	Depressed Control	30 30	15/15 15/15	36.00 ± 8.00 38.00 ± 9.00	Drug-free, antidepressants	Serum	Switzer Land
Karlovic D (44)	2012	Depressed Control	122 142	56/66 76/66	46.50 ± 12.40 44.80 ± 14.20	Drug-naïve	Serum	Croatia
Kim Y (46)	2007	Depressed Control	64 30	23/41 13/17	33.90 ± 15.70 44.30 ± 15.63	Antidepressants	Plasma	Korea
Kobayakawa M (47)	2011	Depressed Control	81 81	57/24 57/24	65.10 ± 8.30 65.00 ± 8.30	Drug-free	Serum	Japan
Laske C (50)	2010	Remitted Control	35 20	0/35 0/20	61.10 ± 7.20 58.90 ± 6.60	Drug-free, antidepressants	Serum	Germany
Lee B (52)	2007	Depressed Control	77 95	27/50 37/58	35.60 ± 11.80 34.40 ± 9.20	Drug-naïve, drug-free	Plasma	Korea

Matrisciano F (56)	2009	Depressed Remitted Control	21 21 20	11/10 11/10 9/11	41.30 ± 7.90 41.30 ± 7.90 31.80 ± 5.90	Drug-free, antidepressants	Serum	Italy
Molendjik (57)	2012	Depressed Control	541 382	360/181 233/149	39.80 ± 12.60 45.70 ± 12.30	Drug-free	Serum	Nether Lands
Monteleone P (58)	2008	Depressed Remitted Control	11 24 22	9/2 5/19 8/14	45.70 ± 13.60 49.20 ± 12.70 40.10 ± 16.40	Drug-free, lithium, antidepressants, valproate, carbamazepine	Serum	Italy
Neumeister A (59)	2005	Remitted Control	27 22	9/18 9/11	39.80 ± 12.70 32.70 ± 9.11	Drug-free	Plasma	United States
Oral E (61)	2012	Depressed Control	39 40	11/28 14/26	26.30 ± 4.00 27.20 ± 4.00	Drug-free	Serum	Turkey
Ozam E (62)	2010	Depressed Control	66 56	47/19 38/18	33.10 ± 2.10 23.90 ± 2.30	Drug-free	Serum	Turkey
Papakostas G (64)	2011	Depressed Control	36 43	23/13 15/19	42.60 ± 9.80 30.00 ± 8.60	Drug-free	Serum	United States
Piccinni A (65)	2008	Depressed Control	15 15	13/02 12/03	47.00 ± 10.80 39.90 ± 9.20	Drug-free	Serum	Italy
Pillai A (66)	2012	Depressed Remitted Control	28 17 43	NA NA NA	67.10 ± 5.70 67.10 ± 5.70 67.00 ± 5.30	Drug-free, antidepressants	Plasma	United States
Satomura E (73)	2011	Depressed Control	109 163	45/64 54/109	54.40 ± 14.50 52.50 ± 14.90	Antidepressants	Serum	Japan
Serra-Millas (74)	2011	Depressed Control	18 14	15/3 11/3	38.50 ± 16.08 39.07 ± 16.12	Drug-free	Plasma	Spain
Shi Y (75)	2010	Depressed Control	24 30	9/15 10/20	62.21 ± 6.46 70.00 ± 6.90	Drug-free	Plasma	China
Shimizu E (76)	2003	Depressed Control	33 50	21/12 26/24	40.80 ± 13.60 41.90 ± 15.90	Drug-free, antidepressants	Serum	Japan
Sozeri-Varma G (78)	2011	Depressed Control	30 40	6/24 13/27	39.75 ± 16.26 34.60 ± 7.59	Drug-free	Serum	Turkey
Su S (79)	2011	Depressed Control	18 21	NA NA	21.90 ± 2.00 25.00 ± 3.00	Drug-free	Serum	Taiwan
Terracciano A (81)	2011	Depressed Control	114 1985	101/13 NA	51.70 ± 15.20 51.40 ± 15.30	Drug-free, antidepressants	Serum	Italy
Wolkovitz O (88)	2011	Depressed Remitted Control	30 30 28	10/20 10/20 10/18	39.10 ± 10.00 39.10 ± 10.00 39.00 ± 10.30	Drug-free, antidepressants	Serum	United States
Umene-Nakano	2009	Depressed	36	28/8	46.80 ± 8.50	Drug-free, antidepressants	Serum	Japan

W (85)		Control	20	15/5	43.00 ± 7.00			
Varanbally S (86)	2013	Depressed Control	43 24	24/19 11/13	33.00 ± 8.50 31.90 ± 9.80	Drug-free	Serum	India
Yoshida T (90)	2012	Depressed Control	69 78	37/32 46/32	40.50 ± 9.70 37.20 ± 9.80	Drug-naïve, antidepressants	Serum	Japan
Yoshimura R (91)	2007	Depressed Control	42 30	15/27 10/20	47.00 ± 19.00 45.00 ± 15.00	Drug-free	Serum	Japan
Yoshimura R (92)	2010	Depressed Control	20 20	7/13 7/13	39.20 ± 10.60 36.70 ± 10.10	Antidepressants	Plasma	Japan
Ziegenhorn AA (99)	2007	Depressed Control	91 259	NA NA	NA NA	NA	Serum	Germany
Zhou L (97)	2013	Depressed Control	40 50	0/40 0/50	42.67 ± 9.58 44.30 ± 10.04	Drug-free	Serum	China
Zhou Z (98)	2011	Depressed Control	35 30	19/16 NA	63.50 ± 12.50 NA	Antidepressants	Serum	China
Schizophrenia								
Buckley P (7)	2007	SZ Control	15 14	8/7 9/5	21.00 ± 8.83 25.00 ± 5.72	Drug-naïve	Plasma	United States
Carlino D (8)	2011	SZ Control	40 40	20/20 20/20	48.00± 10.00 44.00± 10.00	Drug-naive	Serum	Italy
Chen C (9)	2009	SZ Control	88 90	NA NA	30.75± 10.52 34.00± 4.70	Drug-naïve	Serum	China
Fernandes BS (22)	2010	SZ Control	7 21	2/5 6/15	35.79 ± 10.34 35.27 ± 10.20	Antipsychotics	Serum	Brazil
Gama C (23)	2007	SZ Control	30 26	18/42 15/11	35.35 ± 10.36 40.68 ± 12.12	Typical and atypical antipsychotics	Serum	Brazil
Gonzalez-Pinto A (26)	2010	SZ Control	13 18	NA NA	24.39± 6.53 25.19± 5.05	Drug-naive	Plasma	Spain
Goto N (28)	2011	SZ Control	18 18	9/9 9/9	29.00 ± 11.00 30.00 ± 11.00	Antipsychotics	Serum	Japan
Grillo R (29)	2006	SZ Control	44 25	19/25 12/13	35.50 ± 12.50 34.11 ± 13.00	Antipsychotics	Serum	Brazil
Huang T (35)	2006	SZ Control	126 96	72/54 36/60	34.00 ± 10.30 29.10 ± 5.30	Drug-naïve	Serum	Taiwan
Ikeda Y (36)	2008	SZ Control	74 87	39/35 47/40	41.90 ± 11.10 39.80 ± 10.70	Antipsychotics	Serum	Japan
Jindal R (38)	2010	SZ	24	17/7	22.40 ± 5.47	Drug-naïve	Serum	United

		Control	41	25/16	22.31 ± 5.67			States
Jockers M (39)	2004	SZ Control	102 61	NA NA	NA NA	Drug-naïve	Serum	Germany
Kalmady SV (40)	2013	SZ Control	59 60	31/28 29/31	30.40 ± 7.50 26.40 ± 4.70	Drug-naïve	Serum	India
Kuo F (48)	2012	SZ Control	33 30	19/14 12/18	32.18 ± 8.78 38.29 ± 10.29	Antipsychotics	Serum	Taiwan
Lee A (51)	2011	SZ Control	22 22	13/9 13/9	39.14± 14.00 39.20± 14.00	Drug-free	Serum	Germany
Lee B (53)	2009	SZ Control	36 36	15/21 15/21	31.30 ± 7.80 31.30 ± 7.90	Drug-naïve, atypical antipsychotics	Plasma	Korea
Mackin (55)	2007	SZ Control	20 14	18/2 12/2	42.1 ± 10.30 43.7 ± 12.90	Antipsychotics	Serum	United Kingdom
Niitsu T (60)	2011	SZ Control	63 52	26/37 25/27	35.90 ± 8.20 34.90 ± 7.30	Antipsychotics	Serum	China
Palomino A (63)	2006	SZ Control	21 21	NA NA	23.70 ± 5.72 25.50 ± 5.40	Drug-free, mood stabilizers, typical and atypical antipsychotics	Plasma	Spain
Pillai A (67)	2010	SZ Control	47 44	15/19 13/23	32.18 ± 8.78 38.29 ± 10.29	Drug-naive	Plasma	United States
Pirildar S (68)	2004	SZ Control	22 22	7/15 7/15	27.81 ± 9.54 25.70 ± 7.80	Atypical antipsychotics	Serum	Turkey
Reis H (69)	2008	SZ Control	40 20	40/0 20/0	52.30 ± 9.80 52.30 ± 9.80	Typical antipsychotics	Serum	Brazil
Rizos E (70)	2010	SZ Control	37 21	32/15 29/15	43.63 ± 10.91 46.50 ± 14.90	Drug-naive	Serum	Greece
Rizos E (71)	2010	SZ Control	47 44	32/15 29/15	43.70 ± 10.54 46.50 ± 14.90	Antipsychotics	Serum	Greece
Shimizu E (76)	2003	SZ Control	40 40	20/20 20/20	35.50 ± 14.90 35.60 ± 14.60	Drug-naïve, Antipsychotics	Serum	Japan
Toyooka K (82)	2002	SZ Control	34 35	17/17 14/21	48.60 ± 14.00 45.60 ± 11.30	Antipsychotics	Serum	Japan
Vinogradov F (87)	2009	SZ Control	56 16	10/6 42/14	43.95 ± 9.30 44.50 ± 11.69	Typical and atypical antipsychotics	Serum	United States
Yang Y (89)	2011	SZ Control	264 323	281/83 228/95	49.90 ± 9.90 50.90 ± 9.10	Antipsychotics	Serum	China
Yoshimura R (91)	2007	SZ Control	89 103	52/37 48/55	37.00 ± 13.00 40.00 ± 23.00	Drug-free	Plasma	Japan
Zhang X (95)	2012	SZ Control	657 445	578/79 263/182	48.40 ± 13.70 44.90 ± 13.60	Antipsychotics	Serum	United States

Zhang X (96)	2012	SZ Control	251 206	187/64 143/63	52.10± 8.30 51.80± 9.20	Antipsychotics	Serum	China

Abbreviations: BDNF, brain-derived neurotrophic factor. NA, not available.

Annotations: Some studies contribute to more than one diagnostic group. * Mean ± standard deviation. ǂ Mania and Depression groups together.

This study had only the euthymic group included due to high heterogeneity of the manic group as assessed by the *I2* test.

Table 2: Summary of included studies (some studies contributed to more than one diagnostic group).

Characteristics of the study	Bipolar Disorder			Schizophrenia	Major Depressive Disorder	
	Mania (n=9)	Depression (n=7)	Euthymia (n=14)	(n=31)	Depressed (n=50)	Remitted (n=16)
Total number of patients	171	136	600	2436	2851	941
Total number of controls	220	149	576	2083	4954	813
Age of patients*	33.88 ± 6.03	38.00 ± 8.73	41.43 ± 7.62	35.63 ± 9.11	41.53 ± 9.18	42.50 ± 9.90
Age of controls*	32.88 ± 5.48	36.29 ± 6.62	41.29 ± 8.00	36.37 ± 8.92	41.57 ± 9.96	40.37 ± 9.99
Number involving drug-free/naïve patients (%) #	33.30	28.60	0.00	52.00	78.30	30.00
Source (Serum/plasma)	5/4	6/1	9/5	25/6	41/9	12/4

* Mean ± standard deviation.
# We considered studies involving drug-free/naïve patients studies with any subjects without psychiatric medication for at least 7 days.
Male and female numbers not reported for all studies.

Table 3: Studies that evaluated serum or plasma brain-derived neurotrophic factor (BDNF) levels in healthy subjects and in subjects with bipolar disorder, schizophrenia, and major depressive disorder. Some studies contribute to more than one diagnostic group.

Studies according pathology

Bipolar Disorder			**Bipolar Disorder**			**Control**		
Mania *vs.* Control	**Effect Size**	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Cunha AB (12)	-0.79	pg/ug protein	32	0.14	0.08	32	0.20	0.07
Gonzalez-Pinto (26)	-0.78	ng/ml	05	3.66	2.56	18	5.80	2.66
Huang T (33)	-0.29	ng/ml	26	4.20	4.00	56	6.70	10.10
Kapczinski F (40)	0.00	pg/ug protein	20	0.13	0.01	20	0.13	0.01
Machado-Vieira R (54)	-0.95	pg/ml	30	224.80	76.50	30	318.50	114.20
Oliveira GS (14)	-1.03	pg/ug protein	22	0.28	0.11	24	0.40	0.12
Palomino A (63)	-1.34	ng/ml	14	3.79	1.99	12	7.92	3.95
Tramontina JF (83)	-0.61	pg/ug protein	10	0.21	0.10	10	0.31	0.05
Yoshimura R (84)	-0.10	pg/ml	12	24.30	7.9	20	25.40	11.7
Total			**171**			**220**		
Depression *vs.* control		**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Cunha AB (12)	-0.50	pg/ug protein	21	0.15	0.13	32	0.20	0.07
Fernandes BS (21)	-2.30	pg/ug protein	40	0.15	0.08	30	0.38	0.12
Kapczinski (40)	-0.98	pg/ug protein	20	0.12	0.01	20	0.13	0.01
Mackin P (55)	-0.01	pg/ml	20	13,755.2	7,932.2	14	13,800.4	9,107
Oliveira GS (14)	-1.21	pg/ug protein	20	0.22	0.17	22	0.40	0.12
Su S (79)	-1.91	ng/ml	10	5.40	4.70	21	12.50	3.00
Yoshimura R (93)	-0.81	pg/ml	06	16.10	8.5	20	25.40	11.7
Total			**136**			**149**		
Euthymia *vs.* control		**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Barbosa I (4)	0.87	pg/ml	25	3500.00	2500.00	25	1800.00	1200.00
Barbosa I (3)	1.12	pg/ml	19	2695.80	1570.10	38	1211.00	1043.40
Chou Y (10)	-0.02	pg/ml	23	328.00	242.40	33	334.60	353.60
Cunha AB (12)	-0.13	pg/ug protein	32	0.19	0.08	32	0.20	0.07
Dias VV (17)	0.19	pg/ug protein	65	0.28	0.21	50	0.24	0.21
Gama C (23)	0.12	pg/ug protein	30	0.20	0.08	26	0.19	0.08
Kapczinski (40)	-0.03	pg/ug protein	20	0.11	0.01	20	0.13	0.01
Kauer-Sant'Anna M (EaS) (45)	0.66	pg/ug protein	26	0.91	0.22	26	0.77	0.20

Kauer-Sant'Anna M (LaS) (45)	-1.16	pg/ug protein	30	0.33	0.16	30	0.57	0.24
Langan C (49)	0.23	ng/ml	24	35.92	8.23	22	33.55	11.86
Monteleone P (58)	-1.04	ng/ml	28	27.9	14.8	22	42.5	12.5
Rybakowski J (72)	-0.43	ng/ml	13	23.60	13.30	30	28.90	10.90
Suwalska A (80)	-0.22	ng/ml	141	24.20	17.00	75	27.40	10.40
Tramontina J (83)	-0.25	pg/ug protein	114	0.14	0.08	137	0.16	0.08
Tramontina JF (84)	0.64	pg/ug protein	10	0.38	0.14	10	0.31	0.05
Total			**600**			**576**		

Major Depressive Disorder			**Major Depressive Disorder**			**Control**		
Depressed *vs.* Control	**Effect Size**	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Aydemir C (1)	-0.94	ng/ml	20	27.70	13.70	20	41.20	15.10
Aydemir O (2)	-1.01	ng/ml	24	21.20	11.30	26	31.40	8.80
Basterzi A (5)	-0.49	pg/ml	43	42,005.00	12,630.00	15	47,727.00	7,698.00
Bocchio-Chiavetto (6)	-1.06	ng/ml	25	29.60	12.41	59	40.78	11.34
Chu C (11)	-1.64	pg/ml	12	115.10	57.20	122	548.80	370.60
Dalby R (13)	-0.23	pg/ml	22	4,745.00	2,091.00	22	5,398.00	3,245.00
Deuschle M (15)	0.17	ng/ml	55	7.29	4.00	14	6.64	2.11
Deveci A (16)	-1.00	ng/ml	24	21.20	11.30	26	31.40	8.80
Diniz B (18)	-0.51	pg/ml	29	478.50	373.50	42	711.30	534.70
Eker C (19)	-0.86	ng/ml	25	21.70	6.60	22	27.00	5.70
Elfving B (20)	0.27	pg/ml	162	31206.00	7280.00	289	29274.00	6806.00
Fernandes BS (21)	-0.26	pg/ug protein	10	0.35	0.08	30	0.38	0.12
Gervasoni N (24)	-1.06	ng/ml	26	22.60	3.60	26	26.40	3.60
Gonul A (25)	-0.75	ng/ml	28	20.80	6.70	18	26.80	9.30
Gorgulo Y (27)	-2.47	ng/ml	41	19.54	4.26	33	33.83	7.14
Gustafsson G (30)	0.16	pg/ml	18	324.00	176.00	18	298.00	142.00
Harvey B (31)	0.06	pg/ml	89	1,390.00	710.25	111	1,352.61	570.49
Hu Y (32)	-1.89	ng/ml	28	5.66	2.07	28	9.17	1.63
Huang T (34)	-0.46	ng/ml	111	10.90	7.10	107	14.10	7.00
Jeon H (37)	0.19	ng/ml	105	16.20	5.60	50	15.20	4.60
Karege F (42)	-0.73	ng/ml	30	22.60	3.00	30	26.50	7.00
Karege F (43)	-0.90	ng/ml	43	10.10	2.30	35	12.20	2.40
Karlovic D (44)	-1.86	ng/ml	122	37.50	13.30	142	56.80	6.30
Kim Y (46)	-0.42	pg/ml	64	652.50	530.00	30	889.40	611.30
Kobayakawa M (47)	-0.19	ng/ml	81	29.10	13.60	81	31.40	10.60
Lee B (52)	-0.63	pg/ml	77	579.46	414.25	95	819.20	347.05
Matrisciano F (56)	-1.98	ng/ml	21	35.40	15.20	20	64.10	13.10

Molendijk (57)	-0.19	ng/ml	541	8.75	3.24	382	9.35	3.19
Monteleone P (58)	-1.43	ng/ml	11	20.10	18.40	22	42.5	12.5
Oral E (61)	-1.31	ng/ml	39	1.75	0.16	40	1.95	0.14
Ozan E (62)	-0.94	ng/ml	66	22.47	5.50	56	27.49	5.2
Papakostas G (64)	0.67	pg/ml	36	15,174	8,163	43	10,096	6,946
Piccinni A (65)	-1.65	pg/ml	15	19,300	8,800	15	33,600	8,600
Pillai A (66)	-0.31	pg/ml	28	210.84	132.45	43	248.90	117.55
Satomura E (73)	-0.84	pg/ml	109	20231.20	8180.00	163	27105.50	8310.20
Serra-Millas (74)	-1.67	pg/ml	18	458.5	163.90	14	793.80	232.70
Shi Y (75)	-0.55	pg/ml	24	859.83	211.36	30	958.83	150.20
Shimizu E (76)	-0.73	ng/ml	33	17.60	9.60	50	25.40	11.7
Sozeri-Varma G (78)	-0.83	pg/ml	30	1453.42	144.51	40	1632.23	252.93
Su S (79)	-1.21	ng/ml	18	6.40	6.50	21	12.50	3.00
Terracciano (81)	-0.30	ng/ml	114	13.2	3.00	1985	14.1	3.01
Umene-Nakano W (85)	-2.09	ng/ml	36	9.00	4.30	20	21.10	7.00
Varanbally S (86)	-0.97	ng/ml	43	18.59	4.90	24	23.60	5.60
Wolkovitz (88)	-0.96	ng/ml	30	14.88	5.41	28	20.91	7.07
Yoshida T (90)	-0.36	ng/ml	69	21.09	5.60	78	23.11	5.90
Yoshimura R (92)	-1.54	ng/ml	42	9.5	7.8	30	23.4	10.1
Yoshimura R (94)	-1.35	ng/ml	18	11.90	4.90	20	19.30	6.00
Ziegenhorn AA (99)	-0.30	pg/ml	91	20023.30	11463.30	259	23331.00	10729.20
Zhou L (97)	-3.68	ng/ml	40	13.04	1.23	50	18.37	1.58
Zhou Z (98)	-0.48	ng/ml	35	21.70	10.30	30	26.20	8.40
Total			**2,821**			**4,954**		

Remmitted *vs*. control	**Effect Size**	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Aydemir C (1)	-0.17	ng/ml	20	38.57	15.30	20	41.20	15.10
Basterzi A (5)	0.22	pg/ml	17	50,011.00	12,060	15	47,727.00	7,698.00
Gervasoni N (24)	-0.41	ng/ml	26	24.90	3.60	26	26.40	3.60
Gonul A (25)	0.66	ng/ml	28	33.30	9.90	18	26.80	9.30
Gorgulo Y (27)	2.64	ng/ml	41	52.29	6.76	33	33.83	7.14
Huang T (34)	-0.13	ng/ml	58	13.10	9.10	107	14.10	7.00
Laske C (50)	-0.94	ng/ml	35	24.40	6.10	20	30.50	6.90
Matrisciano F (56)	-0.70	ng/ml	21	54.90	12.20	20	64.10	13.10
Molendijk (57)	-0.02	ng/ml	539	9.30	3.17	382	9.35	3.19
Monteleone P (58)	-1.02	ng/ml	24	31.10	9.50	22	42.5	12.5
Neumaister A (59)	0.39	pg/ml	27	132.00	126.00	20	90.00	60.00

Piccinni A (65)	0.02	pg/ml	15	33,732.00	1,206.0	15	33,600	8,600
Pillai A (66)	0.35	pg/ml	28	248.80	117.65	43	210.12	103.55
Serra-Millas (74)	-0.01	pg/ml	18	791.2	221.90	14	793.80	232.70
Wolkovitz O (88)	-0.30	ng/ml	30	18.75	6.97	28	20.91	7.07
Yoshimura R (92)	-0.14	ng/ml	14	22.00	8.50	30	23.4	10.1
Total			**941**			**813**		

Schizophrenia			**Schizophrenia**			**Control**		
	Effect Size	**Unit**	***N***	**Mean BDNF**	**SD**	***N***	**Mean BDNF**	**SD**
Buckley P (7)	-4.85	pg/ml	15	135.00	21.77	14	290.50	38.81
Carlino D (8)	-1.03	ng/ml	40	25.60	2.00	40	28.90	4.00
Chen C (9)	-0.93	ng/ml	88	9.00	4.20	90	12.10	2.20
Fernandes B (22)	-0.45	pg/ug protein	7	0.14	0.05	21	0.16	0.04
Gama C (23)	1.40	pg/ug protein	60	1.21	0.98	26	0.19	0.08
Gonzalez-Pinto (26)	-0.70	ng/ml	13	4.15	1.68	18	5.80	2.66
Goto N (28)	-0.41	ng/ml	18	15.00	4.50	18	17.00	5.00
Grillo R (29)	-1.35	pg/ml	44	112.20	47.90	25	168.80	26.30
Huang T (35)	0.01	ng/ml	126	14.20	6.92	96	14.18	6.86
Ikeda Y (36)	-0.66	ng/ml	74	37.08	20.42	87	52.24	25.28
Jindal R (38)	-0.53	pg/ml	24	97.58	31.41	41	116.78	38.42
Jockers M (39)	-0.02	pg/ml	102	13.10	5.90	61	13.20	5.20
Kalmady SV (40)	-0.60	ng/ml	59	28.80	11.70	60	34.90	8.20
Kuo F (48)	-3.59	ng/ml	33	4.45	0.63	30	21.47	1.05
Lee A (51)	-2.41	ng/ml	22	4.38	2.10	22	15.39	6.00
Lee B (53)	0.35	pg/ml	36	1030.95	546.32	36	880.61	244.57
Mackin (55)	-0.05	pg/ml	20	13436.00	7979.00	14	13800	9107.00
Niitsu T (60)	0.17	ng/ml	63	15.30	3.8	52	14.60	4.40
Palomino A (63)	-0.96	ng/ml	21	4.19	2.26	21	7.55	4.31
Pillai A (67)	-2.68	pg/ml	34	750.00	80.80	36	980.00	90.00
Pirildar S (68)	-1.75	ng/ml	22	14.53	2.93	22	26.80	9.30
Reis H (69)	1.77	pg/ml	40	7751.00	1847.00	20	3500.00	2048
Rizos E (70)	-1.30	ng/ml	37	18.87	8.23	21	29.20	7.73
Rizos E (71)	-0.98	ng/ml	47	19.19	8.58	44	27.50	8.17
Shimizu E (77)	-0.21	ng/ml	40	26.40	11.00	40	28.50	9.10
Toyooka K (82)	-0.85	ng/ml	34	6.30	3.40	35	11.40	7.70
Vinogradov F (87)	-0.60	ng/ml	56	25.27	10.34	16	31.30	8.95
Yang Y (89)	-1.35	ng/ml	264	8.80	2.30	323	11.90	2.30
Yoshimura R (93)	-0.50	ng/ml	89	1.40	0.63	103	1.85	1.35

Zhang X (97)	-0.92	ng/ml	657	9.50	2.90	445	11.90	2.10
Zhang X (98)	-0.93	ng/ml	251	9.90	2.00	206	11.90	2.30
Total			**2,436**			**2,083**		

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DISCUSSÃO

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 técnicas de metanálise e metarregressão, fomos capazes de demonstrar que os níveis periféricos de BDNF no soro e no plasma estão moderadamente reduzidos em pessoas com esquizofrenia, quando comparadas com controles saudáveis a partir do primeiro episódio psicótico, e que esta diminuição é acentuada com a progressão da doença. Além disso, a diminuição do BDNF periférico não se correlaciona com a gravidade dos sintomas positivos e negativos. No plasma, mas não no soro, os níveis periféricos de BDNF são sempre aumentados após o tratamento com antipsicóticos, independentemente da resposta do paciente ao medicamento. Além disso, em uma metanálise comparativa de BDNF no soro e plasma na esquizofrenia, transtorno bipolar e transtorno depressivo maior, verificamos que os níveis periféricos de BDNF estão igualmente reduzidos em todas essas condições, mas que eles retornam ao normal durante a fase de remissão dos transtornos bipolar e depressivo maior.

Biomarcadores têm um lugar-comum na maioria das especialidades médicas, não só por melhorarem a nossa compreensão da fisiopatologia das diversas doenças, mas também porque podem ser um instrumento útil para apoiar decisões clinicas: 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 TB, MD e esquizofrenia. Com base nos dados encontrados nesta tese, 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, tanto no TB quanto na DM, sendo discriminatórios dos estados de doença. 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 relativa não-invasividade da técnica, uma vez que o material para dosagem do BDNF pode ser acessado na periferia através de uma venopunção.

Outra aplicação potencialmente interessante do BDNF sérico ou plasmático poderia ser como um biomarcador substituto de eficácia farmacológica. Nossos resultados fornecem evidências de que os níveis séricos de BDNF aumentam após o tratamento da esquizofrenia com antipsicóticos, semelhante ao que é visto com a expressão do BDNF em regiões especificas do cérebro em um modelo animal de mania com lítio ou valproato (Frey at al., 2006). Porém é interessante salientar que, no nosso estudo, o BDNF aumentou após o tratamento com antipsicóticos tanto na ausência quanto na presença de resposta clínica. Isto possivelmente limite o uso do BDNF como biomarcador substituto para resposta farmacológica.

Seria interessante analisar se os níveis de BDNF na esquizofrenia no início do tratamento diferem entre respondedores e não-respondedores, porém tal análise não foi possível no nosso estudo. Caso ele difira, poderia possivelmente ser usado como preditor de resposta ao tratamento.

Verificamos nesta tese que os níveis de BDNF no soro e plasma estão diminuídos nas fases maníacas e depressivas do TB, e na DM nos episódios agudos, mas que os mesmos são normais na eutimia no TB e na remissão da DM. Porém, não podemos determinar no presente estudo causalidade. As mudanças no BDNF em relação a um episódio de humor poderiam seguir, teoricamente, três padrões diferentes. Primeiro, o BDNF sérico ou plasmático poderia diminuir após o início de um episódio de humor, com a recuperação do BDNF após o alcance da eutimia ou remissão. Neste caso, as mudanças do BDNF seriam uma conseqüência dos episódios de humor e sua avaliação poderia ser útil como um biomarcador substituto. Segundo, o BDNF sérico ou plasmático poderia diminuir antes do início de um episódio de humor, recuperando-se antes do alcance da eutimia ou remissão, o que tornaria o BDNF um preditor de episódios de humor e de resposta ao tratamento. Em terceiro lugar, diminuições no BDNF seriam concormitantes aos episódios de humor, refletindo atividade da doença, e sendo possivelmente um epifenômeno nestas patologias. O comportamento do BDNF e a sua relação temporal com os episódios de humor no TB e na DM permanecem desconhecidos. Na DM, 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 at al., 2006; Marano at al., 2007; Lee et al., 2008). No TB há evidências de alguns

poucos estudos longitudinais de que o BDNF aumenta após a eutimia ser alcançado (Palomino et al., 2006), mas não há nenhum estudo abordando se o aumento do BDNF é um pré-requisito para a melhorar clínica ou vice-versa.

Por último, o BDNF poderia desempenhar um papel como biomarcador de progressão da doença na esquizofrenia. Mostramos em nossa análise que o BDNF diminui com o tempo de doença na esquizofrenia. Atualmente, o conceito de neuroprogressão na esquizofrenia engloba características clinicas e neuropsicológicas, mas os biomarcadores permanecem um campo pouco explorado nesse cenário. Em um estudo sobre TB 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, tanto no TB quanto na esquizofrenia.

Concluindo, esta tese resolve as discrepâncias encontradas em estudos anteriores sobre BDNF na esquizofrenia, e mostra que os níveis de BDNF estão igualmente reduzidos, sendo, portanto, inespecíficos, durante os episódiso de humor no TB e na DM, mas não durante a eutimia ou remissão nestas patologias, refletindo atividade de doença. Os níveis de BDNF na esquizofrenia diminuem com o tempo de doença, e aumentam após tratamento com antipsicóticos independente da resposta clínica. Estes resultados são de grande importância para o campo, considerando a crescente evidencia da participação do BDNF na fisiopatologia destas patologias. Além disso, eles apóiam a idéia da utilização dos níveis de BDNF

perférico como um marcador biológico da atividade da doença durante os episódios de humor. 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 clinica.

CONCLUSAO

Em conclusão, há evidências de que a esquizofrenia está relacionada com níveis alterados de BDNF periférico. Se estes níveis de BDNF estão causalmente relacionados com o desenvolvimento da esquizofrenia ou se eles são apenas um epifenômeno nesta patologia ainda precisa ser determinado. Além disso, os níveis de BDNF no soro e plasma são inespecíficos para a esquizofrenia, transtorno bipolar e transtorno depressivo maior, mas podem ser considerados um biomarcador de atividade de doença nessas condições.

PARTE IV

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ADENDOS

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

a) yes, with independent validation ✸
b) yes, eg record linkage or based on self reports
c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases ✸
b) potential for selection biases or not stated

3) Selection of Controls

a) community controls ✸
b) hospital controls
c) no description

4) Definition of Controls

a) no history of disease (endpoint) ✸
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for _____ (Select the most important factor.) ✸
b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure

a) secure record (eg surgical records) ✸
b) structured interview where blind to case/control status ✸
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description

2) Same method of ascertainment for cases and controls

a) yes ✸
b) no

3) Non-Response rate

a) same rate for both groups ✸
b) non respondents described
c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

1) Is the Case Definition Adequate?
a) Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records)
b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record
c) No description

2) Representativeness of the Cases
a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)
b) Not satisfying requirements in part (a), or not stated.

3) Selection of Controls
This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.
a) Community controls (i.e. same community as cases and would be cases if had outcome)
b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population
c) No description

4) Definition of Controls
a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.
b) No mention of history of outcome

COMPARABILITY

1) Comparability of Cases and Controls on the Basis of the Design or Analysis
A maximum of 2 stars can be allotted in this category
Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.
There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = , Other controlled factors =

EXPOSURE

1) Ascertainment of Exposure
Allocation of stars as per rating sheet

2) Non-Response Rate
Allocation of stars as per rating sheet

CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort
Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users users of estrogen).
Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort
Allocation of stars as per rating sheet

3) Ascertainment of Exposure
Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study
In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis
A maximum of 2 stars can be allotted in this category
Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences

between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.
There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)
Age = , Other controlled factors =

OUTCOME

1) Assessment of Outcome
For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.
a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)
b) Record linkage (e.g. identified through ICD codes on database records)
c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)
d) No description.

2) Was Follow-Up Long Enough for Outcomes to Occur
An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3) Adequacy of Follow Up of Cohorts
This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.
Allocation of stars as per rating sheet

BDNF Meta-analysis: Checklist summarising compliance with MOOSE guidelines

Reporting background should include	
Problem definition	Yes
Hypothesis statement	Yes
Description	Yes
Type of exposure or intervention used	Yes
Type of study designs used	Yes
Study population	Yes
Reporting of search strategy should include	
Qualifications of searches (e.g. librarians and investigators)	Yes
Search strategy, including time period included in the synthesis and keywords	Yes
Effort to include all available studies, including contact with authors	Yes
Databases and registries searched	Yes
Search software used, name and version, including special features	Yes
Use of hand searching (e.g. reference lists of obtained articles)	No
List of citations located and those excluded including justification	Available on request
Method of addressing articles published in languages other than English	Yes
Method of handling abstracts and unpublished studies	No
Description of any contact with authors	No
Reporting methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Yes
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes
Assessment of heterogeneity	Yes
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes
Provision of appropriate tables and graphics	Yes
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Yes
Table giving descriptive information for each study included	Yes
Results of sensitivity testing (eg, subgroup analysis)	Yes
Indication of statistical uncertainty of findings	Yes
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Yes
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes
Assessment of quality of included studies	Yes
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Yes
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes
Guidelines for future research	Yes
Disclosure of funding source	Yes