UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

DISSERTAÇÃO DE MESTRADO

FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO NOS TRANSTORNOS POR USO DE SUBSTÂNCIAS – UMA META-ANÁLISE

FELIPE ORNELL

Orientador: Prof. Dra. Lisia von Diemen

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Dissertação de Mestrado a ser apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento como requisito parcial à obtenção do título de Mestre em Psiquiatria e Ciências do Comportamento.

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“Ostra feliz não faz pérola”. A ostra, para fazer uma pérola, precisa ter dentro de si um grão de areia que a faça sofrer. Sofrendo a ostra diz para si mesma:

“Preciso envolver essa areia pontuda que me machuca com uma esfera lisa que lhe tire as pontas…” Ostras felizes não fazem pérolas… Pessoas felizes não sentem a necessidade de criar. O ato criador, seja na ciência ou na arte, surge sempre de uma dor. Não é preciso que seja uma dor doída… Por vezes a dor aparece como aquela coceira que tem o nome de curiosidade (...)

Rubem Alves

À Laís Taffarel.

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RESUMO

Os transtornos por Uso de Substâncias (TUS) estão entre os transtornos psiquiátricos mais prevalentes no mundo. De acordo com a Organização Mundial de Saúde (OMS), cerca de 10% da população dos centros urbanos de todo o planeta usa, abusivamente, alguma substância psicoativa. As causas dos TUS são complexas e multifatoriais, englobando aspectos genéticos, psicossociais, comorbidades psiquiátricas, sensibilidade/resiliência ao estresse, desenvolvimento cerebral, efeitos na neuroplasticidade e no sistema cerebral de recompensa (SCR). Nos últimos anos tem crescido a proposição dos TUS como uma doença do cérebro, caraterizada por alterações disfuncionais no cérebro. Nesse sentido, a identificação de biomarcadores, que indiquem o estado patológico e a gravidade dos TUS, pode auxiliar no direcionamento e no aumento da efetividade do tratamento. O fator neurotrófico derivado do cérebro – BDNF – principal NT cerebral, parece estar implicado na base fisiopatológica de diversas doenças neurodegenerativas e psiquiátricas. Nos TUS, diversos estudos têm avaliado o BDNF em dependentes de diferentes tipos e classes de drogas, todavia os resultados são contraditórios e o papel do BDNF continua sendo um campo pouco compreendido. Nesse sentido, o objetivo deste estudo foi realizar uma meta-análise dos níveis periféricos de BDNF em usuários de substâncias psicoativas, com exceção do tabaco, comparados a controles. Para isso, realizou-se uma busca sistemática no PubMed / MEDLINE, EMBASE e PsycINFO. A seleção dos estudos elegíveis e a extração dos dados foram realizadas por dois revisores independentes; os desacordos foram resolvidos por consenso e com a opinião de um terceiro revisor. As listas de referência de todos os documentos recuperados foram avaliadas, a fim de identificar estudos elegíveis adicionais não detectados na busca inicial. Ao final, trinta estudos foram incluídos na meta-análise totalizando 1698 casos e 1363 controles. As análises foram realizadas levando em consideração o tipo de droga, a matriz de análise e o status do uso no momento da dosagem (uso ativo e abstinência); as meta-análises foram realizadas por subgrupos de acordo com o tipo de droga consumida e, nas meta-regressões, foram avaliados fatores

potencialmente relacionados à alteração do BDNF. Na análise geral não foram encontradas diferenças significativas entre casos e controles. Após ajuste para viés de publicação, encontrou-se níveis menores de BDNF sérico em usuários ativos em relação aos controles; em contrapartida, em usuários abstinentes, os níveis de BDNF foram semelhantes aos controles. A análise por droga mostrou níveis mais baixos de BDNF em dependentes de álcool, em comparação com os controles, e em dependentes de crack/cocaína durante o uso ativo. Nas análises de meta-regressão, os níveis séricos de BDNF foram associados aos anos de uso de drogas, idade, sexo e tempo de abstinência. Em geral, as análises sérica e plasmática apresentaram resultados discrepantes. Essas evidências sugerem que os níveis de BDNF sérico estão consistentemente mais baixos durante o uso ativo de drogas, mas se equiparam aos controles durante a abstinência. Mais do que isso, o BDNF parece diminuir com a idade, com o tempo de doença e, também, sofrer influência do tempo de abstinência e do gênero. Estes resultados indicam que, menores níveis de BDNF podem estar relacionados com a gravidade e com a progressão da dependência de drogas. Assim, é possível que o BDNF seja um biomarcador discriminatório de estadiamento nos TUS, como já descrito para outros transtornos psiquiátricos e doenças neurodegenerativas.

ABSTRACT

Substance Use Disorders (SUDS) are among the most prevalent psychiatric disorders worldwide. According to the World Health Organization (WHO), about 10% of the population in urban centers abuse some kind of psychoactive substance. SUDS causes are complex, multifactorial, and encompass genetic and psychosocial aspects, psychiatric comorbities, sensitivity/resilience to stress, cerebral development, effects on the reward center and on the cerebral neuroplasticity. Over the last years, the proposition of SUDS as a brain disease is growing, as it is being associated to dysfunctional alterations on the brain. In this regard, looking for biomarkers that are able to indicate the pathological status and to identify SUDS severity could be helpful directing treatment and increasing its effectiveness. Brain-derived neurotrophic factor (BDNF), the main neurotransmitter in the brain, appears to be implicated in the pathophysiological basis of various neurodegenerative and psychiatric disorders. In SUDS, several studies have been evaluating BDNF in dependents of different types and classes of drugs. However the results are contradictory and the role of BDNF still remains poorly understood. In this sense, the aim of the present study was to perform a meta-analysis of peripheral levels of BDNF in users of psychoactive substances, with the exception of tobacco, compared to healthy controls. Hence, a systematic search was conducted through PubMed/MEDLINE, EMBASE and PsycINFO. Both the selection of eligible studies and data extraction were performed by two independent reviewers. Disagreements were resolved by consensus and with the opinion of a third reviewer. The reference list of all retrieved papers were evaluated in order to identify additional eligible studies not identified by the initial search. At the end, thirty studies were included in the meta-analysis, with a total of 1698 cases and 1363 controls. The analysis were performed taking into consideration the type of drug used, the biological matrices analysed and the status of use at the moment of the dosage (active use or withdrawn). Meta-analysis were performed by subgroups according to the type of drug used. In the meta-regressions, factors potentially related to BDNF alteration were evaluated. In the general analysis, no significative differences were found between cases and controls. After adjusting for publication bias, we found lower

levels of serum BDNF in active users compared to controls; in contrast, in withdrawn users, BDNF levels were similar to controls. Analysis by tipe of drug showed lower levels of BDNF in alcohol-dependent patients compared to controls, and in crack/cocaine dependents during active use. In meta-regression analysis, serum BDNF levels were associated with years of drug use, age, sex, and withdrawal time. In general, serum and plasma analysis presented divergent results. These evidences suggest that serum BDNF levels are consistently lower during active drug use, but are matched to controls during withdrawal. More than that, BDNF seems to decrease with age and with years of drug use, and also undergo the influence of withdrawal time and gender. These results indicate that lower levels of BDNF may be related to severity and progression of drug dependence. Thus, it is possible that BDNF is a discriminant staging biomarker in SUDS, as already described for other psychiatric disorders and neurodegenerative diseases.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SÍMBOLOS

AIDS – Síndrome da imunodeficiência adquirida, do inglês *acquired immunodeficiency syndrome*

ATP – Adenosina trifosfato

ATV – Área tegumentar ventral

BDNF – Fator neurotrófico derivado do cérebro, do inglês *Brain-derived neurotrophic factor*

CID – Código internacional de doenças

COF – Córtex órbito–frontal medial

CPF – Córtex pré-frontal

CPFdl – Córtex pré-frontal dorsolateral

DA – DA

DC – Dependente de cocaína

DH – Dependente de heroína

DM – Depressão Maior

GABA – Ácido gama-aminobutirico

DSM – Manual diagnóstico e estatístico dos transtornos mentais, do inglês *Diagnostic and statistical manual of mental disorders*

GCA – Girus cingulado anterior

GPx – Glutationa peroxidase

GSH – Glutationa

HIV – Vírus da imunodeficiência humana, do inglês *Human immunodeficiency virus*

MET – Metanfetamina

NAc – Núcleo accumbens

NGF – Fator de crescimento neural, do inglês *Nerve growth factor*

NIDA – Instituto nacional sobre drogas de abuso, do inglês *National institute of drug abuse*

NT – NT

OMS – Organização mundial da saúde

PUBMED – Website da biblioteca nacional de medicina dos Estados Unidos

RC – Circuito de recompensa cerebral, do inglês *Reward circuit*

SNC – Sistema nervoso central

SPA – Substância psicoativa

TB – Transtorno Bipolar

TUS – Transtornos por uso de substâncias

UNODC – Escritório das Nações Unidas sobre Drogas e Crime, do inglês *United Nations Office on Drugs and Crime*

SUMÁRIO

1 Introdução

1.1 Transtornos por uso de substâncias – Epidemiologia

Os transtornos por uso de substâncias (TUS) estão entre os transtornos psiquiátricos mais prevalentes no mundo (1-4). A Organização Mundial de Saúde estima que 10% da população dos centros urbanos de todo o planeta usa abusivamente alguma substância psicoativa, independente de sexo, idade, nível social e de instrução (5).

O tabaco e o álcool são as drogas lícitas mais consumidas no mundo. Estima-se que existam cerca de 1 bilhão e 200 milhões de pessoas fumantes no mundo, fazendo com que o tabaco seja um dos quatro principais fatores de risco para doenças não transmissíveis e a principal causa global de morte evitável, gerando 6 milhões de mortes diretas ou indiretas a cada ano(6). O álcool é consumido por 38,3% da população mundial, havendo diferenças nas prevalências entre as regiões. Em 2010, o consumo de álcool entre pessoas com 15 anos ou mais foi estimado em 6.2 litros de álcool puro por ano (13,5 gramas de álcool puro por dia), um quarto deste consumo (24,8%) refere-se a álcool produzido ilegalmente. O consumo de álcool aumenta o risco de desenvolver mais de 200 doenças, incluindo cirrose hepática e alguns tipos de câncer, além de estar associado à violência e a acidentes. Em 2012, estima-se que tenham ocorrido 3,3 milhões de mortes devido ao uso nocivo do álcool representando 5,9% de todas as mortes ocorridas no mundo (7).

No Brasil, estima-se que entre 14.7% (8) e 16,9% da população é tabagista e 50% consome bebidas alcoólicas, dos quais 17% (11,7 milhões) são abusadores ou dependentes (9). Além disso, o estudo sinaliza para a precocidade do início do consumo de ambas as substâncias que, frequentemente, são apontadas como porta de entrada para drogas ilícitas (10-12).

Dados recentes, publicados pela UNODC, sugerem que, cerca de 5% da população adulta do mundo, ou 247 milhões de pessoas entre 15 e 64 anos, consumiram drogas ilícitas em 2014. Além disso, estima-se que 11,74% desta população (29 milhões de pessoas) apresente critérios para dependência; entre as

substâncias mais utilizadas destacam-se cannabis, opioides, opiáceos, cocaínicos, anfetaminas e êxtase (13). Ressalta-se que, apesar deste relatório ter sinalizado o aumento no número de usuários recreativos de drogas no mundo, se comparado aos relatórios publicados nos anos anteriores, esta estimativa se manteve proporcionalmente estável ao crescimento da população global. Apesar disso, o percentual de pessoas que apresentam critérios para dependência aumentou desproporcionalmente, pela primeira, vez em seis anos (13).

No Brasil, a maconha é a substância ilícita mais utilizada, tanto na população adulta, quanto adolescente; 6,8% dos adultos e 4,3% dos adolescentes referiram uso na vida e 2,5% e 3,4%, respectivamente, relataram uso no último ano. A cocaína inalada ocupa a segunda posição, o uso na vida foi relatado por 3,8% dos adultos e 2,3% dos adolescentes, dos quais 1,7% e 1,6%, respectivamente, relataram uso no último ano. O uso de crack na vida foi relatado por 1,3% dos adultos e 0,8% dos adolescentes, sendo que 0,7% e 0,1% fizeram uso no último ano (14). Outro dado relevante é que, 41,4% da população que relatou uso no ano anterior é dependente (9). Apesar dos índices de consumo de crack serem inferiores, se comparados a outras drogas, observa-se que é a droga ilícita que mais conduz a internações em hospitais psiquiátricos (15) e que mais provoca demanda por atendimento (16), gerando custo expressivo para o sistema público de saúde.

1.2 Diagnóstico e características clínicas dos Transtornos por Uso de Substâncias

Historicamente, observa-se que, os TUS foram mal compreendidos, considerados como uma falha moral, mau hábito ou mesmo hedonismo e não como uma condição de saúde, o que contribuiu para a desassistência à esta população, evidenciada durante muito tempo (17). Atualmente, a OMS define droga como qualquer substância química, lícita ou ilícita, medicinal ou nociva, não produzida pelo organismo, com capacidade de modificar o seu funcionamento (18),

Os TUS constituem transtornos crônicos caracterizados, sobretudo, por um conjunto de sintomas de ordem cognitiva, comportamental e fisiológica, que indicam

um padrão patológico e mal adaptativo de uso que acarreta a continuidade do consumo, apesar das consequências negativas (19, 20).

A avaliação apropriada é essencial, tanto no planejamento do processo terapêutico quanto na pesquisa clínica (23,24). O diagnóstico dos TUS é fundamentalmente clínico, apesar das dosagens de algumas enzimas auxiliarem na avaliação sobre o funcionamento hepático e cardiovascular, não existem análises bioquímicas específicas para o diagnóstico dos TUS. Atualmente, o diagnóstico dos TUS é realizado a partir de critérios estabelecidos no Código Internacional de Doenças (21) ou no Manual Diagnóstico e Estatístico dos Transtornos Mentais (22). Existem diversos instrumentos disponíveis para triar, rastrear, avaliar e diagnosticar, de forma estruturada, o uso problemático de substâncias - a indicação de cada um depende do objetivo a ser alcançado (23, 24).

Diferente do DSM IV e da CID 10, que diferenciam o diagnóstico de abuso ou de dependência, no DSM V o diagnóstico dos TUS enfatiza os prejuízos adjacentes do consumo de substâncias. Neste sentido, a classificação pode ser Leve (2 a 3 critérios são satisfeitos), Moderada (4 ou 5 critérios são satisfeitos) ou Grave (6 ou mais critérios são satisfeitos) e ser aplicada a 10 classes distintas de substâncias: álcool, cafeína, Cannabis, alucinógenos, inalantes, opióides, sedativos, hipnóticos e ansiolíticos, estimulantes (anfetamínicos, cocaínicos e outros), tabaco e outras substâncias (ou substâncias desconhecidas). O diagnóstico dos TUS pode ser aplicado a todas as 10 classes, exceto a cafeína, e é realizado a partir da satisfação de critérios comportamentais, fisiológicos e subjetivos, que podem variar na intensidade e na gravidade

Evidências científicas, pré-clínicas e clinicas, sinalizam que a gravidade dos TUS pode estar relacionada à intensidade de alterações em circuitos cerebrais. Estas alterações podem persistir, mesmo após a desintoxicação, sobretudo em casos mais graves, o que poderia explicar as recaídas e a fissura intensa. Atualmente, acredita-se que quatro sistemas neuronais estejam particularmente envolvidos na fisiopatologia dos TUS (25):

- O sistema de recompensa cerebral (em especial o accumbens)
- O sistema de motivação (córtex orbitofrontal)
- O circuito de memória e aprendizagem (amígdala e hipocampo)

- A área de controle e planejamento (córtex pré-frontal e giro do cíngulo anterior)

Robinson e colaboradores (26, 27) propuseram uma hipótese biopsicológica da dependência, a “Teoria de Incentivo-Sensibilização”, que parte de um tripé de questionamentos fundamental para compreender o motivo de os TUS tornarem-se um problema de saúde pública em todo o mundo:

1. Por que os dependentes desejam drogas? Qual a base neurobiológica e psicológica da fissura por drogas?
2. Por que o desejo por drogas persiste mesmo depois de longos períodos de abstinência?
3. A fissura é atribuível a "gostar" de drogas (aos efeitos prazerosos subjetivos de drogas)?

Sob estes questionamentos discutiram quatro princípios explicativos:

1. Substâncias psicoativas com potencial dependógeno compartilham a capacidade de alterar a estrutura e o funcionamento cerebral;
2. Os principais sistemas cerebrais alterados na dependência são aqueles relacionados ao processo de incentivo motivação e recompensa;
3. As neuroadaptações tornam o sistema de recompensa cerebral hipersensíveis ("sensibilizados") a drogas e a estímulos associados às drogas;
4. Os sistemas cerebrais sensibilizados não são mediadores dos efeitos prazerosos ou eufóricos das drogas, mas sim do subcomponente de recompensa a “saliência de incentivo”.

1.3 Neurobiologia dos Transtornos por Uso de Substâncias

Avanços significativos referentes à psicobiologia dos TUS foram evidenciados nas últimas décadas, o que reforça a compreensão destes transtornos como uma doença crônica, caracterizada por alterações cerebrais (17, 28-31), e que, portanto, necessita de acompanhamento longitudinal. Compreender estas neuroadaptações pode auxiliar no estabelecimento de ferramentas analíticas que potencializem o entendimento da variabilidade interindividual na resposta a drogas de abuso e ao

tratamento (32-34). Identificar parâmetros biológicos, clínicos e neuronais, que reflitam a gravidade dos TUS, pode acarretar implicações importantes na prática clínica, auxiliando na compreensão da fisiopatologia da doença, no rastreamento e identificação de casos mais graves, na avaliação da resposta ao tratamento e do potencial de recaída, possibilitando uma atenção mais individualizada e influenciando significativamente na elaboração de novas estratégias de prevenção e tratamento (30, 33).

Assim como em outras doenças, os pacientes com TUS apresentam sintomatologia heterogênea e respostas diferentes às intervenções terapêuticas (35). Identificar biomarcadores que apontem processos biológicos normais e processos patogênicos, relacionados à dependência, pode constituir instrumentos valiosos na clínica dos TUS, fornecendo medidas objetivas que permitam classificar pacientes, detectar subgrupos e prever a resposta ao tratamento, otimizando os resultados e gerando avanços clínicos significativos (35, 36).

Apesar de os estudos iniciais, sobre a neurobiologia dos TUS, terem enfatizado o impacto agudo das substâncias psicoativas (SPAs), atualmente, a compreensão dos TUS como uma doença crônica fez com que os esforços tenham sido direcionados ao entendimento das alterações neuroadaptativas agudas e de longo prazo. Isso objetiva compreender processos neuroquímicos que auxiliem no entendimento dos mecanismos genéticos, epigenéticos, celulares e moleculares, relacionados ao processo de transição do uso para a dependência e às recidivas crônicas que ocorrem mesmo após períodos longos de abstinência (25).

As drogas de abuso, em geral, compartilham uma característica comum: acarretam o aumento – direto ou indireto – da concentração de dopamina (DA) extracelular no sistema cerebral de recompensa, sobretudo no núcleo accumbens (NAC) estendendo-se, para a amígdala, induzindo assim o estado de excitação (25, 37-41). A DA é um neurotransmissor envolvido na modulação de diversas funções fisiológicas e no desempenho de comportamentos motivados dirigidos a metas. O aumento da sua concentração sináptica, em regiões específicas do cérebro, é associado à sensação de prazer e bem-estar desencadeada diante de certos comportamentos.

A DA também possui papel chave nos processos de aprendizagem, associada a recompensas e a definição de eventos de potencial gratificante. Diante de estímulos desencadeadores de prazer (alimentos, sexo, fuga em situações de perigo, entre outros), a ativação do sistema cerebral de recompensa é desencadeada pela expressão de DA, criando uma memória específica que estimula o organismo a buscá-la novamente (39, 42-45). Desta forma, a DA está fortemente relacionada ao reforço e à consolidação da memória, abrangendo, também, processos como: atenção, aprendizagem, cognição, humor, emoções, regulação do sono, alimentação, controle dos movimentos voluntários entre outros (39, 41, 46).

De acordo com Volkow e colaboradores, o uso de drogas provoca um efeito agudo de superliberação de DA, acarretando concentrações muito superiores aos níveis basais, com intensidade e duração que excedem aquelas desencadeadas por reforçadores naturais (44, 45, 47, 48). Postula-se que, este processo, ocasione o desequilíbrio entre os circuitos dopaminérgicos relacionados à recompensa, prejudicando o condicionamento e as funções executivas de planejamento, regulação emocional e tomada de decisão (47, 49). Por outro lado, acredita-se que, as alterações na neurotransmissão cerebral de DA, adjacentes ao uso crônico de drogas, estariam relacionadas a um estado hipodopaminérgico que conduziria a desregulação dos circuitos de recompensa (50). Possivelmente, a repetição crônica da atividade da DA, no sistema cerebral de recompensa, pode gerar um desequilíbrio neuroquímico e conduzir a uma homeostase alterada, que desenvolverá neuroadaptações estruturais e funcionais permanentes na neuroplasticidade cerebral (51, 52), que por sua vez, estariam relacionadas ao processo de transição do uso recreativo para a dependência (53).

Volkow e colaboradores sugerem que, diferenças marcantes em circuitos cerebrais são evidenciadas em pacientes com dependência de substâncias se comparados com indivíduos sem dependência. De acordo com esse modelo, a dependência envolve outros circuitos além do sistema de recompensa (NAc, CPF, área tegmentar ventral-ATV), como: memória e condicionamento (amigdala, COF, hipocampo e estriado dorsal), controle executivo (córtex pré-frontal dorsolateral (CPFDL), giro cingulado anterior (GCA), córtex frontal inferior e COF lateral e motivação (COF medial para atribuição de saliência, GCA, ATV, estriado dorsal e

córtex motor). Durante o processo de adição, quando a saliência da droga nos circuitos de recompensa, motivação e memória superam os circuitos de controle, ocorre uma retroalimentação positiva - iniciada pelo consumo da droga e perpetuada pelo aumento da ativação dos circuitos de motivação e memória. Além da DA, diversos outros neurotransmissores estão envolvidos nessas neuroadaptações, incluindo glutamato, GABA, norepinefrina, fator liberador de corticotrofina e receptores opióides (49).

Mudanças na plasticidade encefálica podem ser adaptativas, quando associadas a um ganho de função, ou mal adaptativas, quando está associada à perda de funções e a consequências negativas – como é observado em dependentes de drogas. A liberação de DA, desencadeada por drogas de abuso, produz mudanças na forma como os neurônios integram a neurotransmissão excitatória e inibitória, dando início a uma cascata de sinalização complexa, que compromete a neuroplasticidade relacionada tanto a aprendizagem quanto ao desenvolvimento de comportamentos de procura pela droga (51). Este processo envolve neuroadaptações disfuncionais nos sistemas de: recompensa, saliência, motivação, controle inibitório, função executiva, memória e condicionamento, circuitos modulados por vias dopaminérgicas (25, 54, 55).

Evidências apontam para um papel importante das NTs cerebrais nas neuroadaptações induzidas pelo uso de substâncias, podendo estar associadas ao desenvolvimento da dependência, fissura, dano cognitivo e predisposição para recaída (56, 57). O estudo de biomarcadores acende a possibilidade de melhor compreender a fisiopatologia dos TUS, possibilitando prever a gravidade da doença e avaliar o prognóstico e a construção de métodos terapêuticos mais individualizados (58).

1.4 Biomarcadores

Embora existam instrumentos para mensurar se o indivíduo fez uso de substâncias psicoativas – os drogômetros –, esta mensuração limita-se à identificação aguda. Apesar dos avanços na pesquisa, evidenciados nas últimas décadas, ainda não existe nenhum biomarcador que possibilite estimar, de forma

precisa, a trajetória da dependência, os subtipos clínicos, nem a eficácia do tratamento; tampouco, que possa agregar alguma informação preditiva ou que reflita processos neurobiológicos associados com a gravidade da doença (36, 59).

Biomarcadores são características objetivamente observáveis, medidas e avaliadas como indicadores de processos biológicos normais, patogênicos ou respostas farmacológicas para uma intervenção terapêutica (60). A identificação e a utilização clínica de biomarcadores apropriados pode possibilitar uma compreensão mecanicista do processo patológico, constituindo uma ferramenta de medição clínica precisa que possibilite determinar a progressão da doença, os efeitos das intervenções e a resposta clínica, permitindo remodelar o tratamento e potencializar resultados terapêuticos (33, 60).

Existem diversos tipos de biomarcadores: diagnósticos, preditivos, mecanicistas, prognósticos, que podem ser quantificados de diferentes formas (fluidos corporais, soro, plasma, cabelo, urina, sangue, unhas, exames e neuroimagem). A quantificação de substâncias em fluidos corporais, como urina, saliva e sangue, são os biomarcadores mais precisos evidenciados na atualidade. Por outro lado, os dados sobre biomarcadores, com capacidade de prever desfechos clínicos ou processos que se relacionam com a neurobiologia da doença, ainda são incipientes. De acordo com a diretora do NIDA, Nora Volkow, há uma necessidade urgente de biomarcadores que reflitam a exposição crônica a fármacos, bem como, que prevejam ou se correlacionem com as trajetórias de doença e as respostas ao tratamento (36). Neste sentido, os fatores neurotróficos têm sido alvo de investigações na fisiopatologia de diversos transtornos, incluindo os TUS (61, 62).

1.5 BDNF

As NTs (NT) têm papel essencial na regulação de distintas atividades celulares no Sistema Nervoso Central (SNC), como a expressão gênica, o crescimento, a diferenciação e a sobrevivência celular, a apoptose e a plasticidade sináptica (63). O BDNF (64) é a NT com papel na plasticidade sináptica melhor estabelecido na literatura (65). Estima-se que esteja relacionado à mediação dos

principais processos dependentes de estímulo externo, como aprendizado, experiências e memórias, incluindo efeito das substâncias de abuso (66). As NTs, em especial o BDNF, parecem estar implicadas na base fisiopatológica de diversas doenças neurodegenerativas (67-70) e psiquiátricas (70-77)

O BDNF é considerado a principal neurotrofina cerebral, sua produção é realizada principalmente pela glia e pelos núcleos neuronais, sendo altamente expresso na amígdala, neocórtex, hipocampo e cerebelo, áreas relacionadas com funções cognitivas (78, 79). Também, está relacionado à modulação de diversas funções como o crescimento celular, maturação, nutrição, diferenciação, conectividade sináptica, crescimento e integridade neuronal, modulação da transmissão, reparo neuronal, além de processos de neurogênese e neurodegenaração (71, 80-82). O BDNF periférico tem sido amplamente utilizado em pesquisas clínicas, uma vez que parece atravessar livremente a barreira hemato-encefálica e seus níveis no soro e no plasma estão fortemente correlacionados com as concentrações de BDNF encontradas no SNC (83-87). Apesar de estudos prévios apontarem para a associação entre níveis periféricos e cerebrais de BDNF (86-88), em humanos, é difícil estimar de quais áreas encefálicas o BDNF periférico é proveniente, o que torna a transposição dos achados pré-clínicos complexa, compondo uma limitação importante.

Além disso, as matrizes biológicas usados para dosagem do BDNF periférico tem mostrado heterogeneidade. Os níveis do BDNF no soro humano são de 20 - 50 vezes superiores aos níveis no plasma (89, 90). O BDNF do plasma é proveniente, principalmente, dos linfócitos, das células endoteliais, dos linfonócitos e das células periféricas não neuronais, incluindo as células do músculo liso vascular (91, 92). Já o BDNF sérico, mimetiza o total de BDNF armazenado e liberado pelas plaquetas durante o processo de coagulação (93, 94). Tendo em vista que as plaquetas contêm a maior parte do BDNF circulante no sangue, o soro parece refletir melhor a quantidade do BDNF no sangue total, constituindo um marcador mais fidedigno (76, 93).

1.6 BDNF nos Transtornos por uso de substâncias

Estudos pré-clínicos apontam o envolvimento do BDNF na neuroadaptação induzida por drogas, relacionada à transição do uso para a dependência, fissura, recaída e sensibilização à droga (95, 96); isso é evidenciado, principalmente, nos estudos que avaliaram o álcool e os psicoestimulantes (97, 98). Apesar disso, os resultados, de uma forma geral, são controversos. Enquanto a administração prolongada de nicotina, por exemplo, ocasionou o aumento da expressão encefálica do BDNF no cérebro de ratos (99), as anfetaminas diminuíram os níveis de BDNF no hipotálamo e nas regiões corticais (100), e a morfina gerou um aumento imediato na expressão da proteína BDNF no VTA, mas após a retirada, a longo prazo, verificou-se ~~de~~ uma diminuição(101).

Uma revisão verificou que os efeitos do álcool sobre o BDNF cerebral de ratos são controversos entre diferentes estudos (98). As pesquisas pré-clínicas, com cocaína, demonstraram que a administração de BDNF em distintas áreas cerebrais acarreta efeito direto no comportamento de busca por cocaína, todavia, pode ter efeitos opostos dependendo da região cerebral. Infusão de BDNF na ATV e no NAc, durante a abstinência precoce de cocaína, potencializou a procura pela droga e a recaída (102, 103). Em contraposição, a administração de BDNF no córtex pré-frontal de ratos, no último dia de autoadministração de cocaína (realizada por 10 dias) reduziu a procura por cocaína (104).

Acredita-se que o uso de SPA acarrete neuroadaptações e que elas estejam associadas com a reinstalação da busca pela droga, e ocorrem, principalmente, na via CPF-NAc, na qual o BDNF é expresso. Os neurônios piramidais corticais, que saem do CPF, são a principal fonte de BDNF dentro do estriado, incluindo o NAc. A administração aguda de cocaína induz a expressão de RNAm de BDNF no CPFm, córtex cingulado e estriado, que pode representar os estágios iniciais da plasticidade cortical induzida~~s~~ pelos psicoestimulantes. Após a administração repetida de cocaína, o BDNF permanece aumentado nas estruturas prosencefálicas (105). Na abstinência precoce (22h), há diminuição do BDNF no CPF dorsomedial, o que não ocorre na abstinência tardia (21 dias) (96). Além disso, após um período de auto-administração de cocaína, o BDNF está aumentado nas estruturas mesolímbicas, incluindo ATV, NAc e amígdala em períodos prolongados de abstinência (106). Considerando que o BDNF é transportado nas projeções glutamatérgicas do CPF

para o NAc, e que esta via regula a recaída para a busca de drogas, a variação da expressão do BDNF nesta via pode constituir um componente crítico na neuroplasticidade induzida pela cocaína nos neurônios corticais e mesolímbicos (96).

Ao avaliar os níveis de BDNF em dependentes de álcool, em uso ativo, algumas investigações encontraram níveis semelhantes aos controles no *baseline* (107-109), todavia, também há relatos de aumento (61, 110) e redução (111, 112). Já nos dependentes de cocaína, dois estudos recentes avaliaram o BDNF pré-desintoxicação, tendo encontrado níveis diminuídos em relação aos controles (113, 114). Em relação às outras drogas, nos usuários de metanfetamina e de heroína, o nível de BDNF foi encontrado tanto aumentado (115, 116) quanto diminuído (117, 118) em relação a controles. Nos usuários crônicos de maconha, o BDNF não diferiu em relação aos controles (119) e nos usuários de ecstasy foi encontrado elevado (120). Analisados em conjunto, estes estudos revelam que os níveis de BDNF, em indivíduos dependentes de substâncias não abstinentes, são muito variados, tanto entre drogas diferentes quanto entre usuários da mesma substância. Cabe salientar que, a maioria dos estudos foi com tamanhos amostrais pequenos e não há uma boa descrição de como os controles foram selecionados, fatos que podem estar relacionados com achados divergentes.

Mais recentemente, os resultados da variação do BDNF durante a abstinência de cocaína/crack e de álcool têm sido associados à manutenção da abstinência, reforçando o possível papel do BDNF como marcador prognóstico na dependência química (108, 121). O BDNF também tem sido associado com a gravidade dos problemas com cocaína/crack e álcool (122, 123). Estes resultados reforçam a hipótese de que o BDNF é um potencial indicador para a gravidade do uso de drogas e do prognóstico. Portanto, o entendimento do comportamento desta NT pode auxiliar na elucidação do porquê os tratamentos disponíveis funcionam para alguns pacientes e não para outros.

Em dependentes de álcool e cocaína, o BDNF foi avaliado também na abstinência e como preditor de recaída. Durante a abstinência precoce de cocaína (14 dias), o BDNF aumentou durante a desintoxicação e o valor ao final das duas semanas foi correlacionado positivamente com sintomas de abstinência, de

depressão e de ansiedade e com fissura, tendo esse estudo avaliado apenas 23 pacientes e 46 controles (113). Esse achado sugere que níveis maiores de BDNF na abstinência precoce seriam encontrados em indivíduos mais sintomáticos e mais graves. Nessa mesma linha, o valor do BDNF, após 3 semanas de abstinência de cocaína, foi maior no grupo que recaiu em relação ao grupo que se manteve abstinente após 90 dias da alta hospitalar (61). Em dependentes de álcool, o BDNF, avaliado 6 meses após um período de desintoxicação, foi maior nos que estavam abstinentes em relação aos que recaíram, sendo a proporção do aumento também maior nos abstinentes, quando avaliados em relação ao valor do BDNF no primeiro dia da internação (108)

Investigações do nosso grupo de pesquisa apontaram que, a redução no BDNF sérico foi associada à gravidade do uso de crack, além disso, o nível de BDNF estava reduzido na admissão, mas na alta estava semelhante aos controles (122). Outra investigação revelou que, os níveis de BDNF aumentaram durante a abstinência precoce de crack, em uma correlação inversa com o número de pedras de crack usadas nos últimos 30 dias e aos anos de uso de crack (114).

Outro estudo, publicado recentemente, sugeriu uma associação entre níveis mais elevados de BDNF e melhores resultados clínicos, em usuários de crack-cocaína, após desintoxicação (124). Neste sentido, o aumento do BDNF durante a abstinência poderia estar associado à capacidade regenerativa do cérebro após a interrupção do consumo. Esses resultados encontrados são diferentes daqueles descritos por Corominas e D´As, para usuários de cocaína, que associaram o aumento do BDNF durante a abstinência precoce a maiores índices de recaída (61, 121).

Estes resultados mostram a existência de discrepâncias entre os estudos, havendo relatos da redução, do aumento e da não alteração do BDNF em dependentes de drogas. Se considerarmos o fato de estarem ou não abstinentes a controvérsia é ainda maior. Alguns estudos têm ponderado que o BDNF periférico prediz resposta ao tratamento e ao prognóstico, mas os resultados permanecem discrepantes. Ressalta-se que, as inconsistências nos resultados, podem ser decorrentes de diferenças nas características da população estudada ou da ausência de poder estatístico, devido ao reduzido

tamanho amostral. Assim, o papel do BDNF nos TUS permanece sendo pouco explorado.

Uma técnica reconhecida, usada para resolver discrepâncias entre estudos transversais, é a meta-análise; um método quantitativo de combinar os resultados de estudos independentes, visando potencializar o poder estatístico e permitir conclusões mais consistentes. Este método aumenta o poder para se distinguir entre pequenos tamanhos de efeito e ausência de efeito. Além disso, pode ajudar a d*et*erminar se a variação de efeito entre os estudos é devida, apenas, à flutuação estatística esperada ou a diferenças reais na amostra utilizada. Uma análise de meta-regressão, um método estatístico mais sofisticado, pode avaliar fatores moderadores associados a discrepâncias entre os estudos.

2 Objetivo geral:

Avaliar os níveis periféricos de BDNF em pacientes com Transtornos por uso de substâncias, lícitas e ilícitas, exceto tabaco, comparando-os com controles saudáveis a partir de uma revisão sistemática da literatura

2.1 Objetivos específicos:

Verificar se há diferenças nas concentrações séricas e plasmáticas de BDNF de acordo com o tipo e a classe da substância psicoativa utilizada;

Avaliar se a retirada da droga (abstinência) está relacionada com alterações nos níveis periféricos de BDNF;

Avaliar potenciais fatores moderadores (sexo, idade, idade de início do consumo da substância, tempo de uso, e tempo de abstinência);

Confirmação de submissão

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3 Artigo

Brain-derived neurotrophic factor in Substance Use Disorders: a systematic review and meta-analysis.

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Abstract

Background: Changes in brain-derived neurotrophic factor (BDNF) are associated with several neurodegenerative and psychiatric disorders. It is not clear, however, whether BDNF levels are altered in substance use disorders (SUDS) **Methods:** We conducted a systematic search of electronic databases to identify studies comparing peripheral - plasma or serum - BDNF levels in adults with SUDS versus healthy controls. Thirty studies were included in the meta-analysis, accounting for 1698 participants with SUDS and 1363 controls. **Results:** The overall analysis found no significantly different BDNF levels of cases versus controls (SMD=-0.11, 95%CI -0.30 to 0.15, p=0.39, I2=94.02). Subgroupanalysis revealed lower levels of BDNF in alcohol users compared to controls (SMD=-0.45, 95%CI -0.89 to -0.01, p=0.0 4, I2=90.54). Studies using serum or plasma BDNF samples shown different, and sometimes, antagonic results. After adjusting for publication bias, the resoults reveals that serum BDNF in current users was reduced (SMD=-0.51, 95%CI -1.12 to -0.08), but similar to controls in withdrawn. Metaregression analysis revealved that years of drug use, age, gender and length of withdrawn moderate the effects of drug use on peripheral BDNF levels. **Conclusions:** Peripheral BDNF is decreased in alcohol use disorders. However, this effect is not significant across diferent drugs types. Time using the drug, age, gender and the length of withdraw modifies the effects of drug abuse on BDNF levels, indicating that BDNF could be related with the severity and progression of drug dependence, and perhaps be a state biomarker, as already described for other psychiatric and neurodegenerative disorders.

Introduction

Drug addiction consists in a chronic disorder characterized by a set of cognitive, behavioral and physiological symptoms, by the continuity of use despite negative consequences and by high rates of relapse. Regardless of type of drug used, three main characteristics are observed among addicts: 1) Loss of control over use; 2) Tolerance; and 3) Withdrawal symptoms and adverse emotional states when use is interrupted [1, 2]. This can derive from dysfunctional alterations in brain systems, mainly involving memory, reward, motivation and executive functions systems, resulting in compulsion, deficits in decision making, impulsivity and a reduction in inhibitory control [3, 4]. Although it is postulated that chronic use of psychoactive-substances (PAS) entails changes in brain function and structure, leading to dysfunctional neuroadaptations – transitory or permanent –, the time of use and amount of drug necessary to provoke these alterations are unknown [5]. Grasping these neuroadaptations may allow the establishment of analytical tools that enhance the understanding of interindividual variability on drug abuse and treatment responses [5-8].

Significant advances regarding the psychobiology of addictive disorders were evidenced in previous decades, reinforcing the comprehension of addiction as a chronic disease, characterized by structural and functional alterations in different brain systems [8-12]. Brain-derived neurotrophic factor (BDNF) has been studied as a potential biomarker to understand the physiopathology of several psychiatric disorders, including Substance Use Disorder (SUDS) [13, 14]. BDNF is the most abundant neurotrophin found in the brain and it is related to cell growth, differentiation, connectivity and synaptic neuroplasticity, neurotransmission

modulation and neuronal repair, besides neurogenic and neurodegenerative processes [15, 16], learning and memory [17]. Pre-clinical and clinical evidence indicate that neurotrophins are involved in the neuroadaptation process caused by PAS use as well as in different process related to mediation of behavioral effects, including drug sensitization, craving and relapse[18-22]. Peripheral BDNF has been widely assessed in clinical studies since it freely crosses the blood-brain barrier and its peripheral concentration is strongly correlated with concentrations found in central nervous system (CNS) [23, 24].

Previous studies that evaluated BDNF levels in drug addcts evidenced different and even controversial results, indicating that this variation may be related to the type of drug consumed, the pattern of use at the moment of the study and dependence stage [25-33]. However, published studies mostly used small and heterogeneous samples and evaluated, predominantly, only one type of drug, preventing the establishment of a concentration range of this biomarker in patients with a SUD of a different, or of multiple substances. There is not of authors' knowledge the existence of a systematic review that has meta analyzed the difference between BDNF levels in people with SUDS versus controls Therefore, the present study aims to: 1) compare serum and plasma peripheral BDNF levels between subjects with SUDS and healthy controls; 2) evaluate whether this difference occurs in different drugs types, subtypes, withdrawn and blood fraction through subgroup analysis and 3) explore, using meta-regressions, potential moderating factors.

Methods and Materials

The protocol developed for this meta-analytic review followed the

recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [34]. Each element of the search, selection of eligible studies (FO and AGV) and data extraction (FPR and ALT) were performed by two authors. Disagreements were resolved through consensus and with the opinion of a third author (FHPK).

Search strategy

We conducted a systematic search of all potentially eligible references without language restrictions, using PubMed/MEDLINE, EMBASE and PsycINFO computerized databases. The search strategy used was (addiction OR drug abuse OR dependence OR opioids OR heroin OR cocaine OR crack OR inhalants OR methamphetamine OR stimulants OR cannabis OR ecstasy OR club drugs OR alcohol OR alcohol* OR substance-related disorders OR SUDS) AND (BDNF OR brain derived neurotrophic factor OR neurogenesis) NOT (animal OR rat OR mouse OR mice). The last search was performed in June ninth 2016. This search strategy was augmented by tracking manually the reference list of all retrieved papers to identify additional eligible papers.

Study selection

The inclusion criteria were: (1) studies that evaluated individuals with diagnosis of SUDS of alcohol or illicit drugs meeting Diagnostic and Statistical Manual for Mental Disorders or International Classification of Diseases diagnostic; (2) studies comparing BDNF levels between people with SUDS and healthy volunteers or clinical trials using baseline data before drug treatment; (3) studies that measured peripheral BDNF levels; Exclusion criteria were (1) studies that evaluated samples

with baseline clinical comorbidities (e.g: depression, HIV, Parkinson's disease, alzheimer and dementia); (2) genetic studies without information on peripheral BDNF levels; and (3) papers written in the format of letter, poster, review, case reports, opinion or commentary. The authors consensually agreed on the final inclusion of references.

Data extraction

Two reviewers (FPR and ALT) independently extracted data from controls and SUDS group (sample size, mean and standard deviation) from all articles to prevent potential errors. Discrepancies in data entry were double-checked by the reviewers with the original published data and a consensus was reached. We extracted information regarding primary drug, psychiatric comorbidities, scales and/or questionnaires performed to evaluate psychiatric symptoms or disorders, BDNF levels, type of peripheral sample used for BDNF levels measurement and withdrawn length at time of BDNF levels measurement. Information about sex, age, age of first use, years of use, tobacco use, body mass index (BMI), and clinical diseases were also extracted. Furthermore, corresponding authors of included articles were contacted by e-mail in at least two different occasions whenever necessary data were unavailable, requesting the provision of data. In the cases multiple reports pertained to the same participants, we included only the largest data set. When data were available only in graphs, we extracted the data using the Plotdigitalizer software, web version [35].

Assessment of methodological quality

The quality of the 36 studies included in the systematic review was evaluated using the 9-item Newcastle-Ottawa Scale (NOS) for case-control studies[36]. However, the item 3 ("Equivalent non-response rate between groups") was not used in quality assessment because of the proposal of this review. For comparability questions, age was set a priori as the most important matching or adjustment factor. Moreover, other 2 articles were evaluated by Cochrane Collaboration tool using the 7-bias risk assessment of Randomized Clinical Trials, using baseline data/information [37].

Meta-analysis

We conducted random effect meta-analyses due to the anticipated heterogeneity across studies. The analyses were performed with the Comprehensive Meta-Analysis software (CMA, Version 3). The meta-analysis were conducted in the following sequence. First, we conducted a comparative meta-analysis investigating differences on BDNF levels of drug users versus controls using the standardized mean deviation (SMD) together with the 95% confidence intervals (CI) of the effect size. Second, we calculated the subgroup differences according to the 1) drug subtype, 2) withdrawn (we considered in the withdrawn groups those with a minimum of 6 days), 3) drug classification as stimulant (cocaine, crack and methamphetamine), depressant (alcohol, heroine, opiates and ketamine) or hallucinogen (cannabis and amphetamine derivative (±)-3,4-methylenedioxymethamphetamine (MDMA, ecstasy), 4) biological matrix used to measure BDNF (serum or plasma). Third, we investigated potential moderators of BDNF levels with meta-regression analyses. The potential moderators of interest were mean age, % of males, withdrawn length and years of drug use. We assessed heterogeneity using the I^2 statistics for each analysis. Publication bias was verified with the Begg-Mazumdar Kendall's tau and Egger tests.

Trim and fill analyses were conducted to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each interaction until the funnel plot was symmetric about the (new) effect size.

Results

Initially, 925 studies were localized as potentially relevant. Following the application of the eligibility criteria, 56 studies were included for review. After reading the preliminary included papers in full and tracking reference lists for possible missing papers, 38 articles reached the eligibility criteria and were included in this systematic review and 30 of them were also included in the meta-analysis (Figure 1).

Study and participants' characteristics

Across 47 arms of 30 unique studies, there were 2315 blood samples of 1698 participants with SUDS (79% males, mean age of 36.50 years) and 2049 blood samples of 1363 controls (75% males, mean age of 35.24 years) included. The sample size of drug users ranged from 9 [38] to 179 [39]. Fourteen arms evaluated BDNF levels in alcohol (n=600), ten in cocaine (n=532), nine in heroin (n=472), two in cannabis (n=35), five in methamphetamine (n=355), two in ketamine (n=110), and one in MDMA (n=23) users. Twenty arms have blood samples in participants with current/active drug use (n=1119) and other 20 arms in withdrawn participants (n=1102). Twenty-nine arms evaluated participants using depressant drugs (n=1370), 15 in stimulant drugs (n=887) and three on hallucinogen drugs (n=58). Nine arms used data from plasma samples to measure BDNF levels (n=665) while 38 used serum samples (n=1650). Further details of the included studies are summarized in Table 1.

Quality of studies

Quality assessment of the eligible studies using the NOS (Supplemental information).

Four studies scored 8 of 8 possible points [25, 29, 40, 41], 12 scored 7 of 8 possible points [27, 28, 30, 39, 42-49], 13 scored 6 of 8 possible points [25, 50-61], and 7 scored 5 of 8 possible points [26, 40, 42, 62-65]. The quality of the studies was most often compromised by the representativeness of the cases, following by the equivalence in ascertainment for cases and controls. The absence of information about how was the selection criteria of the sample and the validated instruments used to assess psychoactive SUDS without subsequent clinical evaluation was the main compromised points.

Quality assessment of the eligible studies using the Cochrane Collaboration tool (Supplemental information).

None of the 2 studies presented high risk of bias. Nonetheless, they have uncertain risk of bias for allocation concealment and selective reporting[38] and one of them also for random sequence generation[66].

Meta-analysis of overall comparative BDNF levels

Forty-seven studies, including 2315 blood samples of participants with drug use and 1698 controls were pooled and found no significant differences in BDNF levels (SMD=-0.11, 95%CI -0.30 to 0.15, p=0.39, I2=94.02) (Figure 2). No significant publication bias was identified in Begg and Mazumdar (tau=0.02, p=0.79) or Egger tests (intercept=1.03, p=0.60). However, the Duval and Tweedie trim and fill technique adjusted the effect size for 0.22 (95%CI -0.07 to 0.52) trimming nine

studies.

Subgroup analyses

We investigated BDNF levels on plasma or serum separately, as different subgroups (table 3). For each matrix, we investigated the specific role of current substance use status (current use/withdrawn), and the drug subtype – Alcohol (Figure 3), Heroin (Figure 4), Crack/cocaine (Figure 5), Cannabis, Ketamine, MDMA/Ecstasy or Methamphetamine (Figure 6). Following, we investigated the role of drug action and the drug subtype for people with current use or withdrawn, separately, for both serum and plasma BDNF levels. The subgroup analyses are detailed below.

Serum BDNF levels

Twenty-five studies, including 1650 blood samples of participants with SUDS and 1603 controls were pooled and no significant differences in BDNF levels were found (SMD=-0.21, 95%CI -0.51 to 0.08, p=0.16, I2=93.46). No significant publication bias was identified in Begg and Mazumdar (tau=-0.03, p=0.79) or Egger tests (intercept=-0.69, p=0.74). However, the Duval and Tweedie trim and fill technique adjusted the effect size for 0.16 (95%CI -0.16 to 0.49) trimming eight studies. The detailed analysis of BDNF levels can be seen in Table 2, but they will be briefly summarized below.

Analysis of subgroup of serum BDNF

Lower BDNF levels were found for users of depressant drugs (SMD=-0.38, 95%CI -0.76 to -0.03, p=0.04, I2=93.02) and for users of alcohol (SMD=-0.45, 95%CI

-0.89 to -0.01, p=0.04, I2=90.54) and higher levels were found for users of MDMA/Ecstasy (SMD=5.72, 95%CI 4.35 to 7.09, p>0.001, I2=0). After adjusting for publication bias, decreased levels were found for serum BDNF levels in people with current/actual use of drugs (SMD=-0.51, 95%CI -1.12 to -0.08), with one study trimmed, and the difference between users of alcohol and controls was shortened to -0.73 (95%CI -1.22 to -0.25) after trimming 3 studies (Table 2).

Serum BDNF levels in withdrawn participants

No significant effects were found on BDNF serum levels of withdrawn participants. The results remain not significant even analysing drugs with different actions (stimulant or depressant) or at a drug subtype level.

Serum BDNF levels in participants with active use

Lower BDNF levels were found in alcohol (SMD=-0.64, 95%CI -1.16 to -0.13, p=0.01, I2=86.84) and crack/cocaine (SMD=-0.96, 95%CI -1.26 to -0.66, p=0.001, I2=0) users, whilst increased BDNF levels were found for users of Ketamine (SMD=1.37, 95%CI 0.53 to 2.12, p=0.001, I2=0). The publication bias adjusted effect size for people with alcohol use disorder and active use was of -0.97 (95%CI -1.57 to -0.32), after trimming two studies.

Plasma BDNF levels

Eight studies, including 665 blood samples of participants with drug use and 446 controls, were pooled and no significant difference was found in BDNF levels (SMD=0.26, 95%CI -0.36 to 0.90, p=0.40, I2=95.55). Significant publication bias was identified at the Begg and Mazumdar (tau=0.52, p=0.04) and the Egger tests

(intercept=-10.65, p=0.04). However, the Duval and Tweedie trim and fill technique was not adjusted. The detailed analysis of plasma BDNF levels can be seen in Table 3, but they follow briefly summarized below.

Analysis of subgroups of plasma BDNF

Increased BDNF levels were found for users of stimulant drugs (SMD=-0.59, 95%CI -0.12 to 1.05, p=0.01, I2=80.36) and for users of methamphetamines (SMD=0.64, 95%CI 0.24 to 1.04, p=0.002, I2=0) and decreased levels were found for users of Heroin (SMD=-1.01, 95%CI -1.27 to -0.75, p>0.001, I2=0). After adjusting for publication bias, the effect size of stimulant drugs has slightly decreased to 0.47 (95%CI 0.62 to 0.88), after trimming one study (Table 3).

Plasma BDNF levels in withdrawn participants

Decreased BDNF levels were found for depressant drugs (SMD=-0.66, 95%CI -1.32 to --0.00, p=0.04, I2=66.34) and for alcohol (SMD=-0.96, 95%CI -1.26 to -0.66, p=0.001, I2=0), whilst increased BDNF levels were found for users of Methamphetamine (SMD=0.64, 95%CI 0.24 to 1.04, p=0.002, I2=0). No analysis of this subgroup was adjusted for publication bias.

Plasma BDNF levels in participants with active use

Plasma BDNF levels are increased in users of stimulant drugs (SMD=0.97, 95%CI 0.48 to 1.47, p>0.001, I2=0). This subgroup reflects based on the findings of one unique study in users of crack/cocaine. Lastly, users of Heroin presented decreased BDNF plasma levels (SMD=-1.01, 95% CI -1.27 to -0.75, p>0.001, I2=0). No analysis of this subgroup was adjusted for publication bias.

Meta-regressions of potential moderators

We have identified some moderators of the effect of drug use on BDNF serum levels, but not in plasma. In serum samples, sex (k=38 β=-0.02, 95%CI -0.04 to -0.01, p=0.0008, R2=0.07), age (k=38, β=-0.04, 95%CI -0.91 to -0.00, p=0.02, R2=0.02), years of use (k=20, β=-0.06, 95% CI -0.12 to -0.00, p=0.04, R2=0.03) and the length of withdrawn (k=15, β=-0.86, 95%CI -1.71 to -0.02, p=0.04, R2=0.10) moderated the difference of BDNF levels between drug users and healthy controls. The interactions between sex and age (k=38, intercept=3.11, 95%CI 1.24 to 4.98, p=0.001, R2=0.04), sex, age and years of use (k=20, intercept=4.35, 95%CI 1.91 to 6.79, p=0.0005, R2=0.11), but not the interaction between sex, age, years of use and length of withdrawn were significant (k=8, intercept=5.04, 95%CI -1.75 to 11.84, p=0.14, R2=0.27). The full details of the models tested can be found in Table 4.

Discussion

This was the first meta-analysis to assess peripheral BDNF levels in a population with SUDS compared to healthy controls. The main findings of this study were: 1) Peripheral BDNF levels between serum and plasma are divergent; 2) Patients with active drug use show lower serum BDNF levels when compared with controls; 3) There is no difference between BDNF levels of withdrawn individuals and controls in any of the substance groups, except for alcohol at plasma sample; 4) There are differences in peripheral BDNF levels among types of PAS; 5) In depressant drugs, especially alcohol, results are more robust, both in serum and plasma analyses; 6) Meta-regressions showed that sex, age, length of withdrawn and years of drug use modifies the difference in BDNF levels between patients with

SUDS and controls. As a whole, our results suggest that BDNF could be a state-marker in SUDS.

One of the main results of this review and meta-analysis revealed differences in BDNF peripheral levels between serum and plasmatic biological matrices. Only two out of the thirty studies included in this investigation evaluated both biological matrices simultaneously and observed intra-individual and intra-group variations [41, 52]. This difference has already been demonstrated in previous studies with other psychiatric disorders [67-69]. An anterior meta-analysis of subjects with Major Depression verified the reduction in BDNF serum levels and the absence of significant differences in the plasma, showing no correlation of BDNF levels between these biological matrices [68]. Several hypotheses may help the comprehension of the discrepancy in peripheral dosages between the biological matrices. In general, the origin of BDNF in blood is not completely known – although the brain is believed to be the main source of circulating peripheral BDNF –, it is also produced in other regions [70-76]. While plasma BDNF derives mainly from lymphocytes, endothelial cells, monocytes and non-neural peripheral cells, including vascular smooth muscle cells [75, 76], serum BDNF is probably referred to total BDNF stored and released by platelets during blood clotting process [77, 78], generating a concentration of serum BDNF up to 50 times higher than the plasmatic one [77, 79]. Besides that, while plasma BDNF has a half-life of less than one hour, platelets circulate for up to 11 days [80, 81]. Considering that platelets contain the majority of the circulating BDNF in the blood, some investigations point out that serum levels seem to better reflect the amount of BDNF in the whole blood, constituting a more reliable marker [77, 78, 82, 83].

BDNF measurement in both plasma and serum BDNF is also subject to variability during detection due to biological, methodological and analytical factors [84].

The methodology applied to the collection and storage protocol may affect the samples stability[68, 82, 85, 86]. In plasma, the time between puncturing and sample processing, centrifugation condition [77, 85] and anticoagulant used can also interfere with the dosage. While Ethylenediaminetetraacetic acid (EDTA) would cause an increase in the detection of BDNF levels as a result of platelet release [78, 87], heparin would cause a decrease up to 60% in plasma detection [88].

The reduction of serum BDNF during active drug use found in our analyses corroborates with prior data demonstrating lower BDNF levels in manic and depressive episodes and in schizophrenia compared to euthymic subjects and healthy controls, showing that this neurotrophin may be a state-marker in psychiatric diseases. [67, 89-93]. The lack of significant difference in BDNF levels between cases and controls during withdrawal is also in accordance with previously described evidences in other psychiatric disorders where BDNF increased after withdrawn [67, 90]. These results suggest that BDNF could vary between different stages of drug use and be associated with upport the hypothesis that BDNF may be a stage biomarker of the disorder, capable of signaling the cumulative neurological damage of neuroprogressive nature of thepsychiatric conditions [94-97]. In this sense, it is known that during the course of mental disorders the homeostatic functioning is disturbed and the CNS reorganizes itself; in the short term, this reorganization can indicate a mechanism of functional response, but in the long term it can cause dysfunctional and pathological alterations (allostatic load), resulting in inappropriate responses [96, 98-103]. Moreover, in advanced stages of the disease, these inappropriate responses can persist even during remission [104]. In SUDS, the chronic use of PAS generates repeated overactivation of the dopaminergic pathway, leading to neuroadaptive mechanisms that may cause dysregulation in the brain reward system. This would

contribute to the transition from use to dependence [105, 106]. Pre-clinical evidence sustain this hypothesis; ethanol, for example, generates an increase in BDNF during acute administration and decrease when administration is continuous [107].

We have also verified that peripheral BDNF levels are different among users of different drugs, possibly due to factors such as the substance mechanism of action, pattern and duration of drug use, clinical and psychiatric comorbidities of users and polysubstance use. Tobacco, for instance, which is associated with increased peripheral BDNF, was not controlled in 39% of the studies [108, 109]. In crack/cocaine users, for example, polysubstance use is very common: 77% refer alcohol consumption and 85% tobacco in the last year [110]. Considering the use of different drugs, Hilburn et al. have found differences in serum BDNF levels among alcohol, cocaine and methamphetamine users in relation to craving and duration of withdrawn [111].

Meta-regressions showed that reduction in serum BDNF was associated with sex, age, years of drug use and duration of withdrawn. This corroborates with previous investigations that verified the impact of aging and sex on stored and circulating levels of BDNF in peripheral blood [112]. In psychiatric disorders, like bipolar disorder and schizophrenia, meta-analysis have already pointed out that age and duration of the disease are associated with the reduction of BDNF[92, 93]. Moreover, the reduction of serum BDNF during aging was associated with hippocampal shrinkage and memory declining [113]. It should be noted that this process may be different between the sexes. There are reports of higher BDNF levels in elderly women [86], which may result from hormonal differences evidenced between sexes. Estrogen, for instance, interferes in the expression of BDNF, as well as variations in menstrual cycle [73, 112, 114]. It is noteworthy that the only study with an exclusively female sample

found increased BDNF levels in crack users during early withdrawal in relation to controls, and, furthermore, this study showed that more than half of the women had some additional psychiatric comorbidity [49], which may indicate a greater drug use severity.

Evidence suggests that reduced BDNF may be related to the dependence severity [25, 29, 30, 57]. Even in addicted individuals to the same substance, there are differences in BDNF according to severity of drug use and prognosis [29, 32, 58, 115]. In alcohol users, for example, significantly lower levels of BDNF were evidenced in individuals with delirium tremens when compared to those who did not have this condition and controls, which was maintained even after detoxification [25]. In another study, which followed patients for 180 days after detoxification, serum BDNF of patients who maintained withdrawn was higher than baseline and higher than the group that relapsed during this period [57]. Similarly, Scherer et al. found an association between higher levels of BDNF and better clinical outcomes in crack cocaine users during detoxification [115]. In this sense, the increase of BDNF levels, approaching the levels of the controls, during the treatment, may be associated to better clinical outcomes [116, 117].

On the other hand, in young ecstasy dependents, with fewer years of use and more occasional use, BDNF was increased at baseline [26], which may signal the fact that they were in the initial phase of dependence. Another study with controlled administration of THC verified increased serum BDNF in healthy controls, but not in subjects who previously used cannabis [118], signaling that the effect of drugs on BDNF is distinct among recreational use and in early and advanced phases of dependence. In bipolar patients, for example, BDNF serum levels diverging between the early and late stages were previously reported [119]. Beyond bipolar disorder, the

reduction in BDNF levels has also been related to the severity of depression and schizophrenia [90, 93, 120].

The present study has some limitations. First, we have encountered large heterogeneity (80% or higher) for all analysis. In this light, we have explored, using subgroup and moderators analysis, some of the potential sources of this heterogeneity in which age, gender, time using the drug and the drug type and subtype explained some of the heterogeneity. Second, we have encontered publication bias for some analysis. For those, we performed the Duval and Tweedie trim and fill tecnique and recalculated the effect size adjusting for publication bias.

Altogether, these evidences suggest that BDNF could be related with severity and progression of drug dependence, as already described for other psychiatric and neurodegenerative disorders [92, 117, 121-129]. Moreover, when considering BDNF levels interpretation in drug users, factors such as protocol of analysis, drug type and pattern of drug use need to be considered. As shown in the present study, it seems that different drug classes affect BDNF levels in different ways – however, the mechanisms of action of these drugs in BDNF concentration are not fully understood yet. Nonetheless, great progress is being made in order to achieve a better understanding of neuropsychological factors of drug dependence.

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Table 1. Characteristics of the studies included in the meta-analysis of serum or plasma BDNF levels in Substance Use Disorder

Table 2. Brain-derived neurotrophic factor (BDNF) levels from serum samples.

Table 3. Brain-derived neurotrophic factor (BDNF) levels from plasma samples.

Table 4. Meta-regression of potential moderators brain-derived neurotrophic factor (BDNF) in substance use disorders

Figure 1. Flow diagram of the meta-analysis of brain-derived neurotrophic factor (BDNF) in substance use disorders

Figure 2. Overall, plasma and serum Brain-derived neurotrophic factor (BDNF) levels in substance use disorders

Figure 3. Brain-derived neurotrophic factor (BDNF) levels from serum in alcohol users

Figure 4. Brain-derived neurotrophic factor (BDNF) levels from serum in opiate users

Figure 5. Brain-derived neurotrophic factor (BDNF) levels from serum in crack/cocaine users

Figure 6. Brain-derived neurotrophic factor (BDNF) levels from serum in

methamphetamine users

Supplemental information.

S1. Quality assessment of the eligible studies using the Newcastle-Ottawa Scale

S2. Quality assessment of the eligible studies using the Cochrane Collaboration

Table 1. Characteristics of the studies included in the meta-analysis of serum or plasma BDNF levels in Substance Use Disorder**.**

Study	Year	Drug	Withdrawal	Biological Matrix	Mean BDNF (casNenhuma entrada de índice de ilustrações foi encontrada.es)	Mean BDNF (controls)	Unit	Cases (n)	Controls (n)	Gender
Cavus, S.Y.	2012	Alcohol	No Yes	Serum	Baseline: 52.9 ± 19 7º Day: 3.5 ± 8.8	65.3 ± 15.9	ng/Ml	31	29	Men
Costa, M.A.	2011	Alcohol	No Yes No	Serum	Baseline: 22.98 ± 7.95 6 months (withdrawal): 31.9 ±10.1 6 months (no withdrawal): 27.5 ±10.4	24.2 ± 5.1	pg/mL	101	39	Mixed
D'Sa, C. (1)	2012	Alcohol	Yes Yes	Serum / Plasma	Plasma: 1.27+-1.12 Serum: 35.3 +- 11.1	Plasma 1.52+-0.68 Serum: 26.9 ±9.5	ng/mL	16	16	Mixed
Zanardini, R.	2011	Alcohol	No No	Serum / Plasma	Plasma: 4.77 ± 3.50 Serum: 35.97 ± 10.49	Plasma: 4.08 ± 4.00 Serum: 41.70 ± 11.49	ng/mL	37	37	Mixed
Geisel, O.	2016	Alcohol	Yes Yes Yes	Serum	Placebo drug group (baseline): 3446.2 ± 1285.8 Placebo drug group (T1): 3511.9 ± 1493.5 Placebo drug group (T2): 3796.7 ± 2047.4	3716.8 ± 1403.7	pg/mL	28	10	Mixed
Heberlein, A.	2015	Alcohol	No Yes Yes	Serum	Day 1: 647.67 ± 510.13 Day 7: 554.74 ± 398.25 Day 14: 653.81 ± 518.95	623.29 ± 303.03	pg/mL	99	33	Men
Huang, M-C.	2011	Alcohol	No No Yes Yes	Serum	Baseline (Without Delirium TreMens): 12.3± 3.3 Baseline (With Delirium TreMens): 6.2±2.6 After one week (Without Delirium TreMens): 13.4 ± 3.5 After one week (With Delirium TreMens): 8.9 ± 4.4	14.8 ± 4.7	ng/mL	65	39	Mixed
Joe, K-H.	2007	Alcohol	Yes	Plasma	389.5 ± 501.7	822.5 ± 420.7	pg/mL	64	75	Men

Lee, B.C.	2009	Alcohol	No	Plasma	3502.2 ± 1726.9 a	861.75 ± 478.9	pg/mL	41	41	Men
Meng, D.	2011	Alcohol	Yes	Serum	Baseline: 12.69 ± 4.79	Baseline: 11.76 ± 5.05	ng/mL	14	10	Men
D'Souza, D.C.	2009	Cannabis	No	Serum	2552 ± 4067	2552 ± 4932	pg/mL	9	14	Mixed
Angelucci, F. (4)	2008	Cannabis	-	Serum	5984.23 ± 335.9	5683.62 ± 237.65	pg/mL	26	20	Mixed
Ke, X.	2014	Cetamine	-	Serum	9.5 ± 6.68	14.37 ± 6.07	ng/mL	93	39	Mixed
Ricci, V.	2011	Cetamine	No	Serum	12.7 ± 5.48	6159 ± 3.27	ng/mL	17	11	Mixed
Angelucci, F. (2)	2007	Cocaine	-	Serum	5182.46 ± 662.43	5433.32 ± 392.41	pg/mL	15	15	Mixed
Corominas-Roso, M.	2013	Cocaine	No Yes	Serum	Baseline: 51.676± 17.505 After 12 days: 60.643±22.607	76044 ±32.661	ng/mL	23	46	Mixed
D'Sa, C. (2)	2011	Cocaine	Yes	Serum	36 ±9.2	25.8 ± 8.9	ng/mL	35	34	Mixed
Pedraz, M.	2015	Cocaine	Yes	Plasma	274.9±200.3	269.4 ± 242.7	pg/mL	89	85	Mixed
Narvaez, J.C.M.	2013	Crack	No described	Serum	14.21±3.24	12.67 ± 3.74	ng/mL	53	50	Mixed
von Diemen, L.	2014	Crack	Yes No	Serum	Baseline: 28.6 ± 11.0 Discharge: 35.5 ± 12.3	39.5 ±10.6	ng/mL	49	97	Men
Viola, T.W.	2014	Crack	No Yes Yes	Plasma	4 days: 13726.88 ± 5908.50 11 days: 13101.84± 6507.44 18 days: 14137.92 ± 7613.95	8344.90 ± 2662.48	pg/mL	104	20	Women
Chen, S.L.	2015	Opiate (Heroin)	No	Plasma	10.1±7.7	18.6 ±9.4	ng/mL	172	102	Mixed
Heberlein, A. (1)	2011	Opiate (Heroin)	No	Serum	865.14±358.8	556.62 ±174.04	pg/mL	27	21	Men
Angelucci, F. (3)	2007	Opiate (Heroin)	No described	Serum	5091.59±422.91	5433.32 ±392.41	pg/mL	15	15	Mixed
Zhang, K.	2016	Opiate (Heroin)	No Yes	Serum	Baseline: 987.25±915.26 After 26 weeks 2491.54±1397.32	Baseline 3989.07 ±2018.87 After 26 weeks 4003.05± 2011.83	pg/mL	53	52	Men
Schuster, R.	2016	Opiate	No	Serum	48.25±12.95	71.25±17.43	ng/mL	30	51	Mixed

Zhang, J.	2014	Opiate (Heroin)	No No Yes	Serum	Baseline (n=72): 1680±577.37 Baseline (n=37): 1565±511.4 After one month (n=37): 1454± 555.7	1241 ± 335.52	pg/mL	72	90	Mixed
Angelucci, F. (1)	2010	MDMA (ecstasy)	- -	Serum	Non-psychotic: 11.28±0.39 Psychotic:11.36 ± 0.51	8.53±572	ng/mL	23	19	Mixed
Kim, D.J.	2005	Methamphetamine	Yes	Plasma	2536.25±2310.49	1352.61±1188.15	pg/mL	50	50	Men
Chen, P.H.	2014	Methamphetamine	No Yes Yes	Serum	Baseline: 9.84± 4.85 Acute phase: 9.32± 4.33 Subacute phase: 10.45± 5.41	16.26±4.72	ng/mL	59	59	Mixed
Ren, W.	2016	Methamphetamine	No No No	Serum	Baseline (n=179): 1460.28±490.69 Baseline (n=40): 1621.41±591.07 After one month (n=40): 1363.70 ± 580.59	1241.27± 335.52	pg/mL	179	90	Mixed

Table 2. Brain-derived neurotrophic factor (BDNF) levels from serum samples.

Analysis	N subgroups	N participants	SMD 95%CI	Lower and Upper limit		P value	Trim and fill adjusted ES	I²
Serum	38		-0.213	-0.51	0.08	0.16	0.16 (95%CI -0.16 to 0.49) [8]	93.46
User status								
Withdrawn	15		0.326	-0.64	0.21	0.35	-0.31 (95%CI -0.75 to 0.13) [1]	91.64
Active use	16		-0.456	-0.93	0.02	0.06	**-0.51 (95%CI -1.12 to -0.08) [1]**	94.68
Drug subtype								
Alcohol	14		-0.451	-0.89	-0.01	**0.04**	**-0.73 (95%CI -1.22 to -0.254) [3]**	90.54
Cannabis	2		0.346	-1.01	1.70	0.61	N/A	85.27
Ketamine	2		0.281	-1.80	2.36	0.79	N/A	95.08
Crack/cocaine	7		-0.233	-0.79	0.37	0.41	-0.09 (95%CI -0.65 to 0.46) [1]	90.65
Heroin	8		-0.416	-1.24	0.41	0.32	Unchanged	95.88
MDMA/Ecstasy	1		5.723	4.35	7.09	**>0.001**	N/A	0
Methamphetamine	4		-0.423	-1.37	0.52	0.38	-0.11 (95%CI -0.98 to 0.75) [1]	96.24
Serum and withdrawn								
Alcohol	8		-0.287	-1.01	0.43	0.43	-0.47 (95%CI -1.22 to 0.28) [1]	92.58
Crack/cocaine	3		0.076	-0.87	1.02	0.87	Unchanged	92.56
Heroin	2		-0.171	-1.52	1.17	0.80	N/A	95.69
Methamphetamine	2		-0.435	-1.86	0.99	0.55	N/A	95.40
Serum and active use								
Drug subtype								
Alcohol	6		-0.649	-1.16	-0.13	**0.01**	-0.97 (95%CI -1.57 to -0.32) [2]	86.84
Crack/cocaine	2		-0.962	-1.26	-0.66	**>0.001**	N/A	0
Heroin	4		-0.340	-1.91	1.23	0.67	Unchanged	97.87
Methamphetamine	2		-0.418	-2.21	1.37	0.64	N/A	98.22

Table 3. Brain-derived neurotrophic factor (BDNF) levels from plasma samples.

Analysis	N subgroups	N participants	SMD 95%CI	Lower and Upper limit		P value	Trim and fill adjusted ES	I²
Plasma	9		0.269	-0.36	0.90	0.40	Unchanged	95.55
User status								
Withdrawn	5		0.057	-0.58	0.70	0.86	Unchanged	91.78
Active use	4		0.545	-0.83	1.92	0.44	Unchanged	97.70
Drug subtype								
Alcohol	4		0.263	-1.04	1.57	0.69	0.67 (95%CI -0.74 to 2.09) [1]	96.52
Crack/cocaine	3		0.583	-0.06	1.23	0.07	Unchanged	85.83
Heroin	1		-1.011	-1.27	-0.75	**>0.001**	N/A	0
Methamphetamine	1		0.644	0.24	1.04	**0.002**	N/A	0
Plasma and withdrawn								
Drug subtype								
Alcohol	2		-0.668	-1.32	-0.00	**0.04**	N/A	66.34
Crack/cocaine	2		0.398	-0.38	1.17	0.31	N/A	86.46
Methamphetamine	1		0.644	0.24	1.04	**0.002**	N/A	0
Plasma and active use								
Drug subtype								
Alcohol	2		1.128	-0.73	2.99	0.23	N/A	96.41
Crack/cocaine	1		0.977	0.48	1.47	**>0.001**	N/A	0
Heroin	1		-1.015	-1.27	-0.75	**>0.001**	N/A	0

Table 4. Meta-regression of potential moderators brain-derived neurotrophic factor (BDNF) in substance use disorders

Moderator	N subgroups	β	95%CI		P value	R^2
User status						
Active use						
% of males	20	-0.013	-0.03	0.00	0.19	0.00
Mean age	20	-0.004	-0.06	0.05	0.87	0.06
Years of use	9	-0.021	-0.13	0.08	0.63	0.15
Age of the first use	9	0.134	-0.17	0.44	0.38	0.26
Length of abstinence	N/A					
Withdraw						
% of males	20	-0.153	-0.02	-0.00	**0.01**	0.16
Mean age	20	-0.033	-0.09	0.02	0.28	0.03
Years of use	13	-0.025	-0.09	0.04	0.47	0.13
Age of the first use	10	0.058	-0.12	0.23	0.52	0.21
Length of abstinence	10	-0.441	-0.64	0.75	0.46	0.13
Sample						
Serum						
% of males	38	-0.029	-0.04	-0.01	**0.0008**	0.07
Mean age	38	-0.049	-0.91	-0.00	**0.02**	0.02
Years of use	20	-0.064	-0.12	-0.00	**0.04**	0.03
Age of the first use	19	0.013	-0.18	0.21	0.88	0.06
Length of abstinence	15	-0.864	-1.71	-0.02	**0.04**	0.10
Plasma						
% of males	9	-0.005	-0.02	0.01	0.56	0.01
Mean age	9	-0.001	-0.09	0.07	0.81	0.00
Years of use	8	0.041	-0.09	0.18	0.55	0.07
Age of the first use	6	0.021	-0.23	0.27	0.86	0.00
Length of abstinence	4	0.916	-0.81	2.65	0.30	0.04

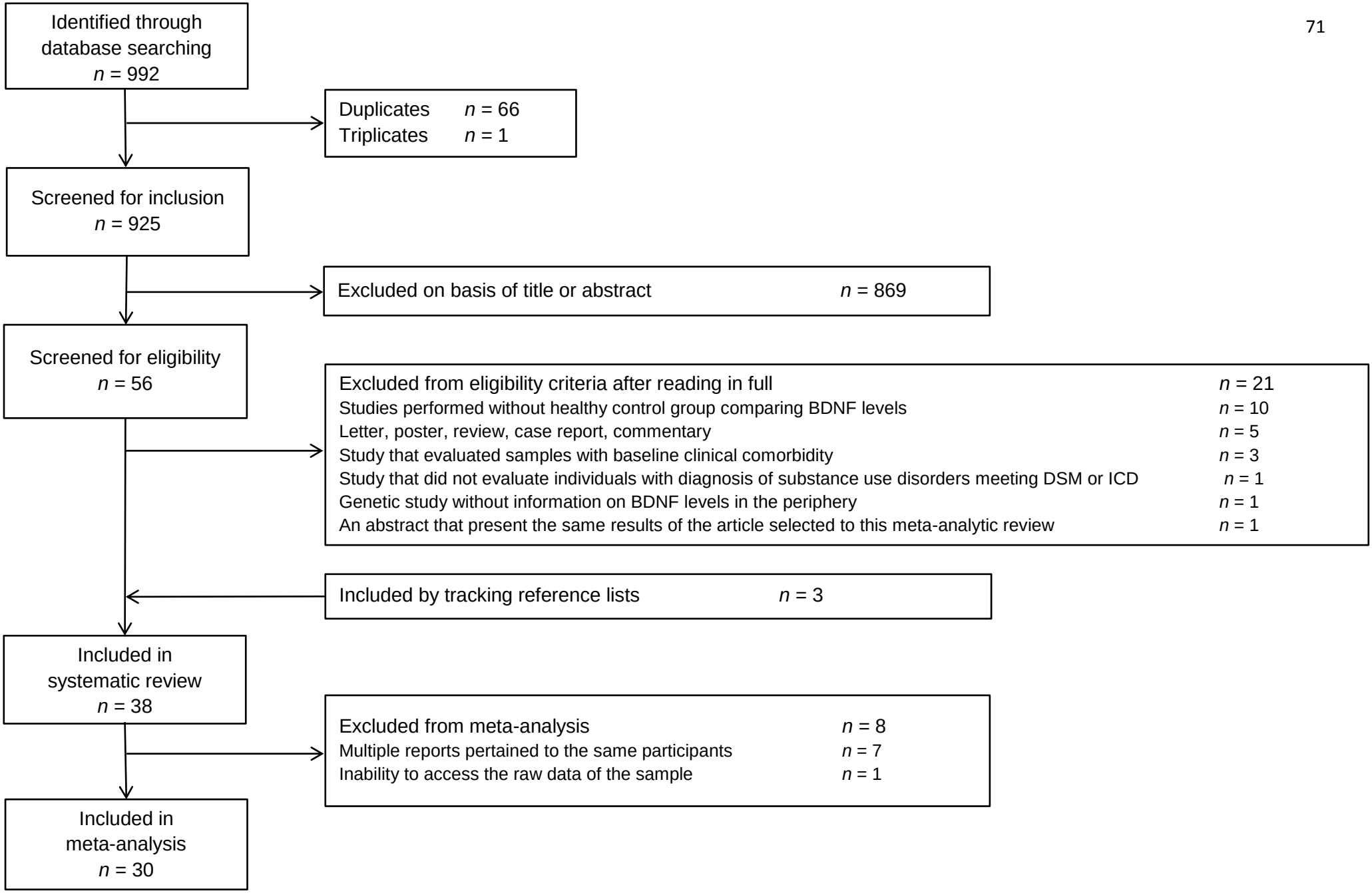


Figure 1. Flow diagram of the meta-analysis of brain-derived neurotrophic factor (BDNF) in substance use disorders.

Group by dosage	Study name	Statistics for each study: Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Plasma	Chen, SL	-1,015	0,132	-1,275	-0,756	0,000
Plasma	D'Sa, C (1)	-0,256	0,355	-0,952	0,439	0,470
Plasma	Joe, KH	-0,942	0,179	-1,293	-0,590	0,000
Plasma	Kim, DJ	0,644	0,205	0,242	1,046	0,002
Plasma	Pedraz, M	0,025	0,152	-0,272	0,322	0,870
Plasma	Viola, TW (2) (withdrawn)	0,822	0,251	0,330	1,314	0,001
Plasma	Viola, TW (2)	0,977	0,253	0,480	1,474	0,000
Plasma	Lee, BC	2,084	0,274	1,546	2,621	0,000
Plasma	Zanardini, R	0,184	0,233	-0,273	0,640	0,431
Plasma		0,269	0,314	-0,357	0,904	0,393
Serum	Angelucci, F (3)	-0,838	0,381	-1,584	-0,091	0,028
Serum	Angelucci, F (4)	1,011	0,316	0,392	1,629	0,001
Serum	Angelucci, F (1)	5,723	0,697	4,357	7,090	0,000
Serum	Angelucci, F (2) (heroin)	-0,838	0,381	-1,584	-0,091	0,028
Serum	Angelucci, F (2)	-0,461	0,370	-1,186	0,264	0,213
Serum	Cavus, SY (withdrawn)	-2,498	0,345	-3,173	-1,822	0,000
Serum	Cavus, SY	-0,706	0,266	-1,228	-0,184	0,008
Serum	Corominas-Roso, M (1)	-0,852	0,265	-1,373	-0,332	0,001
Serum	Corominas-Roso, M (1) (withdrawn)	-0,518	0,259	-1,026	-0,010	0,046
Serum	Costa, MA (withdrawn)	0,945	0,232	0,491	1,400	0,000
Serum	Costa, MA	-0,168	0,189	-0,538	0,202	0,375
Serum	D'Sa, C (1)	0,813	0,368	0,092	1,534	0,027
Serum	D'Sa, C. (2)	1,127	0,259	0,619	1,635	0,000
Serum	D'Souza, DC	-0,381	0,431	-1,226	0,463	0,376
Serum	Geisel, O	-0,206	0,369	-0,929	0,518	0,578
Serum	Heberlein, A (1) (withdrawn)	0,064	0,201	-0,330	0,458	0,749
Serum	Heberlein, A (1)	0,052	0,201	-0,342	0,446	0,795
Serum	Heberlein, A (2)	1,052	0,310	0,445	1,660	0,001
Serum	Huang, MC (2) (with DT) (withdrawn)	-1,286	0,280	-1,836	-0,737	0,000
Serum	Huang, MC (2) (with DT)	-2,140	0,318	-2,764	-1,515	0,000
Serum	Huang, MC (2) (withdrawn)	-0,338	0,227	-0,783	0,106	0,135
Serum	Huang, MC (2)	-0,617	0,230	-1,068	-0,166	0,007
Serum	Ke, X	-0,748	0,196	-1,133	-0,364	0,000
Serum	Meng, D	0,190	0,415	-0,623	1,003	0,647
Serum	Narvaez, JM	0,441	0,200	0,050	0,832	0,027
Serum	Ren, W (withdrawn)	0,288	0,191	-0,086	0,662	0,132
Serum	Ren, W	0,492	0,131	0,235	0,749	0,000
Serum	Ricci, V	1,376	0,428	0,536	2,216	0,001
Serum	Schuster, R	-1,444	0,257	-1,946	-0,941	0,000
Serum	von Diemen, L (withdrawn)	-0,357	0,177	-0,703	-0,011	0,043
Serum	von Diemen, L	-1,015	0,185	-1,378	-0,653	0,000
Serum	Zhang, J (withdrawn)	0,516	0,198	0,128	0,904	0,009
Serum	Zhang, J	0,957	0,167	0,630	1,284	0,000
Serum	Zhang, K	-1,921	0,236	-2,384	-1,459	0,000
Serum	Zhang, K (withdrawn)	-0,861	0,206	-1,265	-0,457	0,000
Serum	Chen, PH (withdrawn)	-1,175	0,249	-1,663	-0,687	0,000
Serum	Chen, PH	-1,342	0,204	-1,741	-0,942	0,000
Serum	Zanardini, R	-0,521	0,236	-0,984	-0,058	0,028
Serum		-0,213	0,155	-0,516	0,083	0,162
Overall		-0,118	0,227	-0,301	0,151	0,388

*DT = delirium tremens

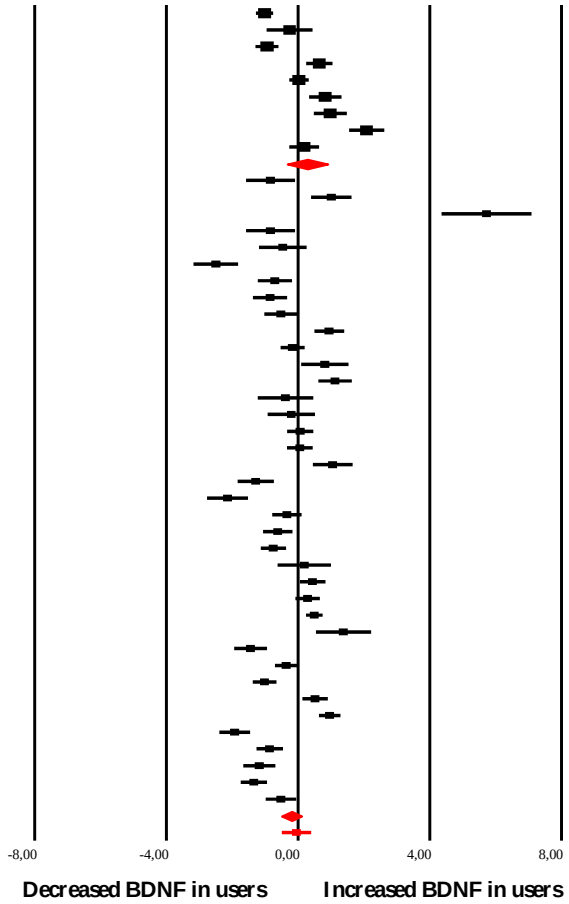
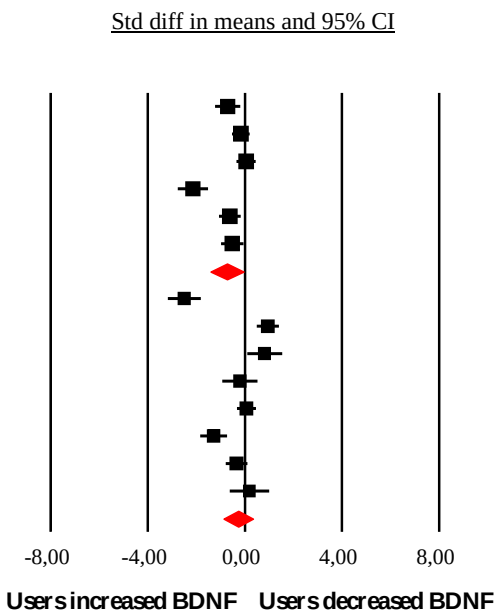


Figure 2. Overall, plasma and serum Brain-derived neurotrophic factor (BDNF) levels in substance use disorders.

Group by withdrawn	Study name	Statistics for each study: Std diff in means	Standard error	Lower limit	Upper limit	p-Value
No	Cavus, SY	-0,706	0,266	-1,228	-0,184	0,008
No	Costa, MA	-0,168	0,189	-0,538	0,202	0,375
No	Heberlein, A (1)	0,052	0,201	-0,342	0,446	0,795
No	Huang, MC (2) (with DT)	-2,140	0,318	-2,764	-1,515	0,000
No	Huang, MC (2)	-0,617	0,230	-1,068	-0,166	0,007
No	Zanardini, R (S)	-0,521	0,236	-0,984	-0,058	0,028
No		-0,649	0,348	-1,165	-0,130	0,001
Yes	Cavus, SY (withdrawn)	-2,498	0,345	-3,173	-1,822	0,000
Yes	Costa, MA (withdrawn)	0,945	0,232	0,491	1,400	0,000
Yes	D'Sa, C (1) S	0,813	0,368	0,092	1,534	0,027
Yes	Geisel, O	-0,206	0,369	-0,929	0,518	0,578
Yes	Heberlein, A (1) (withdrawn)	0,064	0,201	-0,330	0,458	0,749
Yes	Huang, MC (2) (with DT) (withdrawn)	-1,286	0,280	-1,836	-0,737	0,000
Yes	Huang, MC (2) (withdrawn)	-0,338	0,227	-0,783	0,106	0,135
Yes	Meng, D	0,190	0,415	-0,623	1,003	0,647
Yes		-0,287	0,309	-1,010	0,430	0,436



* DT = delirium tremens

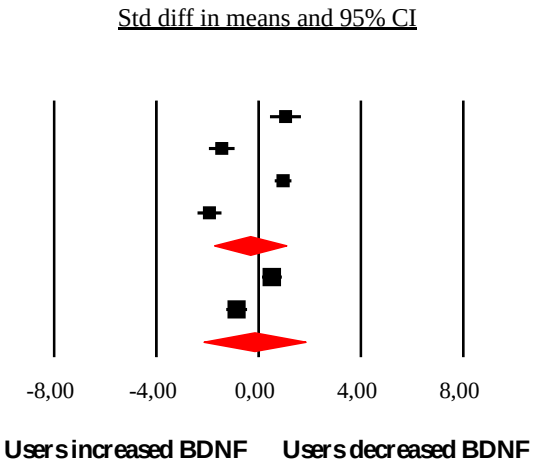
D'Sa, C (1) - Serum and plasma brain-derived neurotrophic factor (BDNF) in abstinent alcoholics and social drinkers

Heberlein, A (1) - Do changes in the BDNF promoter methylation indicate the risk of alcohol relapse?

Huang, MC (2) - Differential Patterns of Serum Brain-Derived Neurotrophic Factor Levels in Alcoholic Patients With and Without Delirium Tremens During Acute Withdrawal

Figure 3. Brain-derived neurotrophic factor (BDNF) levels from serum in alcohol users

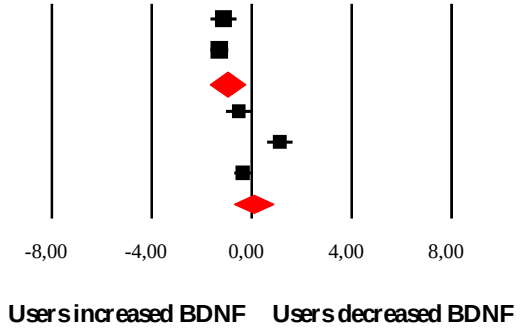
Group by withdrawn	Study name	Statistics for each study				
		Std diff in means	Standard error	Lower limit	Upper limit	p-Value
No	Heberlein, A (2)	1,052	0,310	0,445	1,660	0,001
No	Schuster, R	-1,444	0,257	-1,946	-0,941	0,000
No	Zhang, J	0,957	0,167	0,630	1,284	0,000
No	Zhang, K	-1,921	0,236	-2,384	-1,459	0,000
No		-0,340	0,720	-1,917	1,232	0,673
Yes	Zhang, J (withdrawn)	0,516	0,198	0,128	0,904	0,009
Yes	Zhang, K (withdrawn)	-0,861	0,206	-1,265	-0,457	0,000
Yes		-0,171	1,014	-1,521	1,175	0,805



Heberlein, A (2): Serum levels of BDNF are associated with craving in opiate-dependent patients

Figure 4. Brain-derived neurotrophic factor (BDNF) levels from serum in opiate users

Group by withdrawn	Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
No	Corominas-Roso, M (1)	-0,852	0,265	-1,373	-0,332	0,001
No	Von Diemen, L	-1,015	0,185	-1,378	-0,653	0,000
No		-0,962	0,487	-1,261	-0,667	0,000
Yes	Corominas-Roso, M (1) (withdrawn)	-0,518	0,259	-1,026	-0,010	0,046
Yes	D'Sa, C (2)	1,127	0,259	0,619	1,635	0,000
Yes	Von Diemen, L (withdrawn)	-0,357	0,177	-0,703	-0,011	0,043
Yes		0,076	0,399	-0,879	0,854	0,856



Corominas-Roso, M (1) - Brain-derived neurotrophic factor serum levels in cocaine-dependent patients during early abstinence

D'Sa, C (1) - Serum and plasma brain-derived neurotrophic factor (BDNF) in abstinent alcoholics and social drinkers

Figure 5. Brain-derived neurotrophic factor (BDNF) levels from serum in crack/cocaine users

Group by withdrawn	Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
No	Ren, W	0,492	0,131	0,235	0,749	0,000
No	Chen, PH	-1,342	0,204	-1,741	-0,942	0,000
No		-0,418	0,850	-2,210	1,379	0,642
Yes	Ren, W (withdrawn)	0,288	0,191	-0,086	0,662	0,132
Yes	Chen, PH (withdrawn)	-1,175	0,249	-1,663	-0,687	0,000
Yes		-0,435	0,856	-1,862	1,17	0,559

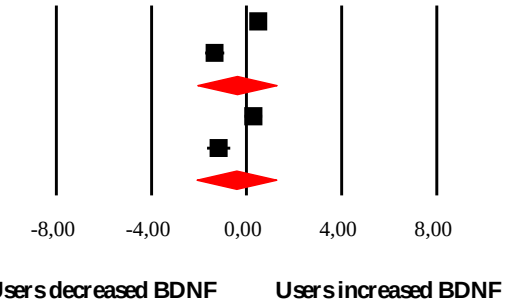


Figure 6. Brain-derived neurotrophic factor (BDNF) levels from serum in methamphetamine users.

Supplemental information 1. Quality assessment of the eligible studies using the Newcastle-Ottawa Scale.

	Selection (max. 4 stars)				Comparability (max. 2 stars)		Exposure (max. 2 stars)			Total stars (max. 8 stars)
	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Control for possible confounding factor (major and any additional ones)		Ascertainment of exposure	Equivalence in ascertainment for cases and controls	Equivalent non-response rate between groups*	
Angelucci, F (1)	✱			✱	✱	✱	✱		do not apply	**5**
Angelucci, F (2,3)	✱		✱	✱	✱	✱	✱		do not apply	**6**
Angelucci, F (4)	✱		✱	✱	✱	✱	✱		do not apply	**6**
Cavus, SY	✱	✱	✱	✱	✱	✱	✱		do not apply	**7**
Chen, PH	✱		✱		✱	✱	✱		do not apply	**5**
Chen, SL	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Corominas-Roso, M (1)	✱		✱	✱	✱	✱	✱		do not apply	**6**
Corominas-Roso, M (2)	✱		✱	✱	✱	✱	✱		do not apply	**6**
Costa, MA	✱		✱	✱	✱	✱	✱		do not apply	**6**
D'Sá, C (1)	✱	✱	✱	✱	✱	✱	✱	✱	do not apply	**8**
D'Sá, C (2)	✱	✱	✱	✱	✱	✱	✱	✱	do not apply	**8**
Han, B	✱	✱			✱	✱	✱		do not apply	**5**
Heberlein, A (1)	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Heberlein, A (2)	✱			✱	✱		✱	✱	do not apply	**5**
Heberlein, A (3)	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Heberlein, A (4)	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Huang, MC	✱		✱	✱	✱		✱	✱	do not apply	**6**
Huang, MC	✱	✱	✱	✱	✱	✱	✱	✱	do not apply	**8**
Joe, KH	✱		✱	✱	✱		✱		do not apply	**5**
Ke, X	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Kim, DJ	✱	✱	✱	✱	✱	✱	✱		do not apply	**7**
Kohler, S	✱			✱	✱	✱	✱	✱	do not apply	**6**
Lee, BC	✱		✱	✱	✱	✱	✱		do not apply	**6**
Meng, D	✱			✱	✱	✱	✱		do not apply	**5**
Narvaez, JM	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Pedraz, M	✱	✱	✱	✱	✱	✱	✱	✱	do not apply	**8**
Ren, W	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Ricci, V	✱			✱	✱	✱	✱		do not apply	**5**
Schuster, R	✱		✱	✱	✱	✱	✱		do not apply	**6**
Sordi, AO	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Viola, TW (1)	✱		✱	✱	✱	✱	✱		do not apply	**6**
Viola, TW (2)	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
von Diemen, L	✱		✱	✱	✱	✱	✱	✱	do not apply	**7**
Zanardini, R	✱			✱	✱	✱	✱	✱	do not apply	**6**
Zhang, J	✱		✱	✱	✱	✱	✱		do not apply	**6**
Zhang, K	✱		✱	✱	✱	✱	✱		do not apply	**6**

Supplemental information 2. Quality assessment of the eligible studies using the Cochrane Collaboration

	Selection Bias		**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Other Bias**
	Random sequence generation	Allocation Concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
D'Souza, DC	low	uncertain	low	low	low	uncertain	uncertain
Geisel, O	uncertain	uncertain	low	low	low	uncertain	low

4 Considerações finais

Esta é a primeira meta-análise a avaliar o BDNF periférico em indivíduos com TUS comparando com controles saudáveis. Nossos resultados indicaram que os níveis séricos de BDNF encontram-se diminuídos durante o uso ativo de substâncias psicoativas, todavia houve variações de acordo com o tipo e a classe de substância e, também, sofreu a influência do sexo, do envelhecimento, dos anos de uso de substâncias e do tempo de abstinência. Além disso, durante a abstinência não houve diferenças entre casos e controles, o que sinaliza que o BDNF, possivelmente, possa normalizar-se com interrupção do uso de SPAs, entretanto, isso pode ser afetada pela gravidade e pela cronicidade do transtorno. Também foi verificada a existência de diferenças entre os níveis séricos e plasmáticos do BDNF, talvez, devido a diferenças metodológicas de mensuração e do fato do BDNF das duas matrizes ser proveniente de locais diferentes, com meia vida distinta.

Nossos resultados corroboram a hipótese que os TUS podem ocasionar alterações neuroprogressivas que afetam, de forma persistente, a neuroplasticidade cerebral - o que parece relacionar-se ao processo de transição do uso recreativo para o a dependência. Neste sentido, o uso agudo de drogas acarretaria o aumento do BDNF; o uso continuado geraria alterações disfuncionais que, em casos mais graves, podem ser irreversíveis mesmo com a abstinência. Sabe-se que os TUS destacam-se pela baixa adesão e altos índices de recaída. Nesse sentido, a identificação de biomarcadores não invasivos, como o BDNF, pode auxiliar na compreensão fisiopatológica dos transtornos, permitindo mensurar o estado patológico e a gravidade da doença e, assim, através da proposição de intervenções mais assertivas, aumentar a adesão do tratamento e a sua efetividade.

Durante a análise dos estudos incluídos no presente trabalho, evidenciamos uma alta heterogeneidade entre os mesmos, principalmente no que se refere a diferenças amostrais e metodológicas. Logo, a realização de uma meta-análise permitiu amenizar as discrepâncias observadas, devido ao fato dessa análise combinar resultados de estudos independentes, controlar fatores de moderação e tamanhos de efeito, potencializar o poder estatístico e proporcionar a formulação de conclusões mais abrangentes.

Em isolado, nossos resultados não permitem inferir que a utilização do BDNF possa se dar na prática clínica, entretanto, funde-se com um amplo corpo de evidências que reforçam a hipótese neurodegenerativa decorrente do uso crônico de SPAS. Assim, espera-se que estes resultados, somados a estudos que investiguem a fisiopatologia dos TUS através do uso de outros potenciais biomarcadores - como o uso da neuroimagem, cortisol, NPY, análise genética, possibilitem o desenvolvimento de tratamentos mais direcionados e específicos.

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Anexo 1 – Projetos em andamento

- Preditores Clínicos, Biológicos e Psicossociais da Recaída Precoce em usuários de crack.
- Projeto cocaínas fumáveis na Argentina, Brasil, Chile, Uruguai e Paraguai. Estudo multicêntrico sobre alterações da função cerebral em usuários de crack.
- Ensaio Clínico Randomizado, Duplo-Cego, Controlado com Placebo, para Avaliar o Efeito da N-Acetilcisteína no Tratamento dos Transtornos por Uso de Álcool e Cocaína.
- Associação da intervenção de cue exposure sobre os níveis de cortisol salivar em dependentes de crack internados no Hospital De Clínicas de Porto Alegre.
- Associação entre o estado nutricional e níveis de leptina e grelina em pacientes internados em uma unidade de adição.
- Vulnerabilidade social em usuários de crack em seis capitais brasileiras
- Fatores de personalidade e emocionais entre usuários de substâncias psicoativas

Anexo 2. Artigos em desenvolvimento:

- Fator Neurotrófico Derivado Do Cérebro (Bdnf) no Transtorno por Uso de Álcool – Uma Meta-análise (título provisório)
- Fator Neurotrófico Derivado Do Cérebro (Bdnf) no Transtorno por Uso de Cocaína – Uma Meta-análise (título provisório)
- Fatores associados a variação nos níveis séricos de BDNF em usuários de crack/cocaína
- Por que é tão difícil fazer pesquisa com usuários de crack (título provisório)
- Diferenças entre nas dosagens do BDNF após 5 anos de congelamento (título provisório)

Anexo 3 – Artigos publicados durante o período do Mestrado

1. **Ornell, Felipe**; Dotta, R. M. ; Scherer, J. ; Dal Cin, V. ; Modena, S. L. ; Halpern, S. C. . Saúde e cárcere: estruturação da atenção básica à saúde no sistema prisional do Rio Grande do Sul. Sistema Penal & Violência (Online), v. 8, p. 107, 2016.

2. Scherer, Juliana N. ; Schuch, Silvia ; **Ornell, Felipe** ; Sordi, Anne ; Bristot, Giovana ; Pfaffenseller, Bianca ; Kapczinski, Flávio ; Kessler, Felix H.P. ; Fumagalli, Fabio ; Pechansky, Flavio ; von Diemen, Lisia . HIGH LEVELS OF BRAIN-DERIVED NEUROTROPHIC FACTOR ARE ASSOCIATED WITH TREATMENT ADHERENCE AMONG CRACK-COCAINE USERS. Neuroscience Letters (Print), p. 169-175, 2016.

3. Scherer, Juliana Nichterwitz ; Silvestrin, Roberta ; **Ornell, Felipe** ; Roglio, Vinícius ; Sousa, Tanara Rosangela Vieira ; von Diemen, Lisia ; Kessler, Felix Henrique Paim ; Pechansky, Flavio . Prevalence of driving under the influence of psychoactive substances and road traffic crashes among Brazilian crack-using drivers. Drug and Alcohol Dependence, p. 255-262, 2016.

4. Steckert, Amanda V. ; Comim, Clarissa M. ; Igna, Dhébora M. Dall ; Dominguini, Diogo ; Mendonça, Bruna P. ; **Ornell, Felipe** ; Colpo, Gabriela D. ; Gubert, Carolina ; Kapczinski, Flávio ; Barichello, Tatiana ; Quevedo, João ; Dal-Pizzol, Felipe . Effects of sodium butyrate on aversive memory in rats submitted to sepsis. Neuroscience Letters (Print), v. 595, p. 134-138, 2015.

Anexo 4 – Artigos submetidos durante o período do Mestrado

1. Avaliação Neuropsicológica das Funções Executivas e do Controle Inibitório nos Transtornos Por Uso de Álcool e Crack

   Autores: Fernanda Rasch Czermainski, **Felipe Ornell**, Luciano Santos Pinto Guimarães, Félix Kessler, Lísia von Diemen e Rosa Maria Martins de Almeida. Revista: Psico, submetido em janeiro de 2016.

2. Histórico de situação de rua como marcador de vulnerabilidades entre usuários de crack em seis capitais brasileiras

   Autores: Silvia C. Halpern, Juliana Nichterwitz Scherer, **Felipe Ornell,** CarlaDalbosco, Sibele Faller, Vinicius Roglio, Félix Kessler, Flavio Pechansky, Lísia Von Diemen .

   Revista: Cadernos de Saúde Pública, submetido em março de 2017.

3. Infrational Act and the inter-relationship with psychic trauma and drug abuse

   Autores: Magda Maria Rodrigues Ferreira Valadares, Laís Rodrigues Valadares, Felipe Ornell, Vinícius Serafini Roglio, Juliana Nichterwitz Scherer, Felix Henrique Paim Kessler, Silvia Chwartzmann Halpern.

   Revista: Trends in Psychology/Temas em Psicologia, 2016

4. Psychiatric disorders in aesthetic medicine: The importance of recognition of signs and symptoms

   Autores: Juliana Nichterwitz Scherer, Felipe Ornell, Joana C. M. Narvaez, Rafael Ceita Nunes

   Revista: Revista Brasileira de Cirurgia Plástica, 2017

Anexo 5 – Capítulos de livros escritos durante o período do Mestrado

1. Comorbidities Associated With the Use and Misuse of Crack Cocaine
   Autores: Narvaez, Joana; **Ornell, Felipe**; Kessler, Felix; von Diemen, Lisia; Magalhães, Pedro.
   Livro: The Neuroscience of Cocaine: Mechanisms And Tretment.
2. Brain-derived neurotrophic factor in cocaine withdrawal
   Autores: Giannotti, Giuseppe; Scherer , Juliana N; **Ornell, Felipe**; Caffino, Lucia; Fumagalli Fabio; von Diemen Lisia.
   Livro: The Neuroscience of Cocaine: Mechanisms And Tretment.

Anexo 6 – Prêmios recebidos durante o período do Mestrado

1. Melhor trabalho da categoria Iniciação Cientifica – Centro de Estudos Luís Guedes – CELG, 2016 – coorientação.
2. Destaque na categoria Psiquiatria Clínica – Centro de Estudos Luís Guedes – CELG, 2016 – coautor.
3. Prêmio Jovens Cientistas, 21st International Council on Alcohol, Drugs and Traffic Safety Conference, 2016 – Coorientação.
4. Destaque XXVIII Salão de Iniciação Científica, UFRGS, 2016 – Coorientação.
5. Destaque da 35ª Semana Científica do Hospital de Clínicas de Porto Alegre, 2015 – Coorientação