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Felipe Cesar de Almeida Claudino

Avaliação de marcadores biológicos e sua associação com desfechos clínicos em pacientes com transtornos mentais submetidos a psicoterapias baseadas em evidências

Porto Alegre
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Orientadora: Profª. Drª. Neusa Sica da Rocha

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BANCA EXAMINADORA:

_____

Prof. Dr. Eugênio Horácio Grevet
Universidade Federal do Rio Grande do Sul

_____

Profª Drª Leticia Sanguinett Czepielewski
Universidade Federal do Rio Grande do Sul

_____

Prof. Dr. Marcelo Tromka
Pontifícia Universidade Católica do Rio Grande do Sul

_____

Profª Drª Neusa Sica da Rocha – Orientadora
Universidade Federal do Rio Grande do Sul

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RESUMO

Psicoterapias baseadas em evidências são tratamentos reconhecidos para diversos transtornos psiquiátricos, como depressão, transtorno afetivo bipolar e transtornos de ansiedade. A psicoterapia, associada ou não a psicofármacos, está relacionada a desfechos clínicos favoráveis, como a remissão de sintomas e estabilização clínica. Além dos desfechos citados, há evidências de que as psicoterapias possam levar a alterações em marcadores biológicos, tais como citocinas, neurotrofinas e metabolismo cerebral. Estudar esses marcadores é uma ferramenta para entender os mecanismos fisiológicos do tratamento psicoterápico e compreender a progressão da doença na vigência dessa terapia. O objetivo desta tese é analisar três marcadores biológicos: fator neurotrófico derivado do cérebro (BDNF), interleucina-6 (IL-6) e imagem por ressonância magnética funcional (fMRI) e suas associações com a resposta ao tratamento de psicoterapias baseadas em evidências. O primeiro artigo desta tese revisou sistematicamente os níveis de BDNF em pacientes com transtornos mentais submetidos a psicoterapias individuais, antes e após o tratamento (k=8). Apesar da heterogeneidade dos estudos, os resultados são promissores nos transtornos estudados, estando o aumento dos níveis da neurotrofina associados à melhora clínica, no entanto os resultados em pacientes com diagnóstico de depressão tenham sido inconclusivos. O segundo artigo investigou um biomarcador de atividade neurológica em pacientes com diagnóstico de depressão submetidos à psicoterapia: a ressonância magnética funcional, com paradigma e em repouso, através de uma revisão sistemática (k=19). Dentre múltiplas áreas, a revisão destacou o sistema límbico na resposta à psicoterapia, área associada ao comportamento e emoções. O terceiro artigo, um estudo naturalístico, analisou 52 pacientes submetidos a uma das três seguintes modalidades de psicoterapias baseadas em evidência: terapia interpessoal, terapia cognitivo comportamental e psicoterapia de orientação analítica em relação aos desfechos de internação psiquiátrica, tentativa de suicídio, qualidade de vida, sintomas depressivos e ansiosos associados aos níveis de IL-6. Os níveis de IL-6 nessa amostra não variaram significativamente e os sintomas de depressão, ansiedade e a qualidade de vida se mantiveram estáveis, mas houve redução de tentativa de suicídio (de 48.07% dos participantes para 3.84%; p=0.003) e internações psiquiátricas no período (de 40.38% para 3.84% p=0.003). Os resultados demonstram o perfil grave dos participantes e o papel da psicoterapia associada à medicação na estabilização desses pacientes. Por fim, o quarto artigo avaliou os níveis de BDNF de um estudo longitudinal naturalístico com amostra de

47 pacientes, considerando variáveis clínicas de histórico de hospitalização psiquiátrica e tentativa de suicídio associada a uso de psicofármacos na resposta ao tratamento e o impacto nos níveis de BDNF. Os resultados mostraram que o uso de lítio está associado ao aumento dos níveis do marcador e que psicoterapias baseadas em evidência reduzem internação (B 0.439; p=0.019) e tentativa de suicídio em pacientes com histórico prévio, porém os níveis de BFNF não se alteraram significativamente na amostra analisada (p=0.855). Os achados obtidos reforçam a hipótese de que as psicoterapias baseadas em evidência podem cursar com alterações fisiológicas na melhora clínica e sintomática de pacientes com transtornos mentais, porém, a interação com biomarcadores é complexa e a literatura ainda incipiente. A expansão do conhecimento destes mecanismos, a partir dos marcadores estudados, é imprescindível para o incentivo à pesquisa e o reforço no tratamento baseado em evidências com uso de biomarcadores.

Palavras-chave: Psicoterapias baseadas em evidência, Biomarcadores, Fator Neurotrófico Derivado do Cérebro, Interleucina-6, Ressonância Magnética Funcional, Terapia Interpessoal, Terapia Cognitivo Comportamental, Psicoterapia de Orientação Analítica

ABSTRACT

Evidence-based psychotherapies are recognized treatments for a variety of psychiatric disorders, such as depression, bipolar affective disorder, and anxiety. Psychotherapy, whether associated with psychotropic drugs, is associated to favorable clinical outcomes, such as symptom remission and clinical stabilization. In addition to the outcomes, there is evidence that psychotherapies can lead to changes in biological markers, such as cytokines, neurotrophins and brain activity. The evaluation of these markers is a tool to understand the physiological mechanisms of psychotherapeutic treatment and understand the progression of the disease during this therapy. Therefore, this thesis aimed to analyze 3 biological markers: brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6) and functional magnetic resonance imaging (fMRI) and their association with response to evidence-based psychotherapies. The first article systematically reviewed BDNF levels in patients undergoing individual psychotherapies, before and after treatment with individual psychotherapy (k=8). Despite the heterogeneity of the studies, the results were promising in the disorders studied, with the increase in BDNF levels being associated with clinical improvement, although the results in patients diagnosed with depression were inconclusive. The second article investigated a biomarker of neurological activity in patients diagnosed with depression undergoing psychotherapy: functional magnetic resonance imaging, with paradigm and at rest, through a systematic review (k=19). The studies highlighted the role of the limbic system in the response to psychotherapy, an area associated with behavior and emotions, which are altered in individuals with depression. The third article analyzed 52 patients undergoing one of the following three modalities of psychotherapies: interpersonal therapy, cognitive behavioral therapy and psychodynamic psychotherapy and the outcomes of reduced psychiatric hospitalization, suicide attempt, improvement in quality of life, associated depressive and anxiety symptoms. to interlekin-6 levels. Interleukin-6 levels in this sample did not vary significantly and symptoms of depression, anxiety and quality of life remained stable, but there was a reduction in suicide attempts (from 48.07% of participants to 3.84%; p=0.003) and psychiatric hospitalizations. in the period (from 40.38% to 3.84% p=0.003). The results demonstrated the severe profile of the participants and the role of psychotherapy associated with medication in patient stabilization Finally, the fourth article evaluated the BDNF levels through a naturalistic longitudinal study with a sample of 47 patients, considering clinical variables of psychiatric hospitalization history and suicide attempt associated with the use

of psychotropic drugs in the response to treatment and the impact on BDNF levels. The results showed that lithium use is associated with increased marker levels and that the therapy reduces hospitalization (B 0.439; p=0.019) and suicide attempts, but that BFNF levels has not change significantly in the analyzed sample (p=0.855). The findings obtained reinforce the idea that evidence-based psychotherapies lead to physiological changes in the clinical and symptomatic improvement of patients with mental disorders. Knowledge of this mechanism is essential for encouraging research and strengthening evidence-based treatment using biomarkers.

Keywords: Evidence-based psychotherapy, Biomarkers, Brain-derived Neurotrophic Factor, interleukin-6, Functional Magnetic Resonance Imaging, Interpersonal Therapy, Cognitive Behavioral Therapy, Analytical Oriented Psychotherapy

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LISTA DE ABREVIATURAS E SIGLAS

APA – American Psychological Association
APAP – Automatic positive airway pressure
BA – Behavioral Activation
BAI – Beck Anxiety Inventory
BATD – Behavioral Activation Treatment for Depression
BDI– Beck Depression Inventory
BDNF –Brain-derived neurotrophic fator / Fator Neurotrófico Derivado do Cérebro
BIS-10 – Barrat Impulsiveness Scale
BOLD- Blood-oxygen-level-dependent
CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CBASP – Cognitive Behavioral Analysis System of Psychotherapy
CBT – Cognitive-Behavioral Therapy
CCMD -3 – Diagnostic Criteria for Mental Disorder in China 3
CGI-CS – Clinical Global Impression Change Scale
CI – Confidence interval
CTQ – Childhood Trauma Questionnaire
DSM V – Diagnostic and Statistical Manual of Mental Disorders / Manual Diagnóstico e Estatístico de Transtornos Mentais
ECT – Eletroconvulsoterapia
EDI – Eating Disorder Inventory
EMDR – Eye movement desensitization and reprocessing
ESS – Epworth Sleepiness Scale
ET – Exposure Therapy
FIPE – Fundo de Incentivo à Pesquisa e Eventos
fMRI – Functional magnetic resonance imaging / ressonância magnética funcional
GEE – Equações de Estimativas Generalizadas
GIR – Guided Imagery with Relaxation
HCPA – Hospital de Clínica de Porto Alegre
HDRS – Hamilton Depression Rating Scale
IL-6 – Interleucina -6
IPT – Interpersonal therapy
LIPO – Longitudinal Investigation of Psychotherapy Outcomes

M.I.N.I. – Mini International Neuropsychiatric Interview

MDD – Major Depressive Disorder

MRI – Ressonância magnética

PCL-M – PTSD Checklist-Military Version

PE – Post-exposure

POA – Psicoterapia de Orientação Analítica

PP- Psychodynamic Psychotherapy

PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses

PSSI – PTSD Symptom Scale-Interview

PTSD – Post traumatic stress disorder / Transtorno de estresse pós-traumático

QIDS-SR – Quick Inventory of Depressive Symptomatology

SCID-II – Screening Interview for Axis II Disorder

SD – Standard deviation

SF-36 – Short Form Health Survey-36

SIDES – Structured Interviews for Disorders of Extreme Stress

SPSS – Statistical Packages for the Social Sciences

STAI – State–Trait Anxiety Scale.

SUS – Sistema Único de Saúde

TCC – Terapia Cognitivo-Comportamental

TIP – Terapia Interpessoal

WHOQOL– World Health Organization Quality-of-Life Instrument

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1 - APRESENTAÇÃO

Esta tese de doutorado, intitulada “Avaliação de marcadores biológicos e associação com desfechos clínicos em pacientes com transtornos mentais submetidos a psicoterapias baseadas em evidências”, foi apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul, em 09 de fevereiro de 2022.

Dois estudos que a compõem foram realizados no ambulatório de Psicoterapia do Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA). O serviço oferece psicoterapias individuais baseadas em evidências como Psicoterapia Interpessoal, Orientação analítica e Cognitivo Comportamental a pacientes oriundos da rede básica de saúde ou de serviços do HCPA. O setor é referência na formação de terapeutas no Rio Grande do Sul faz parte da formação dos médicos residentes de Psiquiatria da instituição. Esta tese faz parte de um projeto “guarda-chuva”, denominado “Estudo longitudinal de pacientes atendidos em psicoterapias baseadas em evidência em um ambulatório especializado para transtornos mentais do SUS”, cujo objetivo é analisar longitudinalmente psicoterapias baseadas em evidências, com foco em preditores e marcadores de resposta ao tratamento, fornecendo substrato para o fortalecimento das terapias e o conhecimento sobre seus mecanismos de ação.

A motivação do estudo foi a necessidade de aumento de investimentos em estudos sobre psicoterapias que, embora sejam reconhecidamente indicadas no tratamento de diversos transtornos mentais, possuem baixos recursos para estudos no tema. O reconhecimento pela American Psychological Association sobre a necessidade de esforços no desenvolvimento de pesquisas em psicoterapias, associada ao investimento do setor de saúde, ensino e pesquisa na oferta do serviço aos usuários do Sistema Único de Saúde (SUS) demonstram a relevância do projeto. Exemplo disto foi o reconhecimento do projeto “guarda-chuva” no edital 62/2014 da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), que consistia na formação em pesquisa médica de alunos de medicina, que iniciaram o doutorado durante a graduação, estimulando a produção acadêmica e a qualificação de pesquisadores, contribuindo para o desenvolvimento científico do país.

Quanto ao perfil dos participantes, os pacientes do serviço de psicoterapia do Hospital de Clínicas de Porto Alegre apresentam características distintas do perfil dos

pacientes da maioria dos estudos na área, devido ao concomitante de psicofármacos, sintomas graves, histórico de internações psiquiátricas e tentativas de suicídio. Esse perfil representa a complexidade e realidade da saúde mental da população. A indicação de tratamento não-farmacológico associado, mesmo em casos complexos e em vigência de tratamento com psicofármacos, é fundamental e efetiva e o conhecimento dos mecanismos de ação das psicoterapias se faz ainda mais necessário. Considerando a pertinência do tema, foram realizados quatro estudos de marcadores biológicos associados a psicoterapias baseadas em evidências (duas revisões sistemáticas e dois estudos naturalísticos), avaliando-se marcador inflamatório (interleucina-6), neurobiológico (neuroimagem funcional) e atividade neurotrófica (BDNF) em estudo naturalístico e a partir de uma revisão sistemática.

O primeiro artigo consistiu em uma revisão sistemática para avaliar a atividade neurotrófica (BDFN) em pacientes com transtornos mentais submetidos a psicoterapias individuais. Os níveis de BDNF foram mensurados antes e após as psicoterapias, sendo, em sua maioria, correlacionados com a melhora clínica. Foram consultados artigos das principais bases de dados, seguindo o PRISMA (guia de revisão sistemática), considerados os seguintes termos: “transtorno mental”, “neurotrofina” e “psicoterapia”.
No segundo artigo, foi realizada uma revisão sistemática de ressonância magnética funcional (fMRI) estática e com paradigmas em pacientes com diagnóstico de depressão submetidos a psicoterapias individuais. Os achados foram correlacionados com os desfechos clínicos após as psicoterapias. Foram consultados artigos das principais bases de dados, seguindo o PRISMA (guia de revisão sistemática). Foram considerados os termos: “transtorno mental”, “ressonância magnética funcional” e “psicoterapia”.

O terceiro artigo foi realizado a partir dos dados obtidos do estudo longitudinal de psicoterapias baseadas em evidências em pacientes submetidos a psicoterapia interpessoal, cognitivo comportamental e orientação analítica no baseline e seis meses após o início do tratamento. Os desfechos primários foram a redução de internação psiquiátrica e de tentativa de suicídio, e os desfechos secundários foram a melhora de sintomas depressivos (mensurados pela Inventário de Depressão de Beck), sintomas ansiosos (Inventário de Ansiedade de Beck) e qualidade de vida (World Health Organization Instrument to Assess Quality of Life Brief Version), todos os dados correlacionados com os níveis de interleucina-6.

O quarto artigo foi realizado a partir dos dados obtidos do projeto guarda-chuva em pacientes submetidos a psicoterapias baseadas em evidências nos estágios iniciais e

seis meses após o início do tratamento. Os desfechos foram os níveis do BDNF, sintomas depressivos e impacto da terapia na internação psiquiátrica, tentativa de suicídio e uso de psicofármacos.

Essa tese está organizada na seguinte ordem: Introdução, Objetivos, Artigo 1 (publicado na Frontiers in Psychiatry), Artigo 2 (submetido no Journal of Affective Disorders), Artigo 3 (submetido na Psychotherapy Research), Artigo 4 (submetido na Psychiatry Research), Considerações finais e Anexos.

2 - INTRODUÇÃO

Transtorno mental pode ser definido como uma condição de saúde que modifica cognição, emoção e pensamento de um indivíduo, causando dificuldade no funcionamento e na realização das atividades diárias (Manderscheid et al., 2020). Os transtornos psiquiátricos são prevalentes em todo o mundo, com início na juventude, o qual impacta social e economicamente a população ((Kessler et al., 2009; Trautmann, Rehm, Wittchen, 2016). Embora prevalentes, uma minoria tem o diagnóstico adequado e a disponibilidade de oferta de tratamentos de qualidade (Wang et al., 2007; Whitley, Palmer, Gunn, 2015), o que contribui para a cronicidade da doença.

Embora haja um aumento expressivo da prevalência de transtornos mentais, sobretudo nos últimos meses em decorrência da pandemia de COVID-19, levando a um aumento global da discussão acerca da importância do diagnóstico dessas patologias, observa-se historicamente uma dificuldade de acesso ao tratamento dessas enfermidades (Demyttenaere et al., 2013; Wu et al., 2021). O manejo dos transtornos mentais evoluiu muito nas últimas décadas, destacando-se o advento da psicofarmacologia na década de 50, e, posteriormente, as terapias de neuromodulação, como eletroconvulsoterapia (ECT) e (Staudt et al., 2019), classicamente, a psicoterapia - foco deste estudo. Apesar disso, os tamanhos de efeito de psicoterapias e farmacoterapias para transtornos mentais ainda são limitados, sugerindo uma limitação de tratamento como atualmente conduzida (Leichsenring et al., 2022).

Dentre diversas definições apresentadas na literatura, a psicoterapia pode ser caracterizada como um tratamento em que o terapeuta e o paciente atuam conjuntamente, para melhorar as condições psicopatológicas, o comprometimento funcional, atitudes, pensamentos, afeto e o comportamento do paciente (Brent, Lolko, 1998). A psicoterapia é uma modalidade de tratamento exclusivo ou adjuvante em diversos transtornos mentais, como transtornos depressivos (Health Quality Ontario, 2017), de ansiedade (Bandelow, Michaelis e Wedekind, 2017), afetivo bipolar (Swartz, Swanson, 2014), de personalidade (Banyard, Behn e Delgadillo, 2021), abuso de substâncias (McHugh, Hearon e Otto, 2020), dentre outros.

Embora as evidências sustentem que tratamentos psicológicos baseados em evidências sejam eficazes, o acesso a essa modalidade de tratamento está em queda. Nas últimas décadas nos Estados Unidos, por exemplo, houve uma redução de mais de 50% de gastos com psicoterapia, seja isolada ou concomitante ao tratamento farmacológico

(Olfson, Marcus, 2010), enquanto, no mesmo período, se observou um crescimento exponencial em gastos com psicofármacos (Lindsley, 2012).

O avanço no tratamento de doenças sofreu importante impacto após a difusão da prática baseada em evidências, na década de 90 (Claridge, Fabian, 2005). O termo "baseado em evidências" foi definido por Sackett (Sackett et al., 1996) como o uso consciente, explícito e judicioso das melhores evidências atuais na tomada de decisões sobre o cuidado de pacientes individuais. Em consonância com as normativas científicas vigentes, a American Psychological Association definiu em 2005 a prática da psicologia baseada em evidências, destacando a experiência clínica, características do paciente e a pesquisa como fundamentais para bons resultados em psicoterapia. Destacou-se que, para uma melhor evidência de indicações do tratamento, são necessárias pesquisas, revisões, ensaios clínicos randomizados, estudos de eficácia e processo, pesquisa qualitativa e observação clínica em psicoterapia (APA, 2006).

Um dos principais desafios das psicoterapias baseadas em evidências está relacionado à condução de pesquisas clínicas. A população dos estudos não apresenta a complexidade de comorbidades e variabilidade clínica do mundo real, o que dificulta a generalização dos resultados (Cook et al., 2017). Além disso, é fundamental conhecer os mecanismos funcionais dos processos biológicos das psicoterapias para maior sustentação da sua eficácia (Carey et al., 2020).

Um estudo naturalístico sueco conduzido entre os anos de 2007 e 2010 avaliou desfechos de pacientes de serviços ambulatoriais em atendimento psiquiátrico submetidos a três modalidades de psicoterapias individuais: terapia cognitivo-comportamental, psicodinâmica ou integrativa, com desfechos as foram analisadas a gravidade dos sintomas, qualidade de vida e autoavaliação da saúde. Os autores destacaram o número expressivo de perda de seguimento ao longo do seguimento, de 36%. Além disso, não houve diferença nos desfechos clínicos se comparadas as três modalidades de terapia, tempo de tratamento ou diferença entre os terapeutas. Os pacientes apresentaram melhora na redução dos sintomas e recuperação clínica. (Werbart et al.,2013). Os achados do estudo incentivaram a criação deste projeto para avaliação dos desfechos em outro serviço, no contexto de saúde brasileiro.

2.1 Psicoterapias baseadas em evidência

A psicoterapia é uma modalidade de tratamento adjuvante ou isolada empregada

amplamente em saúde mental, sendo sua eficácia comparada ao de psicofármacos em diversos transtornos (APA, 2006).

Uma metanálise de 2014 envolvendo mais de 137 mil participantes comparou o efeito da farmacoterapia e da psicoterapia em pacientes com diagnóstico de transtornos mentais. Os resultados mostraram que não havia diferenças consistentes na eficácia dos tratamentos com medicações ou psicoterapias nos estudos analisados. Além disso, os autores destacaram que há necessidade de investimento público para maior compreensão e comparação dos efeitos desses tratamentos (Huhn et al., 2014). Por fim, refletem que o benefício maior aos pacientes é a associação dessas modalidades terapêuticas.

Com o avanço das terapias baseadas em evidência e o crescente aumento de diferentes técnicas de psicoterapia, a American Psychological Association (APA) criou em 2006 uma política para as diretrizes de psicoterapias baseadas em evidências, definida como integração das pesquisas disponíveis na área de psicoterapia, a experiência clínica, a cultura e, por fim, as preferências do paciente (19). O resumo destes pilares está descrito na tabela 1.

Tabela 1 - Políticas e definições de Psicoterapias baseadas em evidências (APA,2006-adaptado)

Políticas	Definição
Melhor evidência de pesquisa	Resultados científicos das estratégias de intervenção, avaliação e problemas clínicos.
Prática clínica	Relacionados às competências que geram resultados terapêuticos positivos, que envolvem aspectos como avaliações clínicas, tomadas de decisões, conhecimentos interpessoais, competências profissionais, utilização de evidência de pesquisas científicas, compreensão da influência das diferenças individuais, busca de recursos e estratégias clínicas.
Características, valores e contexto do paciente	Consideração das características do paciente, tais como variações clínicas dos transtornos, estágios da vida, fatores socioculturais e familiares, contexto ambiental, preferências e valores.
Implicações clínicas	Tomada de decisões em colaboração com o paciente, o monitoramento do progresso e ajustes ao tratamento.

Um dos principais desafios das psicoterapias baseadas em evidências é conhecer os mecanismos de atuação das intervenções, as diretrizes clínicas que necessitam ser desenvolvidas e disseminadas, a mensuração da qualidade de intervenção e metodologias bem definidas para sistematização e implementação de intervenções baseadas em evidências (The National Academies Press, 2015), o que reforça a necessidade de investimento e pesquisa na área.

Com o objetivo de compreender a ação das psicoterapias nos diferentes diagnósticos de transtornos psiquiátricos, há uma linha de pesquisa direcionada aos mecanismos funcionais dos processos das psicoterapias a partir de marcadores biológicos.

2.2 – Psiconeuroimunologia - teoria inflamatória e neurotrófica da depressão

A fisiopatologia da depressão é complexa. Dentre as teorias que procuram explicar a origem, manutenção, piora e remissão dos sintomas dessa patologia, estão a teoria inflamatória e neurotrófica.

No papel inflamatório da depressão, as citocinas inflamatórias estão alteradas na depressão aguda, associadas à resistência ao tratamento monoaminérgico. Citocina, como a IL-6, atua em vários tecidos-alvo diferentes em todo o corpo, podendo precipitar uma infinidade de eventos relevantes para a depressão e bloquear seus efeitos pode evitar uma maior escalada de respostas inflamatórias (Roohi, Jaafari e Hashemian., 2021) Moduladores de citocinas, por outro lado, apresentam potencial de cura da depressão em pacientes cronicamente inflamados (Kappelmann et al., 2018). Embora um nexo de causalidade ainda não tenha sido estabelecido, há evidências, pacientes com depressão apresentam aumento níveis de citocinas pró-inflamatórias, mas os resultados conflitantes tenham sido descritos. (Marques, Cizza e Sternberg, 2007).

O fator neurotrófico derivado do cérebro, assim como as citocinas, apresenta papel importante na fisiopatologia e tratamento da depressão. Há evidências dos efeitos opostos do estresse e do tratamento antidepressivo nos níveis de BDNF em áreas corticais e subcorticais cerebrais. A redução do BDNF evocada pelo estresse está implicada na atrofia dendrítica, declínio na neurogênese hipocampal, e comportamento tipo depressivo. O efeito antidepressivo do BDNF está implicado na remissão da atrofia neuronal e do declínio neurogênico (Chiou Y-J eHuang, 2019).

Considerando o papel inflamatório e da degeneração neuronal em determinadas regiões cerebrais, o uso de marcadores como citocinas, neurotrofinas e neuroimagem se

mostram potenciais marcadores do transtorno depressivo e sua remissão após tratamento.

3 - REVISÃO BIBLIOGRÁFICA DA LITERATURA

3.1 Marcadores biológicos em psicoterapias

Em 1994, Schussler (Schussler, 2004) destacou que as abordagens para o conhecimento da psicoterapêutica derivada de dados neurobiológicos em psicoterapia eram escassas, mas fundamentais para o avanço no tratamento de transtornos mentais. Nos últimos anos, observou-se crescimento nos estudos de marcadores biológicos neste processo.

Transtornos mentais, como a depressão, estão intimamente relacionados com comorbidades como doenças cardiovasculares, diabetes, doenças neurológicas e inflamatórias (Cristea et al., 2019). A utilização de marcadores biológicos, inicialmente utilizados para o diagnóstico e acompanhamento dessas patologias, começaram também a ser utilizados nos estudos dos processos fisiopatológicos dos transtornos mentais e no seu tratamento, como hemoglobina glicada (Doering et al., 2007), citocinas inflamatórias (O'Toole et al., 2018), cortisol (Fischer, Cleare, 2017), neurotrofinas (Lester et al., 2012), eletroencefalograma (Unterrainer, Chen e Gruzelier, 2014), ocitocina (Zilcha-Mano et al., 2020) exames de neuroimagem (Chakrabarty, Ogrodniczuk e Hadjipavlou, 2016), entre outros.

Biomarcadores são definidos como indicadores de processo biológico normal, processo patogênico ou respostas a uma intervenção (FDA-NIH,2016). Têm sido empregados em complemento ao diagnóstico de doenças e tratamentos oncológicos, cardiovasculares, genéticos, imunológicos e psiquiátricos (Hulka, Griffith, Wilcosky, 1990). Na psiquiatria, podem ajudar a elucidar a etiologia dos mecanismos funcionais dos mecanismos de ação das psicoterapias, permitindo uma escolha de modalidade mais precisa, juntamente com a compreensão sobre os processos envolvidos no seu tratamento, seja como preditor ou marcador de resposta à terapia.

3.1.1 Fator neurotrófico derivado do cérebro (BDNF)

Neurotrofinas são peptídeos responsáveis pela sobrevivência, desenvolvimento, função e plasticidade neural (Lewin, Barde, 1996). Também estão relacionadas com a fisiopatologia e mecanismos de ação dos tratamentos farmacológicos e psicológicos (Castrén, 2014). Dentre as neurotrofinas conhecidas até o presente momento, uma das

mais estudadas é o fator neurotrófico derivado do cérebro (BDNF), presente no sistema nervoso central, é capaz de atravessar a barreira hematoencefálica, o que permite estimar seus níveis a partir de amostras de sangue periférico (Sanchez et al., 2011).

Os níveis de BDNF estão alterados em diversos transtosnos mentais, como transtornos de ansiedade (Suliman, Hemmings e Seedat, 2013), depressivos (Yu, Chen, 2011) e alimentares (Hashimoto et al., 2005). Seus níveis apresentam variações após farmacoterapia e psicoterapia (Emon et al., 2020), estando associados a melhora clínica.

Esta neutrofina possui um precursor chamado de pré-próBDNF, convertido em pro-BDNF e, por fim, convertido em BDNF (Autry, Monteggia, 2012). O BDNF atua quando se conecta ao receptor TrkB, que é abundante no hipocampo, desencadeando cascatas de fosforilação e sinalizações, que vão atuar em neurônios hipocampais (Phillips et al., 2014). O hipocampo faz parte do lobo límbico, importante na aprendizagem, memória e comportamento emocional (Anand, Dhikav, 2012). Estudos de neuroimagem, por exemplo, demonstram aumento do volume do hipocampo e aumento da sua atividade funcional após terapia cognitivo comportamental (Moustafa, 2013; Chalah, Ayache, 2018).

A ativação do hipocampo e de outras regiões cerebrais em pacientes com transtornos mentais submetidos a psicoterapias desencadeia o aumento do BDNF. Uma vez que os níveis periféricos de BDNF representam a concentração no sistema nervoso central (Klein et al., 2011) esta neurotrofina representa um potencial marcador biológico de resposta à psicoterapia. Apesar disso, antes da realização desta tese, não identificamos na literatura uma revisão sistemática avaliando os níveis de BDNF pré e pós-psicoterapias em pacientes com diagnósticos de transtornos mentais. O esquema de modulação dos níveis de BDNF em função de estressores e impactos no humor, cognição e afeto estão ilustrados na figura 1.

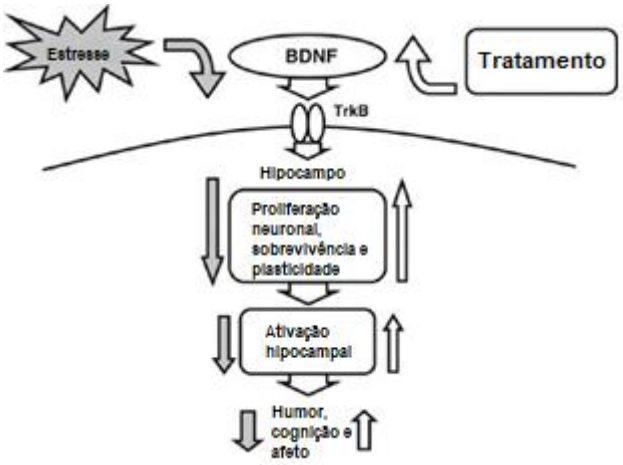

Figura 1 – Mecanismo da fisiologia do BDNF na psicoterapia (Groves, 2007)

3.1.2 Interleucina-6

A interleucina é uma citocina responsável pela ativação e diferenciação de células imunes, apresentando propriedades pró-inflamatórias e anti-inflamatórias (Justiz, Qurie, 2021). Embora o papel das interleucinas como a IL-6 seja bem conhecido na fisiopatologia de doenças autoimunes como a artrite reumatoide (Srirangan, Choy, 2010), osteoartrite (Shimura et al., 2017) e esclerose múltipla (Koutsouraki et al., 2011), sabe-se também que as interleucina-6 tem ações na fisiologia do sistema nervoso central, com alteração da sua expressão em doenças neurodegenerativas como Alzheimer e Parkinson (Spooren et al., 2011).

Associado ao padrão inflamatório nas doenças autoimunes, observou-se nesses quadros a presença de sintomas depressivos, levando à teoria de que o componente inflamatório pudesse estar envolvido na fisiopatologia desse transtorno mental (Ratnayake et al., 201). Em situações de estresse, que podem desencadear transtornos como ansiedade e depressão, ocorre aumento dos níveis de IL-6, levando a disfunção do eixo hipotálamo-hipófise-adrenal, causando alterações na neurotransmissão sináptica e redução de fatores neurotróficos, como BDNF e aumento dos níveis de interleucinas (Ting, Yang e Tsai, 2020), conforme ilustrado na figura 2.

Revisão sistemática avaliou efeito da terapia cognitivo comportamental nos níveis de citocinas pró-inflamatórias em pacientes com depressão maior, demonstrando redução dos níveis séricos de IL-6 após a intervenção (Lopresti, 2017), embora outros estudos não tenham demonstrado alteração nos níveis desta citocina (Moreira, Cardoso e Mondin, 2015; Keri, Szabo, Kelemen, 2014)

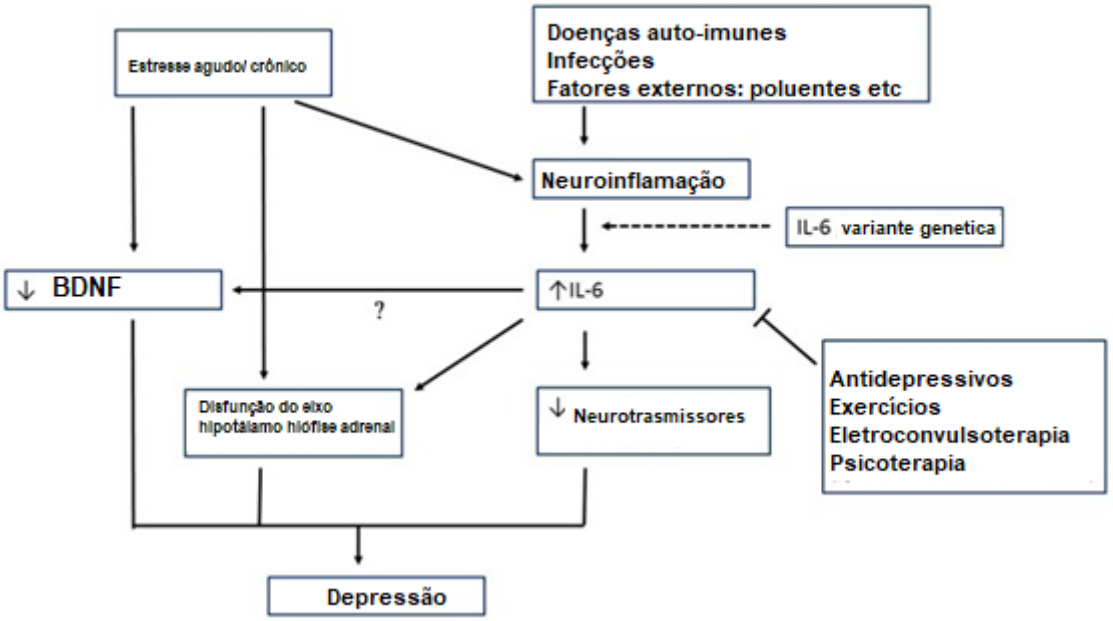

Figura 2- Papel da interleucina no tratamento de depressão (Ting, 2020)

Estudo que analisou tratamento experimental com Tocilizumab, que atua bloqueando a via de sinalização da interleucina-6 não resultou em redução de sintomas depressivos e sim no aumento dos sintomas, indicando a complexidade do envolvimento dessa interleucina nos transtornos mentais (Knight et al.,2021).

Embora se espere uma relação antagônica dos níveis de BDNF e de interleucina-6 em resposta ao tratamento psicoterápico, estudos demonstram que não há, necessariamente, correlação entre esses fatores, podendo os níveis de BDNF se elevarem após o tratamento, enquanto os níveis de IL-6 se mantêm estáveis (Patas et al., 2014), o que pode ser explicado pela ação anti-inflamatória da interleucina ou seu potencial como marcador inflamatório em fase aguda (Tanaka, Narazaki, Kishimoto,2014).

3.1.3 RESSONÂNCIA MAGNÉTICA FUNCIONAL

A ressonância magnética funcional é um método de imagem que avalia mudanças regionais e variações no metabolismo cerebral, a partir da concentração da desoxihemoglobina. As alterações do nível de oxigênio no sangue (BOLD) podem ser analisados quando o indivíduo se encontra em repouso (resting-state) ou quando executa

alguma atividade (paradigma) (Glover, 2011).

O método de análise do estado de repouso ou em atividade possui diferentes metodologias. Os modelos vão desde interação psicofisiológica, quando áreas cerebrais apresentam variação a depender da atividade executada até a estimativa de correlação das áreas de interesse previamente definidas. Um resumo esquemático dos métodos empregados na análise de fMRI em paradigma ou repouso está apresentado na figura 3.

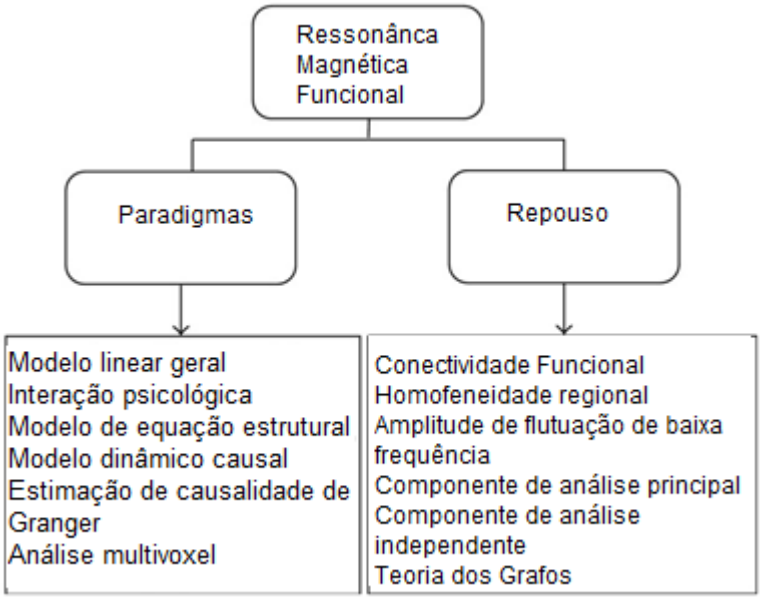

Figura 3 – Métodos de imagem de fMRI (Zhan, Yu, 2015)

Cada vez mais a ressonância magnética funcional tem sido utilizada para monitorização, diagnóstico e acompanhamento de resposta a tratamento. É possível, por exemplo, comparar a diferença de ativação de determinadas regiões cerebrais entre indivíduos saudáveis e aquele com transtornos mentais (Zhan, Yu, 2015), permitindo uma maior compreensão da fisiopatologia e sintomas relacionados aos diferentes transtornos.

Seu uso no entendimento de transtornos mentais na área de neuropsiquiatria tem se mostrado promissor. Meta-análise de 2017 de estudos de reavaliação cognitiva utilizando fMRI em pacientes com transtornos de humor ou ansiedade demonstrou ativação em regiões relacionadas à experiência emocional e mecanismos compensatórios, estratégias de regulação da emoção de reinterpretação e estratégias de distanciamento, permitindo maior compreensão acerca da reavaliação cognitiva nessas patologias (Picó-Pérez et al., 2017).

O exame de neuroimagem como biomarcador em transtornos psiquiátricos também se mostra promissor, avaliando atividade em regiões cerebrais ou conectividade entre áreas do cérebro para suscetibilidade à psicose (Andreou, Borgwardt, 2020) depressão ansiosa (Andreescu et al., 2009), diagnóstico e prognóstico em transtorno afetivo bipolar (Houenou et al., 2012), entre outros.

Assim como biomarcador de transtornos psiquiátricos a ressonância magnética funcional tem potencial como marcador no tratamento de transtornos mentais, especialmente de psicoterapias. Revisão sistemática de 2018 avaliou mecanismos neurais e preditores de resposta à psicoterapia em pacientes com depressão e ansiedade, diminuição da ativação nas regiões límbicas (Marwood et al., 2018). Apesar disso, a utilização do exame de neuroimagem como marcador de resposta à psicoterapia em depressão permanece no campo de pesquisa, sendo fundamental mais estudos para ampliação do conhecimento na área.

4 - JUSTIFICATIVA

As psicoterapias baseadas em evidência são uma modalidade de tratamento indicada para diversos transtornos mentais e seus desfechos clínicos têm sido relacionados com alterações em marcadores biológicos. Existe uma lacuna na literatura no que tange à compreensão dos mecanismos neurobiológicos da ação das psicoterapias para corroborar a efetividade desta prática, contribuindo para a redução em investimento nesse tipo de intervenção. Além disso, os estudos que correlacionam diferentes variáveis nessa modalidade terapêutica ainda são escassos, se comparado aos estudos farmacológicos, o que compromete o conhecimento sobre seus mecanismos de ação e maior recomendação desta modalidade terapêutica. Portanto, é fundamental aprofundar a análise de marcadores reconhecidamente associados aos referidos transtornos e avaliar criticamente como seu potencial indicador de resposta ao tratamento.

5 - OBJETIVOS

5.1 OBJETIVO GERAL

Estudar os marcadores biológicos: BDNF, Interleucina-6 e neuroimagem: ressonância magnética funcional (fMRI) em pacientes com transtornos mentais submetidos a psicoterapias individuais.

5.2 OBJETIVOS ESPECÍFICOS

5.2.1 - Objetivo 1

Revisar sistematicamente a literatura no que tange aos níveis de BDNF antes e após psicoterapias baseadas em evidências e a relação com desfechos sintomáticos em pacientes com diagnóstico de transtornos mentais através de uma revisão sistemática da literatura (artigo #1)

5.2.2 - Objetivo 2

Revisar sistematicamente a literatura no que se refere às alterações funcionais avaliadas por fMRI em pacientes com diagnóstico de depressão submetidos a psicoterapias baseadas em evidências através de uma revisão sistemática da literatura (artigo #2);

5.2.3 - Objetivo 3

Investigar alterações nos níveis de interleucina-6 em pacientes com transtornos mentais submetidos a psicoterapias individuais e a relação com desfechos clínicos e sintomáticos, especialmente quanto ao número de internações psiquiátricas prévias e tentativa de suicídio a partir de um estudo naturalístico (artigo #3);

5.2.4 - Objetivo 4

Investigar alterações nos níveis de BDNF em pacientes com transtornos mentais submetidos a psicoterapias baseadas em evidência e a relação com desfechos sintomáticos, especialmente quanto ao número de internações psiquiátricas prévias, tentativa de suicídio e efeitos de psicofármacos nos níveis da neurotrofina em um estudo naturalístico (artigo #4).

6 - METODOLOGIA

Para os artigos 1 e 2 foram realizadas revisões sistemáticas, com busca nas principais bases de dados: PubMed, EMBASE, PsycArticles, SciELO, Web of Science, and CENTRAL, e protocolo publicado previamente no PROSPERO (CRD42018108144 e CRD42020169652).

Os dados dos artigos 3 e 4 foram obtidos a partir do projeto guarda-chuva, denominado LIPO (Longitudinal Investigation of Psychotherapy Outcomes) (Gonçalves et al., 2019), com pacientes submetidos a psicoterapias individuais no serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre. O projeto previa seguimento por 6 meses, com pacientes maiores de 18 anos, diagnóstico de transtorno mental, submetidos a psicoterapias individuais no Ambulatório de Psicoterapia do Hospital de Clínicas de Porto Alegre (HCPA), Rio Grande do Sul, Brasil, entre os anos de julho de 2016 a agosto de 2019.

Os pacientes com indicação de psicoterapia foram avaliados por médico residente, com a aprovação de um preceptor e após, encaminhados para um dos seguintes três tipos de psicoterapias individuais: psicoterapia psicodinâmica, terapia cognitivo-comportamental (TCC) e terapia interpessoal. A terapia era realizada por médicos residentes do serviço de psiquiatria do HCPA, sob supervisão, dentro da instituição. O grupo de pesquisa não influenciou na escolha da terapia e não houve exclusão por diagnóstico de transtorno mental para adesão à pesquisa.

Os critérios de inclusão e exclusão das psicoterapias estão detalhados nas metodologias dos artigos 3 e 4. Os instrumentos e análises estatísticas de cada estudo estão detalhados em cada um dos estudos, na sessão de metodologia. As amostras coletadas foram computadas através dos questionários de qualidade de vida, sintomas depressivos e ansiosos para correlação com a interleucina-6 e sintomas depressivos para mensurar os níveis de BDNF, conforme figura 4.

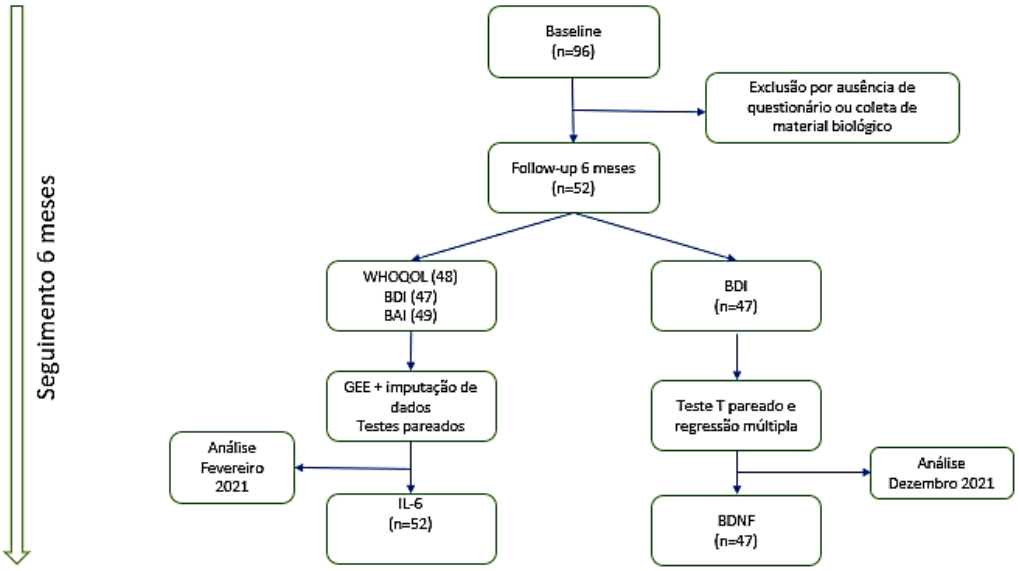

Figura 4 – Coleta de dados e estratificação de análise de BDNF e IL-6

6.1 Aspectos éticos

O projeto faz parte de do projeto guarda-chuva intitulado ‘Estudo longitudinal de pacientes atendidos em psicoterapias baseadas em evidência em um ambulatório especializado para transtornos mentais do SUS´, aprovado pelo cujo Comitê de Ética e registrado sob o número 15-0097. As revisões sistemáticas, por utilizarem dados de artigos já publicados, não necessitaram de aprovação pelo Comitê de Ética.

7 - ARTIGOS

7.1 – ARTIGO 1

Publicado na Frontiers Psychiatry
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The Effects of Individual Psychotherapy in BDNF Levels of Patients With Mental Disorders: A Systematic Review

Felipe Cesar de Almeida Claudino [1] , * Leonardo Gonçalves, [1] Felipe Barreto Schuch, [2] Hugo Roberto Sampaio Martins, [3] Neusa Sica da Rocha [1]

[1] Center of Clinical Research and Center of Experiamental Research, Hospital de Clínicas de Porto Alegre (HCPA), Post-Graduation Program in Psychiatry and Behavioral Sciences, Federal University of Rio Grande do SUl (UFRGS), Porto Alegre, Brazil,

[2] Department of Sports Methods and Techniques, Federal University of Santa Maria (UFSM), Santa Maria, Brazil,

[3] Department of Internal Medicine, Federal University of Health Sciences of Porto Alegre (UFCSPA), Porto Alegre, Brazil,

Edited by: Takeshi Terao, Oita University, Japan

Reviewed by: Kenji Hashimoto, Chiba University, Japan; Reiji Yoshimura, University of Occupational and Environmental Health Japan, Japan

*Correspondence: Felipe Cesar de Almeida Claudino: felipeaclaudino@gmail.com

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Abstract

Background: Brain-derived Neurotrophic Factor (BDNF) is considered the main cerebral neurotrophin and is produced in the central neural system and peripherals. Its levels are reduced in patients with several psychiatric disorders, but it is unclear if the response to psychotherapy can alter its concentration.

Objective: To carry out a systematic review evaluating the effects of individual psychotherapy in BDNF levels in patients with mental disorders.

Methods: The databases PubMed, EMBASE, PsycArticles, SciELO, Web of Science, and CENTRAL; the last search was performed on October 2019 for trials evaluating the effects of individual psychotherapy in BDNF levels in adults with mental disorders. PROSPERO registration: CRD42018108144.

Results: Eight of 293 studies were included. A rise in BDNF levels was observed in depressive patients when psychotherapy was combined with medication. Patients with

post-traumatic stress disorder (PTSD) who responded to therapy presented a raise in BDNF levels mostly when combined with physical activity. There was a rise in BDNF levels in those who responded to psychotherapy in patients with bulimia, in borderline patients, and in insomniacs.

Conclusions: The BDNF seems to present variations after psychotherapy especially in patients with bulimia, PTSD, insomnia, and borderline. These subjects also have symptom reduction. Thereby, BDNF could be a supplemental tool to analyze the success to psychotherapy. BDNF levels in patients with major depression after therapy are still controversial and the short follow-up of most studies is a limiting factor.

Keywords: psychotherapy, brain derived neurotrophic factor, BDNF, mental disorders, systematic review

Introduction

Psychotherapy is a well-grounded treatment for mental disorders with outcomes similar to pharmacotherapy (1). Psychotherapeutic interventions consist of exposure to stimuli, content resignification, and behavioral changes via interpersonal interaction (2). It acts on cognition and leads to symptoms remission, the formation of new neural networks, and can consequently lead to changes in demeanor (3). The neurotrophins are peptides in the central nervous system, and the most abundant is brain-derived neurotrophic factor (BDNF) (4), which stands out among the responsible factors in the formation of new neural networks that result in improved symptomatology.

BDNF is a neurotrophin that is more concentrated in certain regions of the brain such as the pre-frontal cortex and the hippocampus (5)—regions where complex cognitive processes occur including memory, personality, and emotional control. Therefore, psychotherapy stimulates these areas (6) reflecting on psychological symptom remission and resulting in a rise in BDNF levels.

Peripheral BDNF concentrations are lower in people with neuropsychiatric and neurodegenerative diseases (7, 8) versus matched controls. There is also signaling interference of this peptide in limbic areas related to emotion such as the hippocampus (9) that may contribute to the maintenance of the diseases.

BDNF levels also rise after antidepressant treatment, and increase in BDNF are associated with symptom improvements (10, 11); thus, it might be a potential mediator of the antidepressant treatment (12). Beyond pharmacological treatment, it is possible to observe increases in this neurotrophin's levels via electroconvulsive therapy (13) and physical activity (14) concurrent to the remission of psychological symptoms. Previous

reviews of psychotherapies showed few potential response biomarkers for this treatment in patients diagnosed with PTSD such as the 5-alfa-reductase, heart rate changes (15), glucocorticoid metabolism, gene methylation, (16) and structural brain changes (17).

Despite the promising effects of psychotherapy response biomarkers, there is no systematic review evaluating the effects of individual psychotherapy in BDNF levels. Therefore, the objectives of this study are to: 1) evaluate if there are any changes in BDNF levels in people with mental disorders following individual psychotherapy and 2) evaluate if these changes are associated with symptom improvement.

Methods

Study Eligibility

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18). The protocol was registered on PROSPERO: CRD42018108144.

Inclusion Criteria

The study population defined: patients over 18 years old, both genders, previously diagnosed with psychiatric disorders and/or mental disorders by qualified professionals and with its pathology described in the Diagnostic and Statistical Manual of Mental Disorders (DSM V).

The interventions of interest for the study: in-person individual psychotherapy: cognitive behavioral therapy, psychoanalysis, eye movement desensitization and reprocessing (EMDR), dialectical behavior therapy, interpersonal psychotherapy, analytically-oriented psychotherapy, and acceptance/commitment therapy, without limit of sessions or length of treatment.

Control groups defined: patients with no mental disorders or patients with psychiatric disorders submitted to other comparative treatments that are not psychotherapy, such as physical activity, meditation, and electroconvulsotherapy.

For the outcome, BDNF levels and disorder symptoms (according to symptom scales) were measured at two different times before and after psychotherapy exposure. Only serum or plasma BDNF levels were considered.

We included longitudinal randomized or non-randomized clinical trials as well as prospective and retrospective cohort studies; there was no language restriction, and any

year of publication was considered including studies in progress.

Exclusion Criteria

Patients undergoing only group therapy, online therapy, those without pre and post intervention BDNF serum or plasma levels, and patients who did not have their symptoms evaluated pre and post intervention were not included. Cross-sectional or case reports were not considered.

Search Strategy and Study Selection

The titles and/or abstracts were obtained by two independent evaluators (FC and HM) by searching the following databases in October 2019: PubMed, EMBASE, PsycArticles, Scielo, CENTRAL, and Web of Science. The following terms were used for the research in PubMed: ("cognitive behavioral therapy" OR CBT OR "cognitive behavior therapy" OR "cognitive behavior treatment" OR "cognitive-behavioral treatment" OR "cognitive behavior therapy" OR "cognitive behaviour treatment" OR "cognitive behavioral therapy" OR "cognitive behavioural treatment") OR [(psychotherapy OR "psychotherapeutic processes") OR "Cognitive Therapy" OR ("psychotherapy, brief" OR "short-duration psychotherapy") OR "interpersonal therapy" OR "analytical psychotherapy" OR "eye movement desensitization and reprocessing" OR EMDR] AND ("brain derived neurotrophic factor" OR BDNF OR neurotrophin OR neurogenesis OR "nerve cell plasticity" OR "brain plasticity" OR "nerve plasticity" OR "neural plasticity" OR neuroplasticity). The terms were adjusted according to the protocols in each database.The searches in each database were realized twice by two independent evaluators, adapting pre-defined terms following the protocol for each base (such as Mesh terms for PUBMED and thesaurus for Embase, for example). In any divergence regarding the abstracts of each database, an independent third party realized a new search. Independent search results were confronted and divergences were resolved by a third independent party. Abstracts from "grey literature" were only considered if available in the evaluated databases.

The study selection was conducted in two steps. First, the title and abstract of the articles obtained in the search were analyzed by two independent authors (FC and HM) and selected according to the inclusion and exclusion criteria. Next, the remaining articles were read in full. A third reviewer was recruited in case of any disagreement on the inclusion or exclusion of studies at any stage.

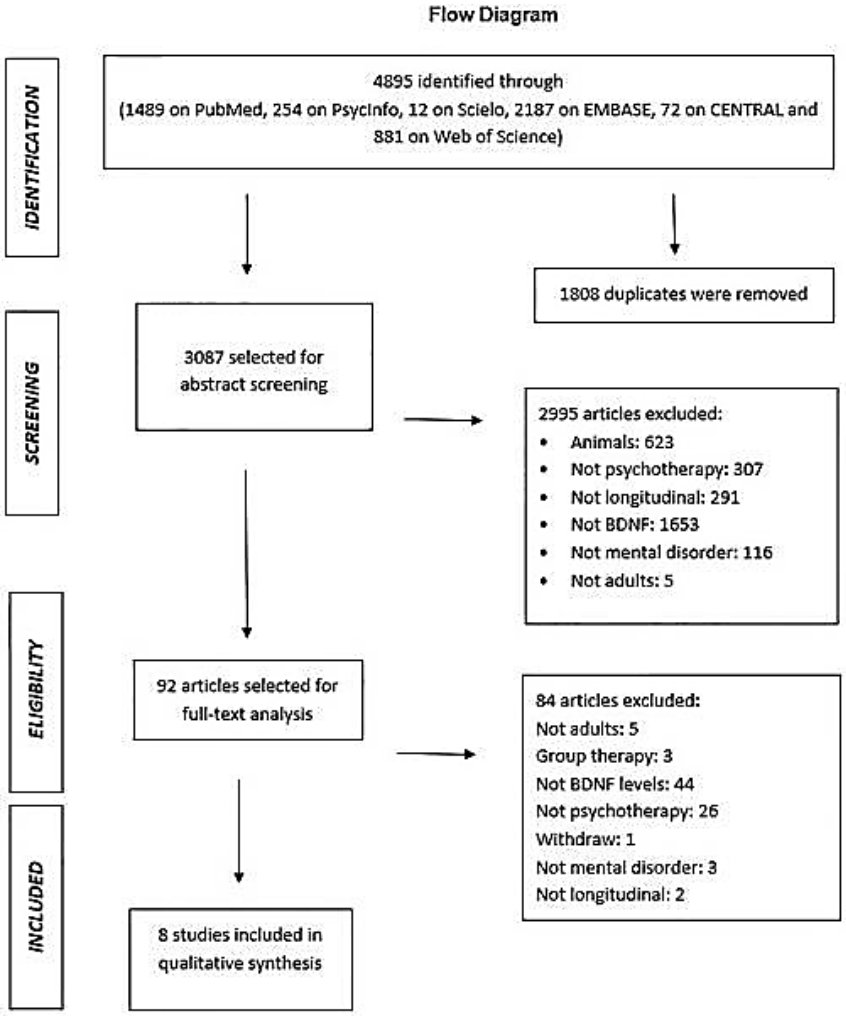
Data Extraction and Analysis

Two authors, independently, extracted data on the following metrics, previously defined in pilot forms: year of publication, country, study design, patient precedence, sex, number of participants, disorder type, therapy type, therapy length, total of sessions, BDNF (plasma or serum), mean and standard deviation of BDNF levels (pre and post intervention), symptom measures, and complementary therapies (pharmacotherapy or else).

Assessment of Risk of Bias

Two instruments were used to evaluate the "Assessment of risk of bias": The New Castle-Ottawa (19) was indicated for longitudinal non-randomized studies. It evaluates aspects such as selection, comparability, and outcome (Table 1). Its scores vary between 0 (highest bias) to 9 points (lowest bias). The Cochrane Collaboration's tool assessed risk of bias for randomized studies (Table 2) (28). This allows evaluation as "high", "low", or "unclear" risk of bias for each domain: selection, attrition, detection, performance, reporting, and others. The intra-study risk of bias was also included (Table 3). There was no exclusion of articles, regardless of the score, due to the small number of studies obtained, but the restrictions were considered when analyzing the individual results.

Searches Results



A total of 4,895 references were found. Of these, 1,808 were duplicates and excluded. Thus, 3,087 abstracts were evaluated in terms of title and abstract followed by exclusion of 2,995 by criteria shown in the figure below. At the full-text stage, 92 articles were read in full, and 8 articles were added to the review and inspected followed by two proofreaders (Figure 1).

Main Mental Disorders Studied

The main features of the studies are detailed in Table 4. We found studies evaluating BDNF levels in people with major depressive disorder (k=3), PTSD (k=2), bulimia (k=1), borderline disorder (k=1), and sleep disorder (K=1) with a predominance in women in five studies (55, 5–100%); three studies have a predominance of male patients. The number of patients varied between n=7 and n=115. Most patients came from outpatient clinics (k=4), and the treatment extent was 4 weeks to 12 months.

TABLE 1 | Evaluation of the methodological quality of longitudinal studies using the Newcastle-Ottawa scale.

Study	Selection				Comparability	Outcome			Total
	Representativeness	Selection of the non exposed	Ascertainment	Outcome of interest was not present at start of study	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow up	
Koch et al. (20)	*		*		**	*		*	6
Yamada et al. (21)	*		*		**	*		*	6
Park et al. (22)	*		*		**	*		*	6
Perroud et al. (23)	*	*	*		**	*		*	7
Rusch et al. (24)	*		*		**	*	*	*	7

*Correspond to criteria (1 point).
**Correspond to criteria (2 points).

TABLE 2 | Evaluation of the methodological quality of randomized studies using Cochrane Collaboration's tool for assessing risk of bias for studies.

	Silva et al. (25)	Powers et al. (26)	Yan et al. (27)
Domain			
Random sequence generation	Low risk	Low risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk
Blinding of participants and personnel	Low risk	Low risk	Low risk
Blinding of outcome assessment	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other sources of bias	Low risk	Low risk	Low risk

TABLE 3 | Evaluation of Intra-study bias risk of studies included.

Study	Clear definition of the study population?	Clear definition of results and evaluation?	Independent results evaluation? (by a third party, for example)	Sufficient follow-up time?	Selective loss during follow up?	Identified and clear limitations?
Koch et al. (20)	YES	YES	NO	NO	NO	YES
Silva et al. (25)	YES	YES	NO	YES	NO	YES
Powers et al. (26)	YES	YES	NO	YES	NO	NO
Yamada et al. (21)	YES	YES	NO	NO	NO	YES
Park et al. (22)	YES	YES	NO	NO	NO	YES
Perroud et al. (23)	YES	YES	NO	NO	NO	YES
Yan et al. (27)	YES	YES	NO	YES	NO	YES
Rusch et al. (24)	YES	YES	NO	YES	NO	YES

Main Clinical Measures Evaluated and Diagnosis Criteria

The diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (29, 30) (k=3), SIDES (Structured Interviews for Disorders of Extreme Stress) (31) (k=1), Mini International Neuropsychiatric Interview (MINI-PLUS) (32) (k=1), Classification and Diagnostic Criteria for Mental Disorder in China 3 (CCMD-3) (33), and Epworth Sleepiness Scale (ESS) (34) were used. Different scales were used for the symptom evaluation: Hamilton Depression Rating Scale (35), (BDI) Beck Depression Inventory (36, 37), PTSD Symptom Scale-Interview Version (38), State–Trait Anxiety Scale (39), Clinical Global Impression Change Scale (CGI-CS) (40), (BIS-10): Barrat Impulsiveness

Scale (41), (CTQ): Childhood Trauma Questionnaire (42), (SCID-II): Screening Interview for Axis II Disorder (43), (PSIQI): Pittsburgh Sleep Quality Index (44), (QIDS-SR): Quick Inventory of Depressive Symptomatology (45), (PCL-M): PTSD Checklist-Military Version (46), and (SF-36): Short From Health Survey-36 (47).

All studies presented symptom reduction on these scales. Three articles branched the patients into responders depending on the reduction of 50% of the HAMD (20) or BDI (23). baseline and CGI-C scores above the "much improved" level after therapy (22).

Complementary Psychopharmacotherapy

Three of the articles included psychopharmacotherapy as a complementary therapy. Those diagnosed with insomnia could use automatic positive airway pressure (APAP). Only one study included physical activity versus complementary therapy (19). Six of the eight studies analyzed plasma levels of BDNF, and two opted for serum levels.

Psychotherapy, Scales, and BNDF Levels

The main results of individual studies are described in Table 5. No significant changes in BDNF levels were observed in depressive patients and those who submitted to interpersonal therapy: [baseline responders (mean ±SD): 3.3±.3.7 x non-responders 2.8±1.3 p=0.68; Day 21-responders: 3.4 ±3.6 x non-responders 3.1±2.3 p=0.97] (17) or Cognitive-Behavioral Therapy [pre-treatment (mean ±SD) 1.387±0.26; post-treatment 1.328±0.3, p= 0.294] (18). However, the responders initially had a higher level of neurotrophin and a higher increase versus non-responders (17). In a study of medication associated with therapy, the group using only vortioxetine had a significant difference in BDNF levels between intervention and control groups in baseline and after. The group who underwent CBT associated with medication had a significant increase versus the control group ($p<0.001$) (27).

Two studies (19, 28) in PTSD patients have shown increased levels of BDNF after intervention in different modalities: exposure therapy (19) and eye movement desensitization and reprocessing (28). The first study related elevation of neurotrophin when psychotherapy was associated with physical activity (mean ±SD) (pre: 1.38 x post: 3.73). Their values were not expressive in isolation (pre: 1.77 x post: 1.75) and PSSI: PE (prolonged exposure therapy): (mean ±SD) 37.00 (8.25); PE+ Exercise: 42.00 (5.2) (19). However, the second study indicated that patients who presented a clinical response or symptom remission symptoms had higher increases in BDNF than those who did not

respond to treatment [responders: (mean ±SD 4435.6±1273.4; non-responders 2789±643.2; p 0.025)]. There was an association between the increase of BDNF levels and symptoms reduction such as anxiety, phobia, and dissociation after EMDR in patients with PTSD (19).

TABLE 4 | Characteristics of included studies.

Study	N (M/F)	Design	Complementary Therapy	Setting patient	Time	BDNF extraction	Clinical Measure
Koch et al. (20)	27 (12/15)	Not randomized	Without medication	Inpatient and outpatient	12-16 sessions (6 weeks)	Plasma	HAMD
Silva et al. (25)	42 (7/35)	Randomized clinical trial	Without medication	Outpatient	16 sessions (12 weeks)	Serum	BDI-II
Powers et al. (26)	9 (1/8)	Randomized clinical trial	ET + Exercise psychopharmacological	No information	12 sessions (12 weeks)	Plasma	PSSI
Yamada et al. (21)	8 (8/0)	Not randomized	Without medication	Outpatient	4 weeks	Plasma	EDI, BDI and STAI
Park et al. (22)	7 (0/7)	Not randomized	Without medication (*)	No information	8 sessions	Plasma	CGI
Perroud et al. (23)	115 (7/108)	Not randomized	psychopharmacological	Outpatient	4 weeks	Plasma	BDI, BIS-10, CTQ, SCID-II
Yan et al. (27)	41 (22/19)	Randomized clinical trial	psychopharmacological	No information	12 months	Serum	HAMD
Rusch et al. (24)	44	Not randomized	APAP psychopharmacological	Outpatient	4-8 biweekly	Plasma	PSQI, QIDS-SR, PCL-M, SF-36

APAP, automatic positive airway pressure; BDI II, Beck Depression Inventory II; BDI, Beck Depression Inventory; BIS-10, Barrat Impulsiveness Scale; CGI-CS, Clinical Global Impression Change Scale; CTQ, Childhood Trauma Questionnaire; EDI, Eating Disorder Inventory; ET, Exposure therapy ; HAMD, Hamilton Depression Rating Scale; PCL-M, PTSD Checklist-Military Version; PSIQI, Pittsburgh Sleep Quality Index; PSSI, PTSD Symptom Scale-Interview; QIDS-SR, Quick Inventory of Depressive Symptomatology; SCID-II, Screening Interview for Axis II Disorder; SF-36, Short Form Health Survey-36; STAI, State–Trait Anxiety Scale. (*) 2 mg lorazepam or 10 mg diazepam was allowed for sleep management.

At baseline, patients with bulimia nervosa undergoing eye movement desensitization and reprocessing had reduced BDNF values versus controls (p = 0.02)—this has been established in previous studies. This sample presented elevation of BDNF levels which were more expressive among responders than non-responders. The pre and post therapy scale scores of responders are listed here: BDI pre (mean ±SD) 22±11.9, post: 17.4±15.2, p=0.22, STAI-state pre: 56±12.9, post 50±17.7, p=0.07, STAI-trait pre: 65.8±10.1, post: 55.2±18.5, p 0.08 (13).

Borderline personality diagnosed patients had a higher BDI mean than the healthy control group (mean ± SD 34.10±11.8) similar to other symptom scales. Responders had an insignificant increase in plasma BDNF levels (p=0.062), as non-responders had insignificant reduction (p=0.78) (23).

Finally, patients with sleep disorders were divided between those who presented an improved sleep pattern and those who got worse. The first group presented an insignificant BDNF increase (pre: 80.2± 28.6; post 89.1±36.3; p =0.089). BDNF levels were stable in the group with no improvement (pre: 91.7±38.1; post 100.2±44.4; p=0.155) (27).

TABLE 5 | Main results.

Study	Diagnosis	Therapy	MAIN RESULTS
(20)	Major Depressive Disorder	(IPT)	• 17 patients had a reduction of the least 50% on the baseline Hamilton scale score and were defined as "responders" after psychotherapy. • BDNF had no meaningful difference between the responders and non-responders groups. • Age, sex, HAMD, subject as inpatient or outpatient, number of previous depressive events, or pharmacological treatment before the therapy had no meaningful correlation with BDNF levels. • There were no association between BDNF levels and depression severity
(25)	Major Depressive Disorder	(CBT)	• There was a significantly depression symptoms reduction after psychotherapy. • There were no significant differences between pre and post psychotherapy intervention BDNF levels.
(26)	Post-traumatic stress disorder	(ET)	• Psychotherapy, as only treatment, in patients with PTSD did not change BDNF levels in 12 weeks. • Exposure therapy associated with physical activity increased the BDNF levels in patients.
(22)	Post-traumatic stress disorder	(EMDR)	• There were no meaningful changes on BDNF plasma levels after psychotherapy, but responders presented higher BNDF plasma levels than non-responders. • Anxiety, phobia, and dissociation levels were significantly reduced after EMDR. • BDNF basal levels presented correlation with the depression and anxiety estimated response
(21)	Bulimia Nervosa	(CBT)	• BDNF levels in patients with bulimia increased after treatment. • There were no differences between BDNF levels in inpatients and outpatients • There was a reduction in the frequency of self-induced vomiting, laxatives using, and compulsive eating episodes after therapy. • There were no significant changes on the Beck Depression Inventory and Eating Disorder Inventory scores, except for "Drive for Thinness".
(23)	Borderline Disorder	(I-DBT)	• Plasma BDNF levels in subjects with BPD were higher than in the control group • There was an inversely proportional decrease of BDNF levels in response to psychotherapy • Non-responders had a reduction of BDNF levels after psychotherapy and, responders, had an increase, both, not significant.
(27)	Major Depressive Disorder	(CBT)	• After the treatment, the group that underwent pharmacotherapy combined with psychotherapy presented a most expressive depressive symptom reduction in comparison to the submitted only to the pharmacological treatment. • Before the treatment, both control and intervention group had BDNF levels with no significant differences. After intervention, the group with psychotherapy associated presented a significantly higher increase of BDNF
(24)	Sleep Disorder	(CBT)	• The group that had an improvement on sleep patterns had a not significant BDNF increase, while in the group that its sleep patterns got worse, BDNF levels did not change.

CBT, Cognitive-Behavioral Therapy; EMDR, Eye Movement Desensitization and Reprocessing; ET, Exposure Therapy; I-DBT, Intensive dialectical behavior therapy; IPT, Interpersonal therapy.

Discussion

To the best of our knowledge, this is the first systematic review to evaluate the relation between BDNF levels in response to psychotherapies. The results showed that, in general, there was a reduction of clinical symptoms in patients with mental disorders that went through different kinds of psychotherapies. In most cases, there was also a concurrent rise in BDNF levels.

In central nervous system, the levels of BDNF are higher in structures of the limbic system, such as the hippocampus (48) and, in patients with mental disorders, the neurotrophin concentration in this region is reduced (49). Meanwhile, the psychotherapy has the potential for stimulation of the limbic system and (50), although the physiology is not clear until this moment, we can assume que psychotherapies act in this system, stimulating a higher BDNF production, reducing psychiatric symptoms.

While this present review showed that there is no absolute consensus regarding BDNF levels rise after psychotherapy, there is meta-analysis that shows evidence of the increase of BDNF after pharmacological treatment (51, 52). Although both treatments are recognized as effective, this difference can be explained by the short follow-up time of the patients. The response to pharmacological therapy tends to occur faster (53), while the response to psychotherapy may take months (54), depending on factors such as

therapeutic relation, for example (55).

These findings showed initial evidence that BDNF could be a potential tool to evaluate the effect of psychotherapies on patients with mental disorders. The BDNF levels could be used with symptom evaluation and other tools such as clinical symptom scales to confirm that there is a satisfactory response to therapy. Furthermore, BDNF levels tend to be stable over time (56), and psychotherapy can be a variable course. Thus, such levels might change at a different rate versus those observed here. Only one of our manuscripts had a follow-up longer than 12 weeks. Prior reviews and meta-analyses have shown that there is an increase in BDNF levels in depressive patients treated with pharmacologically (57) or with physical activity (58). Healthy patients have stable BDNF levels over time, which favors the theory that patients with mental disorders submitted to therapies have an increase in neurotrophins as an outcome. However, in this review, only patients using medication associated with psychotherapy had an increased BDNF.

Although there is initial evidence for the role of BDNF as an individual psychotherapy response biomarker, the heterogeneity across the studies limit the conclusions of this meta-analysis—the groups had different disorders, types of therapies, therapy exposure times, and others boundary conditions that may affect the results. The literature is restricted to depression, PTSD, bulimia, insomnia, and borderline disorders. Thus, the conclusions cannot be extended to other disorders like bipolar disorder and anxiety disorders.

We also cannot disregard the relevance of polymorphism knowledge in response to psychotherapies. A biological response marker could also be expanded to other biomarkers. Longitudinal studies evaluating BDNF levels in response to psychotherapy could facilitate the performance of a meta-analysis of such candidate biomarkers.

Limitations

The conclusions of this review must be cautious because the studies included in this review are small, most of which with a short follow up period. As to BDNF values, the included studies quantified serum and plasma BDNF levels and there is evidence that the levels of these molecules change according to analyzed tissue and organs (59, 60) Also, it isn't possible to quantify the proBDNF precursor and its derivatives values: mature BDNF and pro-peptide BDNF. It is relevant to know this data, for there is evidence that they have different effects in the physiopathology of psychiatric disorder (61). As well, age (62) and ethnicity (63) may interfere in BDNF levels and also were not considered while quantifying the neurotrophin

Conclusion

In conclusion, there is a nascent body of evidence evaluating the effects of individual psychotherapies on BDNF. These neurotrophins seem to present variations after psychotherapy especially in patients with bulimia, PTSD, insomnia, and borderline personality, and that show reductions in symptoms. In patients with depression, those who submitted only to psychotherapy had no increase in BDNF levels while patients with associated medicine usage showed an obviously higher increase versus those who submitted solely to pharmacological treatment. There is only one study with a higher than 12-week follow-up period, which suggests that a longer follow-up time is needed for BDNF levels. BDNF could supplement symptom scales to analyze the effects of psychotherapy

Data Availability Statement

The data set obtained for this study are available from corresponding author on request.

Author Contributions

FC: preparation and registration of the review protocol, extraction of articles in the databases, selection of articles, analysis of results, and article production. LG: protocol production, results analysis, and article production. FS: protocol production, results analysis, and article production. HM: preparation of the review protocol, extraction of articles in the databases, selection of articles, analysis of results, and article production. NR: main orientation, protocol production, review of articles in case of divergence, analysis of results, and article production.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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7.4- ARTIGO 2

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Functional Magnetic Resonance Imaging of Patients with Major Depressive Disorder Undergoing Psychotherapy: A Systematic Review

Authors: Felipe Cesar de Almeida Claudino [1,2,3], Gianfranco Rizzotto de Souza [2,4,] Reebeca Menegol [2,3], Josiane Maliuk dos Santos [1,2,3], Victória Machado Scheibe [2,5], Augusto Madke Brenner [2,4], Juliana Avila Duarte [3,6], Neusa Sica da Rocha [1,2,3]

1-Postgraduate Program in Psychiatry and Behavioral Sciences, Federal University of Rio Grande do Sul (UFRGS) - Porto Alegre, Brazil
2-Innovations and Interventions for Quality-of-Life Research Group (I-QOL) - Brazil
3- Hospital de Clínicas de Porto Alegre (HCPA) - Porto Alegre, Brazil
4- Federal University of Health Sciences of Porto Alegre (UFCSPA) - Porto Alegre, Brazil
5- Lutheran University of Brazil (ULBRA) - Canoas, Brazil
6 - Postgraduate Program in Medical Sciences, Federal University of Rio Grande do Sul (UFRGS) - Porto Alegre, Brazil

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Corresponding Author:
Felipe Cesar de Almeida Claudino
E-mail adress: felipeaclaudino@gmail.com Phone: +55 51 985512263
Rua Ramiro Barcelos, 2350, Porto Alegre, RS, Brazil

Functional Magnetic Resonance Imaging of Patients with Major Depressive Disorder Undergoing Psychotherapy: A Systematic Review

Highlights

- Limbic system is a predictor of clinical improvement in depression.
- Functional magnetic resonance imaging is a potential marker of response to psychotherapy.
- Brain areas stimulated in psychotherapy are related to emotion and behavior.

ABSTRACT

Background: Psychotherapy is considered one of the main treatments for Major Depressive Disorder. There is evidence that clinical improvement after therapy is associated with changes in brain function, observed using functional magnetic resonance imaging. To evaluate the findings observed in resting-state and task-based functional magnetic resonance imaging in adult patients diagnosed with Major Depressive Disorder undergoing individual psychotherapy.

Methods: PubMed, Embase, PsycInfo, SciELO, Cochrane Library, and Web of Science were searched until June 3, 2021, to analyze changes in Functional Magnetic Resonance Imaging in Patients with Major Depressive Disorder in Psychotherapy. PROSPERO registration: CRD42020169652.

Results: Task-based fMRI showed changes in the basal nuclei and amygdala, whereas resting-state fMRI showed changes in the subcallosal cingulate. Considering the common findings between the two methods, alterations were observed in the temporal lobe, frontal lobe, parietal lobe, occipital lobe, insula, cerebellum, and limbic gyrus.

Limitations: The studies had different follow-up times, ranging from 2 weeks to 8 months. Different types of psychotherapies were used, which makes comparison difficult. It was impossible to compare the effects between paradigm-based studies since the stimuli vary between studies.

Conclusions: Functional magnetic resonance imaging showed clinical improvement of patients with depressive disorder undergoing psychotherapy with functional variations at

the brain level, demonstrating the potential of neuroimaging as a biological marker of response to treatment. Although task-based studies, although they are the majority in the findings of this review, such studies show variability between the applied paradigms, which limits the comparison between studies.

Keywords: fMRI, psychotherapy, Major depressive disorder

INTRODUCTION

Major Depressive Disorder (MDD) is a considerable cause of disability worldwide (Gutiérrez- Rojas et al., 2020). Clinical variations, unpredictable course, and varied responses to treatment make it a challenging disorder (Malhi, Mann. 2018). Pharmacological treatment and psychotherapy are the main therapeutic choices for this disorder. Systematic reviews have shown that psychotherapy reduces depression severity and, when combined with antidepressants, reduces depressive symptoms compared to patients undergoing pharmacological treatment alone (Ijaz et al. 2018; Farah et al., 2016). MDD is associated to functional changes in brain activity, seen in neuroimaging tests. There is evidence of brain alteration in patients diagnosed with MDD regarding the volume of the frontal regions (Zhang et al., 2018), in addition to a significant reduction in the volume and shape of the left thalamus (Lu et al., 2016). The hippocampus, for example, is smaller in depressed patients than in healthy controls (Ballmaier et al., 2008) and the striatal area shows variability in these individuals (Zhang et al., 2018) – associated with a higher risk of impulsive and suicidal behavior (Ballmaier et al., 2008). The amygdala has also been reported to be reduced, particularly in unmedicated patients (Kronenberg et al., 2009).

Neuroimaging tests are potential tools used to analyze brain areas before, during, and after treatment in psychotherapy, to identify whether there have been structural or functional changes in the brain, which help to improve the understanding of both the therapeutic process and of its results (Weingarten et al., 2015. It is possible to observe, for example, brain alterations in depressed patients (Sanka et al., 2018) with obsessive-compulsive disorder (Thorse et al., 2015), schizophrenia, anxiety disorders, and post-traumatic stress disorder (Roffman et al., 2015) via neuroimaging, measuring differences in blood flow, oxygenation, metabolic levels, functional connectivity, among other variables (Weingarten et al., 2015).

Functional magnetic resonance imaging (fMRI), the object of analysis in this study, is a non- invasive imaging test that allows the assessment of brain activation from its metabolism (Bandettini et al., 1992), analyzing tissue perfusion and brain oxygen concentration (Logothetis et al., 2008). The exam can be performed with the patient under stimuli (task-based magnetic resonance imaging) or at rest, without stimuli (Glove, 201; Phan et al., 2004). The mapping of metabolic changes in brain areas, together with other techniques, allows us to infer the cognitive mechanisms involved in different activities or evidence-based therapies, for example.

Evidence-based psychotherapies are considered effective for many mental disorders (APA, 2006), including MDD (Cook et al., 2017). Reviews in recent years (Fonseka, 2018; Porcu, 2016; Frankli et al., 2016) have demonstrated the potential of neuroimaging tests as markers of treatment response in anxiety and depressive disorders, especially in areas such as the anterior cingulate cortex, the amygdala, insula (Chakrabarty et al., 2016), and the left rostral anterior cingulate. (Sanka et al., 2018). However, as far as we know, no recent study conducted a comprehensive search, within the literature, focusing exclusively on the functional analysis of patients diagnosed with MDD (without psychiatric comorbidities), attending different forms of individual psychotherapy, undergoing fMRI.

Considering that psychotherapies may be able to modulate certain brain regions, which have a potential relationship with the pathophysiology of MDD, the objectives of this systematic review are to observe brain areas that show activity changes after therapy, to analyze whether these differences are associated with clinical improvement, and to discuss the potential use of neuroimaging markers associated with treatment response in patients diagnosed with MDD undergoing individual psychotherapies in longitudinal studies, case-control studies, and randomized and non-randomized clinical trials

METHODS

This review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009. The review protocol was registered on PROSPERO under the code CRD42020169652 before study selection and data extraction.

Studies with the following characteristics were considered: 1) randomized and non-randomized clinical trials, 2) longitudinal studies and case-control studies, 3) study

protocols that provided outcome data for more than one point in time, 4) adult patients over 18 years of age, 5) diagnosis of unipolar depression, defined by validated protocols / instruments), 6) submitted to individual psychotherapies (specified below), 7) with clinical measurements obtained through cutoff points in validated instruments 8) performance of functional magnetic resonance examination. There were no restrictions on gender, ethnicity or nationality. As for the language, the analyses were restricted to articles in English, Portuguese, Spanish, French, and Italian.

Studies with the following characteristics were excluded: 1) group psychotherapies 2) studies with patients with clinical or psychiatric comorbidities 3) children/adolescents, under 18 years of age 4) patients diagnosed with bipolar depression 5) patients with depressive disorder who did not attend psychotherapy 6) cross-sectional studies.

Data were extracted on sex, study design, diagnosis, number of participants, therapy type and time, total of sessions, neuroimaging, clinical measures, and complementary therapies, by two independent groups. Considering the different areas of the central nervous system, some areas of the brain were grouped into larger areas, facilitating the analysis and understanding of the functional brain processes.

Risk of Bias Assessment

Two instruments were used to assess the risk of bias: The New Castle-Ottawa Quality Assessment Scale (Wells et al., 2013) used for Longitudinal Studies and the New Castle-Ottawa Quality Assessment Scale for studies with Randomized Controlled Trials. Studies are evaluated with scores ranging from 0 to 9, and the higher the score, the less bias. Due to the limited number of articles included in our analysis, no studies were excluded, regardless of the score obtained.

Search Strategy and Study Selection

The titles and/or abstracts were obtained by two independent groups searching the subsequent databases on June 3rd, 2021: PubMed, EMBASE, PsycArticles, COCHRANE CENTRAL, and Web of Science. The terms below were used for the search in PubMed: (((“cognitive behavioral therapy” OR “CBT” OR “cognitive behavior therapy” OR “cognitive behavior treatment” OR “cognitive behavioral treatment” OR “cognitive behavior therapy” OR “cognitive behavior treatment” OR “cognitive behavioral therapy”

OR “cognitive behavioral treatment” OR “psychotherapy” OR “psychotherapeutic processes” OR “Cognitive Therapy” OR “psychotherapy, brief” OR “short-duration psychotherapy” OR “interpersonal therapy” OR “analytical psychotherapy” OR “eye movement desensitization and reprocessing” OR “EMDR”) AND (“Depression”[Mesh] OR “Depressions” OR “Depressive Symptoms” OR “Depressive Symptom” OR “Symptom, Depressive” OR “Symptoms, Depressive” OR “Emotional Depression” OR “Depression, Emotional” OR “Depressions, Emotional” OR “Emotional Depressions”) AND (“Magnetic Resonance Imaging”[Mesh] OR “Imaging, Magnetic Resonance” OR “NMR Imaging” OR “Imaging, NMR” OR “Tomography, NMR” OR “Tomography, MR” OR “MR Tomography” OR “NMR Tomography” OR “Steady-State Free Precession MRI” OR “Steady State Free Precession MRI” OR “Zeugmatography” OR “Imaging, Chemical Shift” OR “Chemical Shift Imagings” OR “Imagings, Chemical Shift” OR “Shift Imaging, Chemical” OR “Shift Imagings, Chemical” OR “Chemical Shift Imaging” OR “Tomography, Proton Spin” OR “Proton Spin Tomography” OR “Magnetization Transfer Contrast Imaging” OR “MRI Scans” OR “MRI Scan” OR “Scan, MRI” OR “Scans, MRI” OR “fMRI” OR “MRI, Functional” OR “Functional MRI” OR “Functional MRIs” OR “MRIs, Functional” OR “Functional Magnetic Resonance Imaging” OR “Magnetic Resonance Imaging, Functional” OR “Spin Echo Imaging” OR “Echo Imaging, Spin” OR “Echo Imagings, Spin” OR “Imaging, Spin Echo” OR “Imagings, Spin Echo” OR “Spin Echo Imagings”))).

In the case of discrepancies regarding the abstracts in the databases, an independent third party (NSR) searched anew. Search results were then confronted and disparities were resolved by a third independent evaluator.

RESULTS

Searches Results

In total, 4,643 references were found. Of these, 1,226 were excluded for being duplicates. Thus, 3,417 references were evaluated in title and abstract, and 3,229 were subsequently excluded due to the criteria shown in Figure 1. During full-text reading, 188 articles were assessed, and 19 articles were included in the review and examined by two proofreaders (Figure 1).

Main Clinical Measures Evaluated and Diagnosis Criteria

The studies included in this review used the following scales to assess depressive symptoms: Beck Depression Inventory (BDI) (Beck, Sterr., 1987), (K=14), Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) (K=13), and Low Resistance Thought Induction Montgomery- Asberg Depression Rating Scale (MADRS) (K=1) (Montgomery, Åsberg., 1979).

Psychotherapies

Six types of psychotherapies were included in this study. Cognitive Behavioral Therapy (CBT) was the most used in the articles found. CBT is a psychotherapy created by Aaron T. Beck and is based on the cognitive model, in which the therapist tries to produce a change in the patient's thoughts to enable a lasting emotional and behavioral change (Beck, 2013. Another therapy used was Behavioral Activation Treatment for Depression (BATD), which focuses on changing and activating behaviors (Mazzucchelli et al., 2009). Different concepts of Behavioral Activation (BA) as important treatment for depression were developed following the concepts of Lewinsohn and the idea that the behavior of depression is the result of a loss, or lack, of response-contingent positive reinforcement (Mazzucchelli et al., 2009; Fuhr et al., 2016).

A study on Psychodynamic Psychotherapy (PP), a study on Guided Imagery with Relaxation (GIR), and one on Cognitive Behavioral Analysis System of Psychotherapy (CBASP) were found. CBASP was developed specially for the treatment of chronic depression and is an integrative therapy that combines components of cognitive, behavioral, and interpersonal strategies. Guided Imagery with Relaxation is a cognitive-behavioral self-management technique, it involves the use of verbal suggestions to create a flow of thoughts that focus the individual's attention on imagined sensations; Relaxation is an essential addition to Guided Imagery, as relaxation allows more concentration on the sensory sensations (Baird, Sands., 2006). Finally, Psychodynamic Psychotherapy includes a range of treatments based on psychoanalytic concepts that involve less frequent meetings and may be considerably briefer than psychoanalysis. Essentially, it aims to explore aspects of the self that are not fully known, especially as they are manifested within the therapy relationship (Shedler, 2010). A study on Low Resistance Thought Induction Psychotherapy (TIP) was also found. TIP is a form of psychological treatment developed in China, which consists of holistic and syndrome differentiation-based

treatment [34].

Figure 1

Table 1

Among the studies included in the qualitative analysis, 6 used resting-state fMRI and 13 were task-based, using several different paradigms. Most of the studies adopted Cognitive- Behavioral Therapy (CBT) (k = 11) or Behavioral Activation Treatment for Depression (BATD) (k = 4) as the chosen psychotherapy. One study used Guided Imagery with Relaxation (GIR), one study used Low Resistance Thought Induction Psychotherapy (TIP), one study used Psychodynamic Psychotherapy (PP), and one study used Cognitive Behavioral Analysis System of Psychotherapy (CBASP). All studies delivered in-person psychotherapy, except for one that used an automated computer program for virtual cognitive-behavioral therapy (iCBT). The duration of treatment ranged from 2 to 15 weeks for CBT and BATD, 5 weeks for GIR, 6 weeks for TIP, and 8 months for PP. The main findings of the included studies are described in table 2.

Table 2

Considering the variability between stimulated and non-stimulated functional magnetic resonance imaging, the results were divided between resting-state and task-based, grouping the findings into correlated areas, based on a neuroanatomical division.

Task-based fMRI

BASAL NUCLEI activity was reported as being a predictor of outcomes after CBT (positive outcomes were associated with lower load-response activity in the putamen (Fu et al., 2008) and with greater pretreatment activity in the right striatum (Queirazza et al., 2019), while negative outcomes were associated with activity in a cluster including the right caudate and putamen (Queirazza et al., 2019)) and after BATD (connectivity

between some clusters spanning around the basal nuclei and a series of other brain regions such as the subcallosal cortex and the temporal pole predicted declines in BDI scores (Walsh et al., 2017)). Activity in the basal nuclei was also reported as having increased after CBT (in the left putamen and in the left caudate, during certain phases of a reward task (Dichter et al., 2009)), as having decreased after CBT (in the left putamen and in the left caudate, but during different phases of the same reward task (Dichter et al., 2009)), and as having decreased after psychodynamic psychotherapy (hyperactive basal nuclei at baseline were normalized after eight months of treatment (Wiswede et al., 2014)). TEMPORAL LOBE activity was reported as being a predictor of outcomes after BATD (better outcomes were associated with less connectivity attenuation between a large cluster spanning the right temporal and parietal lobes and the left middle frontal gyrus, after two successive task runs (Walsh et al., 2017)) and as having increased after CBT (during a reward task, several areas had increased activation following treatment (Dichter et al., 2009)). Activity in the temporal lobe was also reported as having decreased after CBT (in areas such as the right inferior temporal gyrus [38] and the fusiform gyrus (Fu et al., 2008)). FRONTAL LOBE activity was reported as being a predictor of outcomes after BATD (connectivity between areas such as the right orbitofrontal cortex and the temporal pole was associated with greater declines in BDI scores (Walsh et al., 2017)) and after CBT (increased activity in the dorsolateral prefrontal cortex was associated with increased pupillary responses, which were present in more severely depressed patients who had worse outcomes after psychotherapy (Siegle et al., 2011). Parts of the frontal cortices also contributed to the prediction of remission (Costafreda et al., 2009), whereas patients with the greatest clinical improvement after CBT had the lowest mean activity in certain regions spanning the frontal lobe and higher load-response in others (Fu et al., 2008). Diminished connectivity with the left middle frontal gyrus also predicted larger declines in BDI scores (Walsh et al., 2019)). Activity in the frontal lobe was likewise reported as having increased after CBT (in the precentral gyri (Dichter et al., 2009; Sankar et al., 2015) and in the superior frontal gyrus (Fu et al., 2008), for example) and as having decreased after CBT (in the left superior frontal gyrus, for instance (Dichter et al., 2009)). LIMBIC GYRUS activity was reported as being a predictor of outcomes after BATD (greater connectivity attenuation between certain areas and the left nucleus accumbens or the subcallosal cortex predicted greater declines in BDI scores (Walsh et al., 2017), whereas sustained activation of the anterior cingulate cortex was a predictor of better responses to treatment (Carl et al., 2016)) and after CBT (mainly, activity in the anterior

cingulate cortex (Fu et al., 2008; Costafreda et al., 2009; Siegle et al., 2012; Siegle et al., 2006)). Activity in the limbic gyrus was also reported as having increased after CBT (likewise, mainly in the anterior cingulate gyrus (Fu et al., 2008; Dichter et al., 2009)) and as having decreased after CBT (in the posterior cingulate (Fu et al., 2008; Dichter et al., 2009; Sankar et al., 2015), for instance). PARIETAL LOBE activity was reported as being a predictor of outcomes after CBT (in the precuneus and in a large cluster spanning the parietal lobe (Costafreda et al., 2009)) and as having increased after CBT (in areas such as the precuneus (Fu et al., 2008; Dichter et al., 2009)). Activity in the parietal lobe was also reported as having decreased following CBT (in the left postcentral gyrus (Dichter et al.,2009), for instance). CEREBELLUM activity was reported as being a predictor of outcomes after CBT (Costafreda et al., 2009) and as having decreased, following CBT (Fu et al., 2008). AMYGDALA activity was reported as being a predictor of outcomes after CBT (Queirazza et al., 2019; Siegle et al., 2006) and as having increased after CBASP (Klein et al., 2014). Activity in this region was also described as having decreased after CBT (Dichter et al., 2009) and after psychodynamic psychotherapy (Wiswede et al., 2014). OCCIPITAL LOBE activity was reported as having increased after CBT (in areas such as the lingual gyrus and the left lateral occipital cortex (Dichter et al., 2009), during certain phases of a reward task) and as having decreased after CBT (during other phases of the same reward task, in the left occipital pole (Dichter et al., 2009) and in the lingual gyri (Fu et al., 2008)). INSULA activity was reported as being a predictor of outcomes after CBT (Fu et al., 2008) and as having increased after CBT (Dichter et al., 2009).

Resting-state fMRI

FRONTAL LOBE activity increased after psychotherapy and was considered a marker of clinical improvement (after 5 weeks of treatment, change was observed in the ventromedial prefrontal cortex (Huang et al., 2014)) and was also shown to be a predictor of treatment response (the response to therapy was related to connectivity between the left intraparietal sulcus and the frontal orbital cortex (Crowther et al, 2015).The response to CBT was associated with increased connectivity of the subcallosal cingulate cortex with the left ventromedial prefrontal cortex and the left ventrolateral prefrontal cortex (Dunlop et al., 2017)). LIMBIC GYRUS activity increased after psychotherapy (anterior cingulate gyrus area (Huang et al., 2014)) and was shown to be a predictor of treatment

response (dorsal anterior cingulate gyrus activity was correlated with symptom improvement (Huang et al., 2014) and CBT response has been associated with increased connectivity of the subcallosal cingulate cortex with the left midbrain, with left ventromedial prefrontal cortex/insula and that with left ventromedial prefrontal cortex (Dunlop et al., 2017)). Changes in the frontolimbic circuit observed at baseline were modulated by psychotherapy throughout treatment, associated with improvement in clinical symptoms (Lv et al., 2021). The analysis of the division of the area of the subcallous cingulus (anterior rostral cingulum (rACC), anterior subcalosus cingulum (aSCC) and Brodmann's area 25 (BA25)) showed that activation of the rAAC and aSSC areas had an inverse correlation with depressive symptoms prior to therapy, which increase after treatment (Pantazatos et al., 2020). INSULA activity was reported as being a predictor of outcomes (response to BATD was related to the pretreatment connectivity of the right insula with the right middle temporal gyrus (Huang et al., 2014) and response to CBT was associated with positive connectivity scores of the left insula with the subcallosal cingulate cortex (Dunlop et al., 2017)). TEMPORAL LOBE activity was reported as being a predictor of outcomes (response to BATD was related to the pretreatment connectivity of the right insula with the right middle temporal gyrus (Crowther et al, 2015)) PARIETAL LOBE activity was reported as being a predictor of outcomes (response to BATD was related to the pretreatment connectivity of the left intraparietal sulcus with the orbital frontal cortex (Crowther et al, 2015)). OCCIPITAL LOBE activity was described as having its low frequency fluctuation fractional amplitude increased after CBT (Shu et al., 2020). CEREBELLUM activity was described as having its low frequency fluctuation fractional amplitude increased after CBT (Shu et al., 2020).

DISCUSSION

This systematic review aimed to analyze functional changes and connectivity between brain areas associated with clinical improvement in patients diagnosed with MDD, without other psychiatric comorbidities, who underwent individual psychotherapies.

Task-based fMRI showed changes in basal nuclei and amygdala (Fu et al., 2008; Queirazza et al., 2019) whereas resting-state fMRI showed changes in subcallosal cingulate (Pantazatos et al., 2020). Considering the common findings between the two methods, we observed alterations in the temporal lobe (Fu et al., 2008; Walsh et al., 2017; Dichter et al., 2009; Crowther et al, 2015), frontal lobe (Fu et al., 2008; Walsh et al., 2017;

Dichter et al., 2009; Siegle et al., 2011; Costafreda et al., 2009; Walsh et al., 2019; Sankar et al., 2015; Huang et al., 2014; Crowther et al, 2015; Dunlop et al., 2017), insula (Fu et al., 2008 ; Dichter et al., 2009 ; Crowther et al, 2015
; Dunlop et al., 2017), parietal lobe (Fu et al., 2008 ; Dichter et al., 2009 ; Walsh et al., 2019; Crowther et al, 2015), occipital lobe (Fu et al., 2008; Dichter et al., 2009; Walsh et al., 2019; Shu et al., 2020 , cerebellum (Fu et al., 2008; Costafreda et al., 2009; Shu et al., 2020), and limbic gyrus (Fu et al., 2008; Walsh et al., 2017; Dichter et al., 2009; Costafreda et al., 2009; Sankar et al., 2015; Siegle et al., 2012; Carl et al., 2016; Siegle et al., 2006; Huang et al., 2014; Dunlop et al., 2017; Lv et al., 2021; Pantazatos et al., 2020). Many of the included studies reported activity in the limbic system as having varied at the end of treatment or as being predictive of clinical improvement, particularly areas of the cingulate cortex and amygdala. These brain areas are involved in behavioral and emotional responses, which are affected by depression (Pandya et al., 2012). There was no common area for all included studies, pointing to the complexity of the neural pathophysiology of this disorder and the intricate mechanisms of response to psychological treatment.

Studies that examine changes in brain activity that correlate with improvement in symptoms are relevant to increasing our understanding of potential mechanisms. Understanding which areas are affected by treatment allows for a better understanding of the pathophysiology of depression, as well as the mechanisms responsible for the remission of symptoms.

This review has some limitations inherent to the studies that it comprises. The studies had different follow-up times, ranging from 2 weeks to 8 months. Different types of psychotherapies were used, which makes comparison difficult. It was impossible to compare the effects between paradigm-based studies since the stimuli vary between studies. Finally, the studies are heterogeneous, which makes it impossible to carry out a meta-analysis.

As for future perspectives, it is still necessary to understand how the observed functional neuroimaging changes may be related to treatment refractoriness, as well as to assess how other response markers, such as inflammatory markers and neurotrophins, may also be associated with the observed functional changes, as well as points to the need for uniformity between the applied paradigms.

Therefore, functional neuroimaging tests are potential markers of response to psychotherapy treatment in patients diagnosed with major depression and are also

predictors of response to treatment. Thus, it is noteworthy that the identified changes in brain areas reinforce the role of therapy in controlling emotions and the consequent clinical improvement in patients with MDD.

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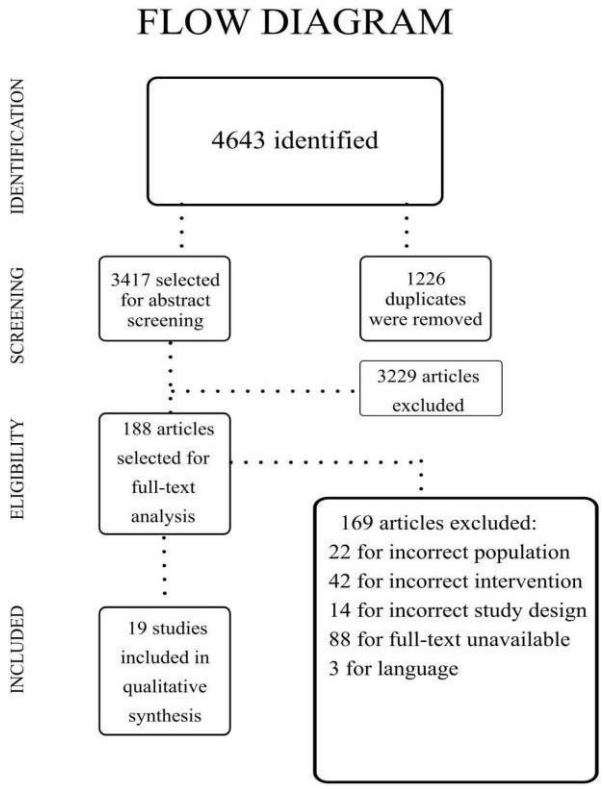

Figure 1- FLOWCHART

Table 1- Description of the characteristics of the included studies

Study	Depression (M/F)	Control (M/F)	Design	Time	Clinical Measure
(Walsh et al., 2017)	33 (11/22)	20 (6/14)	Longitudinal Study	2 - 15weeks	BDI, HDRS
(Dunlop et al., 2017)	37	85	Randomized Clinical Trial	12 weeks	BDI, HDRS
(Siegle et al., 2011)	32(15/17)	51 (15/36)	Longitudinal Study	16 sessions	BDI
(Siegle et al., 2012)	17(4/13); 32(5/27)	15(7/8) 20 (5/15)	Longitudinal Study	12 weeks	BDI, HDRS
(Costafreda et al., 2009)	16 (3/13)		Longitudinal Study	16 weeks	HDRS
(Crowther et al, 2015)	23 (5/18)	20 (6/14)	Longitudinal Study	8 - 15 weeks	BDI, HDRS
(Carl et al., 2016)	33 (11 /22)	20 (6/14)	Longitudinal Study	8 - 15 weeks	BDI, HDRS
(Dichter et al., 2009)	16 (7/9)	15 (6/9)	Longitudinal Study	15 weeks	BDI, HDRS
(Wiswede et al., 2014)	18 (4/14)	17 (3/14)	Longitudinal Study	8 months	BDI
(Huang et al., 2014)	23 (7/16))	20 (8/12)	Longitudinal Study	5 weeks	HDRS
(Klein et al., 2014)	10 (4/6)	10 (4/6)	Longitudinal Study	12 weeks	BDI, HDRS
(Queirazza et al., 2019)	37 (19/18)		Longitudinal Study	6 - 10 weeks	BDI,
(Sankar et al., 2015)	16 (3/13)	16 (3/13)	Longitudinal Study	16 weeks	HDRS
(Fu et al., 2008)	16 (3/13)	16 (3/13)	Longitudinal Study	16 weeks	BDI, HDRS
(Walsh et al., 2019)	33 (29%/71%)	20 (6/14))	Longitudinal Study	2 - 15 weeks	BDI
(Siegle et al., 2006)	14 (7/7)	21 (9/12)	Longitudinal Study	12 weeks	BDI
(Pantazatos et al., 2020)	19 (6/13)	10 (3/7)	Longitudinal Study	12 weeks	BDI
(Shu et al., 2020)	21 (8/13)	38 (17/21)	Longitudinal Study	8 weeks	HDRS
(Lv et al., 2021)	20 (4/16)	20 (7/13)	Longitudinal Study	6 WEEKS	HAMD, MADRS

Legend: BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; MADRS = Low Resistance Thought Induction Montgomery-Asberg Depression Rating Scale.

Table 2- Functional changes observed after psychotherapy in patients diagnosed with MDD

Study	Psychotherapy	fMRI	Task	Main Results
(Walsh et al., 2017)	BATD	task-based	monetary incentive delay	During reward anticipation, better response to BATD could be predicted by greater connectivity between the left putamen and paracingulate gyrus. Patients with greater connectivity attenuation between the left paracingulate gyrus, midline subcallosal cortex, and several frontostriatal seeds had better response to BATD.
(Siegle et al., 2011)	CBT	task-based	emotion identification/digit sorting	Correlations between increased sustained pupillary responses (which were associated with increased activity in dorsolateral prefrontal regions) in more severely depressed patients and worse outcomes after CT were found.
(Siegle et al., 2012)	CBT	task-based	sustained emotional information processing	Participants with the lowest pretreatment subgenual anterior cingulate cortex reactivity in response to negative words exhibited better response to psychotherapy.
(Costafreda et al., 2009)	CBT	task-based	incidental affective processing	Brain areas that had the greatest contribution to the prediction of better outcomes after psychotherapy included the paracentral cortex, the anterior cingulate, middle, and frontal cortices, the superior parietal cortex, the precuneus, and the cerebellum.
(Carl et al., 2016)	BATD	task-based	monetary incentive delay	Patients with greater sustained activation in the anterior cingulate cortex during reward outcomes had better response to psychotherapy.
(Dichter et al., 2009)	CBT	task-based	wheel of fortune	Psychotherapy resulted in functional changes in the paracingulate gyrus (during reward selection), the dorsal striatum (during reward anticipation), and orbital frontal and paracingulate gyri (during reward feedback).
(Wiswede et al., 2014)	PP	task-based	individualized stimuli	Patients initially had enhanced activation in subcortical and limbic regions (such as the amygdala and basal ganglia), which decreased after psychotherapy.
(Klein et al., 2014)	CBASP	task-based	emotional processing	After psychotherapy, there was an increase in the left amygdala reactivity.
(Queirazza et al., 2019)	I-CBT	task-based	probabilistic reversal learning	Greater pretreatment activity in the right amygdala and in the right striatum was displayed by patients who responded to psychotherapy.
(Sankar et al., 2015)	CBT	task-based	modified dysfunctional attitude scale	Extreme responses to dysfunctional attitudes scale statements were associated with greater activation in the inferior parietal lobe, in the left hippocampal region and in the precuneus. After psychotherapy, patients exhibited less attenuation in the left parahippocampal region.
(Fu et al., 2008)	CBT	task-based	implicit sad facial affect recognition	Patients displayed increased amygdala-hippocampal activity. Baseline dorsal anterior cingulate activity was associated with better response to psychotherapy.
(Walsh et al., 2019)	BATD	task-based	positive emotion regulation	Decreased connectivity between right temporoparietal regions and the left middle frontal gyrus, during positive emotion upregulation, predicted greater reduction of anhedonia symptoms after psychotherapy.
(Siegle et al., 2006)	CBT	task-based	sustained emotional information processing	Patients with low sustained reactivity to emotional stimuli in the subgenual cingulate cortex and with high sustained reactivity in the amygdala had better response to psychotherapy.

(Pantazatos et al., 2020)	CBT	Resting-State	-	Anterior subcallosal cingulate (aSCC) had an inverse correlation with depressive symptoms before therapy, which increased after treatment
(Shu et al., 2020)	CBT	Resting-State	-	Cerebellar area functional change after psychotherapy
(Lv et al., 2021)	TIP	Resting-State	-	Frontolimbic circuit changes observed at baseline were modulated, associated with improvement in clinical symptoms after treatment.
(Dunlop et al., 2017)	CBT	Resting-State	-	Resting-state functional connectivity of the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex was differentially associated with remission and treatment failure to CBT and antidepressant medication. Positive summed functional connectivity scores were associated with remission with CBT.
(Crowther et al, 2015)	BATD	Resting-State	-	Better outcomes after psychotherapy were predicted by pretreatment connectivity of the orbital frontal cortex with the left intraparietal sulcus and the right middle temporal gyrus with the right insula.
(Huang et al., 2014)	GIR	Resting-State	-	After psychotherapy, regional homogeneity in the anterior cingulate gyrus and in the ventromedial prefontal cortex increased. Higher pretreatment regional homogeneity, in the dorsal anterior cingulate gyrus, was correlated with better responses to psychotherapy.

Legend: BATD = Behavioral Activation Treatment for Depression; CBT = Cognitive-Behavioral Therapy; CT = Cognitive Therapy; PP = Psychodynamic Psychotherapy; GIR = Guided Imagery with Relaxation; CBASP = Cognitive-Behavioral Analysis System of Psychotherapy; I-CBT = Virtual Cognitive-Behavioral Therapy; tip = Low Resistance Thought Induction Psychotherapy.

AUTHOR CONTRIBUTIONS

FC: protocol production, results analysis, and article production. GR: preparation and registration of the review protocol, extraction of articles from databases, selection of articles, analysis of results, and article production. RM: selection of articles, results analysis, and article production. JM: selection of articles, results analysis, and article production. VS: selection of articles, results analysis, and article production. AB: selection of articles, results analysis, and article production. JD: main orientation, protocol production, review of articles in case of divergence, analysis of results, and article production. NR: main orientation, protocol production, review of articles in case of divergence, analysis of results, and article production.

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7. 3– ARTIGO 3

Submetido na Psychotherapy Research

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Reduction of suicide attempts and hospital readmissions in patients with mental illness undergoing psychotherapy: correlation with interleukin-6 levels

Felipe Cesar de Almeida Claudino[1,2,3], Giovana Bristot [4,5], Shanna Luiza de Castro [3], Neusa Sica da Rocha[1,2,3]

1-Center of Clinical Research, Center of Experimental Research, and Psychiatric Service Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS Brazil
2-Post-Graduation Program in Psychiatry and Behavioral Sciences, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
3- Inovations and Interventions for Quality-of-Life Research Group (I-QOL), Brazil
4- Laboratory of Molecular Psychiatry - Center of Experimental Research, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.
5- Post-Graduation Program in Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

ABSTRACT

Introduction: Mental illness is defined as a disorder that affects cognition, emotion, and behavior. In more severe cases, individuals with this diagnosis have a higher rate of psychiatric hospitalization and a suicide attempt profile. Inflammatory factors, such as interleukin-6, are greater in this group, and their reduction is related to symptom remission, indicating a potential for a biological marker of response to treatment.
Objectives: Longitudinal naturalistic study with 52 patients with mental illness who are undergoing individual psychotherapy and were evaluated 6 months after the study initiation. The patients answered a sociodemographic questionnaire and scales of quality of life, depressive and anxious symptoms. IL-6 levels were measured by immunoassay.
Results: There was an improvement in the four domains of quality of life, depressive and anxious symptoms, but these values were not significant. There was a significant reduction in the frequency of psychiatric hospitalization baseline 21 (40.38%), follow-up 2 (3,84%); p=0.003] and previous attempted suicide [baseline 25 (48.07%), follow-up 2 (3,84%); p=0.003]. Interleukin-6 levels did not show any differences in follow-up and compared to healthy controls

Conclusion: Individual psychotherapy in patients with mental illness has potential in the reduction of psychiatric hospitalization and attempted suicide. In our sample, the Interleukin-6 levels in the analyzed sample are not related to attempted suicide and psychiatric hospitalizations, life quality and anxiety and depressive symptoms.

Keyword: Mental Illness, Psychotherapy, suicide attempts, hospital readmissions, Interleukin 6

Introduction

Mental disorders are one of the biggest causes of ineptitude in the world and one of the most prevalent diseases in the last decade [1]. The diagnosis of these diseases is based on the assessment of signs and symptoms, with the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) being one of the most used instruments for this purpose [2]. These pathologies, when causing severe functional impairment, and affecting vital activities, with diagnosis and long-term treatment, are called serious mental illness, of which almost half of the individuals do not have psychotic symptoms [3]. This patient profile, which has a higher risk of psychiatric hospitalization, relapses, and attempted suicide [4], that are “hard outcomes” [5].

The origin of these disorders is uncertain, but it is believed that their causes are multifactorial, with the implication of social, environmental, and biological factors [4,5]. It is known that genetic factors are related to a higher risk to developing mental disorders throughout life, whether it is because of the genetic heritage or the involvement of neurodegenerative, metabolic, and inflammatory agents that participate in the physiopathology of mental illness [6,7,8]. Inflammatory processes have an important role in the physiological mechanisms involved in mental illness [9]. The inflammatory cascade can be triggered by injuries, pathogens, autoimmune diseases, and stress [10]. A range of cells act in this process, among which interleukin-6 stands out.

Interleukin-6 is a pro-inflammatory cytokine, responsible, in the central nervous system for neuroplasticity and synapse, among other actions [11]. It is often related to autoimmune diseases, such as rheumatoid arthritis [12]. Studies indicate that its suppression can contain the advance of these diseases, by reducing the activation of cytokines. It is also observed that interleukins play an important role in the pathophysiology of psychiatric disorders [13]. The increase in interleukin-6 was observed

in disorders such as Major Depression, Generalized Anxiety, Bipolar Affective Disorder and Schizophrenia [14,15,16]. Patients in psychiatric hospitalization with depressive symptoms have higher levels of IL-6 than healthy controls [17]. IL-6 activity is involved in the activation of the hypothalamic-pituitary-adrenal axis or influence of neurotransmitter metabolism, which are modified in patients diagnosed with depression [18].

Thus, there is evidence that their levels show a significant reduction with consequent clinical improvement of patients, when treatment with psychotropic drugs, such as Fluoxetine [19]. As pharmacotherapy, psychotherapy is a potential therapeutic tool for the treatment of these mental disorders, and as well as the use of medication, they can lead to the reduction of interleukin-6 levels [20]. The results of the effects of psychotherapies on interleukin-6 levels, however, are not yet conclusive [1,22].

Considering the considering the potential change in interleukin-6 levels and the remission of suicide attempts and hospital readmissions after psychotherapy, the objective of this study is compare patients' interleukin-6 levels with healthy control levels and to evaluate the relationship between interleukin-6 levels and the reduction of depression, anxiety symptoms, hospitalization, suicide attempts and increased quality of life in patients with mental illness, submitted to individual psychotherapy.

Materials and methods

A longitudinal naturalistic study was conducted over 6 months, with patients over 18 years old diagnosed with mental disorders undergoing individual psychotherapy at the Psychotherapy Outpatient Clinic of the Hospital de Clínicas de Porto Alegre (HCPA) , Rio Grande do Sul, Brazil, between the years from July 2016 to August 2019. The patients were referred from the primary care or other services at the tertiary hospital [23].

The patients were evaluated by a resident, with the approval of a preceptor and, if there was an indication for psychotherapy, they were referred to one of the following three types of individual psychotherapies: Psychodynamic psychotherapy (PDT), cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). The therapy was carried out by residents of the psychiatric service under supervision, within the institution.

When psychotherapy was indicated, a member of the group, who was not involved in patient care, sent an invitation to the patient so he could participate in the longitudinal study, and, if he agreed to participate, questionnaires were applied to assess anxiety

symptoms (Beck Anxiety Inventory) [24], depressive symptoms (Beck Depression Inventory) [25], quality of life (WHOQOL-Bref) [26] and socioeconomic and clinical data, such as gender, level education, suicide attempts, psychiatric hospitalizations and medication use.

The research group had no role in indicating therapy or choosing the modality, as it is a naturalistic study. The clinical evaluation and collection of biological material was carried out before or shortly after the beginning of psychotherapy, with subsequent follow-up for 6 months. There was no exclusion due to diagnosis of mental disorder for accession to the research.

For the analysis of the control group, volunteers without psychiatric comorbidities were invited to participate in the study, being submitted to the application of social questionnaire. The control group was recruited from the institution's blood bank service. After agreement and signing of the free and informed consent form, a standardized diagnostic interview (M.I.N.I) was carried out by one of the researchers, in which psychiatric history and health history were evaluated. Neurological and psychiatric diseases were considered exclusion criteria. The sampling of venous blood was also performed. For the analysis of this study, volunteers diagnosed with mental disorders or those with autoimmune diseases, infections, cancer, or pregnant women, were not included, as this could influence levels of interleukin-6.

All participants signed an informed consent form. The Research Ethics Committee of Hospital de Clínicas de Porto Alegre approved this study (2015-0097). The present study was conducted in accordance with the Declaration of Helsinki.

Venous blood samples obtained from patients and control were centrifuged for 10 minutes at 1.000 xg and the serum removed, aliquoted and stored at -80 ºC. Serum IL-6 levels were obtained by multiplex immunoassay using the commercial ProcartaPlex kit, following the manufacturer's guidelines. The average fluorescent intensity data were analyzed using a 5-parameter logistic method to determine the concentrations of interleukin-6 in each sample (Luminex Xponent 3.1 software).

Statistical analyzes were performed using SPSS version 24.1. Sociodemographic analyzes of patients undergoing psychotherapy were described using frequency, mean and standard deviation. The Kolmogorov-Smirnov test was performed to assess the distribution of the studied variables, using the Mann-Whitney or Wilcoxon test to compare means in non-parametric data conditions and Student's t tests of paired samples, if the data were parametric. Generalized Estimation Equation (GEE) was performed to

assess interleukin-6 levels after 6 months of follow-up, in addition to other variables of interest: quality of life domains, depressive and anxiety symptoms. Potential confounders of interleukin levels were considered in the analysis, such as time in treatment age, education, number of hospitalizations, suicide attempts and medication use. Paired post-hoc analyzes were performed and adjusted by Bonferroni correction for multiple comparisons. The values of the interleukin levels of the group submitted to psychotherapy were compared to the control group, with a significance of $p < 0.05$.

Results

A total of 52 patients undergoing individual psychotherapy and 48 controls were included in this study. The sociodemographic and clinical information of the patients and the control group are shown in table 1.

Table 1 - Sociodemographic and clinical information of patients undergoing psychotherapy and control group

	Baseline (n=52)	Controls (n=48)	p value
Age	45.50 (10.99)	34.89 (10.96)	0.995
Sex (female)	40 (76.9%)	39 (81.3%)	0.631
Ethnicity (White)	45 (86.5%)	39 (81.3%)	0.588
Education			
Middle school or less	29 (56.9%)	25 (53.2%)	0.001
High school or more	22 (43.1%)	22 (46.8%)	

Table 2 shows that the main therapy implemented in the group was Psychodynamic psychotherapy The most prevalent substance of abuse was alcohol. The number of hospitalizations reported at baseline was over a quarter and over 50% reported at least one suicide attempt. Among the medications in use, it is noteworthy that 69,23% of the sample used antidepressant and the most prevalent percentage of diagnosis was major depressive disorder.

Table 2 - Clinical information of patients undergoing psychotherapy

	Baseline (n=52)
Therapy	
CBT	10 (19.2 %)
IPT	7 (13.5%)
PDT	35 (67.3%)
Diagnosis	
Major Depressive Disorder	27 (51.9%)
Afective Disorder	5 (9.6%)
Anxiety Disorder	7 (13.5%)
Personality Disorder	2 (3.8%)
Post-traumatic stress disorder	1 (1.9%)
Obsessive-compulsive disorder	2 (3.8%)
Eating Disorder	2 (3.8%)
Others	6 (11.5%)

Legends: (CBT): Cognitive-behavior therapy; (IPT): Interpersonal therapy; (PDT): Psychodynamic psychotherapy

Table 3 – Hard outcomes and medications of patients undergoing psychotherapy

	Baseline (n=52)	**Follow-up (n=52)**	**p value**
Hard outcomes			
Psychiatric hospitalizations	21 (40,38%)	2 (3.84%)	0.003
Previous suicide attempts	25 (48.07%)	2 (3.84%)	0.003
Use of Psychiatric medication			
Antidepressant use	36 (69.23%)	38 (73.07%)	0.898
Antipsychotic use	10 (19.23%)	8 (14.81%)	0.642
Mood stabilising	8 (14.81%)	6 (11.53%)	0.773
Benzodiazepines use	9 (17.30%)	7 (13.46%)	0.823

1- Quality of Life (World Health Organization Quality of life -WHOQOL-BREF)

Comparing the Quality of life scores at baseline and at 6-month follow-up, there was an increase in the scores in the 4 domains: physical [53.64 (95% CI, CI: 49.81-57.47) versus [57.77 (95% confidence interval, CI: 53.70-61.85); p=0.818], psychological [50.74 (95%, CI: 46.56-54.93) versus 53.88 (95%, CI: 50.10-57.67); p=0.08], social [54.01 (95% ,CI: 49.50-58.51) versus 55.55 (95%, CI: 51.40-59.70); p=0.140] and environmental [57.90 (95%, CI: 54.63-61.18) versus [58.68 (95%, CI: 55.72-61.63); p:=0.250], although the values were not significant.

2- Depressive symptoms (Beck Depression Inventory-BDI)

Comparing the depressive symptoms between baseline and 6-month follow-up, there was a non-significant reduction in the levels of depressive symptoms [30.91 (95% confidence interval, CI: 28.03-33.79) versus [28.38 (95% confidence interval, CI: 24.86 -31.91; p=0.235]. Longitudinal analysis adjusted for confounding factors showed that age below 45 years and female gender are related to the improvement of depressive symptoms (Table 4).

3- Anxiety symptoms (Beck Anxiety Inventory-BAI)

Comparing the anxiety symptoms between baseline and 6-month follow-up, there was a reduction in the score for anxious symptoms, although the value was not significant [24.59 (95%, CI: 21.59-28.00) versus [20.55 (95%, CI: 16.77-24.33); p=0.686]. The longitudinal analysis adjusted for confounding factors did not show any interaction with this measure (Table 4).

Interleukin-6 (IL-6) levels

For the analysis of interleukin-6 levels, data from 52 patients and 48 controls were analyzed. Scores were compared between baseline and 6-month follow-up, there was a stabilization of interleukin levels, with a non-significant variation, as shown in Table 3. The adjusted longitudinal analysis for confounding factors showed that greater schooling is related to reduction levels of interleukin in the sample, as shown in Table 4.

Table 4 - Variations in quality of life, depressive and anxious symptoms in patients undergoing psychotherapy

Measure	Baseline (n=52)	Follow-up (n=48)	p-value
WHOQOL-Bref Social Relationships domain	54.01 (49.50-58.51)	55.55 (51.40-59.70)	0.140
WHOQOL-Bref Psychological domain	50.74 (46.56-54.93)	53.88 (50.10-57.67)	0.080
WHOQOL-Bref Physical domain	53.64 (49.81-57.47)	57.77 (53.70-61.85)	0.818
WHOQOL-Bref Environment domain	57.90 (54.63-61.18)	58.68 (55.72-61.63)	0.250
Depressive Symptoms (BDI)	30.91 (28.03-33.79)	28.38 (24.86-31.91)	0.235
Anxiety (BAI)	24.59 (21.59-28.00)	20.55 (16.77-24.33)	0.686

Legends: (BDI): Beck Depression Inventory, (BAI): Beck Anxiety Inventory

There was no difference significant difference in the levels of cytokine between the control group and the group undergoing psychotherapy: baseline median 1.18 pg/ml, follow-up median 1.45 pg/ml, controls median 1.36 pg/ml; p>0.05 (table 4).

Table 5 –Interleukin-6 levels in patients and healthy controls

	Groups		**P value**
	Patients baseline (n=52)	**Patients Follow-up (n=52)**	
	Median (IQR)	**Median (IQR)**	
IL-6	1.18 (0.49-1.82)	1.45 (0.63-2.25)	0.132
	Patients baseline (n=52)	**Controls (n=48)**	
	Median (IQR)	**Median (IQR)**	
IL-6	1.18 (0.49-1.82)	1.36 (0.72-2.19)	0.153
	Patients Follow-up (n=52)	**Controls (n=48)**	
	Median (IQR)	**Median (IQR)**	
IL-6	1.45 (0.63-2.25)	1.36 (0.72-2.19)	0.678

To adjust for the confounding effect, variables such as 6-month follow-up time (time), age, education (middle school or less x High school or more), gender (male x female), treatment with mental health medications, psychiatric hospitalizations, and number of suicide attempts throughout life were evaluated (table 6).

Table 6- Covariates tested for adjustment of confounding effect (GEE).

Dependent variable	**Covariates**	**Wald Chi-Square**	**Significance (p-value)**
Physical Domain (WHOQOL)	Time	8.675	0.003
	Time x age	0.373	0.541
	Time x schooling	0.477	0.924
	Time x gender	0.403	0.526
	Time x treatment	1.727	0.189
	Time x hospitalization	1.226	0.268
	Time x suicide attempt	3.296	0.069
Psychological Domain (WHOQOL)	Time	4.350	0.037
	Time x age	0.139	0.709
	Time x schooling	2.175	0.537

	Time x gender	5.809	0.016
	Time x treatment	0.000	0.998
	Time x hospitalization	0.040	0.842
	Time x suicide attempt	0.018	0.894
Social relationships Domain (WHOQOL)	Time	0.615	0.433
	Time x age	4.702	0.030
	Time x schooling	5.50	0.138
	Time x gender	0.006	0.940
	Time x treatment	2.50	0.109
	Time x hospitalization	1.70	0.192
	Time x suicide attempt	3.477	0.062
Environment Domain (WHOQOL)	Time	0.167	0.683
	Time x age	1.909	0.167
	Time x schooling	1.406	0.704
	Time x gender	0.990	0.320
	Time x treatment	3.080	0.079
	Time x hospitalization	1.571	0.210
	Time x suicide attempt	0.904	0.342
BDI	Time	3.699	0.054
	Time x age	2.045	0.153
	Time x schooling	1.692	0.639
	Time x gender	4.335	0.037
	Time x treatment	0.136	0.712
	Time x hospitalization	1.353	0.245
	Time x suicide attempt	0.012	0.913
BAI	Time	7.160	0.007
	Time x age	13.179	0.000
	Time x schooling	3.856	0.277
	Time x gender	0.456	0.449
	Time x treatment	1.673	0.196
	Time x hospitalization	2.500	0.144
	Time x suicide attempt	0.795	0.373
IL-6	Time	0.556	0.452
	Time x age	0.014	0.906
	Time x schooling	11.243	0.010
	Time x gender	1.326	0.250
	Time x treatment	1.396	0.237
	Time x hospitalization	0.085	0.771
	Time x suicide attempt	0.134	0.714

Legends: (BDI): Beck Depression Inventory, (BAI): Beck Anxiety Inventory; (IL-6): Interleukin-6

The data in table 5 show that there is a significant increase in the scores of the physical and psychological domains in the interaction with the 6-month follow-up, sex and time interaction in the psychological domain and depressive symptoms, age in social relationships and anxiety symptoms and schooling in IL-6 levels.

Discussion

To our knowledge, this is the first study that aims to evaluate the clinical response, suicide attempts, hospital readmissions, and their association with inflammatory markers (IL-6) in patients with diagnosis of mental disorders who underwent 3 different types - Psychodynamic psychotherapy (PDT), cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) - of psychotherapy with a six-month follow-up. Although clinical diagnosis varied, mainly concentrated in Major Depressive Disorder, Generalized Anxiety Disorder and Bipolar Affective Disorder, a common pattern was observed in these groups, with high depressive and anxiety scores, reduced quality of life, significant percentages of previous suicide attempts and previous psychiatric hospitalizations e, as listed in table 2.

The main findings of the study showed that individual psychotherapy can stabilize the disease. The group presented characteristics such as a significant number of previous psychiatric hospitalizations [21 (40.38%), follow-up 2 (3,84%); p=0.003] and previous attempted suicide [baseline 25 (58.07%), follow-up 2 (3,84%); p= 0.003]. The frequency of these events showed a significant reduction in the 6-month follow-up, $p<0.05$.

The 4 domains of quality of life had an increase in their score, concomitant to the reduction in the score of depressive and anxious symptoms, but these results were not related to a significant variation in the levels of interleukin-6. The model for factors such as time, age, gender, education, medication, history of psychiatric hospitalization and previous suicide attempt showed that the scores of physical and psychological domains vary positively with time, as well as the improvement of social function and reduction of depressive symptoms was observed in individuals over 45 years old.

Patients with mental disorders, such as those with treatment resistant major depressive disorder [27], generalized anxiety disorder [28] and affective bipolar disorder [29] showed reduction in the life quality [30]. Psychotherapy has been shown to be effective in improving these outcomes in patients with different psychiatric disorders [31].

Patients diagnosed with severe depression have high BDI scores, results also observed in the sample of this study, since almost half of the sample had a score above 29 points on the scale, which is a value considered within the range of most severe depressive symptoms [32]. Although there is evidence that patients diagnosed with treatment-resistant depression while on pharmacotherapy experienced clinical improvement for more than 12 months after starting CBT [33], resistance to treatment is a sign of worse prognosis in patients [34].

Interleukin levels, especially interleukin-6, are potential markers of response to treatment of patients with mental disorders undergoing psychotherapy. One of the first studies to assess the impact of psychotherapy on interleukin-6 demonstrated that cytokine levels decreased in women in the first depressive episode, and in patients with severe depressive symptoms [32]. However, later studies have shown that cognitive behavioral therapy did not change interleukin levels and, even when there was a variation in IL-6 levels, this finding was not maintained after 12 months [33].

Patients with psychiatric hospitalization, with more severe acute illness, have higher levels of IL-6 compared to healthy controls [33]. The low levels in the study sample and values without significant difference when compared to the healthy control group may indicate the potential of IL-6 as an inflammatory marker in acute conditions [33], which would not apply to the sample, in which more than 80% started psychotherapy while on medication, with diagnosis and previous treatment, therefore, with diagnosis chronic of mental disorders. Treatment with medications in effect before the start of therapy may have impacted the low levels of IL-6 in the baseline sample, with no changes in follow-up and no changes compared to the control group.

It is necessary to consider that in a population with severe diagnosis, symptoms stabilization, suicide attempts and hospital readmissions reduction, like suicide attempt and hospitalization, are markers of response to treatment, since not all patients are going to have significant clinical remission [33]. The improvement in quality of life, reduction of depressive symptoms, remission of anxious symptoms and the reduction of psychiatric hospitalizations and suicide attempts, are, therefore, disease control markers.

The study has some limitations. In the current context of the pandemic, it was impossible to maintain the collection of sample follow-up from 2020. The introduction of online psychotherapy in this sample, which was previously submitted to face-to-face psychotherapy, could be an unanticipated confounding factor, which is why we chose not to perform the follow-up in this treatment modality. Hospital collections were also a

limitation in the context of the pandemic, which reduced the total number of patients with dosed interleukin levels. There is also a need to correlate clinical findings and levels of interleukin-6 with other factors, such as functional changes in the level of the central nervous system, levels of neurotrophins and the measurement of other inflammatory cytokines levels. The small number of patients who were not undergoing drug treatment limited the effects of the exclusive analysis of the effects of psychotherapies in the sample, since it is known that antidepressants, antipsychotics, and mood stabilizers act to reduce inflammatory cytokines [33].

Conclusion

The introduction of psychotherapy in patients with mental disorders undergoing drug treatment has the potential to reduce psychiatric hospitalizations and attempted suicide. The association of outcomes and changes in interleukin-6 levels was not observed in the sample.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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7.2 – ARTIGO 4

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Evidence-based therapies in patients with mental disorders: a naturalistic study of clinical outcomes and biological marker

Felipe Cesar de Almeida Claudino[1,2,3], Giovana Bristot[4,5], Neusa Sica da Rocha[1,2,3]

1-Center of Clinical Research, Center of Experimental Research, and Psychiatric Service Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS Brazil
2-Post-Graduation Program in Psychiatry and Behavioral Sciences, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil
3- Innovations and Interventions for Quality-of-Life Research Group (I-QOL), Brazil
4- Laboratory of Molecular Psychiatry - Center of Experimental Research, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.
5- Postgraduate Program in Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

ABSTRACT

Evidence-based psychotherapies are effective in the treatment of mental disorders, with results equivalent to pharmacological treatment. There is evidence that treatment response is associated with altered levels of brain-derived neurotrophic factor (BDNF), a neurotrophin associated with neuronal plasticity.

The aim of the present study is to evaluate the BDNF levels of patients diagnosed with severe mental disorders undergoing individual psychotherapies at a 6-months period.

BDNF levels were collected at the beginning of the study and 6 months after the first collection, in addition to the application of a socioeconomic survey and Beck's depression questionnaire.

Amongst the total of 47 patients, 25 (53.19%) had a history of at least one psychiatric hospitalization and 21 (44.68%) suffered at least one suicide attempt in the initial evaluation. The number of hospitalizations and suicide attempts dropped to 2 (4.25%; p= 0.003) during follow-up. The BDI scores indicate severe symptoms, which did not show any significant change over the 6-month follow-up ((29.93 (10.43) 29.25 (12.83); p= 0.253), as well as BDNF levels (77.28 (34.31); 72.68 (36.61); p=0.855)). In multiple linear regression (variables: psychotropic drugs, previous psychiatric hospitalization, and suicide attempt), BDNF levels were associated with the use of mood stabilizer B (0,439;

p=0.019).
The study reinforces that the association of psychotherapy and psychotropic drugs is associated with a reduction in hospitalization and suicide attempts, with no impact on BDNF levels.
Keywords: Psychotherapy, Depression, BDNF

INTRODUCTION

Mental disorders are among the most frequent and disabling pathologies of the last decades [1]. The global prevalence estimate was 28.0% for depression; 26.9% for anxiety; 24.1% for post-traumatic stress symptoms; 36.5% for stress; 50.0% for psychological distress; and 27.6% for sleep problems only during the year of 2020, in the advance of the COVID-19 pandemic [2]. With varied progression, these pathologies are associated with reduced quality of life [3], decreased ability to work [4], and, in more severe cases, increased risk for hospitalization and suicide attempt [5,6].

Currently, there are several lines of treatment for these disorders according to the established diagnosis, the most recommended lines of treatment being pharmacological therapy and psychotherapy [7]. Among non-pharmacological therapies, evidence-based psychotherapies have been shown to be effective in reducing psychological symptoms, as well as physical activity, for example [8]. Systematic review data indicate that the association between treatments is more effective than their application alone, reinforcing the importance of joint and multimodal treatments [9].

Among the various modalities of psychotherapies used in the treatment of mental disorders, the American Psychiatric Association established criteria for defining the concept of Evidence-Based Therapies, characterized by scientific studies, proving their effectiveness through longitudinal studies, systematic reviews, and clinical trials [10].

Within this context, studies have sought to analyze biological markers associated with remission of symptoms after therapy [11]. These markers allow an objective assessment of outcome, in addition to patient self-report [12]. It is observed, for example, the potential in the use of ciytokines [13], neuroimaging [14], and neurotrophins such as brain-derived neurotrophic factor (BDNF) [15], either as a marker of results or as a predictor of response to treatment.

Among these markers, BDNF stands out: a neurotrophin related to neuronal plasticity [16]. It is mainly related to brain areas such as the hippocampus [16], which is associated

with mental illness [18]. Its levels are altered in disorders such as depression [19], anxiety [20], and bipolar disorder [21] compared to the healthy population. On the other hand, an increase in serum and plasma values is observed after therapy and use of psychotropic drugs and psychotherapies in the short term, associated with remission of symptoms [22,23] thus being a potential marker of response to psychiatric treatment [24]. A 2020 systematic review showed that only 8 studies analyzed BDNF levels in patients undergoing individual psychotherapies, with varying results in cases of depressive symptoms and/or diagnosis of major depressive disorder [25].

Most studies carried out with this population undergoing psychotherapies, to date, have not considered the benefits of psychotherapies in a community with a history of more severe mental disorders and with interleukin dosages greater than 12 weeks. Considering this context, the objective of this study is to analyze BDNF levels at 6 months of patients diagnosed with mental disorders undergoing evidence-based psychotherapies in a specialized service outpatient clinic, considering the impact of variables such as medication use and previous psychiatric history on interleukin levels.

METHODOLOGY

A naturalistic longitudinal with a 6-month follow-up of adult patients diagnosed with mental disorder undergoing individual psychotherapy- Psychodynamic psychotherapy (PDT), cognitive behavioral therapy (CBT), and interpersonal therapy (IPT) - at the Psychotherapy Outpatient Clinic of the *Hospital de Clínicas de Porto Alegre* (HCPA), Rio Grande do Sul, Brazil, was carried out in July, 2016 to August 2019.

When psychotherapy was required, the patient was contacted by the research group and, after free and informed consent, there were questionnaires to assess socioeconomic and clinical data, such as sex, education level, suicide, psychiatric hospitalizations, and use of medications. To measure depressive symptoms, the Beck Depression Inventory (BDI) was used, consisting of 21 items that assess hopelessness, guilty feelings, worthlessness, punishment feelings, self-dislike, physical symptoms, suicidal thoughts, appetite, interest in sex and sleep [26].

The control group was recruited from the institution's blood bank service. Neurological and psychiatric illnesses were considered the exclusion criteria. For an analysis of this study, those with mental disorders or those with autoimmune diseases, cancer, or pregnant women were not included.

BDNF serum levels were measured by sandwich-ELISA using a commercial kit, according to the manufacturer's instructions (Millipore, USA). Briefly, microtiter plates (96-well flat-bottom) were incubated overnight at 4 ºC with the samples diluted 1:75 in sample diluent and standard curve ranging from 15.63 to 1000 pg/mL of BDNF. Thus, plates were washed four times with a wash buffer followed by the addition of biotinylated mouse anti-human BDNF monoclonal antibody (diluted 1:1000 in sample diluent), which was incubated for 2 hours at room temperature. After washing, incubation with streptavidin-horseradish peroxidase conjugate solution (diluted 1:1000 in sample diluent) for 1 hour at room temperature was carried out. After the addition of substrate and stop solution, the amount of BDNF was determined (absorbance set at 450 nm). The standard curve demonstrates a direct relationship between optical density and BDNF concentration.

All participants signed an informed consent form. The Research Ethics Committee of *Hospital de Clínicas de Porto Alegre* approved this study (2015-0097). The present study was conducted in accordance with the Declaration of Helsinki.

The Kolmogorov-Smirnov (KS) test was applied to assess the normality of the sample distribution. A paired t-test analysis was performed to determine whether there were differences between BDNF levels at baseline and 6 months later. A multivariate analysis of variance was performed to test the effects of medications -psychotropic drugs - previous psychiatric hospitalization, and previous suicide attempt on BDNF samples. Variables were listed based on the potential for altering BDNF levels, according to literature data, as well as the inclusion of hospitalization and suicide attempt. Statistical analyzes were performed using SPSS version 20 software. Data are presented as means ± standard deviations, frequency, or percentages.

RESULTS

Clinical and demographic characteristics of patients and controls are shown in Table 1. There was no significant difference in age and education between the groups, as for sex, there was a greater predominance of women among the participants. The average number of therapy sessions was greater than 35 over 6 months, especially for analytically oriented therapy. More than half of the patients used some psychotropic drug, whether benzodiazepine, mood stabilizer, antipsychotic or selective inhibitor, the latter being used by 10 patients.

Table 1- Sociodemographic and clinical characteristics of patients and control group

	Patients (n=47)	**Controls (n=48)**	
Age	46.59 (11.09)	34.89 (0.99)	0.002
Ethnicity - White	40 (87%)	39 (81.3%)	0.612
Gender	F: 36 (78.3%)	F: 39 (81.3%)	0.514
Medication usage	Baseline	6-month	p
ISRS	36 (76.5%)	38 (80.8%)	0.486
Mood stabilizer	10 (21.2%)	6 (12.7%)	0.533
Antipsychotic	8 (17.0%)	7 (14.8%)	0.420
Benzodiazepines	9 (19.1%)	7 (14.8%)	0.420
Suicide attempt	21 (44.6%)	2 (4.2%)	0.003
Psychiatric hospitalization	25 (53.2 %)	2 (4.2%)	0.003
BDI	29.93 (10.43)	29.25 (12.83)	0.253
Number of sessions		35.61 (7.19)	
CBT		9 (19.6%)	
POA		31 (67.4 %)	
IPT		6 (13 %)	
Diagnosis			
Depressive Disorders		29 (61.7%)	
Anxiety Disorders		5 (10.6%)	
Bipolar Disorder		5 (10.6%)	
Personality Disorders		3 (6.4%)	
Others Disorders		5 (10.6%)	

Legend: CBT: Cognitive Behavior Therapy; Analytical Oriented Psychotherapy (AOP); IPT: interpersonal Therapy. Other disorders: obsessive compulsive disorder, Post-traumatic stress disorder, Addiction.

BDNF levels did not show significant variation during follow-up [baseline (77.28 (34.31); follow-up 72.68 (36.61); controls 69.60 (23.89); p> 0.05) Its levels at the beginning of the follow-up and after 6 months did not vary significantly, there was also no difference compared to the group of healthy controls. Beck's depression inventory scores, used to measure depressive symptoms did not vary significantly in the analyzed period.

Table 2- BDNF levels of patients and control group

	Groups		P value
	Patients baseline (n=47)	**Patients Follow-up (n=47)**	
BDNF	77.28 (34.31)	72.68 (36.61)	0.314
	Patients baseline (n=47)	**Controls (n=48)**	
BDNF	77.28 (34.31)	69.60 (23.89)	0.211
	Patients Follow-up (n=47)	**Controls (n=48)**	
BDNF	72.68 (36.61)	69.60 (23.89)	0.772

BDNF (ng/ml)
Legend: BDNF: Brain-derived neurotrophic fator; BDI: Beck Depression Inventory.

In the multiple linear regression, used to assess variables – medications, previous psychiatric hospitalization – related to BDNF levels at the end of the 6-month follow-up, the use of a mood stabilizer was shown to be significant for the increase in neurotrophin levels (B 0.439; p=0.019). Drug use, psychiatric hospitalization history or suicide attempts did not impact neuromarker levels in the studied sample.

Table 3: Multivariate tests of serum BDNF levels (ng/mL), pharmacological treatment and psychiatric predictors

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	**t**	**Sig.**
Selective inhibitor	19.371	16.760	.212	1.156	.255
Antipsychotic	-5.794	14.624	-.066	-.396	.694
Mood stabilizer	42.018	17.108	.439	2.456	.019
Benzodiazepine	-9.077	14.269	-.099	-.636	.529
Psychiatric hospitalization	1.530	7.562	.041	.202	.841
Suicide attempt	7.467	7.104	.209	1.051	.300

R^2 = 0.168, adjusted R^2 = 0.037, p = 0.290

Dependent Variable: BDNF after 6 months

Independt variables: medications: selective inhibitor, antipsychotic, mood estabilizer, benzodiazepine.

Psychiatric Predictors: Psychiatric hospitalization and suicide attempt

Discussion

The study followed patients undergoing individual psychotherapies in 3 different

modalities over 6 months, with different diagnosed disorders. Patient results showed that depression scores and brain-derived neurotrophic factor levels did not vary significantly during the follow up period. To date, this is the first study to analyze 3 different modalities of psychotherapies – Cognitive Behavior Therapy; Analytical Oriented Psychotherapy (AOP); IPT: interpersonal Therapy – simultaneously for a period longer than 12 weeks, in patients with a more severe profile, with a high history of suicide attempts [(21 (44.6%) and psychiatric hospitalizations (25 (53.2 %)], using or not using psychotropics.

The use of medication remained stable throughout the follow-up, as well as there was a low percentage of hospitalizations or suicide attempts in the 6-month follow-up after the start of psychotherapy, with only 2 cases reported (4.2%) p=0.003. The use of mood stabilizers was associated with an increase in BDNF in the analyzed sample, which is consistent with the literature [27, 28, 29]. Neurotrophin levels showed no variation compared to the control group. This may have been due to the previous use of psychotropic drugs, which led to an increase in the marker prior to the follow-up of this study.

Leet et al. showed that BDNF levels were reduced in patients with a history of suicide attempts, which may explain the stable values found in the follow-up, who started the follow-up, mostly using psychotropic drugs that can lead to changes in BDNF levels [30]. The severity of the diagnosis and prognosis of these patients can be observed by the maintenance of high values of BDI scores, even after 6 months of follow-up and medication use. Similar studies showed that there was no change in neurotrophin values after psychotherapy in patients diagnosed with depression [15, 22].

This study has some limitations. Not all patients were treated exclusively with psychotherapy. The use of mood stabilizers and associated SSRIs has the potential to raise BDNF levels [31]. The BDNF methylation analysis of the collected samples was not performed, which may lead to changes in neurotrophin levels [32]. Nutritional factors, physical activity, external stressors were also not considered in the analysis of this study. The study expands the discussion on neurotrophin as a long-term response marker in response to psychotherapy associated with drug treatment, which is still conflicting in the literature. Understanding the physiology of treatment response through markers is a potential to reinforce the relevance and effectiveness of psychotherapies as treatments for mental disorders. The results, however, must be considered based on the profile presented, with patients with indicators of severity in the course of the disease, as well as considering that serious outcomes showed a significant reduction in the follow-up period

of the sample.

As a future perspective, the insertion and comparison with other biological markers in the same sample and the analysis of BDNF methylation in this sample will be allies in understanding the pathophysiology of mental disorders in patients with severity factors in mental disorder, as in this study.

Data Availability

Datasets for this manuscript are not publicly available. This study integrates a cohort of patients undergoing psychotherapies in a specialized outpatient clinic of a tertiary hospital, with the confidentiality of the information remaining confirming the free and informed consent form signed by the participants.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Study conception and design: FC, GB and NR. Acquisition of data: FC and NS. Analysis and interpretation of data: FC and NR. Drafting of manuscript: FC, GB and NR. Critical revision: FC, GB, and NR.

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8.0 CONSIDERAÇÕES FINAIS E CONCLUSÃO

Este trabalho teve como objetivo ampliar o entendimento dos mecanismos neurobiológicos das psicoterapias baseadas em evidência em pacientes com transtornos mentais. Os principais achados desta tese são:

A revisão sistemática da literatura evidenciou que o BDNF é um potencial marcador de resposta ao tratamento psicoterápico, abrindo caminho para a elucidação do mecanismo de ação das psicoterapias a nível de sistema nervoso central. Entretanto, os resultados não são consistentes em pacientes com depressão, doença altamente prevalente, o que reforça a necessidade de mais estudos sobre o tema.

O segundo artigo demonstrou que a ressonância magnética funcional permite avaliar áreas associadas à remissão de sintomas no diagnóstico de depressão. A heterogeneidade das áreas encontradas pode ser explicada pelas diferentes técnicas empregadas durante a realização do exame funcional ou pela ativação de diferentes vias que convergem na melhora de sintomas.

O estudo três não demonstrou redução de inteleucina-6 em pacientes submetidos a psicoterapias individuais, e seus valores não diferiam estatisticamente dos níveis encontrados em controles saudáveis. Deve-se considerar o perfil dos pacientes do estudo: com alta prevalência de uso de medicações, além de número expressivo de histórico de internação psiquiátrica e tentativa de suicídio, que são considerados agravantes no prognóstico. Sendo assim, a psicoterapia pode estar associada à estabilização do quadro psiquiátrico e a manutenção dos níveis de interleucina-6 pode ser explicada pela ação anti-inflamatória da citocina, além do fato de que a IL-6 pode ser um marcador de resposta aguda nos diagnósticos estudados, o que não é o caso da amostra avaliada, além do mecanismo complexo de interação entre diversas citocinas inflamatórias, o que ainda não está bem elucidado pela literatura atual.

O estudo quatro não encontrou alterações significativas dos níveis de BDNF e o uso de estabilizados de humor foi associado ao aumento deste marcador. Os escores de sintomas depressivos não variavam significativamente no seguimento, embora o número de internações e tentativa de suicídio tenha reduzido significativamente. Os valores de BDNF no início do seguimento não apresentou diferença se comparado ao grupo controle, o que levanta a hipótese de que o uso prévio de psicofármacos pelos pacientes pode ter elevado os níveis do fator neurotrófico.

Portanto, os biomarcadores têm potencial no seguimento de resposta às

psicoterapias baseadas em evidência. Os estudos apresentados contribuem para a divulgação, conhecimento e valorização das psicoterapias, permitindo uma indicação mais precisa de determinadas técnicas, a partir da utilização de marcadores neurobiológicos. Com isso, abrindo espaço para um importante e incipiente linha de pesquisa que permita indicações mais precisas de determinadas intervenções a partir da utilização de marcadores neurobiológicos

9.0 LIMITAÇÕES

Os estudos apresentados possuem algumas limitações metodológicas. A primeira, relacionados às revisões sistemáticas é a carência de estudos que avaliem os níveis de BDNF em pacientes submetidos a psicoterapias. A quantidade limitada de resultados (k=8), número pequeno de participantes, associada a heterogeneidade das psicoterapias empregadas e dos diagnósticos dificulta um resultado mais preciso, o que inviabilizou realização de uma metanálise.

Em relação ao segundo artigo, a heterogeneidade das psicoterapias e paradigmas empregados nos diferentes estudos limitou uma análise mais abrangente dos dados, tornando necessária a segmentação das ressonâncias funcionais. Importante destacar que, juntamente com a metodologia empregada e softwares utilizados para as análises, que divergiram entre os estudos, as técnicas de psicoterapia empregadas também apresentam variações, que impedem a generalização dos resultados.

No que tange ao terceiro e quarto artigo, houve redução do número de participantes esperados em decorrência da pandemia da COVID-19, fazendo com que os pacientes passassem a realizar psicoterapia na modalidade virtual e impossibilitando a coleta de material biológico para as análises posteriores dos pacientes que já haviam realizado as coletas iniciais.

10.0 PERSPECTIVAS FUTURAS E IMPLICAÇÕES CLÍNICAS

O estudo reforça as necessidades apontadas para os investimentos e pesquisa em psicoterapias baseadas em evidência. O reconhecimento de marcadores biológicos, seja como preditores de resposta ao tratamento ou marcador de tratamento associado aos desfechos clínicos é um instrumento a mais para corroborar os benefícios desse recurso terapêutico. O estudo também destaca a necessidade e relevância de investimento na área, considerando os poucos trabalhos encontrados nas revisões realizadas. Considerando os achados descritos, pretende-se futuramente realizar análise das metilações de BDNF e neuroimagem na amostra desta tese.

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ANEXO A- TERMO DE CONSENTIMENTO LIVRE ESCLARECIDO

Você está sendo convidado para participar de um estudo que se propõe a avaliar o efeito das psicoterapias em longo prazo. O efeito positivo das psicoterapias (de orientação analítica, interpessoal e cognitivo-comportamental) já foi determinado por inúmeros estudos internacionais e em populações brasileiras, mas seus efeitos a longo prazo ainda são pouco estudados.

Caso aceite participar, você será avaliado em 3 momentos (hoje, em 6 meses de terapia e em 1 ano de terapia). Será feita uma coleta de amostra de 10 ml de sangue (aproximadamente 1 colher de sopa), no início da terapia e outra em sua alta. Estas amostras serão utilizadas para medir o BDNF, uma substância produzida pelo corpo associada ao funcionamento cerebral. O sangue coletado será armazenado para uso apenas nesta pesquisa. Os riscos envolvidos neste procedimento são os de uma coleta de sangue usual, que são mal-estar passageiro ou mancha roxa no local da coleta de sangue.

Além desta coleta de sangue, você fará uma avaliação psiquiátrica e psicológica, composta por seis questionários, que serão repetidos nos próximos 3 momentos da pesquisa. Também solicitamos sua autorização para consultar alguns dados clínicos registrados no seu prontuário na instituição. O preenchimento dos questionários não envolve maiores riscos e levará em torno de 60 minutos. O preenchimento poderá ser feito por telefone, caso você não consiga vir até o Hospital. Algumas perguntas podem trazer algum desconforto e você tem a liberdade de não respondê-las.

Não se conhece benefícios diretos por fazer parte desta pesquisa, mas você estará contribuindo para melhor conhecer os efeitos a longo prazo das psicoterapias.

O nome do participante será mantido confidencial pelos pesquisadores, sendo estes dados utilizados apenas para esta pesquisa.

A participação no estudo é totalmente voluntária, a não participação ou desistência após ingressar no estudo não implicará em nenhum tipo de prejuízo para o participante.

Você não terá nenhum custo pela participação neste estudo e não receberá nenhum tipo de compensação financeira.

Em caso de dúvidas, antes e durante o curso da pesquisa, entrar em contato com Dra. Neusa Sica da Rocha, pesquisadora responsável, pelos telefones 33598294 ou 33598413. Serviço de Psiquiatria- HCPA Ramiro Barcelos, 2350- 4º andar, sala 400 N.

Caso tenha dúvidas sobre questões éticas desta pesquisa, o Comitê de Ética em Pesquisa poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227,

ou através do telefone 33597640, das 8h às 17h, de segunda à sexta.

Este documento foi elaborado em 2 vias, uma ficará com você e outra ficará arquivada com o pesquisador.

_____ _____

Nome do participante Assinatura do participante

_____ _____

Nome do pesquisador Assinatura do pesquisador

Porto Alegre, _____de _____de_____

CAAE 43345815.0.0000.5327

Anexo B– Protocolo de pesquisa

Universidade Federal do Rio Grande do Sul

Programa de Pós-Graduação em Ciências Médicas: Psiquiatria

Hospital de Clínicas de Porto Alegre

Avaliação de Pacientes Atendidos em Psicoterapia (GPPG 15-0097)

NOME DO PACIENTE

NÚMERO DE PROTOCOLO

DATA DA INCLUSÃO

DATA DA AVALIAÇÃO

BASELINE

Hospital de Clínicas de Porto Alegre
Serviço de Psiquiatria

Protocolo n°

Data do preenchimento: ☐☐ ☐☐ ☐☐

Entrevistador: ☐☐☐☐☐☐☐☐☐☐

Qual psicoterapia está realizando? ☐ **1 POA** ☐ **2 TIP** ☐ **3 TCC**

Quantas sessões já realizou? ☐

1. Identificação

1.1.Prontuário HCPA: ☐☐☐☐☐☐☐☐

1.2.Nome Completo: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.3. Religião: [1] católica [2] evangélica [3] espírita
[4] judaica [5] outra :_____________ [9] não quer informar

1.4. Origem: [1] Triagem [2] Em acompanhamento

1.5. Sexo: [1] Masculino [2] Feminino

1.6. Data de nascimento: ☐☐ ☐☐ ☐☐☐☐

1.7. Idade: ☐☐ anos

1.8. Etnia: [1] branco [2] não-branco

1.9 Orientação Sexual: [1] heterossexual [2] homossexual [0] sem condições de responder
[3] bissexual [9] não quer informar

1.10. Situação Conjugal: [1] solteiro [2] casado ou companheiro fixo
[3] separado ou divorciado [4] viúvo

1.11. Ocupação: [1] estudante [2] com ocupação remunerada
[3] sem ocupação (não aposentado) [4] dona de casa
[5] em auxílio-doença [6] aposentado por invalidez
[7] aposentado por tempo serviço

1.12. Escolaridade:
- 0 Sem escolaridade
- 1 Fundamental incompleto
- 2 Fundamental completo
- 3 Médio Incompleto
- 4 Médio completo
- 5 Superior incompleto
- 6 Superior completo
- 7 Pós-graduação

1.13 Anos de estudo completos (contar a partir da primeira série, excluindo repetências) [ ][ ]

1.14. Repetência escolar: 1 sim 2 não [ ][ ] anos repetidos

1.15. Sabe ler e escrever? 1 sim 2 Não

1.16. Endereço :

1.17. Cidade:

1.18. Telefone para contato: 1- celular

2- convencional

PESSOA DE REFERÊNCIA:

TELEFONE:

2. Características da Doença

2.1 Qual o motivo da procura de tratamento psicoterápico?

1 Alívio de sintomas 2 Crise vital 3 Relacionamento interpessoal 4 Luto
5 Trauma 6 Queixas físicas

2.2 (com as palavras do paciente):____

____-
____

2.3 Diagnóstico Atual (prontuário)

2.4. Hospitalizações Psiquiátricas: 1 sim 2 não 0 sem condições de responder

Se sim, quantas: [ ][ ]

2.5. Tentativa de suicídio: 1 sim 2 não 9 não quer informar

0 sem condições de responder

Se sim, número: ☐ vezes

Tipo tentativa: ☐1 arma fogo ☐2 enforcamento ☐3 cortar pulsos

☐4 medicação ☐5 pular de local alto

☐6 outro, qual:_____

3. <u>Hábitos</u>

3.1. Tabagismo Passado: ☐1 sim ☐2 não Se sim, tempo de uso: ☐☐ anos

3.11 Tabagismo Atual: ☐1 sim ☐2 não Se sim, ☐☐ maços/dia:

3.2. Uso Atual Chá: ☐1 sim ☐2 não

Chimarrão: ☐1 sim ☐2 não

Café: ☐1 sim ☐2 não

3.3 Já usou ou usa drogas de abuso: ☐1 Sim ☐2 Não

Se sim, qual?

☐1 Maconha	☐1 Uso Atual	☐2 Uso passado	
☐2 Cocaína	☐1 Uso Atual	☐2 Uso passado	
☐3 Crack	☐1 Uso Atual	☐2 Uso passado	
☐4 Alucinógeno	☐1 Uso Atual	☐2 Uso passado	
☐5 Anfetaminas	☐1 Uso Atual	☐2 Uso passado	
☐6 Álcool	☐1 Uso Atual	☐2 Uso passado	
☐7 Benzodiazepínico sem prescrição	☐1 Uso Atual	☐2 Uso passado	
☐8 Outro. Qual? ☐☐☐☐☐☐☐☐☐☐	☐1 Uso Atual	☐2 Uso passado	

4. <u>Tratamento Psiquiátrico</u>

4.1. Você já foi submetido a algum tratamento psiquiátrico? ☐1 Sim ☐2 Não

4.2. Você já foi submetido a algum tratamento psicoterápico? ☐1 Sim ☐2 Não

4.2.1 Qual? ☐1 TCC ☐2 POA ☐3 TIP ☐4 Não sabe

4.2.2.Frequência? [1] semanal [2] quinzenal [3] 2x/semana

4.2.3 Quanto tempo? _____ (número de meses)

4.2.4 Trocou de terapeuta? _____ (número de vezes)

4.3 Você está submetido a algum tratamento psiquiátrico medicamentoso?
[1] Sim [2] Não

4.3.1 Se sim, quais **medicamentos** você tomou para qualquer dos comportamentos/ problemas psiquiátricos (por pelo menos 6 meses)?

[1] Antidepressivos [4] Anticolinérgico

[2] Antipsicóticos [5] Benzodiazepínico

[3] Estabilizador do Humor [6] Metilfenidato [7] Não sabe informar

(Preencher de acordo com prontuário):

Medicação	Uso Atual		Dose	Medicação	Uso Atual		Dose
	0- Não	1-Sim			0- Não	1-Sim	
	0- Não	1-Sim			0- Não	1-Sim	
	0- Não	1-Sim			0- Não	1-Sim	
	0- Não	1-Sim			0- Não	1-Sim	
	0- Não	1-Sim			0- Não	1-Sim	

5. História Familiar de Doença Psiquiátrica:

Filho adotivo? [1] Sim [2] Não [9] Não Sabe [0] sem condições de informar

Código para transtorno: 1 – Transtorno Bipolar 2- Depressão 3- Esquizofrenia 4- Ansiedade 5-Problemas com álcool 6-Problemas com drogas
Código para desfecho: 1- Tentativas de suicídio 2-Suicídio completo 3-Internação psiquiátrica 4- Uso de medicação psiquiátrica

1 Mãe Transtorno: [ ] Desfecho: [ ]

2 Pai Transtorno: [ ] Desfecho: [ ]

3 Irmãos Quantos afetados? [ ][ ] Transtorno: [ ] Desfecho: [ ]

4 Avó/Avô Materno Quantos afetados? [ ][ ] Transtorno: [ ] Desfecho: [ ]

5 Avó/Avô Paterno Quantos afetados? [ ][ ] Transtorno: [ ] Desfecho: [ ]

6 Tios Maternos Quantos afetados? [ ][ ] Transtorno: [ ] Desfecho: [ ]

7 Tios Paternos Quantos afetados? [ ][ ] Transtorno: [ ] Desfecho: [ ]

6. Uso de método contraceptivo:

6.1 [1] sim [2] não [0] sem condições de informar

[ ] [ ]

6.2. Se sim, qual(is): 1 Anticoncepcional oral (pílula) 2 DIU

[3] Camisinha [4] Diafragma [5] coito interrompido [6] L.Tubária

[7] Vasectomia [8] tabelinha [9] Anticoncepcional Injetável

[10] outro, qual: _____

7. <u>Fatores relacionados ao sexo feminino</u> (Obs: codificar para sexo masculino: 9- não se aplica)

7.1. Gravidez atual? [1] Sim [2] Não

7.2. Gestações: [ ]

7.3. Partos Normais: [ ]

7.4. Partos cesáreos: [ ]

7.5. Abortos: Espontâneos [ ]

Provocados [ ]

7.6. Menopausa: [1] sim [2] não Se sim, idade: [ ][ ] anos.

7.8. Terapia de Reposição Hormonal (atual): [1] sim [2] não

7.9. Data da última menstruação: [ ][ ][ ][ ][ ][ ][ ][ ]

8. Moradia:

Vive: [1] Sozinho [2] Com familiares [3] Em pensionato [4] Em instituição

Qual? _____

9. Classificação Econômica

9.1 Posse de Itens

	0	**1**	**2**	**3**	**4 ou +**
Televisão em Cores	0	2	3	4	5
Rádio	0	1	2	3	4
Banheiro	0	2	3	4	4
Automóvel	0	2	4	5	5
Empregada Mensalista	0	2	4	4	4
Aspirador de Pó	0	1	1	1	1
Máquina de Lavar	0	1	1	1	1
Vídeo Cassete e/ou DVD	0	2	2	2	2
Geladeira	0	2	2	2	2
Freezer (aparelho independente ou parte da geladeira duplex)	0	1	1	1	1

9.2 Grau de Instrução do **chefe da família**

Analfabeto /Primário incompleto	0
Primário completo / Ginasial incompleto	1
Ginasial completo / Colegial incompleto	2
Colegial completo / Superior incompleto	3
Superior completo	5

Classe:

1 A1 (30-34) 2 A2 (25-29) 3 B1 (21-24) 4 B2 (17-20)

5 C (11-16) 6 D (6-10) 7 E (0-5)

BAI

Data: _____

Nome: _____ Estado Civil: _____ Idade: _____ Sexo: _____

Ocupação: _____ Escolaridade: _____

Abaixo está uma lista de sintomas comuns de ansiedade. Por favor, leia cuidadosamente cada item da lista. Identifique o quanto você tem sido incomodado por cada sintoma durante a **última semana, incluindo hoje,** colocando um "x" no espaço correspondente, na mesma linha de cada sintoma.

	Absolutamente não	**Levemente** Não me incomodou muito	**Moderadamente** Foi muito desagradável mas pude suportar	**Gravemente** Dificilmente pude suportar
1. Dormência ou formigamento.				
2. Sensação de calor.				
3. Tremores nas pernas.				
4. Incapaz de relaxar.				
5. Medo que aconteça o pior.				
6. Atordoado ou tonto.				
7. Palpitação ou aceleração do coração.				
8. Sem equilíbrio.				
9. Aterrorizado.				
10. Nervoso.				
11. Sensação de sufocação.				
12. Tremores nas mãos.				
13. Trêmulo.				
14. Medo de perder o controle.				
15. Dificuldade de respirar.				
16. Medo de morrer.				
17. Assustado.				
18. Indigestão ou desconforto no abdômen.				
19. Sensação de desmaio.				
20. Rosto afogueado.				
21. Suor (não devido ao calor).				

INVENTÁRIO DE DEPRESSÃO DE BECK (BDI)

Este questionário consiste em 21 grupos de afirmações. Depois de ler cuidadosamente cada grupo, faça um círculo em torno do número (0, 1, 2 ou 3) diante da afirmação, em cada grupo, que descreve melhor a maneira como você tem se sentido nesta semana, incluindo hoje. Se várias afirmações num grupo parecerem se aplicar igualmente bem, faça um círculo em cada uma. Tome o cuidado de ler todas as afirmações, em cada grupo, antes de fazer a sua escolha.

1. Tristeza

0 Não me sinto triste.

1 Eu me sinto triste grande parte do tempo.

2 Estou triste o tempo todo.

3 Estou tão triste ou tão infeliz que não consigo suportar.

2. Pessimismo

0 Não estou desanimado(a) a respeito do meu futuro.

1 Eu me sinto mais desanimado(a) a respeito do meu futuro do que de costume.

2 Não espero que as coisas dêem certo para mim.

3 Sinto que não há esperança quanto ao meu futuro. Acho que só vai piorar.

3. Fracasso passado

0 Não me sinto um(a) fracassado(a).

1 Tenho fracassado mais do que deveria.

2 Quando penso no passado vejo muitos fracassos.

3 Sinto que como pessoa sou um fracasso total.

4. Perda de prazer

0 Continuo sentindo o mesmo prazer que sentia com as coisas de que eu gosto

1 Não sinto tanto prazer com as coisas como costumava sentir.

2 Tenho muito pouco prazer nas coisas que eu costumava gostar

3 Não tenho mais nenhum prazer nas coisas que costumava gostar.

5. Sentimentos de culpa

0 Não me sinto particularmente culpado(a)

1 Eu me sinto culpado(a) a respeito de várias coisas que fiz e/ou que deveria ter feito.

2 Eu me sinto culpado(a) a maior parte do tempo.

3 Eu me sinto culpado(a) todo o tempo

6. Sentimentos de punição

0 Não sinto que estou sendo punido(a).

1 Sinto que posso ser punido(a).

2 Eu acho que serei punido(a).
3 Sinto que estou sendo punido(a).

7. Auto-estima
0 Eu me sinto como sempre me senti em relação a mim mesmo(a).
1 Perdi a confiança em mim mesmo(a).
2 Estou desapontado(a) comigo mesmo(a).
3 Não gosto de mim.

8. Autocrítica
0 Não me critico nem me culpo mais do que o habitual.
1 estou sento mais crítico(a) comigo mesmo(a) do que costumava ser.
2 Eu me critico por todos os meus erros.
3 Eu me culpo por tudo de ruim que acontece.

9. Pensamentos ou desejos suicidas
0 Não tenho nenhum pensamento de me matar.
1 Tenho pensamentos de me matar, mas não levaria isso adiante.
2 Gostaria de me matar.
3 Eu me mataria se tivesse oportunidade.

10. Choro
0 Não choro mais do que chorava antes.
1 Choro mais agora do que costumava chorar.
2 Choro por qualquer coisinha.
3 Sinto vontade de chorar, mas não consigo.

11. Agitação
0 Não me sinto mais inquieto(a) ou agitado(a) do que me sentia antes.
1 Eu me sinto mais inquieto(a) ou agitado(a) do que me sentia antes.
2 Eu me sinto tão inquieto(a) ou agitado(a) que é difícil ficar parado(a).
3 Estou tão inquieto(a) ou agitado(a) que tenho que estar sempre me mexendo ou fazendo alguma coisa.

12. Perda de interesse
0 Não perdi o interesse por outras pessoas ou por minhas atividades.
1 Estou menos interessado pelas outras pessoas ou coisas do que costumava estar.
2 Perdi quase todo o interesse por outras pessoas ou coisas.
3 É difícil me interessar por alguma coisa.

13. Indecisão
0 Tomo minhas decisões tão bem quanto antes.
1 Acho mais difícil tomar decisões agora do que antes.
2 Tenho muito mais dificuldade em tomar decisões agora do que antes.
3 Tenho dificuldade para tomar qualquer decisão.

14. Desvalorização

0 Não me sinto sem valor.

1 Não me considero hoje tão útil ou não me valorizo como antes.

2 Eu me sinto com menos valor quando me comparo com outras pessoas.

3 Eu me sinto completamente sem valor.

15. Falta de energia

0 Tenho tanta energia hoje como sempre tive.

1 Tenho menos energia do que costumava ter.

2 Não tenho energia suficiente para fazer muita coisa.

3 Não tenho energia suficiente para nada.

16. Alterações no padrão de sono

0 Não percebo nenhuma mudança no meu sono.

1a Durmo um pouco mais que o habitual.

1b Durmo um pouco menos do que o habitual.

2a Durmo muito mais do que o habitual.

2b Durmo muito menos do que o habitual.

3a Durmo a maior parte do dia.

3b Acordo 1 ou 2 horas mais cedo e não consigo voltar a dormir.

17. Irritabilidade

0 Não estou mais irritado(a) do que o habitual

1 Estou mais irritado(a) do que o habitual

2 Estou muito mais irritado(a) do que o habitual

3 Fico irritado(a) o tempo todo.

18. Alterações de apetite

0 Não percebi nenhuma mudança no meu apetite.

1a Meu apetite está um pouco menor do que o habitual

1b Meu apetite está um pouco maior do que o habitual

2a Meu apetite está muito menor do que antes.

2b Meu apetite está muito maior do que antes.

3a Não tenho nenhum apetite.

3b Quero comer o tempo todo.

19. Dificuldade de concentração

0 Posso me concentrar tão bem quanto antes.

1 Não posso me concentrar tão bem como habitualmente

2 É muito difícil manter a concentração em alguma coisa por muito tempo.

3 Eu acho que não consigo me concentrar em nada.

20. Cansaço ou fadiga

0 Não estou mais cansado(a) ou fatigado(a) do que o habitual.

1 Fico cansado(a) ou fatigado(a) mais facilmente do que o habitual.

2 Eu me sinto muito cansado(a) ou fatigado(a) para fazer muitas das coisas que costumava fazer

3 Eu me sinto muito cansado(a) ou fatigado(a) para fazer a maioria das coisas que costumava fazer.

21. Perda de interesse por sexo

0 Não notei qualquer mudança recente no meu interesse por sexo

1 Estou menos interessado(a) em sexo do que costumava estar

2 Estou muito menos interessado(a) em sexo agora

3 Perdi completamente o interesse por sexo

Subtotal da página 1_____

Subtotal da página 2_____

ESCORE TOTAL_____

QUALIDADE DE VIDA

Este questionário é sobre como você se sente a respeito de sua qualidade de vida, saúde eoutras áreas de sua vida. Por favor,responda a todas as questões. Se você não tem certeza sobre que resposta dar em uma questão, por favor, escolha entre as alternativas a que lhe parece mais apropriada. Esta, muitas vezes, poderá ser sua primeira escolha.

		Muito Ruim	Ruim	Nem ruim nem boa	Boa	Muito boa
1	Como você avaliaria sua qualidade de vida?	1	2	3	4	5

Por favor, tenha em mente seus valores, aspirações, prazeres e preocupações. Nós estamos perguntando o que você acha de sua vida, tomando como referência as duas últimas semanas.

Por favor, leia cada questão, veja o que você acha e circule no número que lhe parece a melhor resposta.

		Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
2	Quão satisfeito(a) você está com a sua saúde?	1	2	3	4	5

As questões seguintes são sobre o quanto você tem sentido algumas coisas nas duas

últimas semanas:

		Nada	Muito pouco	Mais ou menos	Bastante	extremamente
3	Em que medida você acha que a sua dor (física) impede você de fazer o que você precisa?	1	2	3	4	5
4	O quanto você precisa de algum tratamento médico para levar a sua vida diária?	1	2	3	4	5
5	O quanto você aproveita a vida?	1	2	3	4	5
6	Em que medida você acha que a sua vida tem sentido?	1	2	3	4	5
7	O quanto você consegue se concentrar?	1	2	3	4	5
8	Quão seguro(a) você se sente em sua vida diária?	1	2	3	4	5
9	Quão saudável é seu ambiente físico (clima, barulho, poluição, atrativos)?	1	2	3	4	5

As questões seguintes são sobre quão completamente você tem sentido ou é capaz de fazer certas coisas nestas últimas duas semanas:

		Nada	Muito pouco	Médio	Muito	Completamente
10	Você tem energia suficiente para o seu dia-a-dia?	1	2	3	4	5
11	Você é capaz de aceitar sua aparência física?	1	2	3	4	5
12	Você tem dinheiro suficiente para satisfazer suas necessidades?	1	2	3	4	5
13	Quão disponíveis para você estão as informações que precisa no seu dia-a-dia?	1	2	3	4	5
14	Em que medida você tem oportunidades de atividades de lazer?	1	2	3	4	5

As questões seguintes são sobre quão bem ou satisfeito você se sentiu a respeito de vários aspectos de sua vida nas duas últimas semanas:

		Muito	Ruim	Nem ruim	Bom	Muito

		Ruim		nem bom		bom
15	Quão bem você é capaz de se locomover?	1	2	3	4	5

		Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
16	Quão satisfeito(a) você está com seu sono?	1	2	3	4	5
17	Quão satisfeito(a) você está com sua capacidade de desempenhar as atividades do seu dia-a-dia?	1	2	3	4	5
18	Quão satisfeito(a) você está com sua capacidade para o trabalho?	1	2	3	4	5
19	Quão satisfeito(a) você está consigo mesmo?	1	2	3	4	5
20	Quão satisfeito(a) você está com suas relações pessoais (amigos, parentes, conhecidos, colegas)?	1	2	3	4	5
21	Quão satisfeito(a) você está com sua vida sexual?	1	2	3	4	5

22	Quão satisfeito(a) você está com o apoio que você recebe de seus amigos?	1	2	3	4	5
		Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
23	Quão satisfeito(a) você está com as condições do local onde mora?	1	2	3	4	5
24	Quão satisfeito(a) você está com seu acesso aos serviços de saúde?	1	2	3	4	5
25	Quão satisfeito(a) você está com o seu meio de transporte?	1	2	3	4	5

As questões seguintes referem-se a com que freqüência você sentiu ou experimentou certas coisas nas últimas duas semanas:

		Nunca	Algumas vezes	Frequentemente	Muito frequente-mente	Sempre
26	Com que freqüência você tem sentimentos negativos tais como mau humor, desespero, ansiedade, depressão?	1	2	3	4	5

Alguém lhe ajudou a preencher este questionário? .....

Quanto tempo você levou para preencher este questionário? .....

Você tem algum comentário sobre o questionário?

APENDICE A – Outras produções bibliográficas durante o período do doutorado

Artigos publicados

Trombka M, Demarzo M, Bacas DC, Antonio SB, Cicuto K, Salvo V, Claudino FCA, Ribeiro L, Christopher M, Garcia-Campayo J, Rocha NS. Study protocol of a multicenter randomized controlled trial of mindfulness training to reduce burnout and promote quality of life in police officers: the POLICE study. BMC Psychiatry. 2018 May 25;18(1):151. doi: 10.1186/s12888-018-1726-7. PMID: 29801444; PMCID: PMC5970505.

Schmitt AA Jr, Brenner AM, Primo de Carvalho Alves L, Claudino FCA, Fleck MPA, Rocha NS. Potential predictors of depressive symptoms during the initial stage of the COVID-19 outbreak among Brazilian adults. J Affect Disord. 2021 Mar 1; 282:1090-1095. doi: 10.1016/j.jad.2020.12.203. Epub 2021 Jan 6. PMID: 33601682; PMCID: PMC7832486.

Brenner AM, Claudino FCA, Souza GR, Rocha NS. Time series analysis of suicide from a monthly perspective in the south of Brazil: an ecological study. Trends in psychiatry and psychotherapy, 2021

Artigos submetidos

Brenner AM, Claudino FCA, Burin LM, Scheibe VM, Padilha BL, Souza GR, Duarte JA, Rocha NS. Structural Magnetic Resonance Imaging findings in Severe Mental Disorders adult inpatients: A Systematic Review. (2021)

Januario EM, Valdivia LJ, Schmitt Jr AA, Claudino FCA, Brenner AM, Rocha NS. Protective factor Against depressive symptoms among Brazilian healthcare workers during the initial stages of the COVID-19 pandemic (2021)