INSTITUTO DE PSIQUIATRIA – IPUB
CENTRO DE CIÊNCIAS DA SAÚDE – CCS
UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

RAQUEL MENEZES GONÇALVES

IMPACTO DA TERAPIA COGNITIVO-COMPORTAMENTAL EM MARCADORES BIOLÓGICOS E EFICÁCIA DA TERAPIA DE EXPOSIÇÃO COM REALIDADE VIRTUAL PARA O TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

RIO DE JANEIRO

2015

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Tese de doutorado submetida ao corpo docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do grau de Doutor em Saúde Mental.

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RESUMO

GONÇALVES, Raquel. Impacto da terapia cognitivo-comportamental em marcadores biológicos e eficácia da terapia de exposição com realidade virtual para o transtorno de estresse pós-traumático. Rio de Janeiro, 2015. Tese (Doutorado em Saúde Mental) – Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2015.

O futuro da psicologia se apoia no diálogo com a ciência básica. A convergência das duas áreas é interessante para o avanço na precisão dos diagnósticos, a predição de resposta a tratamentos e o aprimoramento e desenvolvimento de intervenções eficazes. A presente tese de doutorado teve como objetivos: (1) investigar o impacto da Terapia Cognitivo-comportamental (TCC) em parâmetros psicofisiológicos; (2) verificar a eficácia da Terapia de Exposição com Realidade Virtual (TERV) no tratamento do Transtorno de Estresse Pós-traumático (TEPT). Para alcançar o primeiro objetivo, foram publicados três artigos: uma revisão sistemática sobre potenciais biomarcadores de eficácia da TCC no tratamento do TEPT; um estudo experimental que avaliou o impacto de um protocolo de TCC em parâmetros psicofisiológicos basais de pacientes com TEPT; e uma meta-análise sobre o impacto da TCC na frequência cardíaca de pacientes com diferentes transtornos de ansiedade. Para alcançar o segundo objetivo, foi publicado um quarto artigo com o objetivo de avaliar a eficácia de uma variação da técnica de exposição, a TERV. Com relação ao primeiro objetivo, verificou-se que os parâmetros cardíacos são os biomarcadores de eficácia mais estudados no TEPT e que a TCC tem o efeito de reduzir a reatividade cardíaca, comprovadamente no TEPT e potencialmente em outros transtornos de ansiedade. Quando medidos em repouso, esse impacto não foi observado. Apenas a baixa frequência (índice predominantemente simpático) foi impactada pela TCC quando mensurada em repouso, visto que diminui substancialmente em pacientes respondentes ao tratamento. Os níveis de cortisol tendem a variar de acordo com o momento do tratamento, elevando-se no período de exposição e reduzindo ao fim da terapia. Com relação ao segundo objetivo, verificou-se que a TERV é tão eficaz no tratamento do TEPT quanto a TCC com exposição tradicional, podendo ser uma poderosa ferramenta no tratamento de pacientes resistentes.

Palavras-chave: terapia cognitivo-comportamental, terapia de exposição com realidade virtual, transtorno de estresse pós-traumático, biomarcadores

ABSTRACT

The future of psychotherapy relies on the dialog with the basic science. The convergence of these two areas is interesting for the advance of diagnosis accuracy, in predicting response to treatment and for the improvement and development of effective interventions. This doctoral thesis aimed to: (1) investigate the impact of cognitive-behavioral therapy (CBT) in psychophysiological parameters; (2) verify the effectiveness of virtual reality exposure therapy (VRET) in the treatment of post-traumatic stress disorder (PTSD). To achieve the first goal, three articles were published: a systematic review of potential biomarkers of CBT efficacy in the treatment of PTSD; an experimental study that evaluated the impact of a CBT protocol in basal psychophysiological parameters of patients with PTSD; and a meta-analysis on the impact of CBT in heart rate of patients with different anxiety disorders. To achieve the second objective, a fourth article was published with the aim of evaluating the effectiveness of a variation of the exposure technique, the VRET. Regarding the first objective, it was found that cardiac parameters are the most studied biomarkers of efficacy in PTSD and CBT has the effect of reducing the cardiac reactivity in PTSD and potentially in other anxiety disorders. When measured at rest, this trend was not observed. Only the low frequency (a predominantly sympathetic parameter) was impacted by the CBT when measured at rest, since it reduces substantially in treatment respondents. Cortisol levels tend to follow the treatment, rising in the exposure period and reducing by the end of therapy. Regarding the second objective, it was found that the VRET is as effective in the treatment of PTSD as CBT with traditional exposure, and can be a powerful tool in treatment-resistant patients.

GONÇALVES, Raquel. Impacto da terapia cognitivo-comportamental em marcadores biológicos e eficácia da terapia de exposição com realidade virtual para o transtorno de estresse pós-traumático. Rio de Janeiro, 2015. Tese (Doutorado em Saúde Mental) – Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2015.

Keywords: cognitive behavior therapy, virtual reality exposure therapy, post-traumatic stress disorder, biomarkers

DEDICATÓRIA

Dedico esta tese aos portadores de transtorno de estresse pós-traumático. Que este trabalho colabore para remediar o sofrimento causado por circunstâncias tão adversas e de impacto tão grandioso. Contribuir para o alívio do sofrimento dessas pessoas é a maior fonte de motivação desta pesquisa.

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LISTA DE ABREVIATURAS E SIGLAS

TCC: Terapia Cognitivo-Comportamental
TEPT: Transtorno de Estresse Pós-Traumático
TERV: Terapia de Exposição com Realidade Virtual
LINPES: Laboratório Integrado de Pesquisas sobre o Estresse
CIMCYC: *Centro de Investigación Mente, Cérebro y Comportamiento da Universidade de Granada*
COPPE: Centro de Pós-graduação e Pesquisa em Engenharia
DSM: Manual Estatístico e Diagnóstico de Transtornos Mentais
CID: Classificação Internacional de Doenças
NIMH: *National Institute of Mental Health*
RDoC: *Research Domain Criteria*

Apresentação

O interesse pelo estudo do TEPT surgiu na época da graduação em psicologia, durante o estágio no Laboratório Integrado de Pesquisas sobre Estresse (LINPES/IPUB), iniciado em 2007. Interesse anterior havia em compreender a interface entre os transtornos mentais e seus reflexos biológicos. Já estava claro que existia um vasto campo a ser explorado, especialmente com a incorporação de biomarcadores no campo da psiquiatria ocorrida nas últimas décadas (Singh & Rose, 2009). Descobertas recentes já haviam confirmado alterações consistentes em alguns transtornos mentais. Portanto, o próximo passo seria identificar, aprimorar ou desenvolver tratamentos que pudessem regularizar alterações biológicas em conjunção com as sintomatológicas. Seria possível utilizar a psicoterapia como ferramenta para normalizar essas alterações? A terapia cognitivo-comportamental já vinha se mostrando eficaz através de estudos científicos de alta qualidade metodológica. Diversos transtornos mentais, incluindo o TEPT, já se beneficiavam do conjunto de técnicas desenvolvidas a partir do Modelo bifatorial de Mowrer (Mowrer, 1947), que explicava a aquisição e manutenção do medo através dos condicionamentos clássico e operante, e, mais recentemente, Aaron Beck com a terapia cognitiva (Rangé et al., 2007). Portanto, seria possível observar a regularização de alterações biológicas em pacientes acometidos por transtornos mentais através dessas técnicas?

Tendo em mente essas perguntas, iniciei minha pesquisa sobre o tema no mestrado, que resultou no artigo de entrada no curso de doutorado (artigo 1), uma revisão sistemática acerca dos potenciais biomarcadores da TCC para o TEPT. Este foi o primeiro desta compilação de quatro artigos que serão defendidos nesta tese.

Paralelamente, iniciei um projeto no LINPES em parceria com a equipe de psicofisiologia para o atendimento de pacientes com diagnóstico de TEPT e monitoramento de parâmetros psicofisiológicos basais ao longo do tratamento, que culminou no artigo 2.

Durante o período de doutorado sanduíche, no qual aprofundei meus conhecimentos sobre parâmetros cardíacos por seis meses no *Centro de Investigación Mente, Cérebro y Comportamiento* (CIMCYC) da Universidade de Granada, na Espanha, surgiu a ideia de ampliar a pesquisa para outros transtornos de ansiedade, o que culminou na publicação do artigo 3, uma meta-análise sobre o impacto da TCC na frequência cardíaca de pacientes com transtornos de ansiedade.

Finalmente, impulsionada pelo desenvolvimento de um ambiente virtual em parceria com o Centro de Pós-graduação e Pesquisa em Engenharia (COPPE/UFRJ), posteriormente utilizado para o projeto intitulado “A Terapia de Exposição com Realidade Virtual para pacientes com TEPT controlada por um Sistema de Lógica Fuzzy”, surgiu outra questão de pesquisa: a eficácia da TCC se expande a meios não-convencionais de condução da terapia? Para isso, conduzi com meus colegas de laboratório uma revisão sistemática (artigo 4) para verificar a eficácia da TERV no tratamento do TEPT, além de participar da co-autoria de um artigo sobre a montagem do ambiente virtual utilizado para o tratamento de vítimas de acidentes automobilísticos com diagnóstico de TEPT.

Como resultado final da minha produção, foram publicados cinco artigos como primeira autora (Gonçalves et al., 2010; Gonçalves et al. 2011; Gonçalves et al. 2012; Gonçalves et al. 2015a), sendo um em fase final de publicação (Gonçalves et al., 2015b), cinco artigos em parceria com meus companheiros de laboratório (Lages et al., 2011; Rodrigues et al., 2011; Rodrigues et al., 2014; Macedo et al., 2014; Oliveira et al., 2014) e três capítulos de livro (Ventura & Gonçalves, 2011; Porto et al., 2011; Gonçalves et al., 2012). Os trabalhos defendidos nesta tese são os artigos científicos publicados como primeira autora no período de 2011 a 2015. Os trabalhos restantes podem ser localizados na seção de anexos.

Introdução

Relevância

O TEPT é causador de intenso sofrimento aos seus portadores. A incapacidade de viver sem que a memória do evento traumático retorne de forma constante e intensa dificulta e por vezes impede o funcionamento diário do indivíduo acometido. Como consequência da revivescência, são constantes a hiperativação frente a qualquer estímulo que possa desencadear, mesmo que minimamente, a memória traumática. Deste modo, instintivamente o indivíduo se isola, evitando entrar em contato com os gatilhos que geram revivescência. Além disso, o entorpecimento emocional afasta o indivíduo de seu círculo social, incluindo amigos, familiares e cônjuge, o que pode acarretar prejuízo em vários âmbitos, como separações conjugais, demissões de empregos e dificuldades no relacionamento social. Dessa forma, são geradas e reafirmadas alterações cognitivas relacionadas ao medo, raiva, culpa, vergonha, que estimulam ainda mais o isolamento (Cahil et al., 2009).

A estigmatização da doença, em conjunção com as consequências citadas no parágrafo anterior, colaboram para o surgimento ou fortalecimento de crenças de incapacidade e fracasso. Essas crenças influenciam o surgimento de sentimentos disfóricos e comportamentos disfuncionais, podendo levar ao desencadeamento de depressão e outros transtornos que podem agravar ainda mais o quadro e impactar enormemente a qualidade de vida do paciente (Knapp, 2004).

Diante deste contexto, cabe referir a relevância de se estudar profundamente as bases desta patologia, assim como aperfeiçoar os tratamentos existentes, de modo que intervenções mais eficazes estejam disponíveis. A união de diferentes áreas do conhecimento pode auxiliar a descoberta de fatores de predisposição, possibilitando intervenções preventivas, diagnóstico mais preciso e a disponibilização de tratamentos que aliviem o sofrimento desses indivíduos.

Isto posto, a proposta desta tese foi aperfeiçoar o tratamento psicoterápico para o TEPT. A TCC, em especial a terapia de exposição, é atualmente o tratamento de escolha para o transtorno, mas sabe-se que um considerável número de pacientes não responde ou abandona o tratamento e que esta taxa pode chegar a 50% (Schottenbauer et al., 2008). Portanto, sendo o TEPT um grave problema de saúde pública, é fundamental aprimorar o tratamento para que se obtenha maior taxa de sucesso. Este aprimoramento pode ser realizado na medida em que forem identificados os mecanismos de ação da terapia. A regularização de marcadores

biológicos ocasionada pela TCC comprova de maneira objetiva a eficácia da terapia, além de ampliar a possibilidade de aprimoramento do tratamento, o que, por sua vez, pode colaborar para diminuir as atuais taxas de abandono e ineficácia e alimentar a esperança de que mais pacientes sejam beneficiados (Cahil et al., 2009).

Diagnóstico de Transtorno de Estresse Pós-traumático

Informações gerais

O TEPT é o transtorno mais incapacitante e frequente precipitado por um evento traumático (Norris, 2002). Além disso, ele é o terceiro transtorno mental mais prevalente do Brasil, estando atrás somente de fobias específicas e depressão maior (Ribeiro et al., 2013). Em um estudo estadunidense clássico, com 5.692 participantes, foi constatado que a prevalência de TEPT ao longo da vida é de 6,8%, enquanto a prevalência atual é de 3,5% (Kessler et al., 2005). O único grande estudo epidemiológico brasileiro foi conduzido pelo Instituto do Milênio em 2013, que investigou a relação entre eventos traumáticos e as prevalências de transtornos mentais no Rio de Janeiro e em São Paulo. Este estudo multicêntrico entrevistou um total de 3.744 pessoas. 63.6% da amostra havia sofrido ao menos um evento traumático no Rio de Janeiro, enquanto em São Paulo essa taxa foi de 59.4%. Com relação à prevalência de TEPT, os resultados apontaram taxas de 8,7% ao longo da vida e 3,3% em um ano no Rio de Janeiro, enquanto em São Paulo, a prevalência ao longo da vida foi de 10,2% e a atual, de 5% (Ribeiro et al., 2013).

A maioria das pessoas que passa por um evento traumático evolui sem desenvolver TEPT (35-65%) ou se recupera de sintomas iniciais espontaneamente (15-25%). Apenas 5% a 15% passam a preencher critério diagnóstico para TEPT e 0% a 15% desenvolvem os sintomas tardiamente (Bonanno et al., 2011). Não se sabe ao certo o que determina o desenvolvimento do transtorno, mas alguns fatores predisponentes já foram identificados. Um estudo de revisão realizado em 2000 por Brewin e colaboradores verificou 14 fatores de risco: gênero feminino, baixa idade, baixo nível sócio-econômico, baixo nível educacional, baixa inteligência, etnia minoritária, histórico de doença psiquiátrica, abuso na infância, experiências traumáticas prévias, experiências adversas na infância (excluindo abuso), histórico familiar de doenças psiquiátricas, gravidade do evento traumático, baixo apoio social e ocorrência de outros eventos estressantes após o evento traumático. Além disso, alguns fatores que ocorrem durante o evento traumático podem aumentar as chances de desenvolvimento de TEPT, como reações peri-traumáticas (Joseph e cols., 1994) ou a percepção do indivíduo acerca do grau de controle sobre a situação (Whealin, Ruzek & Southwick, 2008).

Características que parecem colaborar para a recuperação após o trauma incluem a resiliência. Este conceito é definido como a capacidade de superar adversidades e é composto por um conjunto de fatores, como capacidade de solucionar problemas, responsabilidade, autoestima, independência, bem-estar, iniciativa, bom humor, *insight*, criatividade, dentre outros. Pessoas resilientes conseguem "deixar o trauma no passado" com mais facilidade que as não-resilientes. Embora este campo careça de estudos de alta qualidade metodológica para a comprovação de eficácia, a maior parte dos estudos existentes encontra resultados promissores (Macedo et al., 2014).

Critérios Diagnósticos

De acordo com a quinta edição do Manual Estatístico e Diagnóstico de Transtornos Mentais (DSM V), o TEPT é classificado como um dos transtornos relacionados a trauma ou estresse (APA, 2013). Nesta categoria, estão incluídos transtornos cuja origem está associada a acontecimentos estressantes ou catastróficos. No que se refere ao TEPT, o evento deve necessariamente ser traumático, o que inclui morte ou ameaça de morte, lesão grave ou violência sexual. A exposição pode ser (1) direta, (2) através de testemunho da situação, (3) saber que o evento ocorreu com alguém próximo, caso seja violento ou acidental, ou (4) ser exposto a pormenores aversivos de um evento traumático que ocorreu com outra pessoa, o que inclui profissionais repetidamente expostos a eventos desta natureza (critério A).

A partir do evento traumático, outros critérios, descritos a seguir, são essenciais para o diagnóstico de TEPT.

Critério B: Estão presentes nesta categoria sintomas relacionados à reexperimentação. Ao menos um dos sintomas deve estar presente para que se preencha o diagnóstico completo.

- Recordações aflitivas, recorrentes e intrusivas do evento;
- Sonhos perturbadores relacionados ao trauma;
- Reações dissociativas, nas quais o sujeito sente como se o evento estivesse ocorrendo novamente (ex. *flashbacks*);
- Mal estar diante de estímulos internos ou externos que lembrem o trauma;
- Aumento da ativação fisiológica diante desses estímulos.

Critério C: Os sintomas relacionados a este critério correspondem a evitação, de modo que deve haver ao menos um para o preenchimento completo do critério diagnóstico.

- Evitar memórias, pensamentos ou sentimentos associados ao trauma;
- Evitar estímulos externos (pessoas, lugares, conversas, situações, objetos, etc.).

Critério D: devem estar presentes ao menos dois sintomas de alterações negativas no humor ou cognição.

- Incapacidade de recordar aspectos importantes do evento;
- Crenças negativas persistentes e exageradas a respeito de si mesmo, do mundo e de outras pessoas;
- Pensamentos distorcidos a respeito da razão e consequência do evento que leva o sujeito a culpar-se ou a culpar outros;

- Emoções negativas persistentes, como medo, horror, raiva, culpa, vergonha;
- Diminuição do interesse ou participação em atividades significativas;
- Sensação de distanciamento dos outros;
- Incapacidade para experimentar emoções positivas;

Critério E: este inclui sintomas relacionados a alterações na excitabilidade e reatividade. Pelo menos dois deles devem estar presentes.

- Dificuldade para iniciar ou manter o sono;
- Condutas imprudentes ou auto-destrutivas;
- Irritabilidade ou rompantes de raiva;
- Dificuldade de concentração;
- Hipervigilância;
- Resposta de sobressalto exagerada.

Preenchidos esses critérios, é necessário que eles estejam presentes por no mínimo um mês (critério F), que causem prejuízo na vida do indivíduo (critério G) e que não sejam ocasionados por uso de substâncias ou condições médicas (critério H).

O DSM V, lançado em 2013, trouxe algumas mudanças nos critérios diagnósticos do TEPT. Como a presente pesquisa teve início anos antes deste período, utilizamos nos artigos publicados os critérios vigentes no DSM-IV-R. Nesta edição do manual, o TEPT era classificado como um transtorno de ansiedade que acomete indivíduos que são expostos, testemunham ou tomam conhecimento de eventos traumáticos extremos envolvendo morte, sério ferimento ou outra ameaça à integridade física. Além disso, o indivíduo deveria apresentar, no momento do trauma, reação de intenso medo, impotência ou horror (critério A). Para ser diagnosticado, o indivíduo deveria apresentar, a partir de quatro semanas após o evento, sintomas de três classes:

1) Critério B: revivescência persistente do evento como se ele estivesse ocorrendo novamente, o que pode vir na forma de pensamentos intrusivos, *flashbacks* ou pesadelos recorrentes;

2) Critério C: evitação ativa de qualquer estímulo associado ao evento, como lugares, pessoas, sentimentos, pensamentos ou situações que ativem memórias do trauma. É comum ocorrer um entorpecimento psíquico ou embotamento (*numbing*) da responsividade geral, no qual ocorre redução na capacidade de experimentar quaisquer sentimentos, tanto os relacionados ao trauma quanto os não relacionados, como sentimentos de intimidade,

ternura e sexualidade. Seria como se o indivíduo ficasse “anestesiado”, afastando-se de atividades e pessoas em geral;

3) Critério D: excitabilidade aumentada, que pode ser observada na forma de respostas de sobressalto exageradas, hipervigilância, irritabilidade, insônia ou agitação frequente.

As principais mudanças entre as duas últimas edições do DSM ocorreram: (1) na modificação da categoria do TEPT, que é retirado do grupo de transtornos de ansiedade e passa a integrar uma nova categoria, a de transtornos relacionado ao trauma e estresse; (2) no critério A, que eliminou a necessidade de reação subjetiva no momento do trauma e modificou algumas especificações sobre os tipos de experiência traumática que podem levar ao diagnóstico. Um exemplo é a exposição indireta ao trauma, que passa a ser restrita a pessoas próximas e a causas súbitas e catastróficas. A definição de trauma mudou consideravelmente nas últimas décadas, sendo o critério A o que mais sofreu alterações nas edições do DSM (Luz et al., 2011); (3) na incorporação de mais uma dimensão diagnóstica, que inclui sintomas de alterações negativas no humor ou cognição e acopla sintomas de entorpecimento emocional, antes incluídos na categoria de evitação. A inclusão de novos sintomas abre caminho para o aumento na heterogeneidade de pacientes diagnosticados com o transtorno (Zoellner et al., 2013).

No manual estipulado pela Organização Mundial da Saúde (OMS, 1993), a décima revisão da Classificação Internacional de Doenças (CID-10), o TEPT encontra-se categorizado nos critérios diagnósticos para reações graves ao estresse e os transtornos de ajustamento, além de haver também o diagnóstico de reação aguda ao estresse, ausente no DSM. Os critérios apresentados no CID-10 para o TEPT são: sintomas iniciados após a vivência de situação ameaçadora ou catastrófica que provocaria: angústia em quase todas as pessoas, revivência do trauma na forma de *flashbacks*, memórias vívidas ou pesadelo; comportamento de evitação persistente de qualquer fator que lembre o trauma; excitabilidade aumentada persistentemente ou incapacidade de relembrar aspectos importantes do trauma. São critérios semelhantes aos do DSM, contudo, mais abrangentes e flexíveis (Kristensen, Parente & Kaszniak, 2005).

Em 2009, foram estipuladas pelo *National Institute of Mental Health* (NIMH) propostas de mudança nas categorias diagnósticas dos transtornos mentais, o que impactará futuras pesquisas em psiquiatria e psicologia. O *Research Domain Criteria* (RDoC) preconiza que sejam priorizadas dimensões de comportamento observável e medidas neurobiológicas, não

considerados nos sistemas de classificação vigentes (Insel et al., 2010). Espera-se que medidas biocomportamentais abram espaço para a criação de categorias diagnósticas mais específicas, que substituiriam os manuais como DSM e CID, aumentando, consequentemente, a precisão nas áreas da psiquiatria e psicologia.

Tratamento

Existem evidências consistentes sobre a eficácia da TCC no tratamento de diversos transtornos mentais. Dentre eles, incluem-se transtornos invasivos do desenvolvimento (*The MTA cooperative group*, 1999), transtornos alimentares (Fairburn, Cooper & Shafran, 2003), dor crônica (Morley, Eccleston & Williams, 1999), depressão maior (Parker, Roy, & Eyers, 2003) e transtornos relacionados ao medo, como transtorno de ansiedade social (Gould, Buckminster et al., 1997), transtorno obsessivo-compulsivo (Van Balcon et al., 1994), transtorno do pânico (Gould et al,. 1995) e transtorno de ansiedade generalizada (Gould et al., 1997).

Em uma revisão de meta-análises que incluiu 16 transtornos, constatou-se tamanho de efeito grande no tratamento com TCC para depressão unipolar, transtorno de ansiedade generalizada, transtorno do pânico com e sem agorafobia, transtorno de ansiedade social, TEPT, depressão infantil e transtornos de ansiedade na infância (Butler et al., 2005).

Desde a inserção do diagnóstico de TEPT no DSM, ocorrida na terceira edição do manual (APA, 1987), um considerável volume de estudos científicos para o tratamento do transtorno foi publicado (Cahill et al., 2006). No tratamento do TEPT, a TCC não só é considerada eficaz (Bisson, 2007), como também é recomendada como tratamento de escolha (*National Institute for Clinical Excellence*, 2005; *Expert Consensus Panel*, 1999; Bisson et al., 2010).

O tratamento da TCC é estruturado, focal e de breve duração, se comparado a terapias psicodinâmicas. Sua abordagem para o TEPT envolve: (1) psicoeducação sobre o transtorno e o tratamento ao qual o paciente será submetido. Em alguns casos, a psicoeducação estende-se aos familiares; (2) técnicas de manejo da ansiedade, que auxiliam a regularização de sintomas físicos provocados pela hiperventilação; (3) reestruturação cognitiva, que envolve a modificação dos pensamentos distorcidos e improdutivos relacionados ao trauma que colaboram para manter os sintomas; (4) exposição a aspectos relacionados ao trauma que não representam perigo real. A exposição é normalmente realizada na forma imaginária, que consiste na recordação ativa do evento traumático através, por exemplo, da fala ou da escrita, e/ou ao vivo, na qual o paciente é encorajado a enfrentar estímulos reais que foram condicionados ao trauma, como objetos, locais ou pessoas (Foa & Rothbaum, 1998).

A evitação encoberta durante a exposição imaginária dificulta o processo de extinção do medo (Jaycox et al., 1998). A TERV é uma opção de exposição em casos em que o paciente tem dificuldade em engajar-se no relato traumático ou no processo de imaginação. Também possui a vantagem de simular cenários do trauma, como guerras ou catástrofes naturais, de maneira segura. Realizada em ambiente totalmente controlado, pode-se reproduzir o evento traumático realisticamente, o que colabora para que a técnica de exposição seja realizada sem a interferência de evitação encoberta.

A TERV teve seu uso iniciado na década de 90 para o tratamento do espectro autista e reabilitação cognitiva. Seu uso em transtornos de ansiedade foi primeiramente realizado em estudo conduzido para o tratamento da fobia de altura (Rothbaum et al., 1995). Este tratamento foi testado com sucesso em outras fobias específicas, fobia social e transtorno do pânico (Meyerbröker & Emmelkamp, 2010).

Apesar de ser uma alternativa interessante para o tratamento do TEPT, os poucos estudos experimentais publicados possuíam protocolos heterogêneos e limitações metodológicas. Além disso, não havia revisões sistemáticas específicas para o tratamento deste transtorno, o que dificultava o entendimento sobre a real eficácia da TERV. Nesse sentido, o campo clamava por artigos de revisão que pudessem estimular novos estudos e compreender as reais vantagens do tratamento com realidade virtual.

Biomarcadores

Um marcador biológico, ou biomarcador, é um parâmetro orgânico objetivo que indica um processo biológico normal, patogênico ou uma resposta a uma intervenção terapêutica (*Biomarkers Definition Working Group*, 2001).

O campo da psiquiatria vem aumentando esforços para incorporar biomarcadores no diagnóstico, predição de resposta e tratamento de transtornos mentais (Insel et al., 2010; Singh & Rose, 2009). O novo olhar sobre os transtornos mentais estipulado pelo RDoC incentiva a criação e aperfeiçoamento de tratamentos que tenham como alvo medidas biocomportamentais específicas. Dentre os benefícios previstos por esse modelo está o aperfeiçoamento do tratamento, tornando-o mais específico ao problema. Investigar de que maneira o tratamento impacta marcadores biológicos abrirá campo para a seleção de técnicas mais direcionadas, desuso de técnicas menos eficazes e aprimoramento de estratégias mais diretamente relacionadas ao transtorno do ponto de vista biológico (Ostergaard et al., 2014).

Ainda que seja incipiente o diálogo com a ciência básica, a psicologia vem buscando a utilização de parâmetros biológicos como forma de obter avanços realizados no campo da comprovação empírica de eficácia. Nesse sentido, é cada vez maior o número de publicações científicas na área da psicologia que envolvam relação com esses parâmetros (Porto, Gonçalves & Ventura, 2011). A figura abaixo representa a comparação entre o número de publicações com neuroimagem e medicação versus neuroimagem e psicoterapia até o ano de 2009.

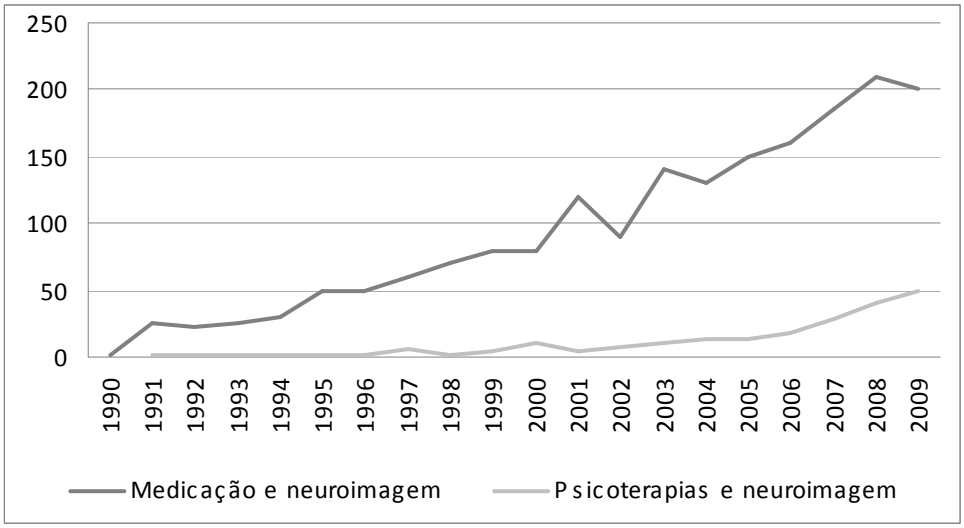

Figura 1: Medicação e neuroimagem versus psicoterapias e neuroimagem. Retirado de Porto, Gonçalves e Ventura, 2011.

De acordo com a figura, é possível observar o número restrito de publicações envolvendo psicologia e neuroimagem em comparação à psiquiatria e neuroimagem. Isto indica que há um vasto campo a ser explorado, embora o número de publicações esteja aumentando nos últimos anos. Em uma revisão sistemática publicada recentemente, Quidé et al. (2012) observaram que em pacientes com diagnóstico de transtornos de ansiedade a TCC tem o poder de modificar a ativação de áreas cerebrais prefrontais, provocando um efeito "de cima para baixo", enquanto o tratamento farmacológico produz efeitos "de baixo para cima", tendo em vista a redução da hiperativação de regiões límbicas após tratamento farmacológico. Este resultado é coerente com a ideia de que a TCC objetiva gerar novos aprendizados flexibilizando pensamentos distorcidos acerca dos estímulos irracionalmente temidos, enquanto a farmacoterapia age mais diretamente em regiões cerebrais "instintivamente" ligadas ao medo.

Espera-se que a pesquisa translacional em psicologia estreite o diálogo com o tratamento farmacológico dos transtornos mentais, colaborando para reduzir a taxa de mortalidade dos transtornos, beneficiando pacientes resistentes aos tratamentos atualmente vigentes e diminuindo o tempo de tratamento de pacientes que já respondem a terapias convencionais.

Objetivos

A presente tese teve como objetivos:

1. Verificar o impacto da TCC em parâmetros psicofisiológicos no tratamento de transtornos de ansiedade, em especial o TEPT.

2. Avaliar a eficácia da TERV no tratamento do TEPT.

Métodos

A investigação do primeiro objetivo foi realizada em três etapas: primeiramente, através da realização de uma revisão sistemática (artigo 1) sobre o impacto da TCC em parâmetros psicofisiológicos geralmente alterados no TEPT. Para tal, foi realizada uma busca sistemática nas bases eletrônicas *ISI Web of Science*, PubMed/MEDLINE e Pilots (a maior base de dados do mundo sobre TEPT). Em seguida, foi realizado um estudo experimental (artigo 2), no qual foi administrado um protocolo de tratamento cognitivo-comportamental em pacientes com o diagnóstico de TEPT atendidos no ambulatório do Instituto de Psiquiatria da UFRJ. Finalmente, foi conduzida uma meta-análise e revisão sistemática (artigo 3) sobre o impacto da TCC na frequência cardíaca de pacientes com transtornos de ansiedade através de buscas eletrônicas nas bases *ISI Web of Science*, PubMed/MEDLINE e PsychINFO.

O segundo objetivo foi alcançado através de uma revisão sistemática (artigo 4) de estudos que administraram protocolos de TERV em pacientes com TEPT. As mesmas bases eletrônicas utilizadas no artigo 3 foram investigadas nesta revisão.

Detalhes dos métodos empregados nos quatro estudos foram descritos nos respectivos artigos incluídos nesta tese.

Artigos
Artigo 1

Revisão da literatura

Potenciais biomarcadores da terapia cognitivo-comportamental para o transtorno de estresse pós-traumático: uma revisão sistemática

Potential biomarkers of cognitive behavior-therapy for post-traumatic stress disorder: a systematic review

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Resumo

Contexto: O estabelecimento de biomarcadores relacionados à terapia cognitivo-comportamental (TCC) é uma maneira de consolidar a eficácia do tratamento de forma mais objetiva, sendo crítico para o avanço desse campo de pesquisa. **Objetivos:** Foi realizada uma revisão sistemática de estudos que: 1) utilizaram parâmetros biológicos para verificar a eficácia da TCC no tratamento do transtorno de estresse pós-traumático (TEPT); e 2) utilizaram esses parâmetros como preditores de resposta à CBT. **Métodos:** Foram conduzidas buscas eletrônicas nas bases PubMed/Medline, ISI/Thompson Reuters e Pilot. **Resultados:** Doze artigos foram selecionados para esta revisão, sendo quatro deles estudos sobre predição de resposta ao tratamento. Foi observada relação entre a eficácia da TCC e modificações nesses parâmetros, sendo a resposta da frequência cardíaca à evocação de sintomas o parâmetro mais utilizado até o presente momento. Sua redução está associada à melhora nos sintomas de TEPT. Potenciais biomarcadores de predição de resposta encontrados incluem 5α-redutase, ativação da amígdala, ativação e volume do córtex cingulado anterior e frequência cardíaca. **Conclusão:** Apesar da escassez de estudos e das limitações metodológicas neles observadas, investigações iniciais sugerem que os biomarcadores da TCC em pacientes com TEPT poderão ser úteis para o monitoramento mais objetivo dos efeitos do tratamento, identificação de predição de resposta e para o desenvolvimento de estratégias mais eficazes de tratamento e prevenção do desenvolvimento de TEPT.

Gonçalves R, et al. / Rev Psiq Clín. 2011;38(4):155-60

Palavras-chave: Transtorno de estresse pós-traumático, terapia cognitivo-comportamental, biomarcadores, revisão sistemática.

Abstract

Background: The establishment of biomarkers related to cognitive-behavior therapy (CBT) is a method to objectively consolidate treatment efficacy, which is critical to advancing the field. **Objectives:** We systematically reviewed studies that used biological parameters to assess the efficacy of CBT for the treatment of post-traumatic stress disorder (PTSD) and studies that used these parameters as predictors of response to CBT. **Methods:** Computerized literature searches were conducted in PubMed/Medline, ISI/Thompson Reuters, and Pilot databases using both thesaurus and free-word search terms. **Results:** 12 articles met the selection criteria. 4 of them were response predictors studies. A relationship was found between CBT efficacy and changes in the measured parameters, with heart rate responses to symptom provocation being the parameter most often studied. The reduction in heart rate was associated with an improvement in PTSD symptoms. The potential biomarkers of response predictions found included 5α-reductase, amygdala activation, activation and volume of the anterior cingulate cortex, and heart rate. **Discussion:** Despite the scarcity of studies and their methodological shortcomings, initial investigations indicate that biomarkers of CBT in PTSD patients hold promise for more objective treatment outcome monitoring, identification of response predictors, and for developing novel treatment and prevention strategies.

Gonçalves R, et al. / Rev Psiq Clín. 2011;38(4):155-60

Keywords: Post-traumatic stress disorder, cognitive-behavioral therapy, biomarkers, systematic review.

Introdução

A eficácia da terapia cognitivo-comportamental (TCC) no tratamento do transtorno de estresse pós-traumático (TEPT) é bem documentada[1-5]. A TCC tem sido considerada um dos tratamentos de primeira escolha para esse transtorno[6]. A base para a avaliação de sua eficácia tem sido a utilização de instrumentos psicométricos (em sua maioria, escalas de autorrelato), que, administrados antes e após ou ao longo do tratamento, apontam para a diminuição dos sintomas experimentados. Entretanto, uma importante limitação de se basear nos autorrelatos é que eles são sujeitos a diversos vieses, particularmente na área da traumatologia. Por exemplo, Marmar[7] aponta que os pacientes com TEPT podem omitir sintomas por causa da estigmatização da patologia, sendo também comum o relato exagerado de sintomas com o objetivo de usufruir benefícios governamentais.

Atualmente, alguns estudos têm se preocupado em obter maior confiabilidade em seus dados. Para isso, estão sendo utilizadas para a avaliação de sua eficácia, além dos instrumentos psicométricos, medidas puramente objetivas, como as alterações de parâmetros biológicos relacionadas à terapia[8]. As medidas de parâmetros biológicos são mais confiáveis do que os resultados provenientes de escalas, uma vez que não estão sujeitos aos vieses que permeiam as medidas psicométricas[7].

Outra preocupação com o uso de medidas psicométricas é relacionada à sua generalização de estudos clínicos sem a utilização de placebo. A utilização de biomarcadores válidos poderá aumentar a confiabilidade de estudos que testam a eficácia da psicoterapia nos quais uma condição controle confiável não é viável[9].

Outro importante papel dos biomarcadores é a sua utilização para o aprimoramento do tratamento. Uma parcela de sujeitos, que pode chegar a 50%, não responde ao tratamento convencional

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com TCC ou desiste dele[10]. Uma possível fonte de aprimoramento da terapia é descobrir quais parâmetros biológicos – cerebral, neuroendócrino e/ou psicofisiológico – são alterados em decorrência da TCC e se os novos padrões de funcionamento são compatíveis com os dados clínicos ao término da terapia. Dessa forma, pode-se personalizar o tratamento considerando-se que uma dada técnica atua na modificação de um determinado biomarcador ou aperfeiçoar o tratamento de modo que atue mais diretamente na modificação desse parâmetro.

Além disso, a identificação de alguns "biomarcadores-chave" em determinados indivíduos pode facilitar a prevenção do desenvolvimento de psicopatologias, o que poderia ser feito mediante a elaboração de programas de intervenção que atuem nesse sentido[11].

O propósito deste artigo é proceder a uma revisão sistemática dos estudos que se utilizaram de parâmetros biológicos para avaliar a eficácia da TCC no tratamento do TEPT, além de investigar preditores biológicos de resposta ao tratamento. A nossa hipótese é de que a TCC é capaz de modificar parâmetros biológicos relacionados ao TEPT.

Metodologia

Seleção dos estudos

Algumas condições foram adotadas para fazer a seleção dos estudos. Primeiramente, foi realizada uma busca eletrônica em 19 de agosto de 2009 nas bases ISI/Thompson Reuters, PubMed/Medline e Pilots. Na base ISI/Thompson Reuters, restringiu-se a busca a *articles* e *notes*. Na base PubMed/Medline, as buscas dos termos TEPT e TCC foram realizadas seguindo a terminologia sugerida pelo *MeSH Database*, enquanto os termos biológicos foram pesquisados diretamente no *Advanced Search*. Dado que a base Pilots é diretamente relacionada a estudos sobre trauma, as palavras-chave relacionadas a TEPT foram omitidas. Posteriormente, os resultados das buscas individuais foram combinados.

Para evitar que artigos que se encaixassem no perfil pesquisado fossem omitidos, além das buscas realizadas nessas bases, foram realizadas novas buscas nas referências bibliográficas de cada artigo selecionado para a revisão, assim como nos artigos que fizeram citação desses estudos. Artigos originais, *brief reports* e cartas ao editor publicados em línguas além da inglesa foram considerados para a inclusão. Artigos de revisão, capítulos de livro, teses e dissertações foram excluídos.

Foram adotados como critérios de inclusão o emprego de técnicas cognitivas e/ou comportamentais, a participação de sujeitos com diagnóstico de TEPT e a avaliação de parâmetros biológicos antes e após a terapia. Artigos que utilizaram técnicas psicoterápicas de outras abordagens foram excluídos. Além disso, foram incluídos estudos que utilizaram pacientes com comorbidades psicopatológicas. Estudos de caso, definidos por Pincus *et al.*[12] como apresentações de 10 casos ou menos, foram excluídos.

Resultados

Dos 308 artigos que se encaixaram nos critérios desta revisão sistemática, foram excluídos 30 artigos que não investigaram TEPT ou nos quais os participantes preenchiam critério diagnóstico somente para TEPT parcial, 77 estudos que utilizaram técnicas de outras abordagens psicoterapêuticas que não a TCC, 82 artigos teóricos, teses ou dissertações, 16 estudos que não fizeram uso de parâmetros biológicos para avaliar a eficácia da terapia, 7 estudos com animais, 3 estudos de validação de instrumentos, 50 revisões e 22 estudos de caso. Cinco artigos foram selecionados a partir das listas de referências. Dessa forma, a análise final foi baseada em 12 artigos, sendo 4 deles estudos de predição de resposta ao tratamento. Os estudos estão sumarizados nas tabelas 1 e 2. Considerando-se todos os estudos selecionados para esta revisão, um total de 333 pacientes foram avaliados, sendo 187 deles selecionados para os grupos experimentais.

Correlatos biológicos dos estudos de eficácia

Estudos com parâmetros neuroendócrinos

Um estudo que utilizou parâmetros neuroendócrinos, conduzido por Smyth *et al.*[13], foi considerado para a nossa análise. O estudo consistiu em um ensaio randomizado-controlado, e o número total de participantes no grupo experimental foi 15. A mensuração dos níveis de cortisol foi realizada somente na etapa de *follow-up*, três meses após o procedimento. Embora os autores não tenham verificado melhora nos sintomas, o resultado apontou maior atenuação de cortisol no grupo experimental diante de lembranças do trauma quando comparado ao grupo controle.

Estudos envolvendo parâmetros psicofisiológicos

Foram identificados sete estudos envolvendo parâmetros psicofisiológicos. Dois deles utilizaram eletromiografia para mensurar a eficácia da TCC, sendo um deles um estudo randomizado-controlado[14], enquanto o outro foi um estudo não controlado[15]. Somando-se o número de participantes submetidos à TCC nos dois estudos, chegou-se a um total de 39 participantes (todos veteranos de guerra). Ambos utilizaram inundação como técnica a ser testada, e os parâmetros analisados incluíram, além de eletromiografia facial, frequência cardíaca e condutância da pele (CP) durante as sessões. Boudewyns e Hyer[14] relataram que a diminuição do EMG não foi estatisticamente relacionada à diminuição das medidas psicométricas. Similarmente, Pitman *et al.*[15] não encontraram relação estatística entre a diminuição no EMG e a diminuição das medidas psicométricas.

Com relação à condutância da pele, três estudos, incluindo os dois estudos acima citados, utilizaram CP para mensurar a eficácia da TCC[16]. Considerando-se todos os estudos, o número de participantes no grupo experimental foi 64. A diminuição da CP em resposta a lembranças do evento traumático foi estatisticamente relacionada à diminuição dos parâmetros psicométricos, sem diferença estatística entre as duas intervenções. Houve, contudo, uma queda mais pronunciada na reatividade no grupo experimental quando comparado ao grupo controle. O grupo experimental mostrou diminuição da reatividade em duas de três repetições do áudio, enquanto o grupo controle mostrou diminuição somente em um dos áudios[14]. Houve uma tendência à diminuição da CP em outro estudo[15], e no terceiro estudo[16] não houve diferença significativa na CP no grupo experimental. Além disso, esse último estudo não detalhou os resultados relacionados à CP.

Sete estudos utilizaram frequência cardíaca para avaliar a eficácia da TCC, sendo quatro deles estudos controlados. No total, 84 pacientes foram submetidos à TCC. Foi observada uma relação entre a redução da frequência cardíaca e a resposta à TCC em seis dos sete estudos selecionados. Houve redução da frequência cardíaca em resposta a lembranças do trauma no grupo submetido ao tratamento comparado ao grupo controle em três estudos[15-17] e tendência à redução em outros três estudos[14,18,19]. Todos esses artigos utilizaram paradigma de provocação de sintomas. O único estudo que não encontrou essa relação empregou metodologia de repouso.

Pressão arterial foi utilizada em dois estudos, sendo ambos os estudos randomizados-controlados. Um total de 37 sujeitos foi submetido à TCC, somando-se o número de participantes nos dois estudos. Em um deles, não houve diferença na pressão arterial após o tratamento[15], enquanto o outro estudo relatou redução significativa na pressão sistólica após o tratamento[20].

Estudos envolvendo neuroimagem

Foi identificado um estudo não controlado que utilizou fMRI em 13 participantes. Após a terapia, houve aumento da ativação de áreas cerebrais envolvidas em cognição social (giro temporal medial esquerdo, relacionado à empatia, giro cingulado posterior, giro frontal medial e giro temporal superior medial esquerdo associado ao perdão), acompanhado de melhora nos sintomas, conforme evidenciado

pelas escalas. A associação dessas áreas cerebrais com empatia e perdão foi previamente identificada pelos autores[21] em um paradigma no qual 10 voluntários foram convidados a fazer julgamentos baseados em cenários sociais. O giro frontal superior esquerdo, giro orbitofrontal e *precuneus* foram ativados por julgamentos de empatia. No estudo conduzido por Farrow *et al.*[21], os sujeitos foram engajados em tarefas que envolviam especulação da intenção de outros, invocando empatia e perdão, e estas eram alternadas com cenas que envolviam julgamentos sociais antes e após a terapia. O tratamento com TCC utilizado nesse estudo incluiu um componente de perdão.

Tabela 1. Estudos selecionados

Estudo	Delineamento	Procedimentos	Medidas biológicas	Eficácia da TCC	Mudanças biológicas
Smyth *et al.*[13], 2008	Randomizado. Placebo (n = 10) ou escrita expressiva (n = 15). Total: n = 25	3 sessões de escrita expressiva (20' cada com 15' de intervalo – todas realizadas em 1 dia). Cortisol analisado somente no *follow-up*	Cortisol (salivar)	Sem mudanças significativas nos sintomas de TEPT. Melhora no humor	Atenuação das respostas de cortisol durante rememoração do trauma no grupo experimental* no pós-tratamento e maior recuperação após 20 min de repouso
Boudewyns e Hyer[14], 1990	Randomizado. Inundação (n = 19) ou aconselhamento (n = 19). Total: n = 38	10-12 sessões semanais de 50 min cada	EMG frontal, frequência cardíaca, condutância da pele	Grupo de inundação mostrou melhora nos sintomas comparado ao grupo controle de acordo com o VET*	Diferença na CP no pós-tratamento comparando ambos os grupos*. FC e EMG mostraram maior tendência à redução no grupo experimental**
Pitman *et al.*[15], 1996	Não controlado. n = 20	12 semanas de inundação/relaxamento	FC, CP, EMG frontal lateral esquerdo e EMG corrugador esquerdo	Diminuição dos sintomas de evitação e intrusões* e melhora em outros sintomas**	Redução em todas as variáveis, mas só a FC mostrou redução*
Blanchard *et al.*[16], 2002	Randomizado. TCC (n = 25), aconselhamento (n = 26) e lista de espera (n = 22). Total: n = 73	8-12 sessões de escrita, exposição *in vivo*, relaxamento, técnicas cognitivas	CP, pressão arterial e FC	Redução no CAPS no grupo experimental*	FC diminuiu no grupo experimental*
Frueh *et al.*[17], 1996	Não controlado. n = 11	29 sessões durante 17 semanas de *Trauma Management Therapy* (exposição, psicoeducação, SST e prática programada)	FC	Efeitos do tratamento no CGI, HAMA, aumento do número de horas de sono e atividades sociais* e CAPS (tendência)	Reatividade da FC diminuiu no pós-tratamento comparada ao pré-tratamento*
Cooper e Clum[18], 1989	Não randomizado. n = 14	6-14 sessões de 90 min cada (uma ou duas vezes por semana) de inundação/relaxamento	FC	Redução da revivescência e distúrbios do sono. Redução no STAI e BDI	FC não se mostrou reduzida no grupo experimental, mas aumentou no grupo controle**
Fecteau e Nicki[19], 1999	Randomizado. TCC (n = 10) ou lista de espera (n = 10). Total: n = 20	8-10 sessões de psicoeducação, relaxamento, exposição, reestruturação e autoinstrução	FC	Efeitos do tratamento detectados pelas entrevistas estruturadas, questionários de autorrelato e testes comportamentais no grupo experimental*	Reatividade diminuiu mais no grupo experimental**
Hinton *et al.*[20], 2009	Randomizado. TCC (n = 12) ou lista de espera (n = 12). Total: n = 24	12 semanas de reestruturação cognitiva, respiração diafragmática, relaxamento muscular, psicoeducação, imageamento guiado, exposição interoceptiva	Pressão arterial sistólica e diastólica, FC	Melhora mais acentuada no grupo experimental. Regulação da emoção e do pânico	Pressão arterial diastólica e FC**. Redução na pressão arterial sistólica*, que foi mais correlacionada à melhora na regulação de estados afetivos negativos
Farrow *et al.*[21], 2005	Não controlado. n = 13	4-10 sessões de TCC incluindo componente de perdão. Não especifica as técnicas empregadas	fMRI (áreas cerebrais)	Redução no CAPS após o tratamento*. Tendência à redução no IRI e EFI**	Aumento da ativação de áreas cerebrais envolvidas em cognição social (giro temporal medial esquerdo, relacionado à empatia; giro cingulado posterior, giro frontal medial e giro temporal superior medial – associado ao perdão)

*: estatisticamente significativo; **: não estatisticamente significativo; VET: *Veterans Adjustment Scale*; CGI: Impressão Clínica Global; HAMA: Escala de Ansiedade Hamilton; CAPS: *Clinician-Administered PTSD Scale*; BDI: Inventário Beck de Depressão; SPAI: *Social Phobia and Anxiety Inventory*; AX: *Spielberger Anger Expression Inventory*; STAI: Inventário Spielberger de Ansiedade Traço-estado; IRI: *Interpersonal Reactivity Index*; EFI: *Enright Forgiveness Inventory*; SST: *Social Skills Training*; FC: frequência cardíaca; CP: condutância da pele.

Tabela 2. Estudos de predição de resposta

Estudo	Delineamento	Protocolo TCC	Procedimentos	Medidas biológicas	Resultados
Pitman *et al.*[15], 1996	Não controlado. n = 20	12 semanas de inundação e relaxamento	Monitoramento durante a primeira e a última série das sessões de inundação	FC, CP, EMG	FC aumentada antes do tratamento foi associada à melhor resposta terapêutica (redução de pensamentos intrusivos)
Yehuda *et al.*[22], 2009	Randomizado. Exposição prolongada (n = 14) ou orientação (n = 14). Total: n = 28	Não especificado	Coletada ao longo de 24 horas pela urina antes e após o tratamento e 3 meses após (*follow-up*). Mensuração em linha de base	Cortisol e alguns de seus metabólitos	5α-redutase (metabólito do cortisol) estava 70% diminuída no pré-tratamento em não respondentes. Nenhum outro hormônio foi preditor
Bryant *et al.*[23], 2008	Não controlado. Diagnosticados com TEPT: n = 14. Total: n = 28	8 sessões semanais de psicoeducação, exposição imaginária, reestruturação cognitiva e prevenção de recaída	Escaneamento antes do tratamento e durante a visualização de imagens de quatro homens e quatro mulheres expressando medo, alternadas com expressões neutras	Áreas cerebrais (fMRI)	Não respondentes tinham maior ativação da amígdala bilateralmente e córtex cingulado anterior ventral direito durante a apresentação de estímulos antes do tratamento
Bryant *et al.*[24], 2008	TEPT: n = 13. História de trauma e sem TEPT: n = 13. Sem história de trauma: n = 13. Total: n = 39	8 sessões semanais de psicoeducação, exposição imaginária, reestruturação cognitiva e prevenção de recaída	Escaneamento antes e após o tratamento (mensuração do volume)	Áreas cerebrais (ressonância magnética estrutural – MRI)	Respondentes tinham maior volume do córtex cingulado anterior rostral comparados a não respondentes

Correlatos biológicos de predição de resposta

Quatro estudos que investigaram predição de resposta à TCC mediante parâmetros biológicos mensurados antes do tratamento foram encontrados. Os parâmetros acessados por esses estudos mostraram-se bons preditores de resposta. Foi observado que os 14 não respondentes à TCC possuíam níveis de 5α-redutase (um metabólito do cortisol) 70% mais baixos que os 14 respondentes[22]. Outro estudo mostrou que os não respondentes à TCC tinham maior ativação da amígdala bilateral e do córtex cingulado anterior direito ventral durante a apresentação de faces com medo e neutras comparados aos respondentes[23]. Além disso, respondentes ao tratamento tinham maior volume no córtex cingulado anterior rostral, em relação aos não respondentes[24]. O aumento da frequência cardíaca antes do tratamento foi preditor de resposta favorável à TCC[15]. Cortisol e alguns de seus metabólitos, contudo, não foram bons preditores de resposta à TCC[22].

Discussão

Até o presente momento, nenhuma revisão sistemática sobre mudanças biológicas como marcadores de eficácia da TCC em pacientes com TEPT ou sobre a utilização desses marcadores como preditores de resposta foi publicada.

Foi observada uma tendência ao aumento de publicações envolvendo medidas biológicas em resposta ao tratamento. De 1985 a 1990, somente dois estudos foram identificados e de 1991 a 1995 nenhum estudo foi identificado. Contudo, de 1996 a 2000, três publicações satisfizeram nossos critérios, e ainda mais estudos foram identificados após 2005 (cinco estudos de 2006-2009).

Correlatos biológicos de estudos de eficácia

Em geral, os resultados da pesquisa desta revisão sistemática apoiam a hipótese de que a TCC é capaz de modificar parâmetros biológicos. A maioria dos estudos observou alguma evidência de mudança nesses parâmetros em associação com a resposta ao tratamento avaliada por escalas psicométricas.

Com relação à frequência cardíaca, a maioria dos estudos mostrou uma correlação entre a resposta à TCC e a redução da reatividade cardíaca associada ao *script* traumático. Até o presente momento, esse parâmetro é o mais promissor biomarcador de eficácia da TCC em virtude da associação com a resposta ao tratamento e ao maior número de estudos que fizeram sua utilização em comparação com outros parâmetros. Esse dado é explicado pela facilidade de implementação desse parâmetro, além da sua alta sensibilidade a pistas traumáticas. Além disso, a frequência cardíaca tem sido considerada um dos mais promissores correlatos biológicos do TEPT[25,26].

EMG e pressão arterial não pareceram ser potenciais indicadores da eficácia da TCC no tratamento do TEPT. Nos dois estudos que foram selecionados para esta revisão sistemática, a avaliação da mudança nesses dois parâmetros após o tratamento não esteve relacionada à mudança observada nas escalas psicométricas, com exceção da pressão sistólica em um dos estudos. É necessária a replicação desses achados para que se possa chegar a conclusões mais consistentes acerca desses dois parâmetros.

A reatividade do cortisol ao *script* traumático também não pareceu estar associada à resposta ao tratamento com TCC. Contudo, sujeitos que receberam sessões de escrita expressiva para o tratamento do TEPT apresentaram menor reatividade ao *script* traumático relacionada ao cortisol, sugerindo que a resposta ao tratamento está associada à melhora na capacidade de regular a resposta ao estresse. Este estudo, contudo, envolveu somente três sessões de escrita expressiva, o que é considerado insuficiente para produzir efeitos terapêuticos[2]. Também é digno de nota o fato de este estudo não informar se os participantes possuíam comorbidades psiquiátricas como depressão maior, considerada uma comorbidade comum no TEPT que está associada a elevados níveis de cortisol[27] e, por isso, pode ter interferido nos resultados do estudo. Níveis de CP mostraram resultados inconsistentes, já que esse parâmetro foi associado à resposta ao tratamento com TCC em apenas um dos três estudos nos quais ele foi mensurado. Dado que o número de estudos ainda é limitado, mais publicações são necessárias para que se chegue a conclusões mais consistentes.

O tratamento eficaz com TCC foi associado ao aumento de áreas neurais envolvidas em cognição social, como o giro temporal medial esquerdo, que foi anteriormente relacionado à empatia, e o giro cingulado posterior, o giro medial frontal e o giro medial superior temporal esquerdo, que foram anteriormente associados ao perdão. É interessante notar que, apesar de ser uma das mais promissoras

tecnologias, o imageamento funcional foi pouco utilizado até o momento em estudos realizados com pacientes com diagnóstico de TEPT[28]. Contudo, a utilização de fMRI envolvendo pacientes com transtorno obsessivo-compulsivo, fobias específicas e transtorno do pânico é mais difundida[28]. Novamente, mais investigações são necessárias para avaliar até que ponto a resposta ao tratamento está associada a determinados padrões de ativação neural, conforme observado em outros transtornos de ansiedade.

Correlatos biológicos de predição de resposta

Apesar do número limitado de artigos encontrados, alguns parâmetros parecem ter potencial clínico para predizer a resposta à TCC, sendo eles a enzima 5α-redutase, ativação da amígdala, ativação e volume do córtex cingulado anterior e frequência cardíaca. As exceções incluem o cortisol e alguns de seus metabólitos. Yehuda *et al.*[29] observaram baixos níveis de 5α-redutase em sobreviventes do Holocausto e sugeriram que essa redução pode ser um fator de risco para o desenvolvimento de TEPT. A maior ativação da amígdala em não respondentes e o maior volume do córtex cingulado anterior em respondentes antes do tratamento são compatíveis com o modelo neural aceito para o TEPT[30,31], que é baseado em dados de neuroimagem que mostram exagerada ativação da amígdala e ativação diminuída em áreas frontais. Apesar de alguns dados demonstrarem que a ativação da amígdala durante o tratamento com exposição é requerida para que o processo de extinção ocorra, dependendo da gravidade do TEPT, a excessiva ativação dessa área é prejudicial ao processamento do medo, talvez porque possa ser mais difícil regular a ansiedade eliciada pela TCC nesses casos[23]. A maior ativação do córtex cingulado anterior pode ser associada à rápida apresentação dos estímulos temidos que não eram percebidos conscientemente, engajando, dessa forma, redes subcorticais. Finalmente, a maior reatividade da frequência cardíaca em respondentes pode ser explicada pelo maior engajamento no processo de exposição a pistas traumáticas.

O estudo conduzido por Hinton *et al.*[20] foi o único que não fez uso do método de provocação de sintomas para mensurar um parâmetro biológico. Todas as outras publicações utilizaram essa metodologia, o que permite maior comparação entre os artigos selecionados. A comparação dos dados presentes nesses estudos ainda assim é limitada por causa da variabilidade no momento da coleta dos dados. Por exemplo, alguns estudos analisaram o primeiro ou o último minuto da provocação de sintomas ou os momentos de pico na resposta aos estímulos.

Limitações metodológicas dos estudos revisados

Várias limitações foram observadas nos artigos incluídos na nossa análise. Amostras pequenas, com 7 de 10 estudos utilizando amostras menores que 30 sujeitos (não incluindo os estudos de predição de resposta), foram a primeira e mais proeminente limitação. O fato de a maioria desses estudos contar com amostra pequena pode explicar a falta de significância estatística observada em alguns parâmetros com relação ao resultado da TCC. Vários estudos relataram tendência à não significância entre seus resultados. Problemas adicionais incluíram a ausência de informação a respeito do uso de medicação psicotrópica por parte dos participantes de três dos estudos selecionados e uso de medicação psicotrópica não estabilizada em quatro dos estudos. Um dos estudos permitiu que os participantes se mantivessem em outros tratamentos psicoterápicos durante a pesquisa[15]. Cinco dos estudos não descreveram a presença de comorbidades psiquiátricas e um estudo relatou a presença de comorbidade, contudo sem especificar a condição comórbida. Além disso, seis dos artigos descreveram comorbidades que incluíam depressão maior. A ausência de controle para comorbidades é relevante por causa da possibilidade de parâmetros biológicos serem alterados em virtude da presença de outros transtornos psiquiátricos, o que pode levar à alteração dos dados. Decidiu-se incluir estudos não controlados em virtude da falta de artigos nesse campo de pesquisa. Entretanto, a possibilidade de efeitos placebo nos ensaios não controlados deve ser considerada, já que esse dado pode invalidar alguns dos achados.

Já que esse é um campo incipiente, os dados devem ser interpretados com cautela. O uso de diferentes metodologias e instrumentos de avaliação torna difícil a generalização dos resultados. Também é digno de nota o fato de a nossa busca ter sido restrita a artigos publicados eletronicamente, o que pode ter omitido estudos que seriam incluídos nesta revisão.

Potenciais implicações clínicas

Apesar dos grandes avanços observados na área da neurociências/neurobiologia, ainda há poucos estudos na literatura psicológica que dialogam com essa área, a qual pode oferecer contribuições extremamente úteis para o entendimento da atuação da terapia no organismo[11]. Segundo Beauchaine *et al.*[11], "o uso de marcadores biológicos em resultados de pesquisas longitudinais representa o primeiro passo rumo a uma ciência de prevenção mais integrada" (p. 747). Apesar da eficácia da TCC, há pacientes que não respondem ao tratamento, continuando a apresentar sofrimento psicológico significativo ao fim da terapia[32]. Portanto, são necessários estudos na área básica que possibilitem o aprimoramento da psicoterapia, de modo que a parcela de pacientes não respondentes ao tratamento obtenha ganhos terapêuticos. O estudo de variáveis biológicas nos transtornos mentais, bem como após tratamento psicológico, é impulsionado pela necessidade de gerar progresso na área clínica. Tal progresso pode ocorrer por meio do desenvolvimento de intervenções mais efetivas para o tratamento e para a prevenção de psicopatologias específicas, a partir dos conhecimentos provenientes do laboratório. Assim, é possível a transposição do conhecimento de área básica para aplicação clínica, ampliando as possibilidades terapêuticas e resposta a tratamentos.

Conclusão

Esta revisão sistemática mostrou que, apesar da eficácia de estudos com esse propósito presentes na literatura atual, existe uma relação entre a eficácia da terapia e mudanças em parâmetros biológicos em pacientes com diagnóstico de TEPT. Contudo, em virtude da tecnologia disponível atualmente, a superioridade dos marcadores biológicos diante dos parâmetros psicométricos tradicionais não está estabelecida. No futuro, é provável que as variáveis biológicas mostrem-se como ferramentas úteis para o desenvolvimento de tratamentos individualizados e mais efetivos.

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O estudo conduzido por Hinton *et al.*[20] foi o único que não fez uso do método de provocação de sintomas para mensurar um parâmetro biológico. Todas as outras publicações utilizaram essa metodologia, o que permite maior comparação entre os artigos selecionados. A comparação dos dados presentes nesses estudos ainda assim é limitada por causa da variabilidade no momento da coleta dos dados. Por exemplo, alguns estudos analisaram o primeiro ou o último minuto da provocação de sintomas ou os momentos de pico na resposta aos estímulos.

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Várias limitações foram observadas nos artigos incluídos na nossa análise. Amostras pequenas, com 7 de 10 estudos utilizando amostras menores que 30 sujeitos (não incluindo os estudos de predição de resposta), foram a primeira e mais proeminente limitação. O fato de a maioria desses estudos contar com amostra pequena pode explicar a falta de significância estatística observada em alguns parâmetros com relação ao resultado da TCC. Vários estudos relataram tendência à não significância entre seus resultados. Problemas adicionais incluíram a ausência de informação a respeito do uso de medicação psicotrópica por parte dos participantes de três dos estudos selecionados e uso de medicação psicotrópica não estabilizada em quatro dos estudos. Um dos estudos permitiu que os participantes se mantivessem em outros tratamentos psicoterápicos durante a pesquisa[15]. Cinco dos estudos não descreveram a presença de comorbidades psiquiátricas e um estudo relatou a presença de comorbidade, contudo sem especificar a condição comórbida. Além disso, seis dos artigos descreveram comorbidades que incluíam depressão maior. A ausência de controle para comorbidades é relevante por causa da possibilidade de parâmetros biológicos serem alterados em virtude da presença de outros transtornos psiquiátricos, o que pode levar à alteração dos dados. Decidiu-se incluir estudos não controlados em virtude da falta de artigos nesse campo de pesquisa. Entretanto, a possibilidade de efeitos placebo nos ensaios não controlados deve ser considerada, já que esse dado pode invalidar alguns dos achados.

Já que esse é um campo incipiente, os dados devem ser interpretados com cautela. O uso de diferentes metodologias e instrumentos de avaliação torna difícil a generalização dos resultados. Também é digno de nota o fato de a nossa busca ter sido restrita a artigos publicados eletronicamente, o que pode ter omitido estudos que seriam incluídos nesta revisão.

Potenciais implicações clínicas

Apesar dos grandes avanços observados na área da neurociências/neurobiologia, ainda há poucos estudos na literatura psicológica que dialogam com essa área, a qual pode oferecer contribuições extremamente úteis para o entendimento da atuação da terapia no organismo[11]. Segundo Beauchaine *et al.*[11], "o uso de marcadores biológicos em resultados de pesquisas longitudinais representa o primeiro passo rumo a uma ciência de prevenção mais integrada" (p. 747). Apesar da eficácia da TCC, há pacientes que não respondem ao tratamento, continuando a apresentar sofrimento psicológico significativo ao fim da terapia[32]. Portanto, são necessários estudos na área básica que possibilitem o aprimoramento da psicoterapia, de modo que a parcela de pacientes não respondentes ao tratamento obtenha ganhos terapêuticos. O estudo de variáveis biológicas nos transtornos mentais, bem como após tratamento psicológico, é impulsionado pela necessidade de gerar progresso na área clínica. Tal progresso pode ocorrer por meio do desenvolvimento de intervenções mais efetivas para o tratamento e para a prevenção de psicopatologias específicas, a partir dos conhecimentos provenientes do laboratório. Assim, é possível a transposição do conhecimento de área básica para aplicação clínica, ampliando as possibilidades terapêuticas e resposta a tratamentos.

Conclusão

Esta revisão sistemática mostrou que, apesar da eficácia de estudos com esse propósito presentes na literatura atual, existe uma relação entre a eficácia da terapia e mudanças em parâmetros biológicos em pacientes com diagnóstico de TEPT. Contudo, em virtude da tecnologia disponível atualmente, a superioridade dos marcadores biológicos diante dos parâmetros psicométricos tradicionais não está estabelecida. No futuro, é provável que as variáveis biológicas mostrem-se como ferramentas úteis para o desenvolvimento de tratamentos individualizados e mais efetivos.

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Artigo 2

Impact of cognitive behavioral therapy on resting cardiac parameters and cortisol in patients with post-traumatic stress disorder: a pilot randomized clinical trial

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Abstract

Post-traumatic stress disorder (PTSD) has been associated with changes in psychophysiological and neuroendocrinal parameters. Cognitive behavioral therapy (CBT) is considered the treatment of choice for PTSD and is able to regularize altered neurobiological parameters. However, little is known about the effects of CBT on these parameters when measured during the therapeutic process. This pilot study aimed to evaluate the impact of CBT on cortisol and cardiac parameters measured at rest during the treatment of PTSD with comorbid major depression. 14 patients were randomized to four months of CBT or a waiting list. As expected, the experimental group had a greater reduction in PTSD symptoms, achieving high effect size. There was a reduction in the low frequency component of heart rate variability, which achieved borderline statistical significance and high effect size. Salivary cortisol tended to track the progress of therapy, rising in the period of exposure and decreasing by the end of treatment. Despite the small sample size, this study opens the way for further research into the impact of CBT on the different biological markers of PTSD during the therapeutic process. This can hopefully help to optimize and personalize therapeutic studies while providing clues about modifications in biobehavioral pathological manifestations.

Key words: Post-traumatic stress disorder, cognitive behavior therapy, cortisol, cardiac parameters, biomarkers

Introduction

Post-traumatic stress disorder, which is usually associated with great impairment of social, work and family life, is a chronic debilitating reaction to a traumatic situation. This reaction involves symptoms of reexperience, avoidance, negative changes in cognition and mood and autonomic hyperarousal (American Psychiatric Association, 2013). Fear processing neural, psychophysiological and behavioral markers (for review, Shvil, 2003) have begun to be investigated in an effort to enable more accurate diagnosis and prognosis, and provide more effective treatments (Singh & Rose, 2009).

Cardiac autonomic dysregulation is considered a psychophysiological marker of PTSD. This disruption can be studied by extracting the sympathetic and parasympathetic components of heart rate variability (HRV) (Berntson et al, 2007). Several studies have shown that reduction of parasympathetic components is associated with poor general health and increased cardiovascular morbidity and mortality (Tsuji et al, 1996; Dekker et al, 2000; Thayer and Lane, 2007; Nunan et al, 2010). In addition, the reduction of cardiac parasympathetic function follows and precedes the development of various risk factors, and therefore high parasympathetic activity is a predictor of good health and good autonomic and emotional regulation (Pumprla et al, 2002; Thayer; Lane, 2007; Vanderlei et al, 2009). The most prominent cardiovascular alterations in PTSD include increased heart rate during the presentation of stimuli conditioned to trauma (Peri et al., 2000) increased rest heart rate (Orr & Metzger & Pitman, 2000), slower heart recovery compared to non-traumatized subjects (Wessa & Florr, 2007; North et al, 2013), and decreased heart rate variability when compared to subjects who have been through a traumatic event, but did not develop PTSD (Norte et al, 2013).

Cortisol is a hormone activated in response to stress, and hence its role in PTSD has been investigated. Prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with deleterious effects (McEwen, 2003). Research involving PTSD and the HPA system has generated inconsistent results (Morris et al, 2012; Meewisse et al, 2007), possibly due to the variety of methods used and the differences between the investigated samples. For example, PTSD and major depression, which has a comorbidity index of 37% (Breslau, Davis, Andreski, and Peterson, 1991) seems to have a different impact on

cortisol activation (Kendall-Tackett, 2000). The most recent meta-analysis on the subject evaluated 47 studies and concluded that baseline morning cortisol levels are lower in patients with PTSD or PTSD comorbid with depression when these groups are compared to subjects who suffered trauma. However, taciturn or evening cortisol levels are lower in PTSD patients compared to non-traumatized subjects, but when there is comorbid depression, cortisol levels are higher.

Research into psychophysiological markers leads to a better understanding of the benefits of existing treatments. It is known that cognitive-behavioral therapy (CBT) has documented efficacy in the treatment of PTSD, significantly reducing psychological symptoms (Bisson, 2007). However, little is known about its impact on biological parameters. In a recent meta-analysis, a reduction in heart rate caused by cognitive behavioral protocols administered in patients with PTSD was found (Gonçalves et al., 2015). However, there are few studies of PTSD which investigate the impact of CBT on biological markers and, although the review was designed to include studies using both symptom evocation methodology and rest methodology, studies that used the second method were not found. The objective of this study was to evaluate possible cardiac and neuroendocrine changes in PTSD patients during treatment with CBT when they are measured at rest.

Materials and methods

Sample

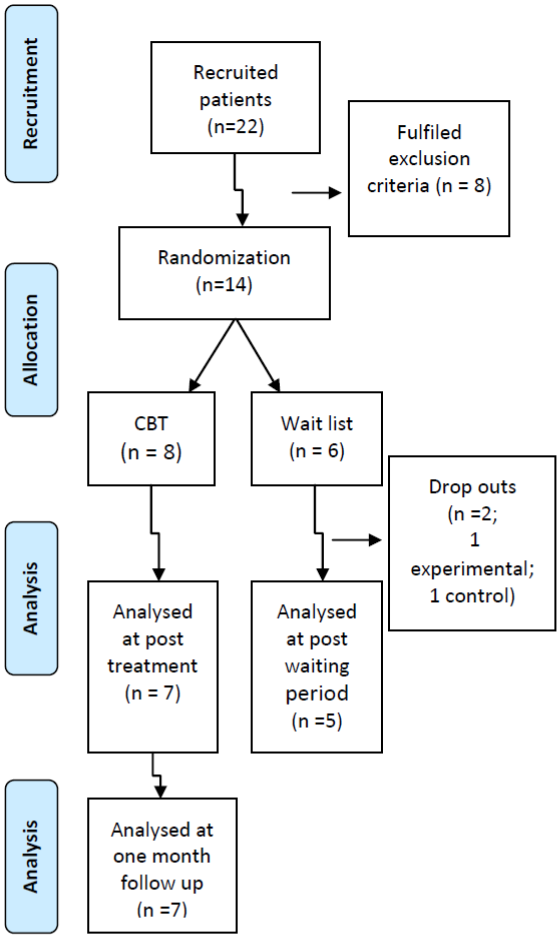
14 adults of both genders took part in the study. They were recruited through the media (newspapers, magazines, television and radio) and by dissemination of the treatment to health professionals. Only patients over 18 years old diagnosed with the full criteria for PTSD, according to the Structured Clinical Interview for DSM-IV (SCID), were included in the study. Pharmacological treatment was allowed during the study.

Excluded subjects were those in parallel psychotherapeutic treatment, who met diagnostic criteria for antisocial personality disorder or borderline personality disorder, were addicted to alcohol or drugs, had serious brain conditions, were pregnant or had primary psychosis. The study was conducted in accordance with the Ethics Committee of the Institute of Psychiatry, Federal University of Rio de Janeiro under the CAAE number 0051.0.249.000-11, and covered the terms of informed consent, questionnaires, treatment protocols and psychophysiological evaluation. Participation in this study was subject to the participants signing a document giving their free and informed consent.

Procedures

Potential participants were assessed using the SCID by a psychiatrist. Participants who fulfilled inclusion criteria were randomized to active treatment (experimental group) or waiting list (control group). Randomization was performed by sequence numbers randomly generated by software. Both groups had monthly psychometric and psychophysiological evaluations, from one week before the beginning of the therapy/waiting period until the end of therapy/waiting time (pre to month 4, totaling 5 evaluations). The experimental group had an extra evaluation, one month after the end of treatment (follow up). After the waiting period (four months), the same treatment was offered to the control group participants. Figure 1 describes the procedures.

Figure 1: Flow diagram for the procedure.



After participants signed the free and informed consent form, the first endocrine and cardiac evaluations were conducted, followed by the completion of the psychometric questionnaire. Each stage of data collection was conducted as follows:

The patient was asked not to eat anything for at least an hour prior to their appointment. They were allowed to drink water during this period. After at least five minutes of sitting without any activity, the following steps were taken: (1) endocrine evaluation; (2) cardiac evaluation; (3) general questions: participants• responded to four questions: if there were any stressful event during that week; what time did he/she sleep the day before and wake up on the day of the experiment; which medicaments were taken on the day of the experiment; and, for women, if she was in the menstrual period; (4) psychometric evaluation.

Endocrine evaluation:

Salivary cortisol is considered to be a reliable and valid measure of unbound ("free") cortisol concentration in the plasma. In each evaluation, one unstimulated saliva sample was collected during the experimental session by the use of a cotton swab. Samples were collected for 1 min at rest. Saliva was extracted from the cotton roll by centrifugation at 5000 rpm for 10 min. Cortisol concentrations were determined by radioimmunoassay using a commercial kit (DIAMETRA).

Cardiac Evaluation:

Accurate analysis of HRV can be performed by different methods: in the time domain, the Root Mean Square of Successive Differences (rMSSD) indicates parasympathetic activity; in the frequency domain, high frequency (HF) is also indicative of vagal influence on the heart, while low frequency (LF) is indicative of the vagal and sympathetic components, predominantly sympathetic. For the present study, a computer running Acknowledge (BIOPAC Systems Inc.) software controlled the data acquisition of the electrocardiographic parameters. Electrocardiographic recordings were collected at a sampling frequency of 1000 Hz and at lead II. An off-line peak detection algorithm (derivative plus threshold) was used to estimate fiducial R-wave points, after which the series was screened by hand and corrected for artefacts. Successive RR intervals were estimated in milliseconds. The cardiac parameters were extracted for 10 min and the last 5 min used for the analysis:

Heart rate (HR): Correlated to increased sympathetic and decreased parasympathetic activity;

- High frequency (HF), from 0.15 to 0.4 Hz: a marker of parasympathetic activity;
- Low frequency (LF), from 0.04 to 0.15 Hz: possibly correlated to sympathetic and parasympathetic activity or to baroreflex sensibility;
- Root mean square of successive R-R interval differences (RMSSD): a marker of parasympathetic activity.

The data processing followed the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. The Matlab software (KARDIA) was used to analyse cardiac parameters.

Psychometric evaluation:

The Post Traumatic Stress Disorder Checklist - Civilian Version questionnaire (PCL-C) is a self-administered instrument used to detect civilians who have high risk for PTSD diagnosis. The Brazilian version consists of 17 items scored 1 to 5, which evaluate the diagnostic criteria described in DSM-IV (Berger et al., 2004). The questionnaire was completed individually by the participants. We chose to do the psychometric evaluation after the cardiac and neuroendocrine evaluations due to the possibility of psychopsysiological reactions caused by the emotional charge associated with the content of the questionnaire.

Treatment Protocol

The study used a treatment protocol for patients with PTSD developed by Drs Edna Foa and Barbara Rothbaum (Foa and Rothbaum, 1998). This protocol was adapted for the Brazilian population by Pedrozo (2008). One psychotherapy session and three co-therapy sessions were performed weekly, all of 90 minutes each, resulting in 16 main therapy sessions and 48 co-therapy sessions, over 4 months. The treatment was conducted as following: psychoeducation about CBT and PTSD, a family session aimed at giving information about the disorder and the therapy, anxiety management techniques (progressive muscle relaxation and diaphragmatic breathing or polarized breathing. The type of breathing that provided more symptoms relief was chosen by the patient), cognitive restructuring of beliefs related to the traumatic event, in vivo exposure and imaginary exposure (listening to a recorded tape with the trauma description).

Statistical analysis

Due to the limited number of participants, the statistical significance of differences between groups was obtained through the Kruskal-wallis test. The effect size (Cohen d) of the mean differences between groups was also calculated. The results of the mean difference between assessments performed before and after treatment / waiting period will be presented. For evaluations carried out between these periods, we will present a qualitative analysis of the data.

Results

Baseline evaluation

Seven patients in the experimental group completed the treatment, while five completed the waiting period in the control group. All participants had comorbid major depression, no history of trauma in childhood and were submitted to pharmachological treatment prescribed by psychiatrists of the PTSD ambulatory clinic at the Federal University of Rio de Janeiro, Brazil. The socio demographic data are shown in Table 1:

Socio demographic data	Experimental group	Control group
Type of trauma		
Motor vehicle acident	2	2
Urban violence	4	3
Witnessing death	1	0
Gender		
Female	4	1
Male	4	3
Marital Status		
Single	4	1
Married	2	4
Divorced	1	0
Years of education		
- 9 years	0	2
9 years	3	2
9-12 years	0	0
12 years	2	1
University education	1	0
Age		
18-30	0	0
31-40	1	1
41-50	4	3
51-60	2	1
Mean	47,43	46,8

Treatment adherence

Two participants withdrew from the study, one from each group. The reasons for the dropouts were not related to adverse effects of exposure techniques.

Effects of treatment

The difference between the average pre and post-treatment / waiting period of the variables, as well as the p value and the effect size, are shown in Table 2.

Table 2: Average differences between pre and post-treatment (total group) / waiting list, p value and effect size.

Variables	**Delta pre-post***	**Delta pre-post***	**P value ****	**Cohen's *d***	**Delta pre-follow up**
	Experimental	Control			Experimental
PCL-C	9.71	-1.67	0.5676	0.859	10.2
Cortisol	1.20	-1.51	0.4561	0.638	1.21
Heart rate	-3.55	-3.3	0.8501	0.015	4.69
High frequency	31.30	-17.81	0.3447	0.54	29.02
Low frequency	15.09	-60.43	0.1859	0.763	58.19
RMSSD	5.75	-2.03	0.2568	0.207	-1.69

*** Difference between before and after treatment/waiting period; ** Kruskal-wallis test**

In order to know the real impact of CBT in psychophysiological parameters, we did a separate analysis of the patients who responded to the treatment according to the PCL-C and compared this data to the control group. We defined this group as the subjects that had a minimal decrease of 15 points in the PCL-C. These data are shown in table 3.

Table 3: Average differences between pre and post-treatment (respondents: n = 3 / waiting list: n = 5), p value and effect size.

Variables	Delta pre-post*	Delta pre-post	P value **	Cohen's *d*	Delta pre-follow up
	Experimental	Control			Experimental
PCL-C	18.5	-1.67	0.1573	1.331	10.2
Cortisol	1.2888	-1.51	0.4795	0.575	1.21
Heart rate	-2.298	-3.3	0.5637	0.408	4.69
High frequency	44.568	-17.81	0.2482	0.578	29.02
Low frequency	102.80	-60.43	0.0833	2.097	58.19
RMSSD	8.656	-2.03	0.2482	0.323	-1.69

***Difference between before and after treatment/waiting period; **Kruskal-wallis test**

Psychometric variable

According to the results of the PCL-C, the mean score of the experimental group was consistently lower at the end of the treatment, and this reduction was maintained in the follow-up period, one month after the end of treatment. The average decrease was 9.71 points. In the control group, there was also a score decrease. However, the average decrease was 6 points.

One of the patients in the control group had a completely different pattern of response. His PCL-C score decreased 42 points from the beginning to the end of the waiting period. This factor is probably due to the effect of pharmacological treatment. If we remove this outlier patient from the analysis, the control group average PCL-C score increases 1.67 points.

The comparison between the group's average scores before and after treatment/ waiting period shows no statistically significant (p = 0.5676) effect of CBT. However, the effect size was large (Cohen's d = 0.859) (Figure 2).

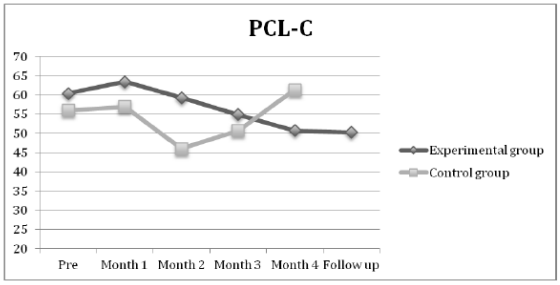


Figure 2: PCL-C scores throughout the treatment/ waiting period

The analysis of patients who responded to the treatment, shows that the result gets closer to statistical significance (p = 0.1573) and the effect size increases (Cohen's d = 1.331).

Cardiac variables

Data from seven subjects in the experimental group and four in the control group were analyzed.

Heart rate

There was no statistically significant difference between the mean heart rate before and after treatment between groups (p = 0.8501). The effect size was small (Cohen's d = 0.015). In the experimental group, there was a heart rate decrease only in the follow up period (Figure 3).

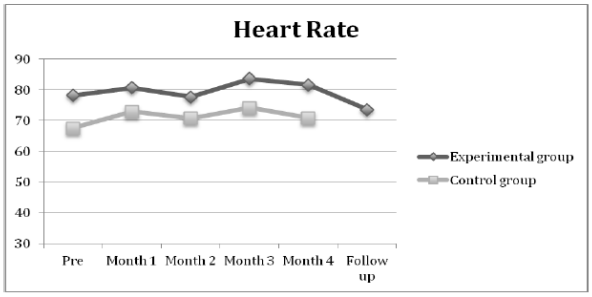


Figure 3: Heart rate throughout the treatment / waiting period

An analysis of the treatment responders indicates that the difference between this subgroup and the control group was not significant (p = 0.5637) and effect size remained small (Cohen's d = 0.408).

High frequency

With respect to HF, the difference between the groups' average scores before and after treatment/ waiting period was not statistically significant (p = 0.3447). The effect size was medium (Cohen's d = 0.54). There was a decrease in the experimental group at month 4 and an increase at follow up (Figure 4).

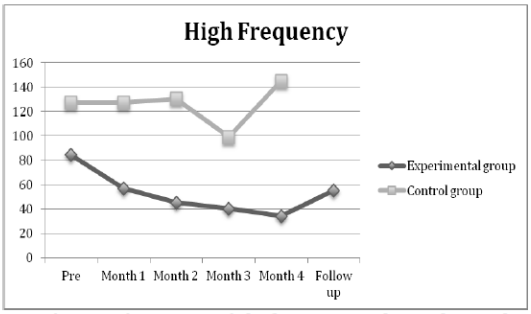


Figure Figure 4: High frequency throughout the treatment/ waiting period

The analysis of patients who responded to treatment indicated that the reduction was not statistically significant (p = 0.2482) and effect size remained medium (Cohen's d = 0.578).

Low frequency

Although there was no statistically significant difference between the group's mean LF before and after treatment/ waiting period (p = 0.1859), there was a score decrease in this parameter in the experimental group. In the control group, the pattern of LF was more unstable. The effect size was medium (Cohen's d = 0 763) (Figure 5).

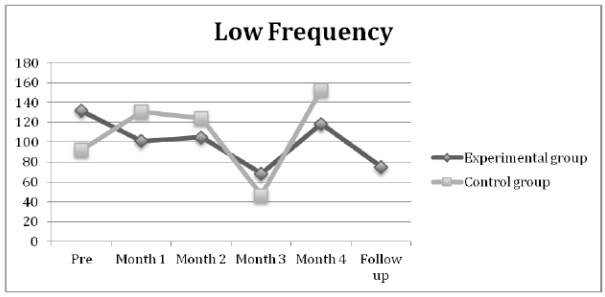


Figure 5: Low frequency throughout the treatment/ waiting period

The analysis of the subjects who responded to the treatment shows that the reduction achieved borderline statistical significance (p = 0.0833) and high effect size (Cohen's d = 2.097).

RMSSD

Regarding RMSSD, there was no statistically significant difference between the mean score of the groups before and after treatment/ waiting period (p = 0.2568). The effect size was small (Cohen's d = 0.207). In the experimental group, this parasympathetic index remained decreased during treatment and increased further in the follow up period. In the control group, this parameter remained more stable (Figure 6).

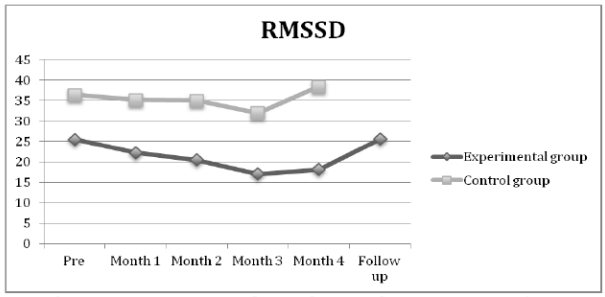


Figure 6: RMSSD throughout the treatment/ waiting period

The analysis of the subjects who responded to the treatment indicates no statistically significant difference when compared to the control group (p = 0.2482). The effect size remained small (Cohen's d = 0.323).

Endocrine variable

Salivary cortisol samples of five subjects in the experimental group and four in the control group were analyzed. The comparison between the average group scores before and after treatment/ waiting period indicates no significant difference (p = 0.4561). The effect size was medium (Cohen's d = 0.638).

In the experimental group, cortisol slightly dropped in month 1, increased in month 2, decreased again towards month 4 and remained lower in the follow up. Cortisol level decreased 1.2 nmol/ L between the first and last evaluation (Figure 7).

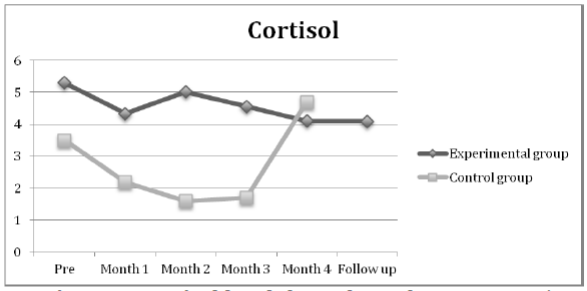


Figure 7: Cortisol level throughout the treatment/ waiting period

The analysis of the treatment responders indicates no statistically significant difference between groups (p = 0.4795). Effect size remained medium (Cohen's d = 0.575).

Discussion

This study differs from the existing literature in two aspects: this is the first randomized controlled trial that evaluates psychometric, cardiac and endocrine parameters at rest in patients with PTSD. The measurement of biological parameters is usually performed during symptom evocation and, when at rest, it is done before symptom evocation (Dunne et al, 2012; Hinton et al, 2009; Fecteau and Nicki, 1999; Sloan et al, 2011). This study is also a pioneer in the evaluation of these parameters throughout the therapeutic process. As far as we are concerned, previous studies involving PTSD evaluated the heart rate or cortisol only before and after CBT treatment (Gonçalves et al, 2015; Gerardi et al, 2010; Smyth et al, 2008).

Psychometric parameter

The results of this pilot study suggest a reduction of the PTSD symptoms in patients treated with a CBT protocol. Although there was no statistically significance difference between groups (p = 0.5676) according to PCL-C, probably due to the low sample power, the effect size was large (Cohen's d = 0.859). Furthermore, a reduction of 18.5 points observed in the treatment responders is considered clinically significant. This result is in accordance with the literature that shows efficacy of CBT in the treatment of PTSD in a wide range of studies (for review, see Bisson, 2007; National Collaborating Centre for Mental Health, 2005). Furthermore, there is a linear decrease of the PTSD symptoms from month 1 to month 4, which is indicative of fast and consistent therapeutic benefit, even when anxiety during the early stages of the exposure technique is present.

Neuroendocrine parameter

Regarding cortisol, although there was no statistically significant difference between groups (p = 0.4561), this hormone level tends to follow the treatment, in that it decreases during psychoeducation, anxiety management and cognitive restructuring periods (month 1), increases during the early period of the exposure technique (month 2), decreases by the end of treatment (from month 3) and remains lower in the follow up. Cortisol peak may be influenced by exposure technique, the most efficacious technique in the treatment of PTSD. It might indicate that engagement in the treatment, which can initially increase anxiety, is important for the future decrease in cortisol level and subsequent improvement of symptoms. This finding is consistent with the increase in the activation of brain areas that initiate HPA axis activity via connection with the hypothalamus during the

exposure period (Gottfried and Dolan, 2004, Knight et al., 2004). Increased anxiety in the early stage of treatment could have an impact on brain structures that release stress related hormones, which would be regularized by the time habituation occurs.

In addition, the decrease in cortisol levels after treatment, which obtained medium effect size both when analyzing the total experimental sample (Cohen's d = 0.638) and only treatment responders (Cohen's d = 0.575), is consistent with the reduction of PTSD symptoms observed in PCL-C. The literature suggests that the levels of this hormone, when measured at rest and in the afternoon, are higher in patients with PTSD comorbid with major depression when compared to subjects who suffered trauma and did not develop PTSD (for review, see Morris et al., 2012). In this sense, the results confirm that the cortisol decrease caused by CBT seems to regularize previously increased levels of this hormone.

Cardiac parameters

In respect of the cardiac parameters, although the literature suggests that PTSD patients have increased baseline heart rate and decreased heart rate variability when compared to subjects who have undergone trauma but did not develop PTSD (Buckley and Kaloupek, 2001; Pole, 2007; Norte et al., 2013), there are no studies measuring the impact of CBT in these parameters at rest. It was expected that heart rate would decrease in month 4 (end of treatment), but we observed this only in the follow up period. In the control group, this parameter remained stable, and there was an increase from the beginning to the end of the waiting period, following the PCL-C. Regarding the parasympathetic components of heart rate variability, contrary to what was expected, there was a reduction in both the HF and the RMSSD at the end of treatment. The HF followed the PCL-C during treatment, decreasing along with the decrease of symptoms, whereas the initial hypothesis was that it would increase. Regarding RMSSD, although there was a decrease in the last assessment, in the experimental group this parameter remained low throughout the treatment, which is consistent with the increased anxiety during the exposure technique. In the control group as expected, this index remained more stable. Regarding subjects who responded to treatment, p-values approximate the statistical significance, although they did not reach statistically significant results. We can therefore say that in the resting state, an increase in parasympathetic activity caused by CBT may not be detected.

With respect to the LF, a predominantly sympathetic index, the hypothesis that it would be reduced by the end of treatment was confirmed. In addition, in the experimental group this parameter followed the decrease in the PCL-C up to month 3 and again at follow up. In the control group, there was an increase in LF at the end of the waiting period, which is also consistent with psychometric variable. The analysis with treatment responders showed a borderline statistical significance (p = 0.0833) and the effect size increased from medium to high (Cohen's d = 2.097). Given the sample size of this pilot study, we must be cautious in generalizing this result. However, replication of this finding will confirm the reduced activation of the sympathetic nervous system caused by CBT. The impact observed on this index possibly reflects the reduction of symptoms of hyperarousal, necessarily observed in PTSD.

It is possible that the parameters measured in this study follow the stages of treatment if they were measured during symptoms evocation. This study has given us the opportunity to observe that in the resting state, this response does not occur in all parameters. Cortisol, even though measured at rest, accompanied CBT throughout the therapeutic process. A larger sample size would possibly produce statistical significance to the results which point in this direction.

Identifying CBT's biological mechanisms of action may encourage the creation and

improvement of techniques that are effective in modifying pathological biobehavioral manifestations. As a result, it will expand the ability to personalize treatment, taking into account different subtypes of the disorder, the techniques, reducing the time required for treatment and the therapeutic intensity for the settlement of maladaptive behaviors.

Limitations

The main limitation of this study is the small sample size, which increases the risk of type 2 error. Another limitations concern the use of pharmacological treatments during the protocol/waiting period and the absence of a blind evaluator. Also, we did not use the original and most widely-used questionnaire for evaluation of symptoms, the Clinician Administered PTSD Scale (CAPS).

Conclusions

The results of this pilot study showed no changes in cardiac and endocrine parameters caused by CBT, when measured in a resting state. However, this is a pilot study with a small sample, which leads to the possibility of false-negative results. In regard to neurobiological parameters, cortisol levels tended to parallel the therapeutic process, rising during the early period of exposure and decreasing in the psychoeducation, anxiety management and cognitive restructuring phases. CBT impact was observed in the LF index of heart rate variability, which may be related to the reduction of autonomic arousal symptoms caused by CBT. The other cardiovascular parameters, on the other hand, when measured in a resting state, did not follow the impact of CBT, suggesting that only cardiac reactivity, measured during the symptoms evocation, responds to the impact caused by the treatment, or that sample was too small to achieve statistical significance.

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Review

Listening to the heart: A meta-analysis of cognitive behavior therapy impact on the heart rate of patients with anxiety disorders

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ABSTRACT

Introduction: The future of psychotherapy relies on the dialog with the basic science, being the identification of psychotherapeutifc biomarkers of efficacy a core necessity. Heart rate (HR) is one of the most studied psychophysiological parameters in anxiety disorders.
Methods: To investigate the impact of cognitive behavior therapy (CBT) on the HR of patients with anxiety disorders, we conducted a meta-analysis and systematic review. Electronic searches were conducted in the ISI/Web of Knowledge, PsychINFO and PubMed/MEDLINE for studies which evaluated HR at least once before and after CBT. Keywords related to anxiety disorders, HR and CBT were used in the search.
Results: 474 studies, of which 47 were selected for the systematic review and 8 for the meta-analysis, were identified. The results provide evidence that CBT significantly decreases the HR of posttraumatic stress disorder patients. In social phobia, obsessive–compulsive disorder and acute stress disorder, the results point in the same direction, although it is still early to attribute the decrease in HR to CBT. In specific phobias, traditional exposure therapy showed greater effect size than exposure with distractors or without psycho-education.
Limitations: Most of the randomized trials have not been conducted in accordance with rigorous methodological quality criteria.
Conclusions: Standardization in the methods used and in treatment protocols, as well as investigations in groups of patients with low physiological reactivity, are necessary in order to reach better conclusions. Notwithstanding these limitations, HR is beginning to emerge as a potential biomarker of efficacy in anxiety disorders.

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1. Introduction

Cognitive-behavioral therapy (CBT), particularly exposure therapy, is considered a first-line treatment for prevalent and often disabling anxiety disorders (Ressler and Mayberg, 2007; Otte, 2011). The treatment involves gradually confronting the feared stimuli in the absence of danger, which generates new learning and consequent extinction of conditioned fear (Konorski, 1967).

The increasing incorporation of biomarkers in psychiatry in an attempt to enhance diagnosis and treatments has generated numerous studies investigating the neurobiological, physiological and neuroendocrine bases of anxiety disorders (Singh and Rose, 2009). Neural circuits of extinction of fear conditioning have been proposed and supported in various disorders (Graham and Milad, 2011; Milad and Quirk, 2012). Psychophysiological parameters – especially heart rate – are among the most studied biomarkers in these disorders (Pittig et al., 2013) and have the advantage of being easily measurable.

The identification of CBT biomarkers of efficacy is therefore a priority. The advantages of identification include the ability: (1) to prove the efficacy of CBT in a more objective manner; (2) to improve interventions through more precise understanding of the CBT mechanisms of action, helping to prevent relapse more consistently and benefit resistant patients (Rodriguez et al., 1999; Mineka et al., 1999; Mystkowski et al., 2002); (3) to precisely select the type of treatment best suited for each patient by understanding the difference between the CBT's and the medication's mechanisms of action. Identifying biomarkers of treatment can promote advances in adapting techniques to better target the underlying biological mechanisms.

Some published reviews observe brain CBT markers of efficacy, which usually involve the regulation of the activation of amygdala, insula, thalamus, the medial prefrontal cortex and hippocampus (Almeida et al., 2013; Porto et al., 2009). However, there are few studies that investigate the impact of CBT on cardiovascular parameters in anxiety disorders. The objective of this meta-analysis and systematic review was to investigate the impact of cognitive-behavioral techniques on heart rate in patients with anxiety disorders.

2. Methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

Any study that measured heart rate at least once before and after treatment with CBT in an anxiety disorder described in DSM IV, such as post-traumatic stress disorder, acute stress disorder, panic disorder with and without agoraphobia, generalized anxiety disorder, obsessive–compulsive disorder, social anxiety disorder, and specific phobia, were selected for this review.

Studies were excluded if they met any of the following exclusion criteria: used other psychotherapeutic approaches or did not use any treatment, theoretical articles, reviews, psychophysiological parameters were not used to assess the effectiveness of therapy, used healthy subjects or patients with subclinical diagnosis, used group therapy, animal studies, case studies including less than 10 subjects (Pincus et al., 1993), studies in pediatric/adolescent patients, questionnaire validation studies, articles that did not present results, articles written in languages other than English, Portuguese or Spanish, articles that presented results of psychotherapeutic intervention and medication simultaneously which made it difficult to distinguish CBT and medication effects.

2.1.2. Types of participants and interventions

The study only included participants who met the full criteria for any of the anxiety disorders mentioned above. The treatment used had to be individual rather than in groups, CBT based and have at least one exposure technique.

2.1.3. Types of outcome measures

In addition to the psychometric parameter, the study should measure heart rate before and after intervention with CBT. Heart rate could be extracted at rest or during symptom evocation.

2.1.4. Databases and search strategy

An electronic search of the literature was conducted in ISI/Web of knowledge, PsychINFO and PubMed/MEDLINE databases in May 2013. The search included all years. We considered articles in English,

Portuguese and Spanish. In addition, manual searches were conducted in the references of included articles. We used keywords related to anxiety disorders (PTSD OR "stress disorder" OR OCD OR "obses*" OR panic OR GAD OR "general* anxiety disorder" OR phobia OR "social anxiety"), psychophysiological parameters ("heart rate*" OR HR) and cognitive behavior therapy ("behavi* therapy" OR "cognitive therapy" OR "cognitive behavio* therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure session*" OR CBT OR "cognitive reest*" OR "anxiety manage*" OR flooding OR "systematic desens*"). In ISI/Web of knowledge database, only articles and notes were considered. Updates in the search were periodically performed until the date of data analysis (April 2014).

2.1.5. Assessment of methodological quality

After the search phase, we did an analysis of the methodological quality of the randomized controlled trials using an adapted version of the Cochrane Collaboration Tool for Assessing the Risk of Bias (Higgins and Green, 2011). This tool analyzes the risk of bias for each study that might interfere with the results.

2.1.6. Statistical analysis

Stata 10.0 software was used to conduct separate meta-analysis for each disorder. Articles were included if they provided either the mean and standard deviation estimates of heart rate at the end of CBT treatment or mean and standard deviation of the change of heart rate from baseline (delta). For each meta-analysis, the effect size was calculated as the difference between the means or deltas between the groups treated with CBT and control groups. Weighted mean differences (WMD) were estimated using fixed-effect models. The magnitude of the heterogeneity between studies was measured by I-squared statistic (Higgins et al., 2003) and the statistical significance evaluated by the chi-squared test for heterogeneity (Borenstein et al., 2009).

3. Results

3.1. Search

474 articles were identified in the three searched databases. Fig. 1 shows the steps of the electronic search that led to 46 articles being included in the systematic review and eight in the meta-analysis. Of the 104 studies whose full text was considered for eligibility, 38 were excluded for a variety of reasons: eight for not using CBT treatment, five for not using participants who met the full diagnostic criteria for an anxiety disorder, five were case studies, 14 for not measuring the heart rate at the beginning and end of treatment, two for using group treatment, one shorter communication, one which performed the processing via the internet, one for not separately presenting the results of both disorders treated and one for not providing results. This left us with 66 studies, which after excluding 27 duplicate studies and adding 8 studies identified through references, gave us our final total of 47.

Of the 47 final studies, 4 used patients diagnosed with post-traumatic stress disorder, 1 with acute stress disorder, 7 with panic disorder with and without agoraphobia, five with obsessive–compulsive disorder, three with social phobia and 21 with specific phobias.

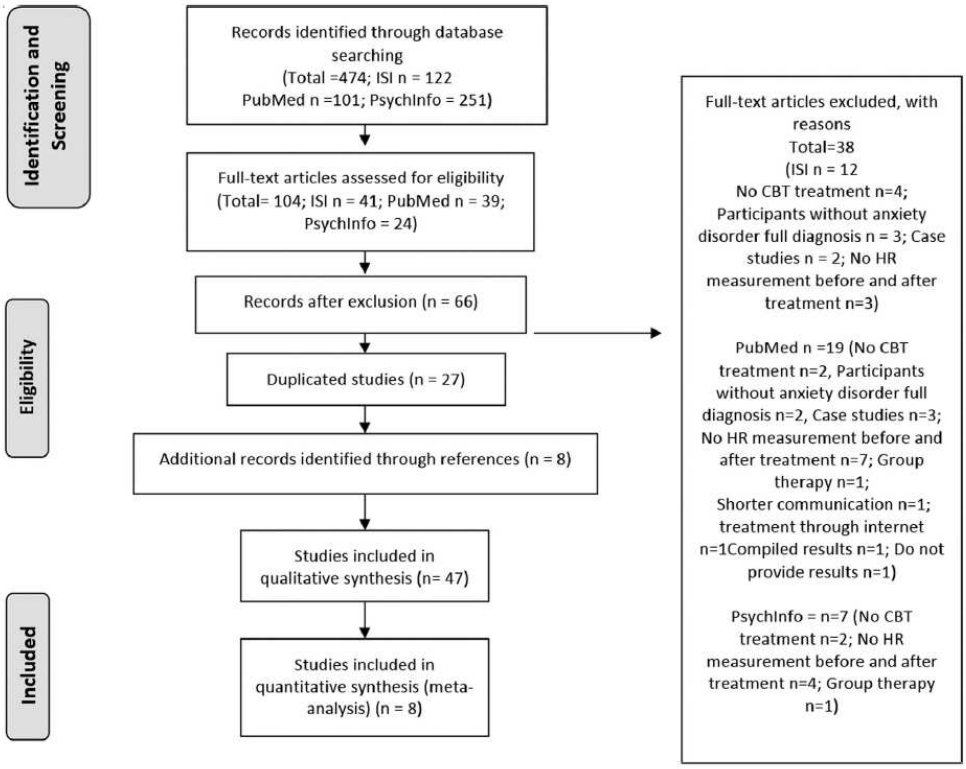

Fig. 1. Flowchart.

3.2. Characteristics of the included studies

3.2.1. Post-traumatic stress disorder

Five studies investigated CBT impact on HR in patients with PTSD. Four were randomized (Dunne et al., 2012; Hinton et al., 2009; Fecteau and Nicki, 1999; Sloan et al., 2011) and one open (Pitman et al., 1996). The results indicate agreement between psychometric and psychophysiological data in four studies, and in three of them CBT was able to reduce PTSD symptoms and heart rate (Dunne et al., 2012; Fecteau and Nicki, 1999; Pitman et al., 1996). In a study using only three written exposure sessions, the intervention produced no impact on any of the parameters (Sloan et al., 2011). Only one study did not find a correlation between psychometric measures and heart rate, producing a decrease only in systolic blood pressure and on symptoms (Hinton et al., 2009).

Fecteau and Nicki (1999) randomized 20 victims of traffic accidents that fulfilled PTSD diagnosis to waiting list (10) or four weekly sessions of two hours of CBT (10). Heart rate was measured before and after listening to a tape with trauma script. Results demonstrated statistically and clinically treatment effects across structured interviews, self-report questionnaires and behavioral test. Heart rate reactivity to trauma stimuli approached significance.

Dunne et al. (2012) randomly allocated 23 motor vehicle crash PTSD participants to 10 weekly one-hour sessions of CBT (12) or waiting list (11). Heart rate was measured before and after listening to the trauma script. Clinically significant reductions in PTSD symptoms were found in the CBT group compared with the waitlist at post-assessment, with further gains noted at 6 month follow-up. The treatment of PTSD was also associated with clinically significant improvements in physiological reactivity to trauma cues.

Sloan et al. (2011) randomized 42 participants with different types of trauma to 3, 20 min sessions of writing about trauma (21) or 3, 20 min sessions of writing about everyday life (21). HR was recorded continuously, for both a 5 min resting baseline period prior to each writing session and during each 20 min writing session. Results indicated that there was no reduction in emotional response for either condition from the first to the last writing session.

Hinton et al. (2009) randomized 24 Cambodian Refugees with PTSD to 12 weekly CBT sessions (21) or wait list (21). HR was recorded during orthostatic test. Orthostatic panic attacks, or panic attacks triggered by standing up, are frequent in this population and are highly associated with PTSD. The patients treated with CBT had much greater improvement than patients in the waitlist condition in all psychometric measures and in one physiological measure – systolic blood pressure response to orthostasis. For the HR, there was a non-significant group effect.

Pitman et al. (1996) treated 20 Vietnam veterans with 12 weekly flooding sessions and relaxation. HR was recorded during the first and last session of each flooding series. The flooding therapy produced only modest overall improvement, which was statistically significant for avoidance symptomatology. Results supported the occurrence of emotional processing, as manifested in significant activation, within-session habituation, and partial across session habituation of HR.

3.2.2. Acute stress disorder

Only one study was identified (Freyth et al., 2010). In this randomized trial, 40 subjects who had undergone a traumatic event which had occurred on average about 20 days before the first assessment were allocated to three weekly prolonged exposure sessions of 90 min each or supportive counseling. Prolonged exposure sessions included psycho-education, progressive muscle relaxation and imaginary and in vivo exposure. Supportive counseling sessions included progressive muscle relaxation and discussion of everyday problems that could have led to the trauma. There was a significant decrease in symptoms as assessed by questionnaires and attenuation of the HR response (marginally significant time effect) of the subjects allocated to the first group at the end of treatment, and at three month follow up.

3.2.3. Panic disorder with or without agoraphobia

Seven studies with Panic Disorder patients were found, four randomized (Meuret et al., 2012; Craske et al., 2005; Riley et al., 1995; Roth et al., 1987), two controlled trials (Garakani et al., 2009; Mussgay and Rüddel, 2004) and one open study (Ehlers et al., 1995).

Two of these studies obtained consistency between psychometric and psychophysiological outcomes. Garakani et al. (2009) observed a significant decrease in both panic symptoms and heart rate. In Mussgay and Rüddel (2004), there was no change in symptoms of panic or heart rate at the end of the treatment. In four other studies (Meuret et al., 2012; Craske et al., 2005; Riley et al., 1995; Ehlers et al., 1995) a decrease in symptoms was observed, but the same was not observed with respect to HR. Finally, in Roth et al. (1987) results indicated a statistically significant reduction in heart rate, while the same was not observed in relation to symptoms.

Meuret et al. (2012) randomized 28 patients to respiratory skill training (17) or cognitive skills training (17). After completing 4 weeks of skills training, all patients underwent three weekly in-vivo exposure sessions plus a fourth session at two-month follow-up. HR was recorded during a five minute baseline just prior to exposure, continuously throughout the exposure, and during a five minute recovery period at the end of the exposure. Significant improvements were found for all the primary and secondary outcome measures across exposure sessions on both treatment conditions. Baseline HR did not change significantly from pre-exposure to follow-up. In relation to HR reactivity, between-session reduction of maximum levels of the HR did not show overall declines.

Craske et al. (2005) randomly allocated 40 participants to 11, 60-min CBT sessions (24) or waiting list (16). HR was recorded during 2-min baseline, cardiac tracking, hyperventilation and meditative relaxation tasks. During cardiac tracking, participants silently counted their heartbeats. There was a greater magnitude of panic disorder severity change in the CBT group. There were no meaningful effects on physiological measures.

Riley et al. (1995) randomized 24 participants to alprazolam moderate dose condition ($M=3.53$ mg/day) or "minimal" alprazolam dose condition ($M=8.1$ mg/day). All patients received 15 twice-weekly CBT sessions for approximately 8 weeks. HR was recorded during baseline relaxation, induction and return to relaxation. Although 83% of the total sample was panic free at the end of treatment, only 50% met the criteria of high end-state functioning (having 0 panic attacks during week 8, the last week of treatment, and a post-test Hamilton Anxiety score of 12 or less). No significant HR differences were found between early and late exposure sessions.

One study used agoraphobia patients with panic disorder (Roth et al., 1987). Twenty-three participants were randomized to imipramine no-exposure (7), imipramine and intensive exposure (8) or placebo and exposure (8). Heart rate was monitored before and during a behavioral approach test (BAT). Results indicated that there was no significant decrease in clinical questionnaires, while heart rate decreased in the placebo and exposure groups. There was no decrease in heart rate in the other groups.

In a controlled and non-randomized study (Garakani et al., 2009), 20 participants chose 12 weekly CBT sessions and 23 chose

CBT plus sertraline. Continuous HR was recorded throughout hyperventilation. All patients had a significant decrease in all clinical measures. Treatment with CBT alone resulted in a statistically significant decrease in HR.

Mussgay and Ruddel (2004) treated 38 participants with psychoeducation and exposure therapy. Physiological signals were recorded throughout the rest phases as well as during neutral and anxiety word-pair presentation. There was no improvement in symptoms through the administered scales. There were also no apparent changes in reactivity due to treatment.

Ehlers et al. (1995) tested 40 panic participants before and after 32 h of massed therapist-assisted and self-guided exposure. HR was recorded while participants were silently counting their heartbeats. Treatment led to significant reductions in agoraphobic avoidance, anxiety and depression. The number of panic attacks also decreased during therapy. No changes in heartbeat perception, heart rate, or confidence ratings were observed.

3.2.4. Obsessive–compulsive disorder (OCD)

Four out of the five articles related to subjects with OCD used symptom evocation methodology to measure heart rate, while in Rabavilas et al. (1979) the measurement was performed before and after the trial. Although all have been successful in the treatment according to the questionnaires or have reduced anxiety during the exposure according to the SUDS, in one of them the improvement of symptoms was not accompanied by a significant decrease in HR (Kircanski et al., 2012).

Three of the five studies were randomized (Kircanski et al., 2012; Grayson et al., 1982, 1986), one controlled, non-randomized (Rabavilas et al., 1979) and one open study (Kozak et al., 1988).

Rabavilas et al. (1979) investigated the difference in treatment response between 6 obsessed OCD personality patients and 6 non-obsessed personality OCD patients. All were treated with eight, twice weekly, flooding sessions and HR measures were obtained before and after completion of the trial. The change observed after the end of the treatment reached significance for both groups. Regarding the changes in the anxiety scores, the obsessional group showed a significant decrement which for the patients' and assessor's ratings reached significance. Also, HR decreased significantly in obsessional group.

Kircanski et al. (2012) treated 50 patients with 3 weekly exposure sessions, while 25 were randomly assigned to blocked and constant exposure (progressing from the lowest to the highest item) and 25 for random and variable exposure (all three contamination items during each exposure session). HR was recorded continuously throughout the three exposure sessions. Significant decreases were observed in the questionnaires from pre to post-treatment, while no main or interaction effects were significant for group and occasion for anticipatory HR or behavior approach test HR.

Grayson et al. (1982) treated 16 OCD patients with two exposure sessions (90 min each). 10 patients were randomized to exposure with distraction on the first day and exposure with attention-focusing on the second day and 6 patients for exposure with attention-focusing on the first day and exposure with distraction on the second day. A 1-min sample of heart rate was taken during the last minute of adaptation. Additionally, heart rate was sampled for the first 20 min following initial contact with the contaminant and thereafter at 10-min intervals. Results indicated that SUDS level decreased at a constant rate over time. As with SUDS, heart rate decreased in a linear manner throughout the session.

In a later study, Grayson et al. (1986) randomized 17 OCD patients to exposure in vivo with attention-focusing or exposure with distraction. Treatment included two exposure sessions (90 min each). HR was sampled for the 20 s before touching the contaminant object (anticipatory) and for the first 20 s of this contact (initial response). Thereafter, 20-s HR samples were taken at 10-min intervals throughout each 90-min session. These samples were collected during the 20-set period immediately after the presentation of the object were instructed to focus on their feared object. Results for both symptoms and the HR indicated a significant main effect of time.

Kozak et al. (1988) treated 14 OCD patients with 15 ninety-minute sessions of imaginal and in vivo exposure plus response prevention over a three-week period and recorded HR during exposure in sessions 6 and 14. Results indicated that peak SUDs decreased significantly within the in vivo exposure. However, during imaginal exposure periods peak SUDs ratings appeared essentially unchanged for both sessions. Also, as expected, across-session habituation emerged for both imaginal and in vivo exposure periods. HR decreased during both imaginal and in vivo exposure. However, no overall across-session decrease in peak heart-rate was found for either imaginal or in vivo exposure.

3.2.5. Social phobia

Three studies (all randomized) were found. In all of them, there was a significant decrease in both HR and symptoms after treatment (Lister et al., 2010; Culver et al., 2012; Harris et al., 2002). Studies conducted by Lister et al. (2010) and Harris et al. (2002) measured the HR before and after the exposure, while the study by Culver et al. (2012) used symptom evocation methodology. In general, the studies were homogeneous. The protocols of the three studies included few sessions, which ranged from one to four. Furthermore, two of them used virtual reality exposure treatment.

Lister et al. (2010) randomized 15 patients to virtual reality therapy (9) or wait list (6). HR was recorded before and after exposure. There was a significant symptom decrease from pre-treatment to post-treatment. Also, there was a main effect for HR pre-treatment versus post-treatment.

Culver et al. (2012) randomized 59 patients to excitors during concurrent exposure (21), excitors during sequential exposure (20) or the excitors during exposure (18). The exposure treatment was comprised of four speeches given during a single day exposure. HR was recorded continuously throughout exposure. BAT, HR and SUDS scores decreased significantly over time.

Harris et al. (2002) randomized 14 patients to virtual reality therapy (8) or wait list (6). The treatment group was submitted to four virtual reality exposure sessions (12–15 min each). Resting HR, before and after exposure HR were recorded. There were significant differences in the questionnaires at post-treatment. Also, results found significant differences in the heart rate during speaking tasks, and the resting heart rate at the end of the 2nd session compared to the resting heart rate at the end on the 4th session.

3.2.6. Specific phobias

20 articles with Specific Phobias were identified, 15 randomized trials, two controlled trials without randomization (Grey et al., 1979; Mühlberger et al., 2005) and three open studies (Côté and Bouchard, 2005, 2009; Muris et al., 1993). 11 studies used patients with animal phobia. Among them, 8 included patients with spider phobia, one with snake phobia and two with various animal phobias. 10 studies used situational phobias, among them, three with claustrophobia, two with dental phobia, two with height phobia, two with flying phobia and one with injection phobia. Protocols involved a few sessions of exposure, ranging from one to five sessions, with the exception of one study with claustrophobia, which included 8–10 sessions (Öst et al., 1982).

18 articles used symptom evocation methodology during HR measurement. Of these, 13 observed coherence between psychometric variables and heart rate at the end of treatment, with decrease of both variables (Rodriguez et al., 1999; Grey et al., 1979; Mühlberger et al., 2005; Côté and Bouchard, 2005, 2009; Muris et al., 1993; Lang et al., 2000; Lang and Craske, 2000; Antony et al., 2001; Elsesser et al., 2013; Telch et al., 2004; Pace-Schott et al., 2012; Steketee, 1989). In one article, there was no reduction in heart rate, or in the symptoms, according to the questionnaires (Wiederhold et al., 2002). In four articles, no consistency between psychometric variables and heart rate was observed: symptoms decreased, but the HR did not accompany these results (Schmidt et al., 2010; Johnstone and Page, 2004; McGlynn et al., 1999; Arntz et al., 1993). In all the articles that used situational phobias, there was correspondence between psychometric and psychophysiological outcomes.

3.2.7. Meta-analysis

Three studies of PTSD and studies of specific phobias were initially included in the two meta-analyzes. However, two of the seven studies with specific phobia were excluded because they used very heterogeneous methodologies, generating inconclusive results. Their results could not be compared to the other specific phobias studies, because these two did not report the heart rate value, but the delta of the value between the beginning and the end of the experiment after treatment. So, in the end, two meta-analyzes were conducted: one with three PTSD studies and another one with five specific phobias studies.

Regarding the three PTSD studies included in the quantitative analysis (Dunne et al., 2012; Hinton et al., 2009; Fecteau and Nicki, 1999), CBT significantly decreased heart rate. The results were homogeneous regardless of the type control group used, i.e. both in studies comparing CBT and wait list and in the study that compared CBT and treatment as usual. ($I^2=9.7\%$; $\chi^2=2.21$ (d.f.$=2$) $p=0.33$). The mean reduction of heart rate from baseline (delta) was 1.81 bpm larger in the CBT groups as compared to controls. (Fig. 2).

Regarding studies with specific phobias, the meta-analysis only suggests efficacy, as weighted mean difference in heart rate at the end of treatment was not statistically significant ($p=0.11$) when compared to groups with exposure with distractors or without psychoeducation. In the only study comparing exposure to the waiting list (Öst et al., 1982), we observed a statistically significant decrease in heart rate in the treated group compared to the waiting list, which suggests that exposure technique plus progressive muscle relaxation can promote a decrease in cardiac reactivity in patients with specific phobias. (Fig. 3).

3.2.8. Risk of bias in randomized-controlled studies

Figs. 4 and 5 summarize the different aspects concerning the methodological quality of the randomized studies.

Regarding selection bias, of the 30 randomized studies selected for this review, only one whose participants had panic disorder (Meuret et al., 2012) and one whose participants had PTSD (Fecteau and Nicki, 1999) performed the allocation of participants in order to reduce the risk of bias. One article relating to acute stress disorder (Freyth et al., 2010) and one to specific phobia (Elsseser et al., 2013) described a non-random component in the sequence generation process, while none of the other 26 articles reported how the allocation was done and whether intervention allocations could have been foreseen in advance of, or during, enrollment.

With respect to performance bias, only five of 30 randomized studies used blinded assessors, one related to panic disorder (Meuret et al., 2012), one to acute stress disorder (Freyth et al., 2010), one to PTSD (Hinton et al., 2009) and two to specific phobias (Arntz et al., 1993; Öst et al., 2001). One study on PTSD reported that it had not used blind assessment (Dunne et al., 2012), while the other studies did not provide information in this regard. In addition, eight studies excluded participants who were receiving concomitant psychotherapy treatment during the trial, decreasing the risk of bias. Of these eight, one of them used participants with OCD (Kircanski et al., 2012), three with panic disorder (Meuret et al., 2012; Craske et al., 2005; Riley et al., 1995), one with PTSD (Dunne et al., 2012) and three with specific phobias (Öst et al., 1992, 1982; Steketee, 1989). One study with PTSD (Hinton et al., 2009) allowed psychotherapeutic treatment during the study, while the remainder did not provid this information.

Regarding attrition bias, 22 out of the 30 randomized studies describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Of these, one were OCD studies (Kircanski et al., 2012), two social phobia studies (Harris et al., 2002; Lister et al., 2010), three panic disorder trials (Meuret et al., 2012; Riley et al., 1995; Roth et al., 1987), one acute stress disorder trial (Freyth et al., 2010), four PTSD studies (Dunne et al., 2012; Hinton et al., 2009; Fecteau and Nicki, 1999; Sloan et al., 2011) and 11 Specific Phobia studies (Lang et al., 2000; Antony et al., 2001; Wiederhold et al., 2002; Johnstone and Page, 2004; McGlynn et al., 1999; Öst et al., 1992, 1982, 2001; Schmid-Leuz et al., 2007; Telch et al., 2004; Arntz et al., 1993; Pace-Schott et al. 2012). Two of

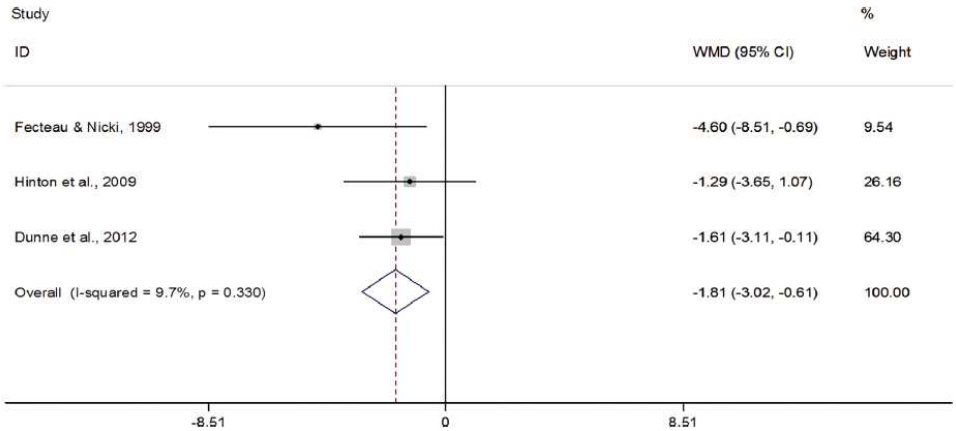

Fig. 2. Weighted mean difference for heart rate between CBT patients and controls.

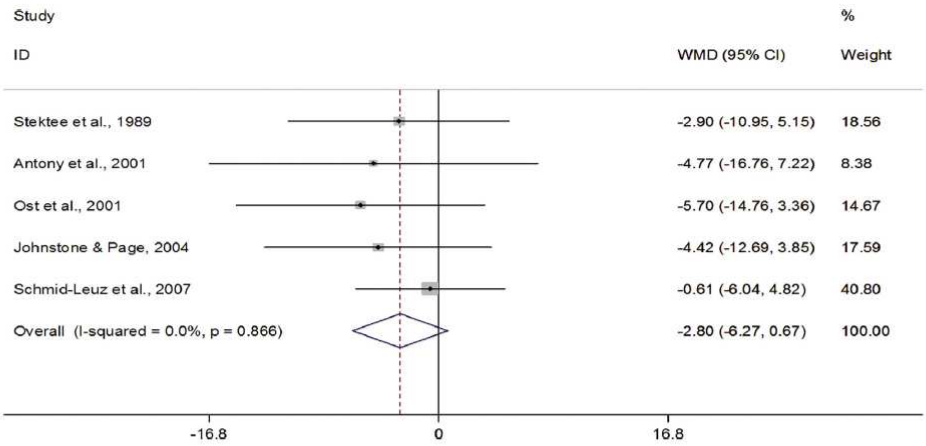

Fig. 3. Weighted mean heart rate differences between control group and patients receiving traditional exposure therapy.

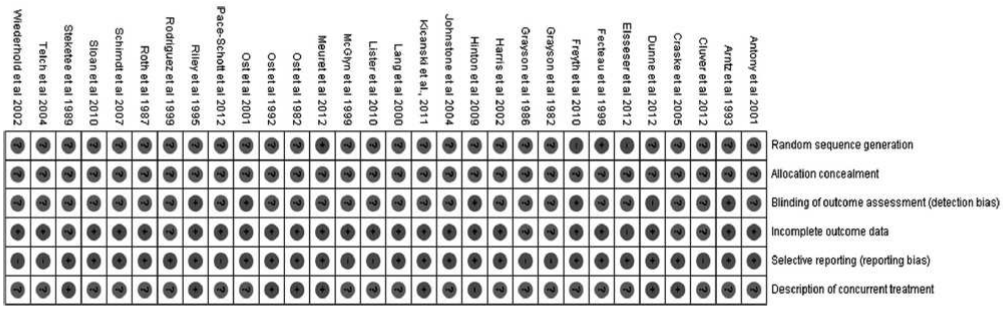

Fig. 4. Risk of bias of the studies.?: unclear risk of bias; +: high risk of bias; −: low risk of bias.

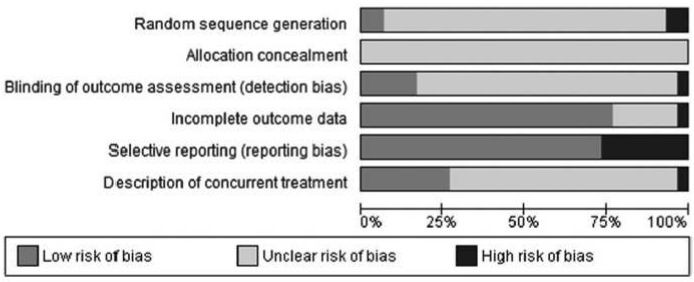

Fig. 5. Percentage of risk of bias.

the 30 studies had high risk of bias in this regard, while six studies did not provide this information, making the analysis impossible.

Finally, with respect to reporting bias, 22 of the 30 randomized studies reported all of the pre-specified primary outcomes, with low risk of bias, being one with OCD subjects (Kircanski et al., 2012), one with social phobia (Harris et al., 2002), four with panic disorder (Craske et al., 2005; Meuret et al., 2012; Riley et al., 1995; Roth et al., 1987), one with acute stress disorder (Freyth et al., 2010), four with PTSD (Dunne et al., 2012; Hinton et al., 2009; Fecteau and Nicki, 1999; Sloan et al., 2011) and 11 with specific phobia (Lang et al., 2000; Rodriguez et al., 1999; Antony et al., 2001; Johnstone and Page, 2004; Öst et al., 1992, 1982, 2001; Schmid-Leuz et al., 2007; Steketee, 1989; Elsseser et al., 2013; Arntz et al., 1993). Eight studies did not show the results of the primary outcomes measures, two with OCD (Grayson et al., 1982, 1986), two with Social Phobia (Lister et al., 2010; Culver et al., 2012) and four with Specific Phobias (Wiederhold et al., 2002; McGlyn et al., 1999; Pace-Schott et al., 2012; Telch et al., 2004).

4. Discussion

4.1. General results

To the best of our knowledge and despite the current relevance of this subject, this is the first systematic review/meta-analysis that evaluates the effects of CBT treatment on heart rate in patients with anxiety disorders.

Most studies measured cardiac reactivity using symptom evocation. The increased cardiac reactivity during coping with phobic stimuli is a consequence of the autonomic system activation related to the fight–flight behavior (Lang et al., 2000). This system allows individuals to react faster and stronger in case of imminent danger. However, in patients with conditions such as specific phobias or PTSD that system does not work properly anymore: it gets triggered in situations that do not suppose a real menace, or when being a real danger the arousal raises so much that complicates the display of any adaptive response. The regularization of cardiac reactivity after treatment with CBT indicates that the defense system no longer reacts to the unrealistic threat. Furthermore, the heart rate changes related to the presentation of a stimulus are also an index of the emotional intensity that the stimulus elicits. So, a decrease of the reactivity in the presence of the phobic stimuli can be also interpreted as a reduction of the emotional impact that they have in the patients, as a consequence of the therapy.

The present results demonstrate a significant decrease in heart rate of patients with PTSD after treatment. Gonçalves et al. (2011) investigated potential CBT biomarkers of efficacy in the treatment of PTSD and found results consistent with this meta-analysis regarding heart rate. In a recent systematic review (Zantvoord et al., 2013), also in patients with PTSD, reduced physiological reactivity was found in line with the decrease in symptoms after treatment with CBT. It is known that heart rate is increased in PTSD patients (but see exceptions below) in a wide variety of methodologies, including resting baseline studies, startle studies, standardized trauma cue studies, and idiographic trauma cue studies (Pole, 2007). This finding could explain why patients with PTSD have a higher risk of premature cardiovascular disease (Blanchard, 1990; Buckley and Kaloupek, 2001). The adjustment of this parameter, as demonstrated in this meta-analysis, points to HR as a potential CBT biomarker of efficacy, representing an important step in the investigation of the treatment's mechanisms of action and its potential in reducing the high cardiovascular disease rate in this population.

Heart rate reactivity to an aversive challenge may be useful in tracking differences in terms of the course of illness and response to treatment for single-versus multiple-trauma PTSD (McTeague et al., 2010). McTeague et al. (2010) showed that despite greater reported arousal, the multiple-trauma relative to single-trauma PTSD patients presented blunted defensive reactivity associated with more chronic and severe PTSD. Furthermore, Lanius et al. (2010), (pg. 4) in an influential review that examined the evidence that supported the DSM-5's decision to create the dissociative subtype of PTSD, called attention to different heart rate reactivity when exposed to trauma cues: "Researchers have suggested that approximately 70% of patients re-experience their trauma with a concomitant increase in heart rate whereas the remaining 30% exhibit states of depersonalization and derealization with no significant concomitant increase in heart rate". Therefore, studies should be careful in distinguishing the PTSD samples; in single-trauma PTSD the heart rate reactivity could be a more useful biomarker for effectiveness of CBT, showing a higher effect size. The use of the heart rate to help to identify and validate biologically homogeneous subtypes that cut across phenotypic diagnoses is another example of what is termed 'stratified psychiatry', a research strategy that aims to improve clinical outcomes across conventional diagnostic boundaries (Fava et al., 2014; Kapur et al., 2012). Additionally, while exposure therapies and other treatments aimed at extinguishing the patient's exaggerated fear response are shown to be effective in helping the recovery of those patients, the treatment of PTSD consequent to cumulative trauma still represents a significant challenge (Lang and McTeague, 2011).

Decreased heart rate reactivity after treatment with CBT was observed in acute stress disorder, specific phobias, social phobia and OCD. According to recent theories about the extinction of fear, continued exposure to irrationally feared stimuli generates a new learning represented by changes in prefrontal-amygdala circuitry (Milad and Quirk, 2012). This change in activation of brain areas involved in the fear circuit would in turn actto regulate the autonomic nervous system by decreasing cardiac reactivity against feared stimuli. In the studies with specific phobias, decrease in heart rate reactivity was observed after treatment with exposure, but this decrease is not statistically significant compared to groups that were treated with this same technique, but without psychoeducation or when distracters were inserted at the time of exposure to feared stimulus. It can be inferred, however, that exposure technique produces an impact on heart rate even when used in an unconventional (impure) way. Studies using control groups treated with placebo techniques are necessary to establish the actual impact of exposure technique in subjects with specific phobias.

In panic disorder studies, the results were inconclusive, and most studies did not find accordance between a decrease in heart rate reactivity and a decrease in symptomatology. It should be noted that treatment protocols varied widely between studies, and medications were tested in three of them. The controversial results could also be connected to differential physiological reactivity among panic patients even before the therapeutic intervention. McTeague et al. (2011) showed increased reactivity in panic patients without, or with moderate, agoraphobia; but observed reduced reactivity to startle probe in panic patients with severe agoraphobia.

McTeague and Lang (2012) examined psychophysiological parameters across the anxiety disorders spectrum, from disorders characterized by focal fear (e.g., specific phobia) to disorders of long-enduring, pervasive apprehension and high distress (e.g., PTSD secondary to cumulative trauma and generalized anxiety disorder). Probing the reactivity to startle, they observed an inverse gradient to that of subjective distress. Startle responses were very high for single-trauma PTSD and specific phobia; and much lower for panic with severe agoraphobia, generalized anxiety and multiple-trauma PTSD, patients with the latterdisorders having much more severe symptoms and higher reports of distress than those of the former. Studies of biomarkers in therapeutic interventions could benefit from taking into consideration the group of patients that present blunted physiological reactivity instead of exaggerated reactivity.

4.2. Methodological issues

4.2.1. Randomized trials

Most of the randomized studies selected for this meta-analysis were not conducted according to strict methodological quality criteria or did not provide information regarding the methodological quality, including participant allocation and use of blind evaluators. The lack of information about the allocation of patients indicates that there is a possibility that randomization was not performed appropriately, indicating a risk of interference by the researcher in the sample selection. Furthermore, only eight studies reported that exclusion criteria included concomitant psychotherapy, which could seriously compromise the results of research. Based on the items discussed above, there were high chances of selection and performance bias.

In contrast, most studies addressed incomplete outcome data adequately and also reported outcome measures free of suggestion, which indicates that there is low risk of bias regarding the balancing of the samples and the omission of possible negative results.

Future studies should follow high methodological criteria and state in the body of the text that these precautions were taken into consideration during the study.

4.2.2. Limitations

Although all 47 studies have evaluated the heart rate before and after treatment, only eight studies could be included in the meta-analysis. The different methodologies employed, the presence of comorbidities in the samples and the lack of standardization in treatment protocols require caution in interpreting the results. Future studies are needed in order to reach more consistent findings.

This systematic review/meta-analysis included only three databases, although the selected bases are the key ones. In addition, we found low statistical power. Due to the limited number of studies included in the meta-analysis, it was impossible to perform a meta-regression.

4.2.3. Clinical implications/future directions

The findings raise questions about the clinical practice of fear extinction. Although heart rate is highlighted as a potential biomarker of efficacy of CBT, the understanding of the process of therapy efficacy is not yet clear. Future studies should investigate both psychometric parameters and psychophysiological parameters in order to clarify how the techniques involved in treatment can regularize them. To achieve this goal, it is necessary to compare the impact of different techniques on these parameters. It is also necessary to compare the use of different methodologies to measure heart rate, such as rest, startle and anticipatory HR.

5. Conclusions

The findings suggest that successful psychological treatment reduces physiological reactivity in patients with PTSD and possibly other anxiety disorders. Therefore, heart rate can be considered a potential biomarker of CBT efficacy for PTSD. In addition, the effect size of the impact of traditional exposure therapy in heart rate in specific phobia is greater than the exposure therapy with distractors or without psychoeducation. These results represent an advance in the investigation of the mechanisms of CBT action and hence in the integration of basic science and clinical psychiatry.

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Conflict of interest

The authors of the article entitled "Listening to the Heart: a Meta-analysis of Cognitive Behavior Therapy Impact on the Heart Rate of Patients with Anxiety Disorders" certify that there is no actual or potential conflict of interest in relation to this paper.

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Artigo 4

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Efficacy of Virtual Reality Exposure Therapy in the Treatment of PTSD: A Systematic Review

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Abstract

The use of Information and Communication Technologies, such as virtual reality, has been employed in the treatment of anxiety disorders with the goal of augmenting exposure treatment, which is already considered to be the first-line treatment for Post-traumatic Stress Disorder (PTSD). To evaluate the efficacy of virtual reality exposure therapy (VRET) in the treatment of PTSD, we performed a systematic review of published articles using the following electronic databases: Web of Science, PubMed, PsycINFO, and PILOTS. Eligibility criteria included the use of patients diagnosed with PTSD according to DSM-IV, the use of cognitive behavioral therapy (CBT) and the use of virtual reality for performing exposure. 10 articles were selected, seven of which showed that VRET produced statistically significant results in comparison to the waiting list. However, no difference was found between VRET and exposure treatment. Of these 10, four were randomized, two were controlled but not randomized and four were non-controlled. The majority of the articles used head-mounted display virtual reality (VR) equipment and VR systems specific for the population that was being treated. Dropout rates do not seem to be lower than in traditional exposure treatment. However, there are a few limitations. Because this is a new field of research, there are few studies in the literature. There is also a need to standardize the number of sessions used. The randomized studies were analyzed to assess the quality of the methodology, and important deficiencies were noted, such as the non-use of intent-to- treat-analysis and the absence of description of possible concomitant treatments and comorbidities. Preliminary data suggest that VRET is as efficacious as traditional exposure treatment and can be especially useful in the treatment of patients who are resistant to traditional exposure.

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Introduction

Post-traumatic stress disorder (PTSD) involves a constant feeling of fear generated by inadequate consolidation of the autobiographical trauma memory [1]. Foa & Kozak [2] suggested that for there to be adequate processing of the traumatic memory and the consequent extinction of the fear, the memory must be activated and safe components must be inserted. Prolonged Exposure Therapy, proved to be highly eficacious in the treatment of PTSD, aims to access the traumatic memory, including information about the traumatic situation and related emotions, thoughts and behaviors. It helps the patient to understand the context of the traumatic experience as well as its impact in the patient's life. It also enables the patient to achieve a realistic perspective on the traumatic event and its aftermath [3].

Despite the fact that exposure therapy stimulates emotional engagement during imaginal exposure, some patients find it difficult to immerse themselves in the traumatic scene and, therefore, may quit the treatment. In some studies, dropouts and non-response rates may reach 50% of the cases [4]. Therefore, the use of Information and Communication Technologies may facilitate exposure for avoidant patients.

In this sense, virtual reality has been used as a tool for exposure and has achieved positive results in the treatment of various anxiety disorders including specific phobias, social phobia, panic disorder and PTSD [5]. Even though this resource has encountered some difficulties because it raises questions about affecting the therapeutic relationship and struggles with personalizing exposure for individuals with different traumas [5], its use has yielded many benefits. Virtual reality exposure therapy (VRET) facilitates the emotional engagement of patients with PTSD during exposures to the multiple sensory stimuli made possible by the virtual environment, bypassing symptoms of avoidance and facilitating control on the part of the therapist [6–7]. The sense of presence provided by a virtual environment that is rich in sensory stimuli facilitates the emotional processing of memories related to the trauma [8]. This technological apparatus allows gradual exposure to the feared environment according to the needs of each patient. In addition, it can be used in situations where time is limited, as well as in situations that are difficult to control or unpredictable [9] or that could put the patient at risk if the exposure were performed in a real situation. Finally, exposure in a virtual reality environment allows for greater methodological rigor in clinical studies as it allows for the standardization of the duration and type of exposure for all patients [10].

The objective of this article is to conduct a systematic review of studies that have used virtual reality in the treatment of PTSD. We

aim to verify the efficacy of Virtual Reality Exposure Therapy for patients diagnosed with PTSD.

Methodology

We performed an electronic search in the following databases: ISI/Web of Knowledge, PUBMED/MEDLINE, PILOTS and PsycINFO in May 2011 with keywords that included the terms PTSD OR "stress disorder*" and "virtual reality". In the ISI/Web of Knowledge, we restricted the search criteria to include only "articles" and "notes". Articles found in the references of the articles selected for this review were also considered for analysis. Independently data collection process was applied. The articles included in the final selection had to fulfill the following criteria.

Criteria for inclusion: the use of patients diagnosed with PTSD according to DSM-IV, the use of cognitive-behavioral therapy (CBT) and the use of virtual reality for performing exposure.

Criteria for exclusion: theoretical articles, reviews, theses, dissertations and book chapters, articles not published in a peer-reviewed journal, articles that used patients who were not diagnosed with full PTSD or techniques that were not part of the repertoire of CBT, case studies, articles that did not include outcome criteria and trials published in languages other than English, Portuguese or Spanish.

After the search phase, we did an analysis of the methodological quality of the randomized controlled trials based on the Cochrane Collaboration Tool for Assessing the Risk of Bias [11]. This tool analyzes the risk of bias for each study that might interfere with the results. In addition, six items were added that also represent risks for biased results. These items were based on the scale developed by Kocsis et al [12] and include description of relevant comorbidities; information on screened, included and excluded subjects; description of treatment (or reference); description of concurrent treatment; an intent-to-treat analysis; and description of dropouts.

Results

The final result of the search can be observed in the flowchart (Figure 1).

Of the 300 articles obtained through the electronic search summed from all the databases searched, 27 were excluded for using samples including non-PTSD disorders or using patients with subclinical PTSD, 36 were excluded for being case studies, 192 were excluded for being theoretical articles, reviews or trials that did not include CBT, two were excluded for using outcome measures that did not include symptoms of PTSD and seven were excluded for using a sample compiled and used in a later study. Thus, 10 articles were considered for the final analysis. This count includes articles found in more than one electronic database, which were, therefore, repeated. Additionally, some studies met more than one exclusion criterion. Each of the studies selected is described below.

Ready et al [7] performed an open trial with 21 Vietnam veterans. The final result combined the samples with those from an earlier study by Rothbaum et al [8], that consisted of a sample of five participants. Nine patients in the most recent study completed the treatment, and six patients dropped out during it. Of the 21 initial participants, 14 completed at least one post-treatment assessment. The questionnaires used included the Clinician Administered PTSD Scale (CAPS), Impact of Events Scale (IES), Beck Depression Inventory (BDI) and Subjective Units of Discomfort Scale (SUDS). The protocol included 8 to 20 weekly sessions, and each lasted 90 minutes. The techniques used included psychoeducation, anxiety management techniques, exposure using VR and imaginal exposure. Follow-ups were performed at three and six months. There was a significant reduction in total CAPS and IES after treatment and during the follow ups. However, for the intrusion cluster on the CAPS scale, no statistical significance was observed at the first measure post-treatment; however, at the follow-ups, there was significant improvement compared to the beginning of treatment. Although there was a significant reduction in BDI during post-treatment and at the follow-up at six months, this was not evident at the three-month follow-up. Gains were maintained for 10 of the eleven patients who completed all of the follow-ups.

Difede et al [13] evaluated the efficacy of treatment with VRET in-patients who developed PTSD after the terrorist attack on the World Trade Center. The participants were assigned to two groups. In the first group, thirteen patients underwent intervention with VRET, and eight matched subjects were assigned to the waiting list. Five of the thirteen participants in the first group were resistant to previous treatments, and four were resistant to imaginal treatment. Because it was decided that these patients would be assigned to treatment, the study became quasi-experimental. The participants in the VRET group were paired with the participants on the waiting list according to the severity of their CAPS scores and socio-demographic characteristics. The study sample was composed entirely of males with severe PTSD. In addition to the use of CAPS, the participants were evaluated by an independent assessor using BDI and Clinical Global Impression (CGI). The treatment combined CBT with VR using techniques including psychoeducation, relaxation training, cognitive restructuring and VRET. The number of sessions was less than 14, with a mean of 7.5. All of the patients received at least six weeks of VRET. The results showed that nine of the 10 participants who completed the training obtained clinically and statistically significant improvements. A large effect size was obtained (Cohen's $d = 1.54$). Compared to the waiting list, the group treated with VRET demonstrated statistically significant improvement based on the CAPS score. The same did not occur for BDI and CGI, for which an interaction between time and group was not noticed. However, the authors stated that the baseline scores were low. At the end of the study, six of the 10 participants in the VRET group no longer met the diagnostic criteria for PTSD. Three patients from the group undergoing VRET did not complete the treatment, and one dropped out due to the anxiety related to the exposure. The dropout rate in the control group was not reported. The results remained the same in the follow-up at six months.

Wood et al [14] examined the effects of VRET on twelve participants in a non-controlled study. 10 sessions that lasted 90 to 100 minutes each were performed once or twice a week. The Post Traumatic Stress Disorder Checklist (PCL-M), the BAI and PHQ-9 questionnaires were used. The techniques and procedures used in the study included psychoeducation, meditation for anxiety management, cognitive restructuring, biofeedback training and gradual exposure using virtual reality. There was a significant reduction in the PCL in 75% of the participants, and these cases no longer fulfilled the criteria for PTSD. The study did not report if there were dropouts over the course of the treatment, as well as averages or standard-deviations and only showed the results with a graph. The study did not perform a follow-up. The focus of this article was on the cost-benefit analysis of using VR; thus, the article may be limited in terms of methodology.

A randomized study by Ready et al [15] compared VRET with Therapy Centered on the Present (TCP) in patients who are veterans of the Vietnam War. Of eleven male participants, nine completed the treatment, with five in the VRET group and four in

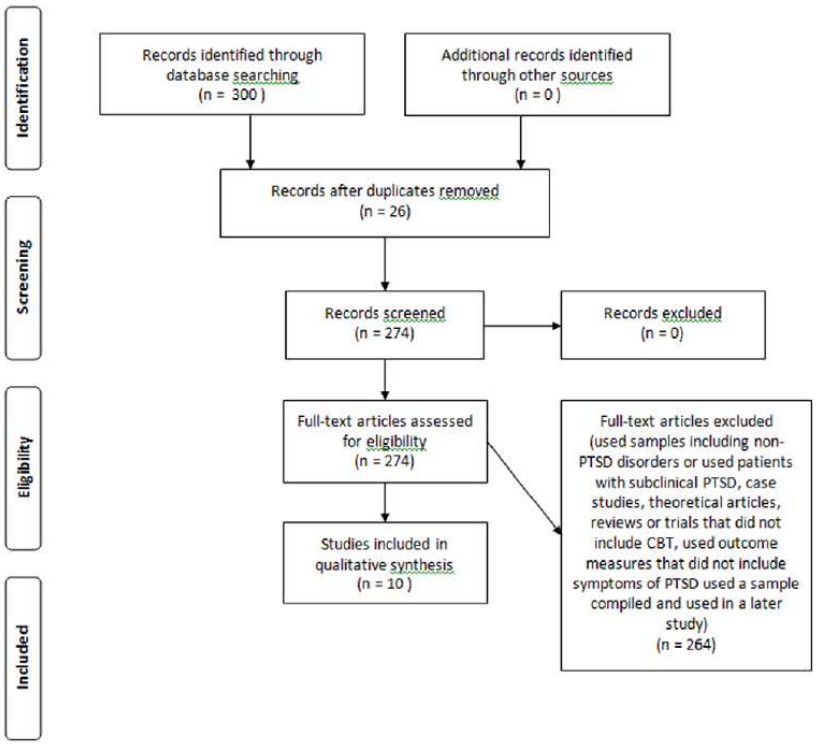

Figure 1. Flowchart of the process of identifying and selecting studies.
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the TCP group. Protocols for both treatments consisted of 10 sessions. The CAPS and BDI scales were administered before and after treatment and during a follow-up six months later by an independent assessor who was unaware of the treatment. There was an improvement of symptoms in both conditions from pretreatment to post-treatment and at the follow-up, performed six months after the end of the study, with scores on the CAPS scale showing greater variations for VRET. However, there was not a statistically significant improvement on the CAPS and BDI scales either within or between groups. It was not possible to compare and find statistically significant differences due to the small sample. There were two dropouts, one from each group.

Roy et al [16] studied soldiers diagnosed with PTSD using functional magnetic resonance imaging (fMRI) in addition to evaluating the effects of VRET. In the first phase of the study, there were 29 subjects who were assigned to four groups: fifteen with both PTSD and Traumatic Brain Injury (TBI), nine with PTSD only, one with TBI only, and four controls. The fMRI was performed before and after treatment and during follow-up periods. In the treatment phase, fifteen participants with PTSD were initially selected at random for VRET (seven) or for Prolonged Exposure (eight). At least twelve sessions lasting 90 min were performed over ≥ six weeks. Both the PE and VRET treatments used psychoeducation, relaxation techniques and some elements of imaginal and in vivo exposure. The groups received equivalent times of exposure (with VR or imaginal exposure), which lasted up to half of each session. The CAPS, PCL-M and BDI scales were administered at the same time as the cerebral scans. It was an ongoing study in which eight participants with PTSD had completed the final scan, and six had dropped out. As the authors considered the number of participants in each group insufficient for a comparison of the efficacy of treatments, the results of the two groups were combined, meaning, in this respect, that the study was non-controlled. There was a non-significant improvement in the clinical symptoms, which could be measured through reductions in CAPS, PCL, CGI and BDI. The results were maintained in the follow-ups performed at one, two and three months with eight patients with PTSD completing the post-treatment scan (five with both PTSD and TBI and three with PTSD only). The brain regions of interest were the amygdala, the hippocampus and the anterior cingulate cortex. Significant improvements are evident on the fMRI scans, which showed a reduced activation of the amygdala, subcallosal gyrus and lateral prefrontal cortex as well as a less-accentuated reduction for the anterior cingulate cortex. These results are corroborated by CGI scores; however, the CAPS score improvements are not statistically significant.

The study by McLay et al [17] is a controlled non-randomized study that shows the results of treatment for PTSD in soldiers from the Iraq War, all male. They compared six cases treated with VRET and four cases with traditional exposure therapy. The treatments were conducted once or twice per week, and the number of sessions varied between six and twelve. There was no standardization in the administration of the techniques or in the number of sessions. The patients were treated according to the clinical judgment of what they required, and they typically

received the treatment to which they were assigned. The scales administered included PCL-M, CAPS, PHQ-9 and BAI. All of the patients who were treated with VRET significantly reduced their scores on the PCL-M (by 67% on average), BAI and PHQ-9. At the end of the treatment, five no longer met the diagnostic criteria for PTSD. The patients who received traditional exposure therapy also showed statistically significant improvement at the end of the treatment (a 74% decrease on the PCL-M), and none showed the diagnostic criteria for PTSD at this stage. There was no statistically significant difference between the treatments. The study didnt perform a follow up. There were no dropouts.

Rizzo et al [18] conducted an open trial with 40 war veterans who were resistant to pharmacological treatment and counseling using virtual Iraq. Sessions lasting 90 to 120 minutes were held twice per week for five weeks. The average number of sessions was less than 11. The techniques used included psychoeducation, anxiety management techniques and imaginal, in vivo and VR exposure. Participants were evaluated based on the PCL-M, BAI and Patient Health Questionnaire (PHQ-9), in addition to physiological monitoring, which included heart rate, galvanic skin response and respiration frequency. However, the results of the psychophysiological monitoring were not reported. A follow-up was performed at three months. Of the 20 participants who completed the treatment, there was a clinical and statistically significant reduction in the PCL-M, with 17 participants showing a reduction of more than 50%. Furthermore, sixteen of the participants did not fulfill the criteria for PTSD after treatment. When looking at the average scores for the BAI and the PHQ-9, there was a statistically significant reduction at the end of treatment. Half of the patients did not complete the treatment.

Seven soldiers dropped out before the first session, six quit after the first session, and seven at the beginning of the VR treatment. Gains were maintained at follow-ups.

The study by Botella et al [19] included subjects who had experienced a broad variety of traumatic events and used EMMA's World as a VR tool. This system used symbols to represent various traumatic events. Their sample included eight men and two women. This was a randomized clinical trial with two groups that used VRET or CBT with in vivo and imaginal exposure. Participants on the waiting list were not included. The study included 10 participants. The authors did not report the number of participants in each group or whether any participant did not complete treatment. Both protocols used from nine to twelve sessions. There was a statistically significant reduction on all the scales administered (CAPS, Davidson Trauma Scale (DTS) and Posttraumatic Cognitions Inventory (PTCI) between pre- and post-treatment conditions for the group that received VRET. VRET proved to be more effective than traditional therapy on the CAPS scale, but the difference was not statistically significant for the CAPS scale or for the others administered. The researchers did not perform follow-ups and did not report the dropout rate for either of the groups.

The study by Gamito et al [20] evaluated VRET as an alternative procedure for reducing symptoms of chronic PTSD in elderly Portuguese veterans who had participated in the colonial war in Africa. 10 participants, all male, were randomly assigned to three groups: five for VRET, two for imaginal exposure, and three for the waiting list. The protocols for VRET and imaginal exposure were based on cognitive desensitization with twelve sessions of exposure with virtual reality for VRET and twelve sessions of traditional imaginal exposure for imaginal exposure group. The first session for both protocols was dedicated to psychoeducation. The CAPS, Impact of Events Scale Revised (IES-R), Symptoms Checklist Revised (SCL-90-R) and BDI scales (only for the VR group) were administered before and after treatment. There was no statistically significant difference in the analysis of the CAPS scale. However, the group treated with VRET obtained a reduction of 8% when measured with CAPS, although there was only a reduction of 1% for the group assigned to imaginal exposure and 6% for the WL. There was a reduction in IES-R for the group with VRET, whereas an increase was observed for the other two groups. There was a significant reduction in symptoms of depression (reduction of 40% on the BDI) and on the SCL-90-R for the VRET group. No follow-up was performed. One dropout was reported in the VRET group, and the dropout rate in the control group was not reported.

The study by McLay et al [21] evaluated the efficacy of VRET in the treatment of 20 Active Duty military personnel in a randomized trial. 10 of these patients were assigned to VRET and 10 to treatment as usual (TAU). The participants of the latter group received a combination of typical treatments for PTSD, which included Prolonged Exposure, Cognitive Processing Therapy, Eye Movement Desensitization and Reprocessing, group therapy, psychiatric medication, substance rehabilitation and inpatient service. The VRET protocol included sessions of psychoeducation, relaxation, attentional and autonomic control training and exposure to a VR simulation of Iraq or Afghanistan. There was no standardization of the treatment protocol, and the number of sessions varied from 10 to 13 weekly sessions for the two groups. The participants were monitored using the CAPS scale before and after treatment. At the end of the treatment, seven of the 10 participants in the VRET protocol showed improvements of greater than 30% on the CAPS scale, whereas only one of the nine participants who completed the TAU showed an improvement greater than 30%. Both treatments showed efficacy and there was no statistically significant difference between the groups. Only one dropout in the TAU group was reported. The researchers did not perform a follow-up.

Figures 2 and 3 summarize the different aspects concerning the methodological quality of the randomized studies. Among these investigations, only one study reported the method used for generating the random sequence and whether the method used to hide the sorting did not allow a prediction of the distribution of the patients into groups. Two of the studies did not use a blind evaluator; one did not report on this, and one made use of a blind evaluator. In addition, only one of the studies included data for all the subjects in the final analysis. In all of the articles, the main scales were also administered at the final evaluation. In one study, the presence of comorbidities was not described, and in three studies, they were partially described. The numbers of subjects screened, included and excluded were described completely in only one study. In three studies, the treatments were sufficiently described or referenced to allow replication. Only two studies clearly provided information on concurrent treatments allowed and administered during the course of the study, and they did not permit concomitant treatments. In one study, this description was partially completed, and in another study, there was the possibility that the participants in group therapy were concurrently taking non-stabilized psychotropic medication. None of the articles performed an intent-to-treat analysis because there were no evaluations over the course of treatment. In fact, there were only pre- and post-treatment evaluations.

Discussion

General results

To the best of our knowledge and despite the current relevance of this subject, this is the first systematic review that evaluates the

	Random sequence generation	Allocation concealment	Blinding of outcome assessment (detection bias)	Incomplete outcome data	Selective reporting (reporting bias)	Description of relevant comorbidities	Information on screened, included, and excluded subjects	Description of treatment (or reference)	Description of concurrent treatment	Intent-to-treat analysis
Botella et al 2010	?	?	–	?	+	?	?	+	?	–
Gamito et al 2010	?	?	?	?	+	?	?	+	+	–
McLay et al 2011	+	+	–	?	+	?	?	+	–	–
Ready et al 2010	?	?	+	+	+	–	+	?	+	–

Figure 2. Methodological Analysis of Randomized Controlled Trials; + Low Risk of Bias; – High Risk of Bias; ? Unclear Risk of Bias.
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efficacy of VRET focused exclusively on patients diagnosed with PTSD. A study conducted by Meyerbroker & Emmelkamp [5] included a systematic review of VRET in various anxiety disorders including PTSD. However, only two studies were considered in their analysis [7–13]. A meta-analysis was performed by Parsons et al [22], and two studies with PTSD were selected. The meta-analysis was based on fewer than 20 subjects. Two different meta-analyses in VRET and anxiety disorders were published [23–24], including only one paper in PTSD [13]. The lack of systematic reviews and meta-analyses on the subject is probably due to the small number of studies in the literature that use VR as a tool for exposure. However, the few published studies are recent, with the first dating from 2006 [7], which indicates rapid growth in this area.

Based on the evaluations of the 10 studies, the results point to the potential efficacy of VRET in the treatment of PTSD. Among the six studies that included a control group, a statistically significant reduction in questionnaires evaluating symptoms of PTSD was observed in four. In comparison to the waiting list, results were significantly better for VRET. However, no difference was found between VRET and exposure treatment. The same result was obtained in the meta-analyses on the efficacy of VRET and classical cognitive-behavioral evidence-based treatment in the treatment of anxiety disorders, performed by Opris & colleagues [24]. We cannot discard, nonetheless, the possibility of a Type 2 error due to low sampling power; that is, if the samples were larger, a difference in efficacy in favor of one of the treatments might have been found. In three of the four non-controlled studies, VRET showed efficacy, which confirms the potential efficacy of this treatment.

Eight of the 10 studies used samples of war veterans. The high utilization of this population was probably due to the high financial and social costs of wars in terms of the number of soldiers who return home with PTSD [14]. In two studies, samples included victims of various traumas, and the remaining study was conducted with victims of the terrorist attack of September 11, 2001. War veterans are considered to be a more resistant sample[7]. Thus, the results obtained might have been even more promising if the studies had used subjects exposed to other types of trauma. A problem involved in using VRET in comparison to traditional exposure is related to the difficulty of constructing a context that refers precisely to the traumatic memory of the patient [5]. Due to its high financial cost, it would be almost impossible to follow the idiosyncratic method, which means personalizing the virtual environment according to the perspective of each patient related to the trauma. By contrast, with a homogeneous sample, only some stimuli elicited by the virtual environment are necessary to produce anxiety sufficient for activation of the traumatic memory [7]. In a study which used individuals that had suffered various types of trauma [19], the virtual environment was even more general, but it still evoked recollections of the traumatic event.

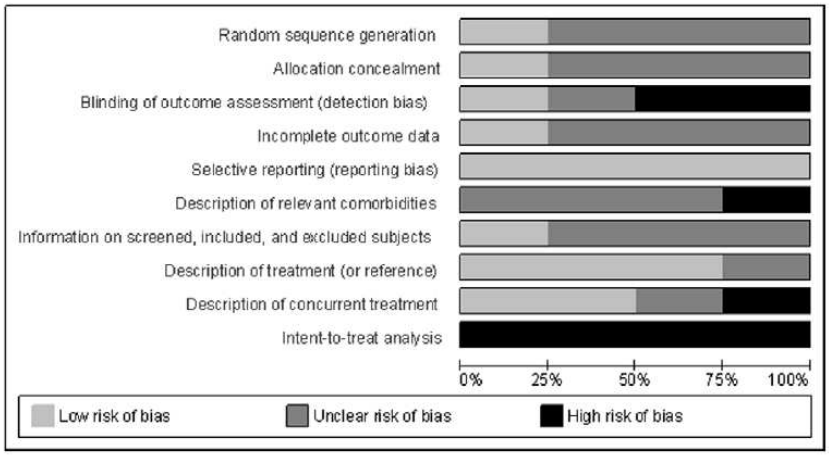

Figure 3. Methodological Analysis of Randomized Controlled Trials.
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The number of sessions varied between 5 and 20. Only four studies set a fixed number of sessions. The others proposed only a minimum number that could be exceeded depending on the needs of the patient. The lack of standardization makes it difficult to evaluate the efficacy of the protocol, although it is understandable considering that these were the first studies to test the efficacy of VRET in the treatment of PTSD. Therefore, there is no standard to follow. The sessions basically consisted of techniques that included psychoeducation, anxiety management (such as diaphragmatic breathing, progressive muscle relaxation and meditation) and *in vivo* and imaginal exposure. Only three studies reported using cognitive restructuring [13,14–21].

The majority of the articles used head-mounted display VR equipment and VR systems specific for the samples. Only one study used an automatic virtual environment, an adaptive VR display called EMMA's World [19]. This system allows for deep immersion into the virtual environment for both the patient and the therapist, which offers a better perception of what the patient is seeing. This VR equipment is non-specific, and different environments could bring the patient into contact with different feelings that serve as triggers for traumatic memories. No other studies used the automatic virtual environment methodology. So, it was not possible to test which of the two methodologies was more efficacious in the treatment of PTSD.

Methodological Issues

Randomized clinical trials. We found that the four randomized studies were not conducted in accordance with rigorous criteria for quality. All of them had methodological limitations that introduced a risk of bias for the final results. Proper reporting of the items that constitute a randomized trial assists in the critical evaluation of internal validity and the generalization of the results [25].

It is striking the absence of information to judge the quality of the trials. The majority of studies omitted data concerning random sequence generation, allocation concealment, description of relevant comorbidities, information on screened, included and excluded subjects and description of incomplete outcome data. Besides, even in the study with the higher amount of items evaluated favorably [15], those items account for less than half of the total of the evaluated items. The items with the lower risk of bias were selective reporting and description of treatment.

Another serious limitation concerns the use of extremely small samples in each of the randomized trials. For example, two studies [19–20], despite being randomized, involved only 10 participants each. The randomized study with the largest sample included 20 subjects [21]. These small samples make a meta-analysis focused on those data impossible. Finally, the absence of effect size makes it difficult to understand to what extent the result is explained by the predictor variable [26]. In addition, none of the studies used the number needed to treat (NTT), which is a more powerful and intelligible statistical tool because it establishes the necessary minimum number of individuals to be treated in the event that one of them no longer fulfills the diagnostic criteria after the treatment [27].

Future studies should take into account the methodological issues mentioned above and presented in figures 2 and 3 in order to improve the quality of the trials in VRET.

All Studies. We observed an absence of key information that is required to understand the evaluation of VRET efficacy because some studies focused on the description of the VR system configured for exposures, thereby placing less emphasis on evaluating the efficacy of the treatment. Some studies did not even present quantitative results but only qualitative information about efficacy [14–18].

In spite of these limitations, all of the articles reported the results of the most important scale at the final evaluation. Therefore, there was no risk of hidden possible negative results. In addition, half of the articles performed follow-ups. Those data were collected from one month to one year after the end of treatment. Although the ideal time suggested for a follow-up begins at twelve months [12], the fact that there was follow-up assessment shows an effort to incorporate a more robust methodology. We believe that, with advances in the study of VRET efficacy in the treatment of PTSD, future studies will achieve better methodology quality.

Another important consideration is treatment adherence. It is known that exposure techniques can have a high rate of non-adherence due to the initial worsening of the symptoms. For there to be extinction of the fear associated with the memory of the traumatic event, it is necessary for the patient to experience anxiety and feel its reduction after a specified period of repetition of the traumatic memory. Because the technique is highly anxiogenic, many patients do not agree to undergo the treatment or give up at the beginning of treatment. Theoretically, VRET appears to partially bypass this problem by providing exposure in a more controlled and safer environment. However, except for two studies [17–21], there were dropouts from the VRET group for all of the studies that supplied this information. Two studies did not report the dropout rate [14–19]. The highest dropout rate occurred in the study by Rizzo et al [18], where half of the total sample of 40 participants did not complete the treatment. Two other studies showed high dropout rates [16–7], with six dropouts in each (out of 21 and 29, respectively).

It is important to mention the low treatment adherence rates found in the active duty military populations. Out of 49,425 veterans diagnosed with PTSD, only 9.5% attended nine or more VA mental health sessions in 15 weeks or less in the first year of diagnosis [28]. This population has issues regarding stigma associated with mental health problems, higher rates of alcohol related problems, and competing responsibilities for preparing for the next deployment that have a dramatic negative effect on adherence to treatment [29–30].

Despite the fact that exposure therapy is considered to be highly aversive [31], in a study by Hembree et al [32], the dropout rates for exposure therapy were not different from the rates found for techniques considered to be less aversive, such as Cognitive Therapy, Stress Inoculation Training and EMDR during the treatment of PTSD. However, due to the high dropout rate that was evident in the selected articles, we believe that there remains a certain loss of control of anxiogenic stimuli during VRET. The loss of control might be related to the need for the therapist or the patient himself to manage the equipment so as to reduce the intensity of the stimulus when anxiety is very high. The use of new technologies, such as physiology-driven adaptive VR stimulation that automatizes the system to make it less dependent on the intervention of the psychotherapist during exposure, may be able to bypass this limitation.

Finally, one potential application of VRET would be for patients who are resistant to traditional exposure. For example, Difede et al [13] included five patients who had not responded initially to traditional exposure, and the results showed a positive response to VRET (for three of them, there was a reduction of at least 25% in CAPS, whereas for the other two, the reduction was greater than 50%). Replicating this finding would provide evidence of the mechanisms by which VRET could be more advantageous than traditional exposure. We believe that the results would be promising because VRET prevents patients from

using safety signals that make engagement difficult, which compromises the adequate extinction of conditioned fear.

Conclusions

The results of this systematic review suggest the potential efficacy of VRET in the treatment of PTSD for different types of trauma. VRET proved to be as efficacious as exposure therapy. VRET can be particularly useful in the treatment of PTSD that is resistant to traditional exposure because it allows for greater engagement by the patient and, consequently, greater activation of the traumatic memory, which is necessary for the extinction of the conditioned fear.

However, there remains a vast field to be explored that requires methodologically stronger trials and replications of those trials, the standardization of treatment, empirical studies with different VR systems and attempts to increase the rate of adherence to treatment. In future studies, the use of VRET for traditional exposure resistant patients would be interesting, as would the use of artificial intelligence to make the system less dependent on the intervention of the psychotherapist at the moment of exposure.

Supporting Information

Checklist S1 PRISMA 2009 Checklist.
(DOC)

Author Contributions

Conceived and designed the experiments: RG ALP IF PV. Performed the experiments: RG ALP. Analyzed the data: RG EC. Contributed reagents/materials/analysis tools: RG EC. Wrote the paper: RG IF PV.

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Conclusões

O investimento em pesquisa translacional nas áreas da psicologia e psiquiatria pode ser a saída para a diminuição da taxa de mortalidade dos transtornos mentais. Tendo em vista a incipiência desta união, especialmente no que diz respeito ao campo da psicologia, esta tese sintetiza alguns avanços obtidos na interseção da psicologia com a ciência básica, além de indicar caminhos para futuras pesquisas na área.

Os achados da presente tese permitem inferir que a TCC é capaz de modificar parâmetros psicofisiológicos anteriormente alterados em pacientes com transtornos de ansiedade. Em parâmetros cardíacos, esse impacto é observado através da redução da frequência cardíaca durante a evocação de sintomas, especialmente no TEPT e em fobias específicas. Em outros transtornos, novos estudos com metodologia padronizada possibilitarão confirmar a tendência de eficácia.

Especificamente com relação ao TEPT, os parâmetros cardíacos estão entre os biomarcadores mais estudados. Quando medidos em repouso, o impacto da TCC não é observado na maioria dos parâmetros. Constatou-se apenas redução de um índice predominantemente simpático mensurado no domínio da frequência, denominado baixa frequência. Ainda assim, este resultado deve ser visto com cautela e carece de replicações.

Com relação ao parâmetro neuroendócrino, mais especificamente o cortisol, observou-se uma tendência de resposta às técnicas utilizadas em diferentes momentos da terapia. Há queda deste hormônio na fase inicial do tratamento, durante a qual os pacientes aprendem técnicas de manejo da ansiedade, compreendem os aspectos do transtorno e do tratamento e aprendem a flexibilizar pensamentos distorcidos. Posteriormente, quando tem início a técnica de exposição, observa-se elevação do nível de cortisol, o que é coerente com o aumento da ansiedade observado durante o estágio inicial de administração da técnica. Finalmente, quando a ansiedade associada à exposição começa a diminuir, tendo em vista o processamento da memória traumática e a consequente extinção do medo condicionado, o nível de cortisol volta a decair, mantendo-se reduzido por um mês após o término do tratamento. Estudos com tamanho de amostra maior poderão confirmar se esta tendência se confirma de maneira estatisticamente significativa.

Outra conclusão inferida a partir dos resultados da presente tese diz respeito à extensão da eficácia da TCC no tratamento do TEPT. Através da revisão sistemática publicada, foi demonstrado que a TERV tem eficácia equivalente à exposição tradicional, apesar de não produzir ganhos extras. Além disso, a técnica parece beneficiar pacientes resistentes ao tratamento convencional. A replicação em estudos com metodologia padronizada e em amostras maiores é interessante para estabelecer esse achado.

A tendência de crescimento do campo é consistente. Diante da publicação exponencial de estudos nos últimos anos, há expectativa de que num futuro próximo conclusões mais robustas possam ser alcançadas. Diante deste panorama, abre-se caminho para a possibilidade de tratamentos novos e mais eficazes, adaptando-os a diferentes tipos de pacientes, incluindo o tempo e intensidade necessários para cada indivíduo, além de possibilitar a personalização de técnicas eficazes a partir de diferentes demandas biocomportamentais.

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Anexos

Termo de Consentimento Livre e Esclarecido:

Eficácia da Terapia Cognitivo-Comportamental para o Transtorno do Estresse Pós-Traumático.

Você está se propondo a participar de um estudo que visa verificar a eficácia da Terapia Cognitivo-Comportamental (TCC), um tipo de atendimento psicológico, no tratamento de pacientes com o diagnóstico de Transtorno do Estresse Pós-Traumático (TEPT).

Este estudo está sendo realizado no ambulatório dos Transtornos Relacionados ao Estresse sediado no campus da Praia Vermelha da Universidade Federal do Rio de Janeiro, e encontra-se soborientação dos professores Dra. Paula Ventura e Dr. Ivan Figueira.

Você será sorteado para um dos dois grupos desta pesquisa. Um grupo receberá tratamento com Terapia Cognitivo-Comportamental que será administrado ao longo de dezesseis semanas (cada semana com 1 sessão de terapia principal e 3 sessões de co-terapia, totalizando 4 sessões de terapia por semana) com uma hora e meia de duração cada sessão. As sessões serão gravadas e será discutido o evento traumático e suas conseqüências para a sua vida. É natural que, ao conversar sobre o evento traumático, você se sinta desconfortável, mas o terapeuta estará disponível para ajudá-lo a se sentir melhor.

O outro grupo aguardará em uma lista de espera e poderá, ao final de dezesseis semanas, se submeter ao tratamento psicoterápico, se desejar.

Independente do grupo que você for selecionado, você receberá acompanhamento psiquiátrico de acordo com sua necessidade. Além disso, você realizará uma avaliação fisiológica detalhada para entendermos como o seu corpo reage. Você ficará em uma sala especialmente preparada (isolamento acústico relativo, ar condicionado, luz indireta) e serão colocados alguns sensores em seu corpo para medir seus batimentos cardíacos, sua pulsação, sua respiração e seu suor, e será feita a coleta de sua saliva. Se você for selecionado para o grupo que ficará na lista de espera, você fará cinco avaliações fisiológicas, sendo uma avaliação a cada quatro semanas. Se você for selecionado para começar a terapia logo, você fará seis avaliações fisiológicas, sendo uma avaliação realizada uma semana antes do tratamento psicoterápico, quatro avaliações durante o tratamento (uma a cada quatro semanas) e uma avaliação um mês após o término do tratamento.

A sua participação é voluntária e participar ou não da pesquisa não trará nenhum prejuízo significativo à sua saúde ou bem-estar. Caso você decida não participar, ou interromper o estudo, o seu atendimento médico não será prejudicado.

Sua identificação, seus dados pessoais e suas respostas serão mantidos como informações confidenciais. Os resultados da pesquisa serão publicados com fins científicos, sem que a sua identidade seja revelada.

A sua participação é muito importante, já que os dados obtidos neste estudo possibilitarão o desenvolvimento de estratégias de tratamento mais eficazes para ajudar pacientes com TEPT, que é um transtorno comum e que causa muitos prejuízos e sofrimento na vida das pessoas.

Caso precise, favor entrar em contato com:

Helga Rodrigues – Psicóloga (CRP:05/32.820)
Telefone: (21) 9946-3130

Raquel Gonçalves – Psicóloga (CRP:05/36.117)
Telefone: (21) 9492-0590
Declaro ter lido o texto acima e concordo com estes termos e com a minha participação nesta pesquisa.

Rio de Janeiro, _____ de _____ de 20_____.

_____

Nome do (a) paciente

_____

Assinatura do (a) paciente

_____Paula Rui Ventura_(CRP:05/16.145)_____
Pesquisador (a) responsável

PCL

Nome:_____
Data de preenchimento_____
Checado por:_____ Pront.: _____

Abaixo, há uma lista de problemas e de queixas que as pessoas às vezes apresentam como uma reação a situações de vida estressantes. Por favor, indique o quanto você foi incomodado por estes problemas durante o último mês marcando em vermelho o espaço correspondente.
.

	1	2	3	4	5
	nada	**Um pouco**	**médio**	**bastante**	**muito**
1. Memória, pensamentos e imagens repetitivos e pertubadores referentes a uma experiência estressante do passado?	○	○	○	○	○
2. Sonhos repetitivos e perturbadores referentes a uma experiência estressante do passado?	○	○	○	○	○
3. De repente, agir ou sentir como se uma experiência estressante do passado estivesse acontecendo de novo (como se você a estivesse revivendo)?	○	○	○	○	○
4. Sentir-se muito chateado ou preocupado quando alguma coisa lembra você de uma experiência estressante do passado?	○	○	○	○	○
5. Sentir sintomas físicos (coração batendo forte, dificuldade de respirar, suores) quando alguma coisa lembra você de uma experiência estressante do passado?	○	○	○	○	○
6. Evitar pensar ou falar sobre uma experiência estressante do passado ou evitar ter sentimentos relacionados a esta experiência?	○	○	○	○	○
7. Evitar atividades ou situações porque elas lembram uma experiência estressante do passado?	○	○	○	○	○
8. Dificuldades para lembrar-se de partes importantes de uma experiência estressante do passado?	○	○	○	○	○
9. Perda de interesse pelas atividades que você antes costumava gostar?	○	○	○	○	○
10. Sentir-se distante ou afastado das outras pessoas?	○	○	○	○	○
11. Sentir-se emocionalmente entorpecido ou incapaz de ter sentimentos amorosos pelas pessoas que lhe são mais próximas?	○	○	○	○	○
12. Sentir como se você não tivesse expectativas para o futuro?	○	○	○	○	○
13. Ter problemas para pegar no sono ou para continuar dormindo?	○	○	○	○	○
14. Sentir-se irritável ou ter explosões de raiva?	○	○	○	○	○
15. Ter dificuldades para se concentrar?	○	○	○	○	○
16. Estar super-alerta, vigilante ou em guarda?	○	○	○	○	○
17. Sentir-se tenso ou facilmente sobressaltado?	○	○	○	○	○

ARTIGOS

Impacto da co-terapia no tratamento do TEPT com Terapia cognitivo-comportamental

Impact of co-therapy in the cognitive behavioral treatment of PTSD

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Resumo

A terapia cognitivo-comportamental (TCC) apresenta eficácia comprovada no tratamento do Transtorno de Estresse Pós-Traumático (TEPT), contando com técnicas tais como psicoeducação, reestruturação cognitiva, relaxamento muscular progressivo, respiração diafragmática, exposição *in vivo* e imaginária. A utilização de co-terapia no tratamento individual de pacientes praticamente não foi investigada. O objetivo deste estudo foi ilustrar a adaptação do protocolo da Edna Foa para TCC no TEPT com destaque para a introdução da co-terapia, não presente no protocolo original. Trata-se da avaliação do tratamento de uma paciente com TEPT que não tolerou os medicamentos de primeira escolha, através de escalas de auto-relato e heteroavaliação realizada por psiquiatras. Observou-se diminuição dos escores do Inventário Beck de Depressão (BDI), Inventário Beck de Ansiedade (BAI), *Clinical Global Impression* (CGI) e do PTSD *Checklist – civilian version* (PCL-C) ao longo do tratamento. O presente caso sugere que a administração do protocolo foi adequada, havendo evidências de eficácia da TCC e da relevância da co-terapia como ingrediente importante neste processo. Ensaios randomizados controlados poderão testar o custo-efetividade da adição da co-terapia ao tratamento, particularmente em casos de TEPT resistentes ou intolerantes aos tratamentos convencionais e com comorbidades psiquiátricas.

Palavras-chave: Transtorno de Estresse Pós-Traumático, Terapia Cognitivo-comportamental, Co-terapia, Relato de caso.

Abstract

Cognitive behavioral therapy (CBT) is an effective treatment for Post Traumatic Stress Disorder (PTSD) and use techniques such as psychoeducation, cognitive restructuring, relaxation, breathing retraining, imaginal and in vivo exposure. The role of co-therapy in individual treatment of patients hasn't been well investigated. The aim of the present study was to illustrate the adaptation of a version of Edna Foa's protocol of CBT for the treatment of PTSD, highlighting the addition of co-therapy, not included at

the original protocol. It was evaluated the treatment of a medication intolerant PTSD patient through self report scales and psychiatric evaluation. It was observed that scores of Depression Beck Inventory, Anxiety Beck Inventory, Clinical Global Impression and PTSD Checklist – civilian version decreased over treatment. This case report suggests that the administration of the protocol was satisfactory, with evidences of CBT efficacy and co-therapy relevance as an important element in this process. Randomized controlled trials are necessary to test the cost-effectiveness of co-therapy addition in the treatment protocol, particularly in patients with treatment-resistant or treatment-intolerant PTSD and psychiatric comorbidity.

Key words: Cognitive Behavioral Therapy, Post Traumatic Stress Disorder, Co-therapy, case report

INTRODUÇÃO

O Transtorno de Estresse Pós-Traumático (TEPT) é desenvolvido após exposição direta, testemunho ou conhecimento de um evento traumático extremo envolvendo morte, sério ferimento ou outra ameaça à integridade física, onde o indivíduo experiencia intenso medo ou horror. Sintomas de três classes devem existir: revivescência, evitação/entorpecimento emocional e hiperestimulação autonômica. (*American Psychiatric Association*, 1994).

O TEPT chama atenção por sua alta prevalência, sendo considerado o quarto transtorno mais comum (Yehuda, 2002). Estima-se que a prevalência do TEPT na população geral ao longo da vida seja de aproximadamente 8%. As comorbidades mais comuns são depressão e outros transtornos de ansiedade precedendo o trauma, e abuso de substâncias após o evento traumático (Vieweg, et al., 2006).

A Terapia Cognitivo-Comportamental (TCC) pressupõe que a maneira como interpretamos as situações influencia nossos sentimentos e comportamentos (Beck, 1997). Portanto, crenças disfuncionais desenvolvidas após o evento traumático ou já existentes anteriormente colaboram para o surgimento de sentimentos disfóricos e

comportamentos desadaptativos, o que pode favorecer o desenvolvimento de patologias. O indivíduo com TEPT pode perder a sensação de segurança e passar a se ver de forma negativa, além de desenvolver um senso de responsabilidade pelo ocorrido (Foa, 1998). Além disso, pode ocorrer condicionamento do local e de elementos presentes na situação, que eliciam respostas de ansiedade não existentes anteriormente. Devido à produção de reações ansiogênicas, esses estímulos são evitados, assim como qualquer lembrança do trauma em si, o que promove alívio momentâneo da ansiedade. Desta forma, a evitação é reforçada negativamente, ocorrendo aumento de sua freqüência. O tratamento, portanto, consiste em fornecer ferramentas que auxiliarão o paciente a identificar, avaliar a realidade de suas cognições e a modificá-las caso não sejam realistas, o que é denominado reestruturação cognitiva. Paralelamente, deve-se expor o indivíduo aos estímulos provocadores de ansiedade, que em realidade não são perigosos, de modo que ocorra habituação da ansiedade. Na exposição *in vivo*, o indivíduo enfrenta os estímulos provocadores de ansiedade. Já na exposição imaginária, há o enfrentamento das lembranças do evento em si, onde o paciente ouve repetidamente o seu relato do trauma até que não sinta mais ansiedade.

A TCC apresenta eficácia comprovada no tratamento do TEPT (Mendes, et al., 2008), sendo considerada o tratamento de primeira escolha (Bisson, 2007, DeAngelis, 2008). O tratamento pode contar com técnicas tais como: psicoeducação, reestruturação cognitiva, relaxamento, exposição *in vivo* e imaginária. A utilização destas técnicas objetiva identificar, avaliar e modificar crenças disfuncionais e expor o paciente a situações e lembranças que ele evita por considerá-las perigosas, mas que em realidade não são.

Muitos estudos demonstraram a eficácia da terapia de exposição em reduzir a gravidade do TEPT, independente do tipo de evento traumático precedente (Hembree et al., 2003). Quando comparada com outras técnicas, como o *Eye Movement Desensitization and Reprocessing* (EMDR) e o treino de relaxamento, a terapia de

exposição produziu redução significativa nos sintomas de evitação e de revivescência, tendendo a ser mais rápida do que as outras técnicas na redução da evitação. Após o tratamento, muitos pacientes deixam de preencher critérios para o TEPT (Taylor et al., 2003).

Apesar das evidências a favor da terapia de exposição, alguns trabalhos salientam dificuldades em aderir e tolerar esta técnica. Hembree, et al. (2003) procuraram verificar essa hipótese e obtiveram como resultado que a taxa comum de desistência era de 20.5% para tratamentos de exposição, 22.1%, para terapia cognitiva ou treino de inoculação do estresse, 26.9% para combinações de exposição e outras técnicas de TCC, e 18.9% para EMDR. Apesar de esses resultados indicarem altas taxas de desistência do tratamento, não foram encontrados na literatura artigos referentes à utilização da co-terapia visando melhorar a adesão do paciente à terapia de exposição.

Este trabalho tem como objetivo apresentar a adaptação do protocolo da Edna Foa para TCC no TEPT em paciente intolerante à medicação de primeira linha para este transtorno. Introduzimos 12 sessões de co-terapia entre as sessões de terapia para auxiliar o tratamento extraconsultório, sendo este o principal diferencial em relação ao protocolo da Foa (1998), no qual não há tal tipo de atendimento. As sessões de co-terapia apresentam potenciais vantagens tais como garantir a adesão ao tratamento, identificar e manejar obstáculos à implementação das técnicas, treinar o paciente na realização dos exercícios de relaxamento e facilitar o engajamento nas exposições (Del Prette, 2007).

Descrição do caso clínico:

B., 50 anos, casada, dona de casa e residente no Rio de Janeiro, procurou atendimento após assalto ocorrido em sua residência, no qual vários pertences foram roubados. Ela estava sozinha e não reagiu. Quando os assaltantes foram embora, apresentou sensação de "congelamento", rosto quente e tremor nas pernas. Após o

assalto, passou a trancar a casa, pôs grade nas janelas e procurava constantemente possíveis maneiras de bandidos entrarem em sua casa.

Além do TEPT, foram diagnosticados a partir da SCID-I (*Structured Clinical Interview for DSM-IV Axis I Disorders*) (Del-Ben et al., 2001) Depressão Maior, Transtorno Obsessivo-compulsivo (TOC) e Fobia Social. Inicialmente foi prescrita paroxetina 20 mg/dia, posteriormente interrompida devido à sonolência e lentificação psicomotora importantes. Foi, então, prescrito citalopram 20 mg/dia. Para o tratamento da cefaléia foi iniciada nortriptilina 25 mg/dia. Após melhora da cefaléia e do quadro clínico, o citalopram foi suspenso e a dose de nortriptilina elevada até a dose de 50 mg/dia. No quinto mês de tratamento, foi relatada piora dos sintomas de depressão e manutenção dos sintomas de TEPT. Neste período foi iniciado o tratamento com TCC.

Os seguintes sintomas foram relatados: ansiedade súbita, aperto no peito, sensação de sufocamento, taquicardia, apetite reduzido, perda de prazer em sair e realizar tarefas domésticas, dificuldade de concentração, choro fácil, cansaço, desânimo, excitabilidade aumentada, pensamentos intrusivos recorrentes sobre "alguém entrar em sua casa, matar, torturar e estuprar sua família". A paciente mostrou-se bastante amedrontada com a possibilidade de sofrer novo assalto. Assim, evitava qualquer situação que a expusesse à violência urbana, relatando grande ansiedade até mesmo ao sair de casa e interpretando qualquer situação como perigosa.

METODOLOGIA E RESULTADOS

Foram realizadas 16 sessões de terapia (realizadas uma vez por semana), intercaladas com 12 sessões de co-terapia (realizadas três vezes por semana). Definimos a co-terapia o trabalho realizado em ambiente extra-consultório que complementa a participação do terapeuta principal, auxiliando a implementação das técnicas cognitivo-comportamentais no período entre as sessões. Foram realizadas

exposições imaginária (ao relato do evento gravado em fita) e *in vivo*, para a qual foi elaborada uma hierarquia de enfrentamento com as situações evitadas pela paciente. A reestruturação cognitiva auxiliou na modificação de crenças de vulnerabilidade pré-existentes que se intensificaram devido ao trauma. Algumas cognições identificadas durante o tratamento foram "o mundo é perigoso", "parece que tudo de errado acontece comigo", "as pessoas não são confiáveis". A reestruturação destas cognições foi efetiva na flexibilização da maneira rígida e extrema de pensar da paciente. Conseqüentemente, observou-se diminuição da ansiedade e aquisição de repertório comportamental mais adaptativo. Após a oitava sessão a sintomatologia já havia diminuído, assim como os sintomas do TOC.

Com o avanço do tratamento, a paciente passou a sair de casa com freqüência, dar liberdade aos filhos e inserir-se em atividades de lazer. Embora o foco do tratamento tenha sido no TEPT, observou-se melhora qualitativa nos sintomas de Fobia Social e TOC.

Tabela I: Evolução dos escores do BDI (*Beck Depression Inventory*), BAI (*Beck Anxiety Inventory*), CGI (*Clinical Global Impression*) e PCL-C (PTSD *Checklist – civilian version)* ao longo do tratamento.

	Pré - TCC	Mês 1	Mês 2	Mês 3	Pós-TCC
BDI	18	19	11	15	9
BAI	25	14	6	18	8
PCL-C (geral)	40	45	27	29	28
PCL-C (revivescência)	10	13	8	9	8
PCL-C (evitação)	16	19	11	11	11
PCl-C (entorpecimento)	5	7	3	3	3
PCL-C (hiperestimulação)	14	13	8	9	9
CGI (gravidade)	4	4	4	4	2
CGI (evolutiva)	3	3	3	3	2

Além da assinatura do termo de consentimento livre e esclarecido, para a avaliação dos sintomas, os inventários Beck de Depressão e Ansiedade (Cunha, 2001), *Clinical Global Impression* (CGI) (Guy, 1970) e o PTSD *Checklist – civilian version* (PCL-C) (Berger, et al., 2004) foram administrados a cada mês de tratamento. Os resultados encontram-se na tabela I:

DISCUSSÃO

O presente estudo pretendeu avaliar a utilização de um protocolo de TCC em uma paciente com TEPT intolerante às medicações prescritas. Para tal, foram mensurados ao longo do tratamento sintomas de depressão, ansiedade, TEPT e avaliações realizadas por psiquiatras.

A adição da co-terapia ao protocolo possivelmente contribuiu para o sucesso do tratamento, visto a grande ansiedade relatada pela paciente frente à possibilidade de exposição aos estímulos temidos. A co-terapia visou garantir a eficácia da terapia de exposição por meio de sua correta aplicação e reduzir a possibilidade de desistência ao tratamento. Pode-se sugerir que a adesão completa ao tratamento relacionou-se ao intenso acompanhamento realizado pela co-terapia.

Este artigo evidencia a necessidade de ensaios randomizados controlados para avaliar a eficácia da introdução da co-terapia no tratamento com TCC. Tal ingrediente pode ser particularmente útil em casos graves, resistentes ou intolerantes aos tratamentos, e com elevadas taxas de comorbidade.

CONCLUSÃO

O presente caso sugere que a administração do protocolo foi adequada, havendo evidências de eficácia da TCC e da relevância da co-terapia como ingrediente importante neste processo. A efetividade da administração do protocolo pode ser evidenciada através da diminuição dos escores dos inventários administrados ao longo do tratamento. Houve redução dos sintomas de TEPT, ansiedade e depressão nos

instrumentos de auto-avaliação, confirmada pela heteroavaliação feita pelos psiquiatras, que mostrou melhora da gravidade e evolução clínica global.

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Marcadores neurobiológicos e psicométricos da eficácia da terapia cognitivo-comportamental no transtorno de estresse pós-traumático associado a sintomas dissociativos: relato de caso

Neurobiological and psychometric markers of the efficacy of cognitive behavioral therapy in post-traumatic stress disorder with dissociative symptoms: a case report

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Resumo

Introdução: O transtorno de estresse pós-traumático (TEPT) tem sido associado à desregulação de diversos parâmetros psicofisiológicos e pode apresentar comorbidade com diversas psicopatologias, inclusive a dissociação, podendo dificultar o tratamento. O objetivo do presente trabalho foi investigar os efeitos da terapia cognitivo-comportamental em um paciente com TEPT e sintomas dissociativos com base em medidas psicofisiológicas e psicométricas em diferentes momentos do tratamento.
Descrição do caso: O paciente é um homem de 38 anos, com diagnósticos de TEPT e transtorno depressivo maior recorrente com sintomas dissociativos e resistência ao tratamento farmacológico. O tratamento psicoterápico teve duração de 4 meses, sendo composto por uma sessão semanal de terapia e três sessões semanais de coterapia. Os parâmetros fisiológicos (frequência cardíaca, tônus vagal, balanço simpático e cortisol) e psicométricos (afeto negativo e positivo, resiliência e sintomas de estresse pós-traumático, depressão, ansiedade e dissociação) foram medidos antes, durante (uma vez ao mês) e após o tratamento.
Comentários: Os resultados mostraram diminuição do balanço simpático e aumento do tônus vagal, da frequência cardíaca e dos níveis de cortisol ao longo do tratamento. O tratamento também promoveu redução no afeto negativo e nos sintomas de estresse pós-traumático, depressão, ansiedade e dissociação, além de um aumento nos escores de resiliência, apoio social e afeto positivo. Esses resultados sugerem que a terapia cognitivo-comportamental é um tratamento eficaz para o TEPT com sintomas dissociativos. Além disso, parece promover a normalização das alterações fisiológicas do sistema nervoso autônomo e neuroendócrino relacionadas ao TEPT.
Descritores: Transtornos de estresse pós-traumáticos, psicofisiologia, transtornos dissociativos, psicometria.

Abstract

Introduction: Post-traumatic stress disorder (PTSD) has been associated with dysregulation of many psychophysiological parameters and may present comorbidity with different psychopathologies, including dissociation, potentially affecting treatment outcome. The aim of this study was to evaluate the effects of cognitive behavioral therapy in a patient with PTSD and dissociative symptoms based on psychophysiological and psychometric measures at different time points throughout the course of treatment.
Case description: Our patient is a 38-year old man diagnosed with PTSD, major depression, and dissociative symptoms, resistant to pharmacotherapy. Psychological treatment lasted for 4 months and consisted of one weekly therapy session and three weekly coaching sessions. Physiological (heart rate, vagal tone, sympathovagal balance, and cortisol) and psychometric measures (negative and positive affect, resilience, and post-traumatic stress, depression, anxiety, and dissociative symptoms) were obtained before, during (once a month) and after treatment.
Comments: Results showed a decrease in sympathovagal balance and an increase in heart rate, vagal tone and cortisol levels during the course of treatment. Treatment also lead to a decrease in negative affect and in post-traumatic stress, depression, anxiety, and dissociation symptoms, as well as to an increase in resilience, social support and positive affect scores. These results suggest that cognitive behavioral therapy is an effective treatment for PTSD patients with dissociative symptoms. Moreover, the treatment seems to be able to normalize PTSD-related physiological parameters in the neuroendocrine and autonomic nervous systems.
Keywords: Post-traumatic stress disorders, psychophysiology, dissociative disorders, psychometrics.

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Introdução

Os achados de que indivíduos com transtorno de estresse pós-traumático (TEPT) apresentam parâmetros psicofisiológicos aumentados em resposta a estímulos relacionados ao trauma quando comparados com indivíduos sem TEPT levaram à inclusão, no Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III)[1], da reatividade fisiológica como um critério sintomático formal para o diagnóstico de TEPT. Dessa forma, os pesquisadores começaram a questionar se pacientes diagnosticados com TEPT apresentariam níveis psicofisiológicos alterados mesmo na ausência de estímulos relacionados ao trauma. Pacientes com TEPT possuem maior ativação psicofisiológica em estado basal em relação aos indivíduos sem TEPT[2,3]. A variabilidade da frequência cardíaca (VFC) tem sido proposta como um indicador de saúde física e mental e de regulação emocional, sendo que a baixa variabilidade indicaria deficiência de adaptação do sistema cardiovascular às demandas do organismo[4]. Recentemente, foi proposto que o aumento da frequência cardíaca (FC) em pacientes com TEPT pode ser mediado por redução da atividade parassimpática, e não pelo aumento da atividade simpática[5].

Parâmetros neuroendócrinos associados à ativação do eixo hipotálamo-pituitária-adrenal também têm sido amplamente investigados nos estudos do estresse. A resposta do cortisol é considerada adaptativa ao estresse, e a desregulação desse eixo tem sido relacionada com uma série de patologias, entre elas o TEPT, em que os níveis de cortisol se encontram reduzidos[6].

Sintomas dissociativos são relativamente comuns em pessoas que vivenciaram situações traumáticas[7], apesar de não fazerem parte dos critérios diagnósticos para o TEPT de acordo com a quarta edição do DSM (DSM-IV)[8]. Indivíduos com TEPT e sintomas dissociativos formariam um subtipo dissociativo do transtorno, em oposição ao subtipo hiper-reativo[9]. As respostas biológicas ao estresse vivido numa situação traumática seriam distintas entre esses subtipos. Em estudo realizado com sobreviventes dos ataques de 11 de setembro de 2001, a dissociação foi relacionada a uma diminuída reatividade autonômica ao estresse e a menores níveis de cortisol[10]. Em um estudo de evocação de sintomas, somente os sujeitos que não dissociaram durante a revivescência tiveram aumento da FC[11]. Em outro estudo, menor FC basal foi observada em vítimas de acidentes com dissociação em comparação às vítimas sem dissociação[12].

A terapia cognitivo-comportamental (TCC) é considerada eficaz no tratamento do TEPT[13]. Uma vez que há evidências na literatura de que a TCC pode promover mudanças neurobiológicas[14], aspectos fisiológicos constituem instrumentos relevantes de avaliação de resposta ao tratamento e, por conseguinte, da eficácia da terapia[15].

O objetivo deste trabalho foi investigar a eficácia da TCC no tratamento de um paciente com diagnóstico de TEPT e sintomas dissociativos que se mostrava resistente ao tratamento medicamentoso, com base na avaliação de medidas psicofisiológicas e psicométricas.

Descrição do caso

Descreve-se o caso de um paciente do sexo masculino, de 38 anos, que procurou atendimento no Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (UFRJ), em 2006, onde recebeu os diagnósticos de TEPT e transtorno depressivo maior recorrente, episódio atual moderado. Em 2005, uma mulher se jogou de uma passarela, na frente do ônibus que dirigia. Após o evento, passou a ter pesadelos e a lembrar-se com frequência da cena traumática. Após o trauma, também começou a apresentar sintomas dissociativos, como perder a noção do tempo e do espaço e sair de casa desorientado. O paciente evitava falar sobre o trauma, sair de casa e andar de ônibus, bem como situações, pessoas e lugares que lembrassem o acidente. Passou a apresentar irritabilidade, desânimo, tristeza, perda de prazer nas atividades habituais, insônia, fadiga, diminuição da concentração e impaciência. Também tinha crises agudas de ansiedade, com taquicardia e sudorese, e chegou a apresentar ideação suicida, além de alucinações visuais e auditivas.

O paciente foi medicado com antidepressivos em doses altas, paroxetina até 60 mg/dia e venlafaxina até 375 mg/dia, sem obter melhora expressiva. Foi, então, iniciado tratamento com tranilcipromina, aumentada progressivamente até se atingir a dose de 120 mg/dia. Devido à ausência de resposta com o tratamento farmacológico, indicou-se associação deste com a TCC a fim de potencializar os resultados. Quando a TCC foi iniciada, em abril de 2008, o paciente utilizava as seguintes medicações: tranilcipromina 120 mg por dia, clonazepam 3 mg por dia, haloperidol 15 mg por dia e trazodona 200 mg por dia. O esquema medicamentoso se manteve estável ao longo de todo o tratamento psicoterápico.

O paciente assinou termo de consentimento aprovado pelo Comitê de Ética do Instituto de Psiquiatria da UFRJ ao início do estudo.

Método

Protocolo de TCC

Foi utilizado um protocolo adaptado de Foa & Rothbaum[16], com duração de 4 meses, composto por uma sessão semanal de terapia, conduzida por psicoterapeutas experientes, e três sessões semanais de coterapia, conduzidas por estudantes de psicologia. No total, foram 64 sessões de terapia e coterapia durante o tratamento. As técnicas utilizadas incluíram psicoeducação, reestruturação cognitiva, manejo de ansiedade e exposição imaginária e *in vivo*[17].

Avaliação psicométrica

A avaliação psicométrica foi realizada em três etapas distintas: antes do início do tratamento (uma coleta), durante o tratamento (quatro coletas, sendo uma por mês) e após o tratamento (uma coleta). A avaliação consistiu no preenchimento de questionários relacionados a aspectos negativos, a saber: Inventário de Depressão de Beck (Beck Depression Inventory, BDI)[18], Inventário de Ansie-

dade de Beck (Beck Anxiety Inventory, BAI)[19], PTSD Checklist - Civilian Version (PCL-C)[20], Escala de Experiências Dissociativas (DES)[21] e Escala de Traço de Afeto Negativo (PANAS-N)[22]. Também foram utilizados os seguintes questionários referentes a aspectos positivos: Escala de Traço de Afeto Positivo (PANAS-P)[22], Escala de Resiliência (ER89)[23] e Escala de Apoio Social do Medical Outcomes Study[24]. Todos os instrumentos foram utilizados em versões previamente validadas para o português.

Avaliação psicofisiológica

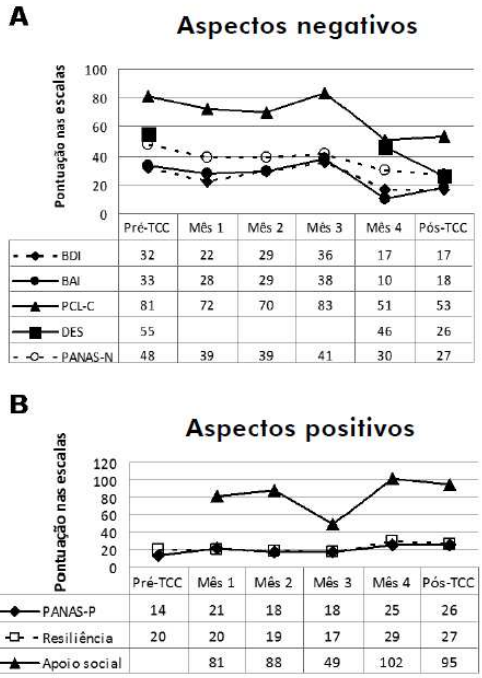
Os parâmetros psicofisiológicos foram avaliados em três etapas distintas: antes do início do tratamento (uma coleta), durante o tratamento (quatro coletas, sendo uma por mês) e após o tratamento (uma coleta). A avaliação consistiu em coleta de cortisol salivar e eletrocardiograma (ECG), com avaliação da FC, do índice parassimpático (VFC em altas frequências) e do índice simpático (balanço simpático). Para a análise dos níveis de cortisol, foram coletadas amostras de saliva utilizando o sistema Salivette®. As amostras foram coletadas e armazenadas a -20 °C até o momento da análise. A dosagem foi realizada através do método de enzimaimunoensaio.

A aquisição e análise dos dados de ECG foram feitas utilizando-se os programas Acknowledge (Biopac Systems, Inc., Goleta, EUA) e Matlab 7.0 (MathWorks, Natick, EUA), respectivamente. Após a aquisição do sinal, foi utilizado um algoritmo para estimar as ondas R e, posteriormente, foi realizada a inspeção visual do sinal para a correção de artefatos. As séries temporais foram reamostradas com interpolação a 2 Hz, e foi gerado o período cardíaco. O período cardíaco (intervalo entre as ondas R do ECG) foi convertido para FC para facilitar a compreensão dos resultados. Foram realizadas análises espectrais utilizando a transformada rápida de Fourier para extrair a amplitude da potência espectral da VFC em altas frequências (VFC-AF: 0.15-0.4Hz) e em baixas frequências (VFC-BF: 0.05-0.15Hz). A VFC-AF medida em repouso tem sido associada à modulação parassimpática e, portanto, tem sido chamada de tônus vagal. A VFC-BF têm sido associada à modulação simpática e parassimpática. Dessa forma, o balanço simpático (índice gerado pela razão entre VFC-BF e VFC-AF) tem sido relacionado a uma modulação predominantemente simpática.

Resultados

Ao início das sessões de exposição *in vivo*, o paciente sentia ansiedade alta, que, com o enfrentamento, foi sendo lenta e gradativamente reduzida. Passou a sair mais, ir a lugares que evitava, sentindo-se mais tranquilo, e passou a conseguir conversar com as pessoas sobre o trauma, o que antes lhe causava grande desconforto. Antes da TCC, tinha as seguintes crenças: "sou um fracasso", "o mundo é perigoso" e "as pessoas não são confiáveis". Ao fim do tratamento, houve a substituição dessas crenças por outras mais realistas e adaptativas, como, por exemplo, "agora acho que fui vítima", evidenciando ausência de culpa pelo que aconteceu, e "quem é fraco não faz esse tratamento".

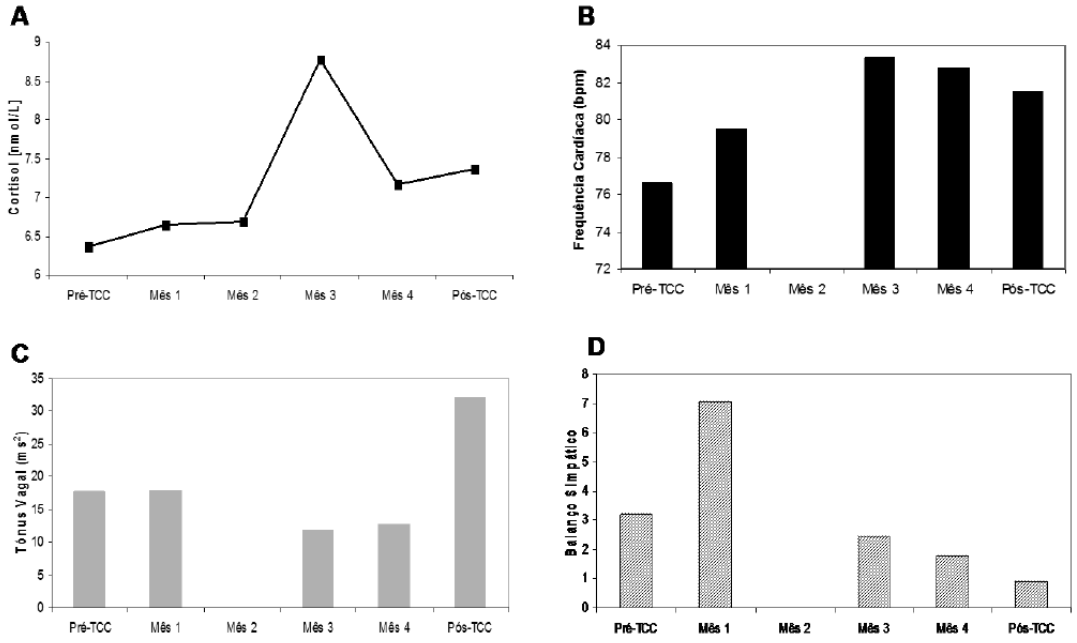
As escalas relacionadas a aspectos negativos mostraram reduções em sua pontuação ao longo do tratamento, resultado que foi mantido após seu término (Figura 1A). Já as escalas relacionadas a aspectos positivos mostraram aumento em suas pontuações (Figura 1B) durante e após o término do tratamento. Foi possível observar piora acentuada no mês 3, com aumento da pontuação nas escalas que avaliam aspectos negativos.



TCC = terapia cognitivo-comportamental; BDI = Inventário de Depressão de Beck; BAI = Inventário de Ansiedade de Beck; PCL-C = PTSD Checklist – Civilian Version; DES = Escala de Experiências Dissociativas; PANAS-N = Escala de Traço de Afeto Negativo; PANAS-P = Escala de Traço de Afeto Positivo.

Figura 1 – Avaliação psicométrica a cada mês: A) aspectos negativos; B) aspectos positivos

A comparação dos níveis basais de cortisol salivar antes (6,36 nmol/L) e após o término da terapia (7,37 nmol/L) evidenciou um pequeno aumento dos níveis hormonais. Além disso, foi observado aumento pronunciado nos níveis basais de cortisol durante o terceiro mês da terapia (8,77 nmol/L) (Figura 2A). Com relação à análise cardíaca, houve aumento progressivo da FC durante o tratamento, resultado que se manteve após seu término (FC antes da TCC: 76,6 bpm; FC após a TCC: 81,4 bpm) (Figura 2B). Foi observada também uma redução do tônus vagal no terceiro (11,8 ms^2) e no quarto mês (12,6 ms^2) em relação à coleta pré-TCC (17,7 ms^2), porém esse quadro se reverteu para um aumento bastante acentuado na coleta pós-TCC (32,0 ms^2) (Figura 2C). Com relação ao balanço simpático, houve aumento no primeiro mês (7,1) em relação à coleta pré-TCC (3,2). Entretanto, nos meses seguintes, houve uma redução progressiva, até atingir os menores valores na coleta pós-TCC (0,9) (Figura 2D).



TCC = terapia cognitivo-comportamental.

Figura 2 – Parâmetros psicofisiológicos a cada mês: A) cortisol; B) frequência cardíaca; C) tônus vagal; D) balanço simpático

Discussão

O presente estudo fornece evidências sobre a eficácia da TCC para o tratamento de TEPT e sintomas dissociativos, visto que ocorreu um aumento nos escores das escalas que medem aspectos positivos e também das variáveis fisiológicas relacionadas a uma melhora da regulação emocional, associado a uma redução nos escores das escalas que medem aspectos negativos.

Houve redução dos sintomas dissociativos ao longo da psicoterapia, caracterizando ausência de dissociação. Esses dados sugerem uma relação entre o tratamento bem-sucedido do TEPT e a redução dos sintomas de dissociação, apesar de o protocolo não ter tido como foco o tratamento dos sintomas dissociativos. Tal resultado se contrapõe a estudos em que a TCC não foi eficaz para a redução dos sintomas dissociativos presentes em outros transtornos[25,26].

Ao longo da terapia, notou-se uma piora significativa no terceiro mês da TCC. Essa piora caracterizou-se por uma queda acentuada na pontuação de escalas que avaliam aspectos positivos e um aumento nas pontuações das escalas que avaliam aspectos negativos. Concomitantemente, houve súbito aumento dos níveis de cortisol, atingindo seu valor máximo durante todo o tratamento, além de redução do tônus vagal. Durante o terceiro mês de terapia, o paciente se mostrou extremamente ansioso com as exposições. Uma vez que não ocorreram eventos negativos significativos em sua vida durante o terceiro mês de terapia que justificassem essa piora, consideramos que essas alterações seriam uma resposta ao próprio tratamento, mostrando uma forte associação entre a avaliação subjetiva e as respostas fisiológicas avaliadas no estudo. No quarto mês, os resultados psicométricos apontaram para um padrão de resposta mais saudável em relação aos meses anteriores, indicando uma possível habituação do paciente ao tratamento. Da mesma forma, no quarto mês, os níveis de cortisol caíram acentuadamente, voltando a aumentar ao fim do tratamento, embora de modo menos abrupto. Podemos inferir que essa melhora indicada pelo cortisol e pelas escalas reflete a queda da ansiedade perante as exposições, o que foi corroborado pela observação clínica dos terapeutas. É interessante notar que as alterações nos níveis de cortisol parecem acompanhar as alterações na avaliação psicométrica do paciente ao longo do tratamento. Apesar de sutil, o aumento nos níveis de cortisol no final do tratamento pode ser considerado um indicativo da eficácia da TCC, uma vez que vai a favor da literatura, que sugere níveis diminuídos de cortisol em pacientes com TEPT[6] e em pacientes com dissociação após trauma[10].

Apesar do aumento progressivo da FC ao longo do tratamento, houve redução do balanço simpático e aumento do tônus vagal. O sistema nervoso autônomo, particularmente o ramo parassimpático, tem um papel tanto na recuperação cardíaca quanto na promoção de resposta mais adaptativa ao estresse[4,27]. O aumento da FC pode ser indicador da redução dos sintomas dissociativos ao fim da TCC, uma vez que a literatura mostra que a FC é menor em pacientes traumatizados com dissocia-

ção[28]. Tem sido proposto que indivíduos com maior tônus vagal possuem maior habilidade de se autotranquilizar em situações ameaçadoras, apresentam mais comportamento de engajamento social saudável[4,27] e menor probabilidade de desenvolver transtornos psicopatológicos[29]. A literatura sugere, ainda, que o aumento do tônus vagal e possivelmente a redução do balanço simpático seriam marcadores biológicos de flexibilidade fisiológica e, consequentemente, bons índices de saúde física e mental. No presente estudo, o tratamento com a TCC parece ter contribuído diretamente para a promoção dessas alterações.

O acompanhamento clínico através da administração de escalas e da observação clínica foi incrementado pelo registro das variações fisiológicas na evolução do quadro do paciente. Por serem medidas objetivas, tais parâmetros podem ser indicadores precisos do quadro clínico, sendo menos vulneráveis a vieses[30]. A estabilização do tratamento farmacológico ao longo da TCC foi fundamental para a comparação dos parâmetros fisiológicos ao longo de todo o estudo. A associação das medidas fisiológicas aos indicadores psicométricos tradicionais, portanto, parece ser uma estratégia útil para o estudo da eficácia de tratamentos terapêuticos.

Conclusão

A associação da TCC ao tratamento farmacológico potencializou a remissão dos sintomas de TEPT e dos sintomas dissociativos do paciente, que não havia apresentado melhora sob tratamento unicamente farmacológico realizado durante 18 meses (paciente considerado resistente à medicação). Apesar dos evidentes ganhos terapêuticos, talvez a resposta ao tratamento não tenha sido ainda mais positiva devido ao foco exclusivo no quadro de estresse pós-traumático e à duração limitada do tratamento, de 16 semanas. Acreditamos que uma proposta de TCC que trate outros aspectos além do TEPT e que não tenha uma duração predeterminada poderia maximizar as respostas do paciente. Contudo, a TCC se mostrou eficaz e promoveu alterações psicofisiológicas importantes, as quais se refletiram em mudanças cognitivas e comportamentais, confirmando a presença de aspectos emocionais, cognitivos, comportamentais e fisiológicos no processamento do medo em pacientes com transtornos de ansiedade.

Esta pesquisa possui as limitações inerentes a um estudo de caso. A fim de melhor compreender o impacto da TCC sobre a fisiologia do TEPT, é imprescindível aumentar a amostra de pacientes, para que seja feito um estudo controlado randomizado.

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Research report

CBT for pharmacotherapy non-remitters—a systematic review of a next-step strategy

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ABSTRACT

Background: Non-remission rates to pharmacotherapy for anxiety disorders are related to higher relapse rates, decreased quality of life and greater functional impairment. Here we sought to investigate the efficacy of cognitive-behavior therapy (CBT) as a next-step strategy in the treatment of patients with anxiety disorders who did not remit after a pharmacological intervention.
Method: We carried out a systematic review in the ISI, Pubmed and PsycINFO/PsychLit databases. Studies that did not use CBT and that did not focus on resistance to drug therapy were excluded. We considered resistant patients who failed to respond (did not fully remit) to an adequate trial of pharmacotherapy and still exhibited residual symptoms of anxiety disorder.
Results: We identified 603 references in our survey, of which 17 were included: eight were on OCD, five on panic disorder, and four on PTSD. No studies were found on social anxiety disorder and generalized anxiety disorder. We observed a lack of standardization of terminology and of definitions of resistance, which makes comparison of results difficult. Finally, all of the identified studies showed benefits from the addition of CBT as a next-step strategy.
Limitations: A limited number of randomized controlled studies were found.
Conclusions: CBT seems to be a promising next-step strategy for patients with anxiety disorders who did not remit with drug-based therapies. However, further clinical trials with strong methodological designs are needed to definitely establish its efficacy in this population.

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1. Introduction

There is consistent evidence about the efficacy of cognitive-behavior therapy (CBT) and pharmacotherapy in the treatment of anxiety disorders. CBT is considered as a first-line treatment for some anxiety disorders. In posttraumatic stress disorder (PTSD), experts' guidelines recommend CBT or drug therapy as the first choice of treatment, which are also effective for the co-morbid depression and anxiety disorders. It has been shown that the addition of CBT to the treatment of patients with resistance to drug therapy leads to better outcomes than standard pharmacological treatment alone (Foa, 2009). For obsessive–compulsive disorder (OCD), the most effective first-line treatments are the selective serotonin reuptake inhibitors (SSRIs) or CBT (particularly exposure and response prevention) (Fenske and Schwenk, 2009; Koran, 2007). In panic disorder as well, there is strong evidence of the efficacy of drug therapy and CBT as initial treatments. However, the available results are not enough to

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recommend combined treatments (drug therapy + CBT) as superior to monotherapy or an intervention as superior to another (Stein, 2009).

CBT has a number of potential gains over pharmacotherapy in the treatment of anxiety disorders: fewer adverse effects, smaller relapse rates (Etten and Taylor, 1998), greater adhesion rate (Mitte, 2005), and greater acceptability (Hofmann, 1998). Pharmacotherapy has such disadvantages as more side effects and rates of relapse with discontinued medication (Simpson, Gorfinkle and Liebowitz, 1999). Nevertheless, in practice CBT is much less used, especially because of the limited availability of specialized practitioners. Moreover, pharmacological treatments have received much more attention from the marketing than psychosocial interventions such as CBT have (Insel, 2009). These reasons account for the fact that drug therapy is now viewed by most clinicians—for bad or for good—as the first choice in the treatment of anxiety disorders.

Non-remission of anxiety disorders to pharmacotherapy or to psychotherapy has turned out to be a crucial issue. The presence of residual symptoms is known to be associated with higher relapse rates, decreased quality of life and greater functional impairment (Fava and Tomba, 2009). It is, therefore, increasingly important to think of therapeutic alternatives for patients with anxiety disorders who do not remit after pharmacological treatment. The purpose of the present article is to find and review the available evidence of the efficacy of CBT as a next-step strategy in the treatment of patients who failed to improve significantly despite drug therapy. As far as we know, this is the first systematic review on the subject.

2. Methods

2.1. Search methods

Electronic searches were performed in the ISI, PubMed and PsycINFO/PsychLit databases, including all languages and all years, until December 08, 2009. The following terms were used:

ISI (advanced search):

- TS = ("behavi* therapy" OR "cognitive therapy" OR "cognitive behavio* therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure session*" OR CBT OR "cognitive reest*" OR "anxiety manage*" OR flooding OR "systematic desens*")
- TS = (anxiety OR phob* OR panic OR OCD OR obsess* OR PTSD OR "stress disorder*" OR GAD)
- TS = (resist* OR refract* OR non-respons* OR non-respond* OR nonrespond* OR augment* OR "sequential treatment" OR "addition of CBT" OR "partial respond*" OR "crossover treatment*" OR "second-line treatment*" OR "second-line recommendation*" OR "fail to respond" OR "second level option*" OR "fail* to respond*" OR "fail* to fully respond*" OR "prior medication trial" OR non-remit* OR nonremit* OR "remain* sympt*")

All of the 3 citation databases were activated [Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) and Arts & Humanities Citation Index (A&HCI)], and we restricted the search criteria in order to include only "articles" and "notes".

PUBMED (advanced search) and PsycINFO/PsychLit:

- ("behavi* therapy" OR "cognitive therapy" OR "cognitive behavio* therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure session*" OR CBT OR "cognitive reest*" OR "anxiety manage*" OR flooding OR "systematic desens*")
- (anxiety OR phob* OR panic OR OCD OR obsess* OR PTSD OR "stress disorder*" OR GAD)
- (resist* OR refract* OR non-respons* OR non-respond* OR nonrespond* OR augment* OR "sequential treatment" OR "addition of CBT" OR "partial respond*" OR "crossover treatment*" OR "second-line treatment*" OR "second-line recommendation*" OR "fail to respond" OR "second level option*" OR "fail* to respond*" OR "fail* to fully respond*" OR "prior medication trial" OR non-remit* OR nonremit* OR "remain* sympt*")

The terms were searched directly in advanced search (All Fields) and the results of each individual search were combined. We used exactly the same strategy in PUBMED and PsycINFO/PsychLit.

Besides the searches in the online databases, manual searches were performed in the reference list of the articles reviewed and times cited lists (Base ISI). Experts on the field were consulted too for additional existing studies that might have not been identified.

2.2. Inclusion criteria

We included only "articles" and "notes"; review articles, book chapters and dissertations were excluded. Studies that used psychotherapeutic techniques other than CBT were excluded. We focused on CBT because it is one of the most extensively researched forms of psychotherapy (Butler et al., 2006) being the most investigated psychotherapeutic intervention for anxiety disorder. We included all types of traditional CBT, as can be seen by the terms used in our search strategy (i.e. cognitive therapy, behavior therapy, exposure therapy, flooding, anxiety managing, cognitive restructuring, cognitive behavior therapy). We excluded studies that employed the term "resistance" with a different meaning (i.e. that did not focus on resistance to pharmacological treatment), because we wanted to have a homogeneous sample. We also included studies that investigated patients with co-morbid psychopathological conditions. Case reports with 10 or fewer cases were excluded, as they represent a major methodological limitation according to the criteria for case series set by Pincus et al. (1993). Studies of CBT as a next-step strategy for pharmacological treatment resistant patients were found only for the three anxiety disorders, namely PTSD, OCD, and panic disorder. Fig. 1 shows the study selection process. Table 1 shows the selected studies.

3. Results

Our search found 603 papers, which were reviewed to identify our final sample of 17 articles (see Fig. 1). Of the selected studies, eight were randomized controlled trials, one was an open controlled trial, six were open, non-controlled trials, two were naturalistic trials, and one was a case series. The results from the selected studies were sorted by primary disorder and all diagnoses were defined according to the

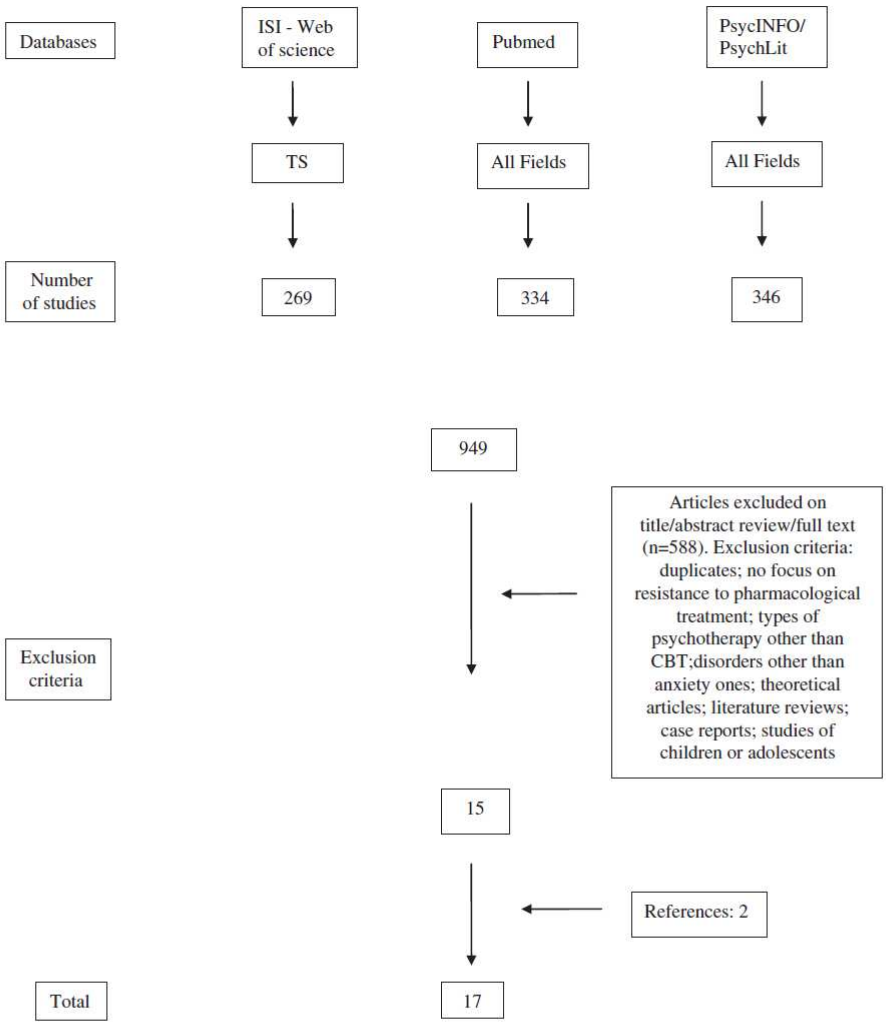

Fig. 1. Summary of the study selection process.

diagnostic criteria of the *DSM-IV*, with the exception of a study by Pollack et al. (1994), in which the criteria were defined by the *DSM-III*. All of the identified studies reported the efficacy of CBT as a next-step strategy for patients with residual symptoms, despite pharmacological treatment refractory to initial pharmacotherapy.

3.1. Studies with post-traumatic stress disorder (PTSD)

We identified four randomized controlled studies and they all indicated that the addition of CBT to pharmacotherapy for PTSD and related symptoms was associated with further clinical improvement, with significantly lower scores at the assessment with the measures used. All selected studies were conducted with Cambodian or Vietnamese refugees and, thus, CBT protocols had to be culturally adapted. The techniques included information about a cognitive-behavioral model of PTSD and panic disorder, muscle relaxation and diaphragmatic breathing, cognitive restructuring, and interoceptive and imaginary exposure.

Hinton et al. (2005) randomized 40 patients with PTSD and comorbid neck-focused and orthostasis-cued panic attacks refractory to initial pharmacotherapy for initial and delayed CBT treatment. Resistance was defined as the presence of PTSD despite receiving supportive counseling and an adequate trial of an SSRI (selective serotonin reuptake inhibitor) (i.e. at least 1 year on the maximally tolerated dose). Twelve individual weekly CBT sessions were conducted and all patients continued supportive psychotherapeutic and pharmacological treatment (an SSRI combined with the benzodiazepine clonazepam). The immediate treatment group showed significantly lower scores, with large effect sizes for all outcome measures. The severity of

Table 1
Description of the included reviews.

Study	n	Disorder	Study design	Criteria for resistance	CBT Protocol	Main outcome measures and results	
Hinton et al., 2005	40	PTSD	Randomized controlled	PTSD, despite supportive counseling and SSRI for at least 1 year at the maximum tolerated dose	12 weeks	Lower scores on the ASI, CAPS and SCL scales. 60% patients in remission	
Hinton et al., 2009	24	PTSD	Randomized controlled	PTSD, despite supportive counseling and an adequate trial of an SSRI at the maximally tolerated dose for at least 6 months	12 weekly sessions	Reduction in the CAPS score and in one physiologic measure. 60% in remission	
Hinton et al., 2004	12	PTSD	Randomized controlled	PTSD, despite at least 1 year with an adequate dose of an SSRI and supportive counseling	11 weekly sessions	Significant main effects for time occurred for ASI, HTQ and HSCL	
Otto et al., 2003	10	PTSD	Randomized controlled	Failure to respond adequately to clonazepam treatment combined with an adequate dose of SSRI other than sertraline	10 sessions	Reduction in CAPS, HSCL and ASI scores. Medium to large effect sizes for PTSD and associated symptoms	
Simon et al., 2009	46	PD	Randomized controlled	Failure to meet remission criteria (no panic attacks for at least 1 week and a CGI-S score ≥ one)	12 weekly sessions	Reduction on the PDSS, CGI-S, HARS and ASI scores. There were no significant differences between the "medication optimization" and CBT groups. 10% in remission	
Heldt et al., 2006b	63	PD	Open non-controlled	Residual symptoms of PD, despite an adequate dose of antidepressants in the previous 4 months	CBGT for 12 weeks	Reduction in CGI-S, PI and HAM-A scores. 81% had no panic attacks and 64% in remission	
Heldt et al., 2006a	32	PD	Open non-controlled	Residual symptoms of PD, despite an adequate dose of an antidepressant in the previous 4 months	CBGT for 12 sessions along 4 months	Decrease in CGI and HAM-A scores. Clinical improvement in 50% of patients for agoraphobia, 47% for anticipatory anxiety, and 38% for HAM-A anxiety symptoms. 75% had no regular panic attacks and 44% patients in remission	
Pollack et al., 1994	15	PD	Open non-controlled	Residual symptoms of PD, despite at least 3 months of adequate pharmacotherapy and CGI score ≥ 3	CBGT for 12 weeks	Reduction in CGI-S score. 47% panic-free patients and 53% panic-free at follow-up. 40% in remission	
Otto et al., 1999	24	PD	Open clinical case series	CGI ≥ 4 and at least 2 months of treatment with any tricyclic antidepressant at the prescribed dose	CBGT for 12 sessions	Decrease in CGI-S and PDSS scores. 60% of the 'adequately-treated' patients and 43% of the 'inadequately-treated' ones in remission	
Tenneij et al., 2005	96	OCD	Randomized controlled	Response to 3 months of pharmacotherapy (reduction of at least 25% in Y-BOCS)	Cognitive therapy for 6 months	Reduction in Y-BOCS score, but not for the HAM-A. Significant increase in anxiety symptoms	
Simpson et al., 2008	94	OCD	Randomized controlled	OCD for at least 1 year, Y-BOCS total score ≥ 16 and some improvement with an SSRI administered for at least 12 weeks before CBT	17 sessions of each modality of CBT, twice a week	Improvements in Y-BOCS and HAM-A scores. 74% achieved responder status. 33% achieved minimal symptoms	
Tolin et al., 2007	41	OCD	Randomized controlled	Chronic symptoms of OCD (at least for 1 year) and at least moderate severity (total Y-BOCS score ≥ 16, along with a CGI score ≥ 4)	15 sessions, twice a week	Decrease in the Y-BOCS and CGI-S scores. 65% of the patients were considered to be responders	
Tundo et al., 2007	21	OCD	Naturalistic	Y-BOCS score ≥ 16, despite at least one adequate SSRI	4 sessions per month during 4 months	19% reduction in Y-BOCS score, and 16% in CGI-S	Significant improvements in Y-BOCS and CGI-S. Increased awareness of OCD symptoms and improvement in the general functioning
Tundo et al. 2009	24	OCD	Naturalistic	Y-BOCS score ≥ 16	12 months	67% was rated as "much improved" or "very much improved" (CGI-S) and 25% had a Y-BOCS total score of ≤ 16	
Tolin et al., 2004	15	OCD	Open controlled	At least moderate OCD (Y-BOCS score ≥ 16), symptoms duration for more than 1 year, and inadequate response to at least two adequate trials with an SSRI	15 sessions, from 1 to 5 times a week	39.5% decrease in Y-BOCS score and 66.6% of patients improved on the CGI	

Table 1 *(continued)*

Study	*n*	Disorder	Study design	Criteria for resistance	CBT Protocol	Main outcome measures and results
Kampman et al., 2002	9	OCD	Open non-controlled	Y-BOCS reduction of less than 25%	12 sessions	41% reduction rate in Y-BOCS score, 32.6% symptom reduction on the HDRS and 43% for the HARS
Simpson et al., 1999	5	OCD	Open non-controlled	Y-BOCS score ≥ 16, despite an adequate dose of an SSRI for at least 12 weeks	17 sessions, 2 times a week	49% mean decrease in Y-BOCS score. Improvement on HAM-D and CGI-S scores

PD = panic disorder; CBGT = cognitive behavioral group therapy; CGI-S = Clinical Global Impressions-Severity; PDSS = Panic Disorder Severity Scale; OCD = obsessive–compulsive disorder; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; SSRI = selective serotonin reuptake inhibitor; PTSD = posttraumatic stress disorder; ASI = Anxiety Sensitivity Index; CAPS = Clinician-Administered PTSD Scale; SCL = Symptom Checklist 90-R subscales; HTQ = Harvard Trauma Questionnaire; HSCL = Hopkins Symptom Checklist; SCL = Symptom Checklist-90-R; HAM-A = Hamilton Anxiety; PI = Panic Inventory; PDSS = Panic Disorder Severity Scale; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale.

both types of panic and flashbacks improved across the treatment. Twelve patients (60%) of the immediate treatment group and 10 (50%) patients of the delayed treatment group did not meet the criteria for PTSD anymore. No difference was found across the groups in the outcome measures at the last evaluation (after the waiting group received CBT), and at the 12-week follow-up.

In a recent study, which included psychophysiological measures evaluation, 24 Cambodian refugees with PTSD and co-morbid orthostatic panic attacks were randomized for initial and delayed CBT treatment [Hinton et al. (2009)]. Resistance was defined as the presence of PTSD symptoms despite supportive counseling and maximally tolerated dosage of an SSRI for at least 6 months. The CBT protocol also consisted of 12 weekly sessions and all patients continued receiving supportive psychotherapy and medication (SSRI and/or benzodiazepine) during the study. Patients randomized for immediate CBT had significant improvements in all psychometric measures and in one physiologic measure (systolic blood pressure response to orthostasis). Patients in the waiting group showed improvements too after receiving CBT.

In a small study by Hinton et al. (2004), 12 traumatized Vietnamese refugees with PTSD and panic attacks were randomized for initial and delayed culturally adapted CBT treatment. Resistance was defined as the presence of PTSD despite treatment with an SSRI at an adequate dose for at least 1 year and supportive counseling. Eleven weekly individual sessions of CBT focusing on PTSD and comorbid panic attacks were held and all patients remained on the usual medications (for the most part, a combination of one SSRI, one benzodiazepine, and gabapentin). Significant main effects for time occurred for all psychometric outcome measures.

Otto et al. (2003), in a pilot study, randomized 10 Cambodian female refugees for treatment with either sertraline alone or combined sertraline plus 10 sessions of CBT. Pharmacotherapy-refractory or nonresponsive patients were defined by the failure to respond adequately to clonazepam treatment combined with an adequate dose of an SSRI other than sertraline. Combined treatment over SSRI-treatment alone was associated with better changes in psychometric measures and provided additional gains in the range of medium to large effect sizes for PTSD and associated symptoms.

3.2. Studies with panic disorder

We identified one controlled randomized study, three open studies and one case series evaluating the efficacy of CBT as an additional treatment for patients with panic disorder who were medication-resistant. All five studies, which included techniques such as providing information on the cognitive-behavioral model of panic disorder, diaphragmatic breathing, muscle relaxation, cognitive restructuring, interoceptive exposure, in vivo exposure, situational exposure and relapse prevention, consistently supported the efficacy of CBT.

Simon et al. (2009) had 46 patients who failed to meet remission criteria randomized to a 24-week treatment comprising three stages: (a) a 6-week lead-in with open-label sertraline flexibly dosed up to 100 mg (or an equivalent dosage of escitalopram) to prospectively define treatment refractoriness ($n = 39$); (b) patients who did not meet remission criteria by the sixth week were randomized in a double-blind fashion for 6 weeks of increased-dose SSRI versus continued SSRI plus placebo ($n = 24$); and (c) patients were randomized for 12 weeks to added CBT or "medication optimization" with SSRI and clonazepam ($n = 19$). Twelve weekly 50-minute individual CBT sessions were held for a total of 12 weeks. Remission status was defined as no panic attacks for at least 1 week and a Clinical Global Impression-Severity (CGI-S) (Guy, 1976) score of 1 or 2. In the first stage, 8 (20.5%) of the patients remitted. In the second stage, increasing the SSRI dose did not result in greater improvement or remission rates. In the third stage, both augmentation with CBT and "medication optimization" were associated with significant reduction in panic disorder and associated symptoms. However, there was no significant difference between groups. Only one patient in each group achieved remission and there was no significant difference between the groups, and the effect sizes were all small. At the naturalistic 3-month follow-up, 6 (35%) of the 17 patients remitted, 3 from the CBT group and 3 from the "medication optimization" group.

In the open trial conducted by Heldt et al. (2006), 63 patients with panic disorder and agoraphobia who were nonresponders to pharmacotherapy received 12 sessions of group CBT along 4 months. Thirty-two patients took part in a previous study (Heldt et al, 2003). All patients were using medication for panic disorder during CBT. The patients included were those with residual symptoms of panic disorder (panic attacks, anticipatory anxiety and phobic avoidance) despite a stable dosage of medication for at least 4 months and CGI-S score ≥ 3. Improvement was defined by at least 50% reduction in the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959), agoraphobia, and anticipatory anxiety scales. Remission was defined as absence of panic attacks and CGI-S score ≤ 2 in

the last 2 months of follow-up. After CBT, there was a significant reduction in symptoms for all measures (frequency of panic attacks, agoraphobia and anticipatory anxiety), with maintenance of gains at 1 year follow-up. Fully 51 patients (81%) had no panic attacks and 40 (64%) met remission criteria (no panic attacks and CGI-S score ≤2). Twenty-eight patients (43%) were not in psychiatric treatment during the follow-up period. Roughly two-thirds of the patients remitted in the follow-up period and the gains were maintained despite medication reductions.

Heldt et al. (2006) found that brief cognitive behavior group therapy was effective in improving panic disorder patients' quality of life. Thirty-two patients who were pharmacotherapy-refractory were treated with 12 sessions of CBT during 4 months. Patients considered refractory had residual symptoms of panic disorder despite a previous pharmacological treatment with an adequate dose of an antidepressant lasting at least 4 months. All patients had been on pharmacological treatment for a long period (mean = 4 years). Improvement was defined as a reduction ≥50% on the PI (Panic Inventory) and HAM-A. Remission was defined as absence of panic attacks and CGI ≤2. Significant improvements were found in all domains of quality of life, which was associated with decreases in general and anticipatory anxiety and in agoraphobic avoidance. Symptoms of anticipatory anxiety had a more significant impact on the quality of life of the patients than the panic episodes themselves. At the end of the treatment, clinical improvement occurred in 16 (50%) patients for agoraphobia, 15 (47%) for anticipatory anxiety, and 12 (38%) for HAM-A anxiety symptoms. Twenty-four patients (75%) had no regular panic attacks and 14 (44%) patients remitted (CGI-S score ≤2 and no panic attack).

Pollack et al. (1994) reported that significant benefits resulted from the addition of CBT to the treatment of patients with panic disorder and agoraphobia who presented incomplete response to pharmacological treatment. Fifteen patients (eight were considered relatively refractory since they received an inadequate dose of medication and seven were deemed refractory because they remained symptomatic despite having received an adequate dose) were treated with cognitive behavior group therapy during 12 weeks. Incomplete response to the pharmacological treatment was defined by the presence, despite at least 3 months of pharmacological treatment, of residual symptoms of panic attacks that were severe enough to interfere with functioning. The study included patients without panic attacks (with CGI-S score ≥ 3), patients who did not receive an adequate dose of medication and patients who received an adequate dose of medication (in accordance with established doses) There was a significant reduction in the CGI-S, in the frequency of panic attacks, increase in the number of patients without panic attacks (from 5 to 7), and attainment of remission in 6 patients (CGI-S ≤ 2). The gains were maintained at the 2 month follow-up.

In the case series reported by Otto et al. (1999), patients refractory to an adequate dose of medication were selected as 'adequately-treated' nonresponders ($n = 10$) and 'inadequately-treated' nonresponders ($n = 14$), i.e. patients refractory to an inadequate dose of medication. The criteria for 'adequately-treated' were: at least 2 months of treatment with any tricyclic antidepressant at a dose ≥150 mg/day, fluoxetine at a dose ≥20 mg/day, sertraline at a dose ≥50 mg/day, paroxetine ≥40 mg/day, nefazadone at a dose ≥300 mg/day, phenelzine at a dose ≥45 mg/day, alprazolam ≥4 mg/day or clonazepam at a dose ≥2 mg/day. Many patients were taking more than one medication. The criteria for resistance also included current CGI-S ≥ 4. Twelve sessions of cognitive behavior group therapy were held. Both groups showed significant decrease in CGI-S and PDSS (Panic Severity Scale) scores. Sixty percent of the 'adequately-treated' patients and 43% of the 'inadequately-treated' ones met remission criteria (a CGI-S score of 1 or 2). Effect sizes tended to be greater for 'adequately-treated' patients, although *t*-test comparisons between improvements in each group did not show any significant differences.

3.3. Studies with obsessive-compulsive disorder (OCD)

We found three randomized controlled trials, three non-controlled open studies and two naturalistic trials; all of them reported gains from the addition of CBT to the treatment of patients with OCD which exhibited residual symptoms despite pharmacological treatment. In all these trials, CBT treatment focused on exposure and response prevention.

Tenneiji et al. (2005) reported that CBT brought additional benefits to patients who responded to drug therapy. Ninety-six patients who responded to 3 months of pharmacotherapy (reduction of at least 25% in Y-BOCS) were randomized to 18 sessions of additional CBT or to continuation with drug therapy alone for 6 months. All patients were treated with fixed doses of 300 mg/day of venlafaxine or 60 mg/day of paroxetine for 12 weeks. Patients with HAM-D (Hamilton Depression Rating Scale) (Hamilton, 1960) score > 16 were excluded. Remission was defined as a total Y-BOCS (Goodman et al., 1989) score ≤ 8. Patients in the medication alone group were submitted, 6 months later, to CBT for another 6 months and did not present a significant decline in the Y-BOCS score. Patients who received additional CBT obtained better results in the Y-BOCS and attained remission more frequently than those which remained on medication only. The results suggest that the outcomes are better when CBT is added immediately after drug treatment.

In a controlled randomized trial, Simpson et al. (2008) compared CBT with two other treatment modalities—exposure and response prevention ($n = 48$) and training of stress management skills ($n = 46$)—as strategies to enhance the effects of pharmacological treatment with SSRI in OCD patients. Patients had OCD for at least 1 year, Y-BOCS total score was ≥16, and some improvement had to be observed with an SSRI administered at an adequate dose for at least 12 weeks before the beginning of the study. Other medications could be used as long as the SSRI had been at a stable level for at least 4 weeks and remained so along the study period. A total of 17 sessions of each CBT modality were held twice a week. The exposure and response prevention group obtained a significantly greater reduction in the obsessive–compulsive symptoms and in the Y-BOCS, Obsessive-Compulsive Inventory and in the HAM-A scores. There was no difference between the groups in the other measures: HAM-D, Social Adjustment Scale and Quality of Life Enjoyment and Satisfaction Questionnaire. A significantly larger number of patients who received exposure and response prevention remained with residual symptoms.

Tolin et al. (2007) randomized 41 patients for self- or therapist-administered exposure and response prevention. All patients were currently using or had already received an adequate trial of an SSRI medication. The determination of what constitutes an adequate medication trial was based on published guidelines and consultation with OCD researchers. In order to be adequate, the medication had to be maintained at the indicated dose for OCD for at least 10 weeks. Other inclusion criteria were: having chronic symptoms of OCD (at least for 1 year) and at least moderate severity, defined as a total Y-BOCS score ≥16, along with a CGI score ≥4 ("moderately ill"). Therapist-administered exposure and response prevention comprised 15 sessions twice a week for 7 weeks and a half. In self-administered exposure and response prevention, patients were told to follow the instructions in a book for 6 weeks. In the cases with prior medication trials, as there were no pre-medication records, the patients were asked to report if they had subjectively experienced no more than a minimum effect of medications. Patients were instructed not to make changes to the medication during treatment and at the 1-, 3- and 6-month follow-ups. There was a significant statistical and clinical reduction in symptoms for all patients. However, among patients who had received therapist-administered exposure and response prevention there was a noticeably larger reduction of the OCD symptoms and a much higher proportion of responders. After treatment, 65% of the patients who received therapist-administered exposure and response prevention were considered to be responders while only 25% of those who received self-administered exposure and response prevention were considered so. At the final follow-up, these proportions were 50% and 25%, respectively.

The naturalistic trial by Tundo et al. (2007) provides further evidence for the effectiveness of CBT as an additional treatment for real-world, medication-resistant nonresponder OCD patients. Patients who had OCD for at least 1 year and did not respond to at least one adequate SSRI trial were selected. Patients were considered nonresponders at the end of the pharmacological treatment if they still met the criteria for OCD and had Y-BOCS total score ≥16. Twenty-one patients completed the treatment with CBT, which consisted of four sessions per month during the first 4 months and then continued with one to four sessions per month. The length of CBT was not established and the pharmacological treatment was not modified during CBT. Statistically significant improvements in Y-BOCS and CGI-S scores were found after the beginning of CBT and at the 1-year follow-up. Four patients had Y-BOCS scores ≤16. There was a slight reduction in OCD symptoms and improvements in patients' insight and general functioning.

Another naturalistic trial by Tundo et al. (2009) investigated the effectiveness of 12 months of CBT using exposure and ritual prevention in association with serotonin reuptake inhibitor (SRI) for pharmacotherapy treatment-resistant patients. Patients who have had OCD for at the least 1 year were included and were nonresponders (Y-BOCS ≥ 16) to al least one adequate trial of SRI. Pharmacotherapy treatment was not changed during the trial period. Statistically significant improvements in Y-BOCS and CGI-S scores were found at follow-up. Patients were considered responders if they were rated "much improved" of "very much improved" on the CGI-S. From 24 patients who completed the treatment, 16 (67%) were rated as "much improved" or "very much improved" and 6 (25%) had a Y-BOCS total score of ≤16.

In another study (Tolin et al., 2004), 15 patients who presented inadequate response to pharmacotherapy at adequate dose, after remaining 1 month in waiting list, received 15 sessions of CBT, from 1 to 5 times a week. The patients had at least moderate OCD (as measured by the Y-BOCS scores ≥ 16), symptoms duration ≥ 1 year, and at least two adequate trials with an SSRI. The determination of adequate medication was based on published guidelines and guidance from OCD researchers. The patients had several comorbidities and were in general characterized by poor insight and putting low effort into CBT, factors that are predictors of poor response. OCD severity (as measured by Y-BOCS) decreased significantly after CBT and the gains were maintained at the 6-month follow-up. One participant did not participate in the 1-month follow-up but returned for the 3-month one. Another patient did not participate in the 3-month follow-up but returned for the 6-month one.

Kampman et al. (2002) investigated the effects of adding CBT to an ongoing treatment with fluoxetine in patients with OCD who were nonresponders to fluoxetine alone. Nine females with OCD symptoms for at least 1 year and Y-BOCS score of at least 16 (or 10 for patients with obsessions only) completed the study. Patients who had previously used an adequate dosage of an SSRI or been submitted to CBT were excluded. The patients were submitted to a 2–6 week waiting period to wash out the usual medications before beginning the study. Treatment was divided in two phases: (a) patients received fluoxetine 60 mg/day for 12 weeks and (b) patients who had a Y-BOCS reduction of less than 25% and were classified as nonresponders received 12 sessions of CBT in addition to the ongoing treatment with fluoxetine. After CBT, OCD symptoms were reduced in 7 of the 9 patients. There was a reduction in OCD symptoms (Y-BOCS) of 8.5% in the first phase and 41% in the second. The general anxiety and depression symptoms diminished as well. There were statistically significant differences between Y-BOCS scores in the first and in the second phases of the treatment, showing a decrease in OCD symptoms in both phases and in general anxiety in phase two.

Simpson et al. (1999) also found benefits from the addition of CBT in 5 patients with residual symptoms (Y-BOCS score of ≥16) despite an adequate trial with an SSRI for at least 12 weeks. Besides the medication, 5 patients completed 17 sessions of CBT twice weekly. The patients had a diagnosis of OCD for at least 1 year and had experienced some improvement (verbal self-report) with adequate dosage and duration of an SSRI treatment. Adequate SSRI dosage was defined as: clomipramine, ≥225 mg/day; fluoxetine, ≥60 mg/day; paroxetine, ≥60 mg/day; sertraline, ≥200 mg/day; and fluvoxamine, 250 mg/day. Among other reasons, patients were excluded if they had received CBT with exposure and response prevention for OCD and were using a psychoactive drug other than an SSRI. Blood drug levels were also checked before and after CBT in order to ensure the maintenance of the prescribed medication. There was no change to blood drug levels in most patients during exposure and response prevention, which suggests the link between improvements and therapy. No patient stopped medication. Follow-ups were performed at 1, 2, 3, 4, 5, 6, 9 and

12 months. There was a significant benefit after exposure and response prevention in all psycometric measures used.

4. Discussion

4.1. Findings

The most important result of this systematic review is that all studies suggest the efficacy of CBT as a next-step strategy for treating patients with anxiety symptoms who do not remit with pharmacological therapy only. However, of the 17 studies selected here only 8 are randomized controlled trials and all had small samples, which is a significant limitation in the field. Thus, performing further randomized controlled trials in resistant patients would be important to provide further evidence of the efficacy of CBT for this population. In PTSD, differently from other disorders, the quality of available evidence is stronger: despite the limited number of conducted studies, all four identified here were randomized controlled trials.

It is important to note that among all anxiety disorders, we could only found studies about CBT as a next-step strategy for pharmacotherapy resistant for OCD ($n=8$), panic disorder ($n=5$), and PTSD ($n=4$). Despite the high prevalence, morbidity and treatment-resistance rates of anxiety disorders like social anxiety disorder and generalized anxiety disorder (GAD), there is a lack of studies in these fields. Actually, there is evidence that this scarcity of studies in social anxiety and GAD is not confined to the theme of next-step strategy in pharmacological treatment resistance. Concerning social anxiety disorder, Crippa (2009) showed a smaller number of studies than for other anxiety disorders. Possible causes include the little attention from the media to social anxiety disorder and the fact that many patients remain undiagnosed and under-treated. The lack of studies in the fields of social anxiety disorder and GAD was also noted in the bibliometric analysis by Boschen et al. (2007), in which the anxiety disorders with the greatest number of publications in the 1980–2005 period were PTSD, panic disorder and OCD. The growing number of publications in PTSD is dominant in this period, this being the anxiety disorder with the highest number of publications since 1980. Boschen et al. (2007) showed that in the 2005–2015 period, the publications on anxiety disorders will continue to be dominated by PTSD, panic disorder and OCD.

4.2. Quality of included studies

We found a lack of standardization in treatment protocols, terminology and definitions used in the reviewed studies. Each study follows a particular CBT protocol, with marked differences regarding, for instance, the length of treatment, CBT techniques and treatment format (individual or group). The terminology for describing non-remission or resistance to pharmacotherapy varied widely too, with use of such different names as resistance, refractory, "not respond", "incompletely responsive", nonresponder and "failure to respond".

Some studies did not define remission at all and failed to assess it as a potential improvement measure [Hinton et al. (2009), Hinton et al. (2004), (Otto et al. 2003), Simpson et al. (2008), Tolin et al. (2007), Tundo et al. (2007), Tolin et al. (2004), Kampman et al. (2002)], while others defined remission through changes to the psychometric measures and absence of clinical symptoms [Heldt et al. (2006), Pollack et al. (1994), Simon et al. (2009), Tundo et al (2007), Hinton et al. (2005) & Heldt et al. (2006)]. The studies also varied regarding the number of patients who achieved remission. In Heldt et al. (2006), 40 (64%) patients presented criteria for remission. In Otto et al. (1999), 60% of the 'adequately-treated' patients and 43% of the 'inadequately-treated' patients presented remission. In Tundo et al (2007), only 4 of the 21 patients with TOC remitted. In Hinton et al. (2005), 12 (60%) patients with PTSD remitted. It should be noted that the criteria for remission were more clearly defined and the remission rates were higher for studies in panic disorder. Therefore, even first-line treatments such as pharmacotherapy and CBT were found to face limitations when the percentage of patients who achieves total remission is considered. Our study highlights the importance of creating a standardized operational definition of resistance, since the diversity of definitions of resistance severely limits the ecological validity of the findings.

We noticed that CBT for PTSD had to be adapted to the cross-cultural characteristics of the sample. All of the patients with PTSD were Cambodian or Vietnamese refugees, with high levels of resistance to pharmacotherapy and severe, complex symptoms due to the several repeated, prolonged traumas. We highlight the importance of the positive results obtained with this sample of patients with specific cultural features in which the protocols were culturally adapted and showed good results.

Other limitations are the reduced number of studies with follow-up evaluation data as well as their relatively brief duration (2–12 months). Out of the 16 selected studies, only eight showed follow-up data: one in PTSD with a 3-month follow-up (Hinton et al., 2005); three in panic disorder, one of which with a 1-year follow-up (Heldt et al, 2006), another with 3-month follow-up (Simon et al., 2009) and another with 2-month follow-up (Pollack et al., 1994); and finally four studies in OCD, of which one had a 1-year follow-up (Tundo et al, 2007), two with 1-, 3- and 6-month follow-up (Tolin et al., 2004 & Tolin et al., 2007), and one with 1-, 2- 3-, 4-, 5-, 6-, 9- and 12-month follow-up (Simpson et al., 1999).

Another methodological issue of the reviewed studies concerns the multiple co-morbidities found. Most of the patients had a clinically relevant secondary diagnosis, for the most part depression and other anxiety disorders, which not only hindered patient response to CBT intervention for a given anxiety disorder but also made the analysis of the results and the comparisons across group more complex. Moreover, anxiety disorders vary widely in their presentations and outcomes obtained with CBT. It is important to emphasize the positive results found in all trials on the efficacy of CBT in patients with residual symptoms and multiple co-morbidities, which represents patients typically found in treatment settings.

Studies also differ concerning the variability of results and the outcome measures used. Some studies used very specific measures and other more global measures, but none used blind assessment of outcome. Furthermore, all studies included psychometric evaluations, but only one trial with

PTSD patients (Hinton et al., 2009) included psychophysiological measures (systolic blood pressure, diastolic blood pressure and heart rate) as additional parameters for assessment of treatment outcomes. The use of such measures, less prone to the kind of bias often associated with the use of self-reporting scales, such as over- or under-reporting of symptoms, is growing, with potentially relevant implications for the development of more individualized and successful treatment modalities.

4.3. Limitations

Some limitations of the present review include the choice of only two electronic databases, albeit the most important ones, and the possibility of overestimation of positive response about the efficacy of CBT, as there is a trend of omitting studies reporting negative results. Moreover, inasmuch as this is a qualitative systematic review, it has some inherent methodological limitations that can be addressed only through quantitative evaluations, a feature that hinders a more accurate evaluation of the efficacy of CBT.

Although all studies indicated that additional benefits can be obtained through the addition of CBT, our results are limited by the fact that we found only eight studies with sound research designs. The take-home message from this systematic review is that more research is necessary to guide the next-step interventions as well as the replication of the findings of the studies in larger samples of patients, with more sophisticated controlled studies, including double-blind evaluation, psychotherapy placebos, and longer follow-up data (Smits & Hofmann, 2008).

4.4. Recommendation

We recommend the development of more randomized controlled studies with larger samples of patients to add evidence of the efficacy of CBT. In particular, social anxiety disorder and GAD are poorly explored research areas, with a demand for future studies, due to the small number of publications and the absence of works investigating CBT as a next-step strategy.

As many of the selected studies do not show long-term data, performing studies with longer follow-ups to demonstrate the maintenance of gains from CBT represents, too, an important area with demand for future investigations.

Because the studies used different words to express the concepts of resistance and remission, we recommend a standardization of these concepts taking into account the specificities of each anxiety disorder.

We observed the need for better summarization of the main outcomes of the studies. For instance, several authors could present their results in a more data focused way (e.g., given the % in remission, etc.).

We also propose, for future research works, studies on pharmacotherapy as a next-step strategy for CBT. In the present review we found few studies with this purpose (Baetz, M. & Bowen, R. C., 1998; Hoffart et al., 1993; Kampman et al., 2002; Hofmann et al., 2006; Kushner et al., 2007; Shim et al., 2008; Simon et al., 2008) which represents a field with relevant studies, in view of the importance of developing next-step strategies for patients who do not remit despite established efficacious, first-line treatments.

Even with the use of next-step strategy and the positive reports of efficacy, there is a room for improvement in CBT interventions among patients treated with drugs, since a substantial number of patients did not present remission.

Conflict of interest

There is no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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Does D-Cycloserine Enhance Exposure Therapy for Anxiety Disorders in Humans? A Meta-Analysis

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Abstract

The treatment of anxiety is on the edge of a new era of combinations of pharmacologic and psychosocial interventions. A new wave of translational research has focused on the use of pharmacological agents as psychotherapy adjuvants using neurobiological insights into the mechanism of the action of certain psychological treatments such as exposure therapy. Recently, d-cycloserine (DCS) an antibiotic used to treat tuberculosis has been applied to enhance exposure-based treatment for anxiety and has proved to be a promising, but as yet unproven intervention. The present study aimed to evaluate the efficacy of DCS in the enhancement of exposure therapy in anxiety disorders. A systematic review/meta-analysis was conducted. Electronic searches were conducted in the databases ISI-Web of Science, Pubmed and PsycINFO. We included only randomized, double-blind, placebo-controlled trials with humans, focusing on the role of DCS in enhancing the action of exposure therapy for anxiety disorders. We identified 328 references, 13 studies were included in our final sample: 4 on obsessive-compulsive disorder, 2 on panic disorder, 2 on social anxiety disorder, 2 on posttraumatic stress disorder, one on acrophobia, and 2 on snake phobia. The results of the present meta-analysis show that DCS enhances exposure therapy in the treatment of anxiety disorders (Cohen d = −0.34; CI: −0.54 to −0.14), facilitating the specific process of extinction of fear. DCS seems to be effective when administered at a time close to the exposure therapy, at low doses and a limited number of times. DCS emerges as a potential new therapeutic approach for patients with refractory anxiety disorders that are unresponsive to the conventional treatments available. When administered correctly, DCS is a promising strategy for augmentation of CBT and could reduce health care costs, drop-out rates and bring faster relief to patients.

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Introduction

Anxiety disorders are the most prevalent mental disorders, in the United States for example, more than 30 million Americans have experienced at least one anxiety disorder in their lifetime [1]. They often present a chronic course and are as disabling as physical diseases [2], significantly compromising the quality of life [3]. They also present high rates of comorbidity with other mental and chronic physical problems [4]. Anxiety disorders have a significant economic impact, leading to marked reduction in productivity and generating high medical and social costs. In the U.S., the direct and indirect cost of anxiety disorders was estimated at 42 billion dollars per year [5]. It is predicted that in 2020 anxiety disorders, together with depressive disorders, will be the second most common disease in the world [6].

Cognitive-behavioral therapy (CBT) and pharmacotherapy represent the front-line interventions for anxiety disorders and exposure is considered the gold standard behavioral intervention. Selective serotonin reuptake inhibitors (SSRIs) are the treatment of first choice for anxiety disorders according to most guidelines and algorithms involving pharmaceutical drugs [7]. The combined treatment of CBT with pharmacotherapy does not appear to present additional benefits as compared to CBT alone for some anxiety disorders [8], such as panic disorder, obsessive-compulsive disorder (OCD) and social phobia [9;10;11]. Even after first choice treatments, the disorder does not remit completely in a high proportion of patient who still require additional treatment [12;13]. Over 40% of patients responding partially to antidepressants suffer from clinically significant residual symptoms [14]. Moreover, a considerable number of patients discontinue treatment for because of the adverse effects of conventional pharmacotherapy. For example, SSRIs induce many undesired effects in the sphere of sexuality, sleep and weight, resulting in treatment interruption or failure to use the correct therapeutic doses [15]. With regard to psychotherapy, 50% of the patients do not respond or abandon the conventional treatment with CBT [16]. Furthermore, many patients do not adhere to the CBT treatment due to the anxiety generated by the exposure technique, which is an essential part of the treatment for anxiety disorders [17]. In this context, it is necessary to develop new effective strategies for the

treatment of patients resistant and/or intolerant to the current treatments.

In translational research, the antibiotic D-cycloserine (DCS), a glutamatergic agent, partial agonist at the glycine recognition site of the *N*-methyl-D-aspartate (NMDA) receptor in the amygdala, emerged as part of a new strategy using a combination of pharmacotherapy and CBT. Originally designed to be a tuberculostatic agent, DCS was later used as a potential treatment for Alzheimer's dementia and negative symptoms in schizophrenia [18;19]. The traditional pharmacological treatment for mental disorders requires the correction of hypothetical biochemical abnormalities in critical structures of the central nervous system. Anxiety disorders have a component of emotional learning. DCS seems to exert an effect on the emotional learning component, accelerating the process of associative learning and contributing to an improvement in symptoms [20]. Studies with animal models strongly suggest that DCS facilitates the process of extinction of conditioned fear [21]. On the other hand, antagonists at the glutamatergic NMDA receptor, which is linked to learning and memory, seem to block learning of extinction of fear. DCS would have a role in enhancing the learning of extinction of fear, a central mechanism in exposure therapy.

The aim of this paper was to perform a systematic review and a meta-analysis of the efficacy of DCS as a strategy of augmentation of CBT in patients with anxiety disorders.

Methods

Search strategy

Electronic searches were performed in the following databases: ISI-Web of Science, Pubmed/Medline and PsycINFO, covering the period from 1974 to November 23, 2012. Articles published in any language were considered. The following terms were used:

ISI (advanced search)

• TS = ("behavio*therapy" OR "cognitive behavio*therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure-based behavior therapy" OR CBT OR flooding OR virtual reality).

• TS = (d-cycloserine OR DCS).

All of the 3 citation databases were activated (Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) and Arts & Humanities Citation Index (A&HCI), and we restricted the search criteria in order to include only "articles" and notes.

Pubmed/Medline (advanced search)

• Cycloserine OR d-cycloserine OR DCS.

AND.

• "behavior therapy" OR "behaviour therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure-based" OR "implosive therapy" OR flooding OR "cognitive therapy" OR "cognitive behavior therapy" OR "cognitive behaviour therapy" OR "cognitive-behavior therapy" OR CBT.

PsycINFO

• "behavio*therapy" OR "cognitive behavio*therapy" OR "exposure therapy" OR "exposure treatment" OR "exposure-based behavior therapy" OR CBT OR flooding OR "virtual reality".

• d-cycloserine OR DCS.

In these databases, the terms were searched directly in advanced search (All Fields) and the results of each individual search were combined. APA Books were excluded.

Besides electronic searches, manual searches were also performed through bibliographical references. We also consulted with experts in the field about the existence of additional studies that could not be located through the electronic search.

Inclusion/exclusion criteria

We included "articles" and "notes" and excluded "review articles", book chapters and dissertations. Our search was based solely on randomized, double-blind, placebo-controlled trials of D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders (with or without comorbidity with others mental disorders) in a human population. We included articles focused on enhancement of exposure therapy through DCS used during and/or at times close to the exposure treatment. Studies that did not focus on CBT (for example, that investigated the neural mechanisms of the process of extinction with DCS) and that did not include anxiety disorders according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) III, III-R, IV and IV-TR [22;23] were excluded. Studies duplicated and listed twice were excluded. Figure 1 shows the study selection process. Table 1 shows the selected studies.

Quality evaluation of the studies and statistical analysis

The use of scales with summary scores for assessing risk of bias has been criticized and discouraged. For this reason we decide to use an adapted model of the graphs proposed by the Cochrane Collaboration to evaluate the methodological quality of the studies included in this review [24]. For this evaluation we mainly took into consideration the following items: randomization, allocation concealment, blinding, selective reporting and type of analysis. Each of these items was classified (Figure 2 and figure 3) as "low risk of bias", "high risk of bias" or unclear (when there was not sufficient information).

Because studies have made use of different scales for anxiety disorders, we estimated the difference of standardized means to obtain the summary measure (effect size) using fixed effects models. Thus, the differences between the final scores in the intervention group and in the control group were expressed in number of standard deviations. Negative values indicate/favor the intervention group. Standardized effect sizes (individual and pooled) were presented using a forest-plot. The heterogeneity between the results of the studies was assessed using the chi-square test for heterogeneity and I^2 statistic. The I^2 represents the proportion of the total variance that is due to inter-study variation (heterogeneity). Values below 30% suggest a low variability in the results across studies (homogeneity) [25]. Analyses were performed using Stata 12. See figure 4.

Results

Our search of the three databases identified 328 publications from which thirteen studies were selected for this review (Figure 1). Most participants had at least one additional DSM Axis I diagnosis and were taking a stable dose of psychotropic medications, which were maintained during the studies. The results of the selected studies were divided by the primary anxiety disorders. Of the thirteen studies identified, four described the treatment of patients with obsessive-compulsive disorder (OCD), two with panic disorder, two with social anxiety disorder, two with post-traumatic stress disorder (PTSD) and three with simple phobia. Table 1 describes the main characteristics of these studies.

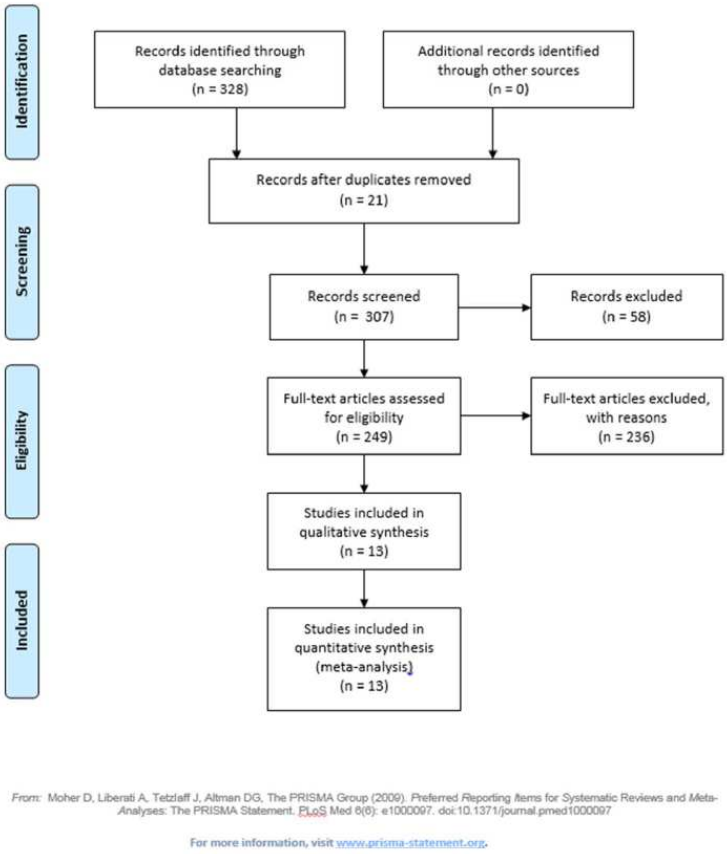

Figure 1. Flow Diagram.
doi:10.1371/journal.pone.0093519.g001

Among the four studies mainly focused on patients with OCD, three found no positive effects for enhancement of exposure therapy with DCS (two found positive results only in mid-treatment) and one reported moderate effect. At least half of the participants were taking psychiatric medications on stable doses just before and during the study. All participants with OCD were diagnosed using the Structured Clinical Interview for DSM-IV [23].

In the only study with children, Storch et al. [26] randomized 30 young people to ten 60-min CBT sessions plus 25 mg of DCS or placebo taken before sessions 4 through 10. The included participants had a diagnosis of OCD, established according to score ≥16 on the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) [27], and were stable on any psychotropic medications for 12 weeks. Evaluations were performed at the end of treatment, after session 6, and within one week post-treatment. Children randomized to DCS augmentation of CBT showed moderate effect size relative to a placebo control on several symptoms severity indexes. For the Clinical Global Impressions-Severity Scale (CGI-S) [28], the effect size was moderate in support of CBT + DCS with a 57% versus 41% symptom reduction. For the CYBOCS, moderate (72%) and small (58%) effect sizes, respectively, were found. For the Anxiety Disorders Interview Schedule - Clinician Severity Rating (ADIS-CSR), the effect size was moderate, with 71% reduction (CBT + DCS) versus 53% reduction (CBT + Placebo).

Kushner et al. [29] randomized 25 participants to 10 doses of DCS (125 mg) or placebo, about 2 hours before each of 10 sessions of exposure and response prevention (twice weekly). Participants were included according to DSM-IV criteria for OCD and for having Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [30] scores ≥18. The evaluations were performed at baseline, after the fourth session, at the last session and at 3-month follow-up. After the fourth session, obsession-related fears declined more rapidly in the DCS than in the placebo group, according to Y-BOCS scores. The DCS group achieved >50% reduction on the Subjective Unit of Distress Scale (SUDS) in all items of the hierarchy in two sessions earlier than the placebo group. However, after the last session of exposure and at the 3-month follow-up, there was no statistically significant difference between the two groups according to the Y-BOCS and SUDS scales, suggesting that the effect of DCS was concentrated in the first exposure sessions.

Wilhelm et al. [31] randomized 22 patients to DCS (100 mg) (n = 10) or placebo (n = 12) administered one hour before each of 10 individual sessions (60 minutes each) of behavioral therapy, twice a week. Before the protocol, participants were interviewed

Table 1. The selected studies.

	NCBT + DCS/PCB + CBT	Disorder	Demographic Age (mean) % of women	DCS Dose (mg) Time Before CBT	CBT protocol	Results
Storch et al. 2007	12/12	OCD	29.0 ± 9.9 50%	250 4 hours	12 weekly sessions of ET	There was no clinically or statistically significant difference between the groups and no difference in remission: 42% (E/RP + DCS) and 58% (E/RP + PCB). There was no difference between groups on CGI: 83% (E/RP + DCS) and 92% (E/RP + PCB) were considered responders.
Kushner et al. 2007	14/11	OCD	Not shown	125 Approximately 2 hours	Up to 10 ET, twice weekly	DCS group showed faster reduction of obsession-related fears (Y-BOCS and SUDS). > 50% reduction on SUDS in all items of the hierarchy in two sessions earlier than the placebo group.
Wilhelm et al. 2008	10/12	OCD	Not shown	100 1 hour	1 psychoeducational/treatment planning session (90 minutes) +10 behavior therapy sessions (60 minutes each) held twice a week	DCS group had significant improvement in OCD symptoms on Y-BOCS compared to placebo group at mid-treatment. There was no statistically significant difference between groups after treatment and at one-month follow-up.
Storch et al. 2010	15/15	OCD	12.2 ± 2.8 63%	25 mg 1 hour (4–10 sessions)	Ten 60-min CBT sessions	Moderate (72% - CBT + DCS) and small (58% - CBT + PB) effect size on CYBOCS. Moderate effect size on CGI-S, in support of CBT + DCS with a 57% versus 41% symptom reduction.
Otto et al., 2010	15/12	Panic Disorder	35.0 ± 11.0 50%	50 1 hour (sessions 3–5)	5 sessions of cognitive-behavior therapy	Better results on PDSS and CGI-S and clinically significant changes (77% DCS vs. 33% PCB). Large effect size.
Siegmund et al., 2011	20/19		Agoraphobia Panic Disorder	37.85 ± 11.3 (DCS) 37.32 ± 13.0 (PCB) 46%	50 1 hour	11 sessions (90 minutes each) of CBT in group
There was no statistical difference between DCS and placebo groups. DCS accelerated reduction of symptoms with in vivo exposure therapy in more severe patients in total score of Panic and Agoraphobia Scale.						
Hofmann et al. 2006	12/15	Social Anxiety Disorder	33.70 ± 10:02 29.62%	50 1 hour (2 to 5 sessions)	5 sessions of individual or group therapy exposure	Group receiving DCS reported significant decrease in anxiety and better social outcomes measured by SPAI, LSAS, and CGI-S.
Guastella et al. 2008	28/28	Social Anxiety Disorder	29.0 ± 8.1 63%	50 1 hour	5 sessions of group ET	DCS enhanced the exposure therapy. Reductions in GAF, SPAI, LSAS, BFNE and LIS, and improvements maintained at one-month follow-up.

Table 1. Cont.

	NCBT + DCS/PCB + CBT	Disorder	Demographic Age (mean) % of women	DCS Dose (mg) Time Before CBT	CBT protocol	Results
Kleine et al. 2012	24/21	PTSD	36.27 ± 11:56 (DCS) 40.26 ± 11.05 (PCB) Not shown	50 1 hour	10 weekly exposure sessions	DCS seems to have enhanced the effects of treatment, but patients who received DCS showed stronger response to therapy. DCS showed greater reduction of symptoms in participants who had more severe pre-treatment PTSD and needed longer treatment.
Litz et al. 2012	13/13	PTSD	32.77 ± 9.85 (DCS) 31.62 ± 9.10 (PCB) Not shown	50 30 min (sessions 2–5)	6 sessions of 60–90 min of exposure therapy	DCS failed to show an overall augmentation effect: 36.4% of the completers in placebo group and 33.3% of those in the DCS condition no longer met criteria for PTSD on CAPS. 50% of the completers met the criteria for status responders: 70% of the placebo group and 30% of the DCS group.
Ressler et al. 2004	17/10	Acrophobia	46.4 ± 2.8 (DCS) 44.8 ± 2.3 (PCB) 59.26%	50/500 "Acutely prior to psychotherapy"	2 sessions of VRE therapy	There was no significant difference between the 50 mg and 500 mg groups. DCS group showed higher percentages of subjects who reported "much improvement" or "very much improvement". Reductions in number of skin conductance fluctuations and greater improvements in measures of symptoms of acrophobia in the real world and improvements maintained at 3-month follow-up.
Tart et al., 2012	15/14	Acrophobia	29.33 ± 14.67 (DCS) 37.71 ± 16.81 (PCB) Not shown	50 After each session	Two-session protocol VRE	"There was clinical improvement in all outcome measures, but there was no significant statistical difference between the groups on DCS versus placebo. 81.8% of placebo group and 66.7% of DCS responded. 63.5% of placebo group and 60.0% of DCS remitted.
Nave et al., 2012	10/10	Snake Phobia	34.60 ± 12.69 (DCS) 39.00 ± 13.91 (PCB) 60%	50 1 hour	Single session of graded exposure therapy	Reduction in both groups on Snake Questionnaire, although DCS group achieved faster reduction in the hierarchy.

ADIS-IV = Anxiety Disorders Interview Schedule for DSM-IV; BFNE = Brief Fear of Negative Evaluation Scale; CGI-S = Clinical Global Improvement Severity; CYBOCS = Children's Yale-Brown Obsessive-Compulsive Scale; DCS = D-cycloserine; ET = exposure therapy; GAF = Global Assessment of Functioning; LIS = Life Interference Scale; LSAS = Liebowitz Social Anxiety Scale; PCB = placebo; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; PDSS = Panic Disorder Severity Scale; SPAI = Social Phobia and Anxiety Inventory; PTSD = Post-traumatic Stress Disorder; SUDS = Subjective Unit of Distress Scale.

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for a diagnosis, pre-treatment evaluation, and a session of psychoeducation/planning of the treatment. The DCS group had a significant improvement in OCD symptoms assessed by the Y-BOCS [30] as compared with the placebo group at mid-treatment (after session 5), with large effect size. However, there was no statistically significant difference between groups after treatment and at the 1-month follow-up. Also, the DCS group showed significant reduction of depression symptoms at the end of treatment, with large effect size. However, there was no statistically significant difference between the groups at mid-treatment and 1-month follow-up.

Storch et al. [32] found no statistically significant difference between the comparison groups although reduction of symptoms occurred in both groups. For this study, 24 participants were randomized to exposure and response prevention (E/RP) + DCS (250 mg) versus E/RP + placebo, administered 4 hours before each of 12 weekly sessions of E/RP (75–90 minutes each). Remission was defined as having reached gravity ≤ 3 on the Anxiety Disorders Interview Schedule for Diagnostic and Statistical Manual of Mental Disorders-IV (ADIS-IV) and ≤ 10 on the Y-BOCS [30]. There was no significant difference in remission between the groups: 42% (E/RP + DCS) and 58% (E/RP + placebo) meeting criteria for remission. The groups did not differ

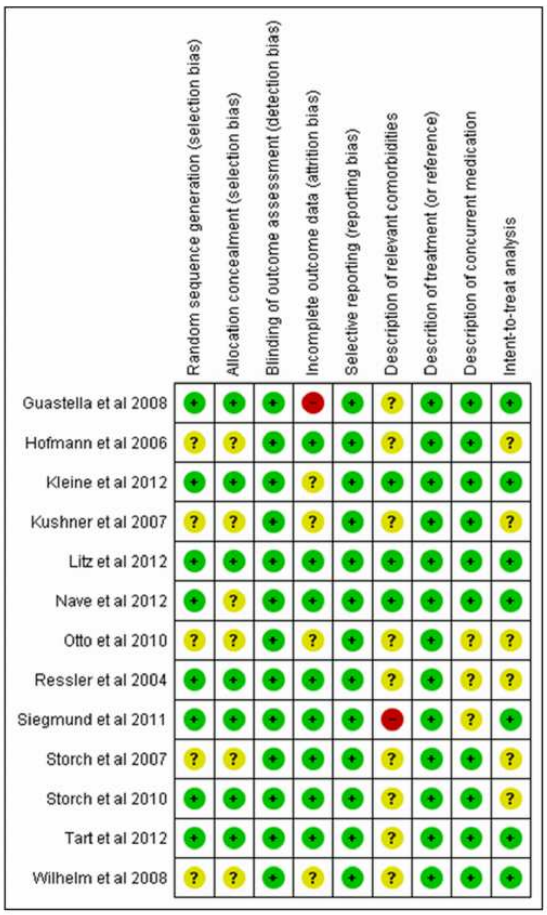

Figure 2. Methodological quality of the included studies (by study).
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on the Clinical Global Improvement Scale (CGI-S) (Guy, 1970), with 83% (E/RP + DCS) and 92% (E/RP + placebo) considered as responders. Follow-up (12 months) also did not show statistically significant differences.

Three controlled trials with patients with specific phobia were identified: two with acrophobia and one with snake phobia. One of the studies with acrophobia reported positive results. The other study with acrophobia and the one study with snake phobia reported negative results.

The study by Ressler et al. [33] was the first to use DCS to facilitate extinction of fear in humans; it was also the only one that used virtual reality and psychophysiological measures. Twenty-seven participants were randomized to three groups: placebo plus Virtual Reality Exposure (VRE) therapy (n = 10), 50 mg of DCS plus VRE therapy (n = 8), or 500 mg of DCS plus VRE therapy (n = 9). The two sessions of behavioral exposure therapy were performed using virtual reality: exposure to height within a virtual glass elevator. The doses of DCS or placebo were administered acutely prior to each of the two sessions. Besides subjective and psychometric measures, an objective measure of fear electrodermal skin fluctuation was used as well. Participants who received exposure therapy plus DCS showed significantly greater reduction in symptoms of acrophobia in almost all primary outcome measures - Acrophobia Questionnaire with Avoidance (AAVQ) and Attitudes Toward Heights Inventory (ATHI) [34]. There was no statistically significant difference in the outcomes between the group that received 50 mg and the group that received 500 mg. The participants who received DCS showed higher proportions of individuals who reported "much improvement" or "very much improvement", significant reduction in number of skin conductance fluctuations per minute of virtual exposure and significantly greater improvements in measures of symptoms of acrophobia in the real world. Improvements in subjective and objective measures were maintained at 3-month follow-up.

Tart et al. [35] replicated the procedures of the first study and randomized 29 participants with height phobia for two sessions of VRE in combination with 50 mg of DCS or placebo. This was the first study, identified in this review, using DCS immediately after the exposure session. The VRE protocol used was the same as in the previous study by Ressler et al. [33]. Participants were selected according to the DSM-IV-TR criteria for acrophobia and a subjective distress score (SUDS) >50 on the Behavioral Avoidance Test (BAT) [34]. Participants using other psychotropic medications or psychotherapy and previous non-response to exposure therapy for acrophobia were excluded. Response was defined as "very much improved" or "much improved" on CGI-I (score ≤ 2). Remission was defined as "normal" or "minimally ill" on CGI-S (score ≤ 2). Evaluations were performed at baseline, at each treatment session, one week post-treatment and at 1-month follow-up. Significant improvements were observed in all measures, with no differences between the groups. The improvement was significant in all outcome measures, but there was no significant statistical difference between the groups on DCS versus placebo on BAT, AAVQ, and CGI scores and other measures. The proportions of responders were 81.8% in the placebo group and 66.7% in the DCS group after treatment, and 80.1% in the control group and 75.0% in the DCS group at 1-month follow-up. Regarding the proportion of patients achieving remission, the authors found 63.5% in the placebo group and 60.0% in the DCS group after treatment, and 63.4% in the placebo group and 66.6% in the DCS group at 1-month follow-up.

In the study by Nave et al. [36], 20 adults with snake phobia received 50 mg of D-cycloserine or placebo 1 hour prior to a single session of graded exposure therapy. All of the participants achieved score ≥18 on the Snake Questionnaire [37], had not undergone treatment for snake phobia previously, and were suitable for functional magnetic resonance imaging (fMRI). Participants were assessed one week before and after treatment through clinical examination and the Snake Questionnaire, CGI-S, CGI-I and Snake-Stimuli Symptom Provocation Functional Magnetic Resonance Imaging Task. The DCS and placebo group responded well to the treatment, although the DCS group reached the top of the exposure hierarchy more quickly.

Two controlled studies were identified involving the combined use of CBT and DCS in the treatment of panic disorder with or without agoraphobia. One found positive results and the other found weak results for enhancement with DCS.

In Otto et al. [38], patients with or without agoraphobia and panic disorder severity of at least 4 (moderate severity) on the CGI-S were selected for 5 sessions of CBT (interoceptive exposure, cognitive, and situational exposure interventions). This was the first study using DCS for a treatment protocol emphasizing exposure to feared internal sensations (interoceptive exposure). Thirty-one participants were randomized to 50 mg of DCS or placebo, administered one hour before 3–5 sessions of CBT. Most

study participants were taking psychoactive medications at stable doses for at least two months before entering the trial without positive results. Soon after the end of treatment and at 1-month follow-up, the group that received DCS instead of placebo showed better results on the Panic Disorder Severity Scale (PDSS) [39] and CGI-S, changes which were clinically significant (DCS = 77%, placebo = 33%), and larger effect size. Treatment gains were maintained at 1-month follow-up, although the difference between the DCS group and the placebo group with regard to participants meeting criteria for clinically significant change was no longer significant at follow-up (DCS = 75% and placebo = 53%). The study suggests that DCS was effective for participants who failed to respond adequately to the traditional drug treatment for panic disorder.

Siegmund et al. [40] randomized 39 participants with panic disorder and agoraphobia. All of them received 11 CBT sessions (8 sessions of 90 minutes each of CBT in a group setting+3 sessions of individual exposure in vivo). This is the only study that used flooding. One hour before the beginning of each exposure session, patients received 50 mg of DCS (n = 20) or placebo (n = 19). After randomization, the baseline assessment showed differences between the groups in three secondary measures; in all of them, the DCS group had less severity than the placebo group. However, comorbidities were significantly higher in the placebo group. Both groups improved after treatment and there was no statistical difference in the primary outcome measure – Panic and Agoraphobia Scale (PAS) [41], or on any of the secondary outcome measures. However, subsequent evaluation showed a statistical tendency to greater reduction of the PAS score in the DCS group. DCS seems to have accelerated the reduction of symptoms with exposure therapy in participants with more severe panic disorder and agoraphobia.

We identified two studies of patients with social anxiety disorder which found positive response to the enhancement with DCS.

Hofmann et. al. [42] found a positive response for the use of short-term dosing of DCS as an adjunctive intervention to exposure therapy. Twenty-seven participants with significant public speaking anxiety were randomized to DCS (50 mg) + 5 sessions of exposure therapy (n = 12) versus placebo+5 sessions of exposure therapy (n = 15). Participants received 5 weekly therapy sessions in individual or group format. DCS or placebo was administered one hour before sessions 2–5. The diagnosis of social anxiety disorder was performed using the Anxiety Disorders Interview Schedule for DSM-IV [43] and the Structured Clinical Interview for DSM- IV. The group that received DCS showed a statistically significantly greater reduction of the general symptoms of social anxiety, assessed through the questionnaires Social Phobia and Anxiety Inventory (SPAI) [44] and Liebowitz Social Anxiety Scale (LSAS) [45], with medium to large effect size (Cohen d); the improvements were maintained at one-month follow-up. They computed controlled effect sizes by dividing the differences between the mean change of the DCS group and the mean change of the placebo group by the pooled standard deviation.

Guastella et al. [46] replicated the study of Hofmann et al. [42] and developed a study of a sample that was two times larger than in previously published studies: 56 patients were randomized to 50 mg of DCS (n = 28) or placebo (n = 28). Participants were given five group sessions (90 minutes each) of an exposure protocol. In sessions 2 through 5 they received the capsules to be taken one hour before each exposure session. Participants were diagnosed with social anxiety disorder using the Anxiety Disorder Interview Schedule for Adults [47]. Improvements were evaluated by SPAI, LSAs, Brief Fear of Negative Evaluation Scale (BFNE), and Life Interference Scale (LIS) [48]. There was a reduction of symptoms in both groups. However, the DCS group had greater reductions of symptoms of social anxiety disorder on LSAs, BFNE and LIS, with moderate effect size (Cohen's d) in most of the measures used; the improvements were maintained at 1-month follow-up. The effect sizes were computed by dividing the difference between the mean change of the DCS group and the mean change of the placebo group by the pooled standard deviation. The results suggest that punctual use of DCS with 3 or 4 sessions of exposure is effective to enhance the treatment of social anxiety disorder.

Two recent studies investigating augmentation of prolonged exposure therapy for post-traumatic stress disorder (PTSD) with DCS were identified. In one of the studies, the DCS enhanced the response of the group of participants who completed all sessions. In the other study, DCS did not enhance the response to treatment.

Kleine et al. [49], from the 75 subjects with mixed traumas selected for randomization, 45 completed the treatment protocol: exposure plus DCS (n = 24) and exposure plus placebo (n = 21). Fifty mg of DCS or placebo were administered one hour before each of 10 weekly exposure sessions. Less than half of the participants (41.8%), equally distributed between the groups, were using other psychotropic medications at a stable dose. In the initial evaluation, 70.1% (47 of the participants) had at least one additional diagnosis, mostly depression (53.7%) and anxiety disorders (41.8%). There was no significant difference between the participants dropping out of the DCS group (n = 9; 27.3%) and the placebo group (n = 13; 38.2%). Response to treatment was defined as decrease from baseline ≥10 points on the Clinician-Administered PTSD Scale (CAPS) and remission was defined as a CAPS severity score <20. Thirty-four participants (50.7%) showed post-treatment response according to the CAPS and the reduction was maintained at 3-month follow-up. There was no difference between the groups regarding the frequency of remission. Nineteen participants (42.2%) were classified as early completers, obtaining recovery before session 8. The regular completers showed more severe self-reported PTSD symptoms at session 1. DCS did not potentiate the overall treatment effects, although the regular completers (the participants who completed all sessions) who received DCS showed a greater reduction in symptoms across sessions than the regular completers on placebo. The use of DCS was associated with a greater reduction of symptoms in participants who had more severe pretreatment PTSD and needed longer treatment.

Litz et al. [50] randomized 26 veterans of the Iraq and Afghanistan wars to exposure therapy plus DCS (n = 13) or to exposure therapy plus placebo (n = 13). Six sessions (60–90 min each) of exposure therapy were conducted. DCS (50 mg) was administered 30 min prior to sessions of imaginal therapy exposure (sessions 2–5). Participants were asked to arrive at least 30 minutes prior to the start of sessions for a medical evaluation, including alcohol breath analyses and to take DCS or placebo. The effect size for primary and secondary outcomes were medium to large, with exposure therapy plus placebo faring significantly better than exposure therapy plus DCS on all outcomes. At post-treatment, 36.4% of the completers in the placebo group compared with 33.3% of those in the DCS condition no longer met criteria for PTSD on the CAPS. Responder status was defined as a reduction of 10 or more points on the CAPS. At post-treatment, 50% (n = 10) of the completers met the criteria for responder status: 70% of the placebo group and 30% of the DCS group. Follow-up evaluations were carried at 3 and 6 months, where 58% and 54% of participants met criteria for responder status, respectively. At the 6-month follow-up, the treatment effects

were clinically significant, with 50% of the participants in the placebo group no longer meeting criteria for PTSD and 66% meeting criteria for respondent status.

Analysis

Methodological quality

In Figure 2 it can be seen that the great majority of the studies presented criteria for "low risk" in the items used for the methodological quality assessment. Most presented at least one "unclear" item, and only two had "high risk" for selected items. Figure 3 shows the proportion of studies fulfilling the quality criteria for each of the selected items.

Combining effect sizes (meta-analysis)

Figure 4 presents the forest plot for the standardized mean differences (SMD) between intervention and control groups of the included studies. The confidence interval of most studies crosses the vertical line of null effect (mean difference equal to zero), indicating that the majority of these studies did not find a statistically significant difference between DCS and placebo.

As we found no evidence of heterogeneity between the results of the different studies ($I^2 = 10\%$ and χ^2 not significant: $p = 0.34$), their SMD were pooled to estimate the overall standardized weighted mean difference. The combined measure in figure 4 shows that the group that received D-cycloserine had an average reduction of 0.34 standard deviations at the end of follow-up as compared to the placebo group. This difference was statistically significant ($p = 0.001$).

Some studies reported large standard deviations, suggesting asymmetry/non-normality of distribution of their means. So, we carried out a sensitivity analysis removing these estimates to evaluate the impact on the overall standardized SMD. The result thus obtained did not differ substantially from the one observed with the 13 studies (Cohen's $d = -0.26$, 95% CI: -0.50 to -0.029, $p = .03$).

Discussion

Overall efficacy

The results of this meta-analysis suggest that D-cycloserine (DCS) enhances the effects of exposure therapy in anxiety disorders. The observed effect size was, however, small to moderate (Cohen's $d = -0.34$). Although we included studies with different types of anxiety disorders, their findings concerning DCS efficacy showed low heterogeneity. Evidence suggests that the use of DCS is effective at low doses, used a limited number of times and at times close to exposure therapy.

Our findings go in the same direction of two other meta-analyses [51;52], one systematic review [53], and two other reviews on the topic [54;55].

In the first published review on the topic, Hofmann et al. [54] analyzed the first two studies with D-cycloserine enhancing CBT in humans and concluded that DCS facilitates the process of extinction of conditioned fear when administered in individual doses and before exposure therapy. They recognized the limitations of their conclusion, calling attention to the fact that the existing literature is composed of relatively small sample sizes and a limited number of studies. Furthermore, they pointed out that although animal and human studies were associated with significant effect sizes, human studies had a small effect size while animal studies had a large effect size.

Norberg et al. [51], in a meta-analysis of DCS augmentation of fear extinction and exposure therapy in non-animal and animal studies, concluded that "DCS is a promising tool for translational research concerned with enhancing (or reducing) NMDA receptor function as a method for improving exposure-based therapy outcomes" (p.1123). DCS showed large treatment effect in animals (Cohen's $d = 1.19$) and small to moderate effect size in humans (Cohen's $d = 0.42$).

One of the factors that may explain a much larger effect size of studies with animal models compared to human studies [51] is the concomitant use of other drugs, as most studies participants were taking other psychotropic medications. Although these drugs have been stably used before the beginning of studies, and their use was controlled in statistical analyses, the mechanisms of possible interaction of DCS with other psychiatric drugs are not yet entirely known; for example, continued use of the antidepressants imipramine and citalopram appears to affect the function of the glycine/NMDA receptor [56]. The only study that established use of other medication that may interfere with DCS (e.g., anticoagulants) as an exclusion criterion was the one by Kleine et al. [49], with PTSD patients. Nevertheless, a study of social anxiety

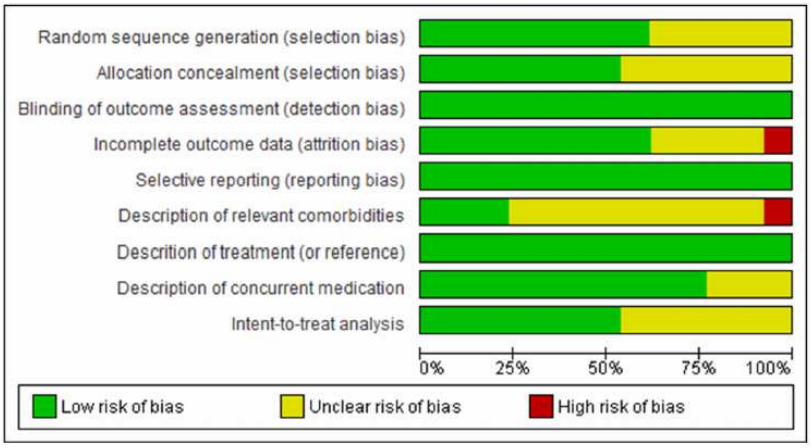

Figure 3. Methodological quality of the included studies (by domain).
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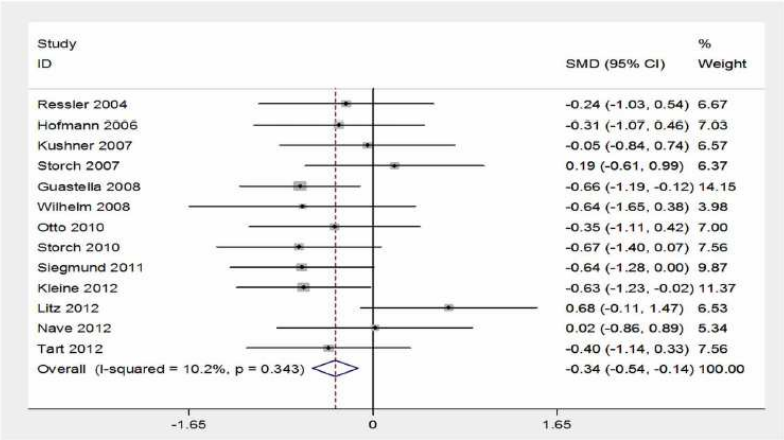

Figure 4. Forest-plot.
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disorder [54] indicated that the use of concomitant medication does not seem to have affected the results, and there is no contraindication for the use of other psychotropic medications with DCS. Another possible explanation for the smaller effect size in humans is the fact that the sample includes human individuals with comorbid disorders, mainly other anxiety disorders and depression.

There is evidence that DCS is effective when administered at low doses (50 mg), a limited number of times, and immediately before (1 or 2 hours) or after exposure therapy [51;53]. Our review is consistent with these findings, since most of the studies used a dose of 50 mg and short CBT protocols. Evidence indicated that DCS does not have anxiolytic properties, not being used as a first strategy, but for the therapeutic enhancement of learning [57]. In the study by Ressler et al. [33] DCS administration did not affect baseline subjective fear levels in patients who received exposure therapy with virtual reality, i.e., administration of DCS during the therapy session did not affect the level of fear or avoidance during it. Despite the evidence with regard to time, dose and protocols, the exact dose indicated for administration of DCS as strategy of potentiation is still unknown.

On the other hand, the meta-analysis performed by Bontempo et al. [52] did not find significant interference of the time of administration and number of doses in the effects of potentiation with DCS. Also, one of the reviewed studies, conducted by Ressler et al. [33], did not find difference between doses of 50 mg and 500 mg.

Most studies in our review (n = 9/13) used 50 mg, but we also observed doses as 100 mg [31], 125 mg [29], 250 mg [32] and 500 mg [33]. Lack of standardization was also found concerning time of administration: 1, 2, 4 hours before or indefinite time [33].

DCS is a partial agonist and high doses may increase the antagonistic effects in NMDA receptors, decreasing the learning effects. A study with animal model suggests that the NMDA receptor can become desensitized after prolonged exposure to DCS [58]. At high doses and/or chronic administration, this substance seems to have a paradoxical antagonistic effect on the NMDA receptor [59], resulting in reduced effect of extinction of fear in animals. Studies with animal models also indicate the rapid development of tolerance to DCS when it is administered repeatedly and at high doses [54].

The possible efficacy of a reduced number of DCS administrations can be explained by the progressive desensitization of receptors with continued use of the substance. This finding is supported by the meta-analysis of Norberg et al. [51] on the use of DCS in animals and humans, in which the rapid development of tolerance is shown. It was also found in that meta-analysis that time of administration of DCS was a predictor of effect size, and the best effects were obtained when the substance was administered immediately before or soon after exposure. Other studies with animal models also support this finding, suggesting that the effects of augmentation with DCS occur during the period of memory consolidation that occurs after exposure rather than during exposure itself [60;61].

In OCD, where the lack of standardization was higher, the results for enhancement with DCS were less promising. These studies used the highest doses for a prolonged period: 100 mg before 10 sessions, 125 mg before 10 sessions, and 250 mg before 12 sessions. A difference between intervention and placebo groups was found when the drug was administered 1 to 2 hours before exposure sessions, but not when administered 4 hours before [32], which may also have contributed to the negative results, since DCS seems to be more effective when used shortly before the exposure sessions [60]. Also, these findings are in accordance with studies with animal models, reinforcing the idea that DCS is effective when administered immediately before or soon after exposure [61]. In this study by Storch et al. [32], DCS was administered at a dose of 250 mg four hours before the session and for a long period of time (12 weeks). The studies that showed positive results used brief protocols. Studies conducted by Wilhelm et al. [31] and Kushner et al. [29], who used twice-weekly sessions, found significantly higher results in the DCS group at the fifth and fourth sessions, respectively, but this effect was not observed at the end of 10 sessions.

In a additional article, Chasson et. al. [62] re-analyzed data from the study by Wilhelm et al. [31] and the outcomes indicated that the group that received DCS achieved results 2.3 times faster than the placebo group and six times faster in the first half of the sessions (1 to 5) of exposure therapy, suggesting that DCS accelerates the gains of exposure in OCD. These data indicate that the effects of DCS are concentrated in the first sessions of exposure. It is possible, therefore, that the period of memory re-

consolidation can be accelerated by DCS. Moreover, the findings of these studies with OCD support the idea that the NMDA receptor can become desensitized with prolonged exposure to DCS [58], and that isolated doses of medication prevent the compensatory changes at the NMDA receptor. Even though DCS did not have more robust effects, accelerating the effects of exposure has important clinical implications. Exposure and response prevention alone require more than 16 sessions to reduce OCD severity. The addition of DCS could reduce to eight the number of sessions. Reducing the required number of sessions and patients responding more quickly to treatment could have benefits to patients and society, such as decrease in treatment refusal, dropout rates, costs (the use of DCS could save over $2100 for each patient), and reduce the anxiety provoked with exposure, facilitating the adherence of treatment [62].

Other hypotheses can also justify the negative findings in OCD, such as the heterogeneity of the disorder and the fact that it is very common for a patient with OCD to be using a Serotonin Reuptake Inhibitor (SRI). In the study by Wilhelm et al. [31], 69.5% of the participants were taking a stable dose of some psychotropic medication, in most cases an antidepressant. In Kushner et al. [29], 64.3% of the group that received DCS and 58.8% in the placebo group were using some other psychotropic medication. The use of concomitant medications, usually an antidepressant, could help to explain the negative findings, as antidepressants seem to modify (desensitize) the function of the NMDA receptor.

In both studies with social anxiety disorder [46;54], we found a higher standardization. Both used the same protocol of 50 mg of DCS one hour before CBT sessions 2 to 5, although Hofmann et al. al. [54] used a format of individual or group sessions. Regarding studies with panic disorder [38;40] both used 50 mg of DCS an hour before the sessions, but differed on the number and format of CBT sessions, which may have influenced the efficacy of DCS in the study with 8 group sessions of Siegmund et al. [40].

With regard to panic disorder, Otto et al. [38] observed statistically significant positive results in the group of DCS as compared to the control group at the end of 5 sessions. These results were not confirmed in the study by Siegmund et al. [40], who found similar results in both groups after treatment. However, this study employed 11 sessions, but it can be observed that the administration of DCS produced better results in the middle of the treatment. This again suggests that the administration of DCS in brief protocols (<5 sessions) can be effective. Another possible explanation for the weak efficacy of DCS discussed in the study refers to the good response to therapy in the placebo group. The participants in the placebo group showed a reduction of symptoms of 58% (PAS) at the last evaluation. This result was not found in the other studies with DCS and suggested a floor effect preventing additional effects with DCS. Siegmund et al. [40] suggested that this effect may be due to the higher dose of psychotherapy: 8×90 min group therapy plus three individual exposures.

PTSD is the only disorder in which DCS seems to have played only a minimal role as an enhancer of CBT. The protocol used by Kleine et al. [49] does not seem to have been effective even in mid-treatment (the study used 10 sessions). This may be due to the specificity of PTSD, which is an anxiety disorder whose time of conditioning is necessarily known. For this reason, it may involve different brain mechanisms that respond differently to the action of DCS. In this study with PTSD, DCS enhanced outcomes in the subgroup of regular completers only, who are the participants who completed all sessions.

Regarding tolerability, DCS was well tolerated with no significant adverse effects found in the reviewed studies. In Hofmann et. al. [42], DCS administration had two spontaneous notifications of acute adverse effects: nightmare the night after administration and exposure session in one participant, and euphoric mood and increased energy in one participant with chronic depression. In Storch et al. [32], only three participants of the DCS group reported adverse events that were considered moderate: Increased anxiety, drowsiness and dry mouth. For the placebo group, these included drowsiness and restlessness. Kushner et al. [29] found mild gastrointestinal distress, dizziness, fatigue, and anxiety in four participants in the DCS group and "jittery feelings", dissociation and dry lips in three participants in the placebo group. In the study by Nave et al. [36], one participant in the DCS group reported mild nausea during the hour following administration. Kleine et al. [49] were the only ones who did not find differences between the participants in the DCS and placebo groups regarding adverse effects. At high doses (500 - 1000 mg) administered chronically, DCS may cause side effects such as headache, drowsiness, confusion, tremors, memory difficulties, paresthesias, and seizure [63]. In this sense, unlike many psychotropic medications, the side-effects of DCS at low doses are minimum [26], and therefore this drug seems to be a safe alternative for enhancing CBT outcome.

Methodological issues

Relating to the methodological quality of the included studies in this meta-analysis, most of the articles presented a low risk of bias (Figures 1 and 2). Figure 1 shows each article separately and figure 2 shows the results of summarized articles. Most part of the studies presented a low risk of bias, with one study showing a high risk of bias for incomplete outcome data [46] and one other [40] for description of relevant comorbidities. A significant number of the studies showed an unclear risk of bias.

With reference to the quality of the included studies, all of them were randomized, double-blind, placebo-controlled trials, although we found a limited number of studies and with relatively small samples sizes. The study by Guastella et al. [46] represents an exception, with a sample twice as large (n = 56) as in previous studies. Furthermore, we did not find any studies with generalized anxiety disorder (GAD). Regarding PTSD, we identified only two studies, both published recently [49;50]. In addition to these, we located another study using DCS for treatment of chronic PTSD [64], but in this case the aim was to investigate the isolated benefit from prolonged use of DCS, without having the main goal of enhancing exposure therapy. In that study, treatment with DCS did not result in significant improvements as compared to the placebo group. That was the first study to investigate the efficacy of the NMDA receptor modulator in PTSD treatment.

Although all studies were double-blind, no count of pills (DCS and placebo) was reported in any study. In Kushner et al. [29], ingestion of the medication at the due time was checked by telephone.

With regard to evaluation of efficacy in the long term, almost all studies had follow-up data for varying periods, including 1 week, 1 month, two months, three months, five months and six months. The results of the action of DCS did not disappear with the discontinuation of treatment and there was no report of discontinuation of the use of DCS in studies in which it was effective. In the study of DCS in OCD by Kushner et al. [29], the improvements were maintained after the last session of exposure and at the follow-up, with no significant difference between the groups treated with DCS and placebo. In Ressler et al. [33], the improvements were maintained too and the group that received

DCS reported less avoidance of heights in their daily activities, after the end of treatment and even at the three-month follow-up. Although the studies presented follow-up data, longer follow-up periods are necessary at least one year so as to confirm the maintenance of the effect of extinction augmented by DCS for a sufficiently long time.

Limitations of the present meta-analysis and recommendation (future directions)

A limitation of this review concerns the use of just three electronic databases, even though they represent the main ones. However, specialists were consulted concerning the existence of non-published studies.

We observed that no study performed a more detailed evaluation of the effects of DCS in each exposure session. We suggest that future studies assess the degree of learning that occurs in each exposure session to better assess the possible causal connection of DCS in the process of extinction. Moreover, because the optimal time and dose for efficacy of DCS has not yet been determined, studies of response control to specific doses are necessary to determine the best dose for using DCS in extinction of fear in humans.

We recommend the development of additional double-blinded randomized trials to validate the findings in this review. With the advances in research, DCS could potentially be used in clinical settings, something that may represent advantages such as cost-efficacy, reduction of dropout and refusal rates, increased access to health care, with more patients gaining access to treatment, acceleration of treatment response with exposure therapy and development of more effective treatments for the general population. According to Otto et al. [65], 5–20% of subjects receiving CBT in randomized, controlled trials drop out of treatment. The drop-out rates for traditional drug treatments of anxiety disorders are higher. Future studies could investigate the relationship of DCS with decreases in the number of drop-out cases.

Further studies are also needed to investigate predictors of response, to determine whether the efficacy of DCS varies according to the type of anxiety disorder, dose or time of administration of DCS and CBT, to determine the long-term results of augmentation with DCS and to assess the effectiveness of the drug and exposure therapy in the real world. It would also be important to evaluate the efficacy of DCS from the psychophysiological point of view, together with the psychometric one, such as in the study of Ressler et al. [33], who evaluated skin conductance during exposure to fear of heights, concluding that the decrease in this parameter was associated with treatment efficacy. This mode of assessment of efficacy has the advantage of being more objective, not suffering interference from subjective biases, improving treatment through the discovery of mechanisms of action of the therapy and preventing the development of disorders [66]. Indeed, the development of biomarkers is crucial to the advance of behavioral treatment research [67].

We located only one study with children, which suggest that this is an area that requires additional studies. This study was the one by Storch et al. [68] with children and adolescents with OCD, and it found moderate effects and did not find significant difference between the group that received DCS and the placebo group.

It is also necessary to investigate the efficacy of DCS for individuals who did not respond sufficiently to exposure therapy. The effects of augmentation occur during the period of memory consolidation, which occurs after the exposure training. Evidence suggests that DCS would enhance the consolidation of emotional learning of exposure therapy. Thus, to maximize the effects of treatment in anxiety disorders, it is important to consider individual differences, including the level of response to exposure therapy achieved in each session so that administration of the drug occurs after successful sessions [69;70]. The effect of DCS seems to potentiate whatever emotional learning has occurred, so there is evidence that DCS can enhance adverse reconsolidation effects, resulting in a poorer outcome relative to placebo. There is some evidence which suggests that the post-session administration of DCS to avoids the possibility of DCS enhancing the reconsolidation of fear memory in cases of unsuccessful therapy. Moreover, the decision to administer DCS would be made post-session, dependent on the level of fear reduced by the end of the exposure session [71]. This evidence could clarify the decision on the use of DCS and the best dose timing. The investigation of the use of DCS after successful and unsuccessful sessions is necessary to support these findings.

Supporting Information

Checklist S1 PRISMA checklist.
(DOC)

Author Contributions

Analyzed the data: EC RG. Wrote the paper: HR IF PV. Conducted electronic searches: AL. Reviewed manuscript: MM.

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Building resilience for future adversity: a systematic review of interventions in non-clinical samples of adults

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Abstract

Background: Potentially traumatic events happen in people's lives, leading to the risk of the development of posttraumatic stress disorder, depression and even suicide. Resilience is an individual's ability to maintain or regain his/her mental health in the face of significant adversity or risk of death. The aim of this study was to conduct a systematic review of studies evaluating the effectiveness of resilience promotion interventions in adults.

Methods: Electronic searches were conducted in databases ISI, PsycINFO and PubMed, including every language and every year until January 20, 2013. We selected studies with nonclinical samples of adults that evaluated the effectiveness of the intervention through randomized and non-randomized controlled trials and open-ended studies. We also considered valid constructs directly related to resilience, such as hardiness.

Results: Among 2.337 studies, 13 were selected for the review, 5 through electronic databases and 8 through search in references or the "times cited list" (list of articles that cited the selected papers). Of these, 7 are randomized controlled trials, 5 non-randomized controlled trials, and one an open-ended trial. Most of the studies included reported some degree of improvement in resilience-like variables among those subjects exposed to resilience-promoting programs. Furthermore, positive findings were more consistent among randomized controlled trials - six out of the seven suggested efficacy.

Conclusion: There is evidence pointing towards some degree of effectiveness of resilience promotion programs, despite the poor operationalization of the construct and great heterogeneity in the studies. Indeed, the analysis of the methodological quality of the selected studies was hampered by the poor quality of reporting. There were faults in reporting in most studies on almost all items (random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, description of concurrent treatment and intent-to-treat analysis), except for the item "selective reporting". Additional efforts should be made to determine the actual effect size of the interventions, since this is crucial for calculating the cost-effectiveness of resilience promotion strategies.

Keywords: Resilience, Prevention, Health promotion

Background

"Bad things happen" [1], as Bonnano et al. put it. Nobody escapes the adversities of life, whether they are potentially traumatic events, such as the sudden death of a loved one, or setbacks in personal or work life. Traumatic events happen frequently [2,3]. Numerous epidemiological studies have shown high lifetime rates of prevalence, for example 90% in the US [4], 76% in Mexico [5], 64.6% of men and 49.5% of women in Australia [6], 81% of men and 74% of women in Canada [7]. Most people are exposed throughout their lives to at least one event capable of eliciting an emotional response of such high magnitude as to be characterized as "psychological trauma", according to the DSM –IV [8]. Despite the high prevalence of traumatic events, there is an evident variability in the adaptation to such events and a natural heterogeneity of the human

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stress response. Posttraumatic Stress Disorder (PTSD) affects 5-10% of individuals exposed to these incidents. According to Bonanno et al. [1,9] among the possible outcomes after exposure to traumatic events, resilience is the most commonly observed response pattern. When the exposure is more prolonged or severe, when it involves interpersonal violence or occurs during childhood, the prevalence of PTSD or other mental disorders can reach higher levels, but it hardly ever exceeds 30% of the sample [10,11].

There is an array of possible ways of defining the key constructs related to resilience, such as positive adaptation to adversities/stress and hardiness. Therefore, studying such a complex construct is a challenge. From the perspective of trauma researchers, resilience is defined as the effective adaptation after significant threats to personal and physical integrity [12]. Hoge et al. [13] characterize resilience as not developing PTSD after a trauma. Bonanno et al. [14] conceptualize resilience as the absence of PTSD symptoms or the presence of a single symptom of PTSD. Masten [15] highlights that the individual needs to receive a significant threat, such as severe adversity or an exposure to a traumatic event, in order for resilience to take place. Moreover, she believes that the quality of adaptation needs to be good. Luthar & Zigler [16] call attention to how best to define a positive adaptation to adversity. Initial studies investigated competence based on external criteria of adaptation, such as social, academic and behavioral competence, expected for a given age and a given culture [16]. Luthar & Zigler [16] argue that internalizing and externalizing symptoms need to be assessed, because although individuals may show competence in behavioural indices, they may have a variety of other psychological difficulties. Masten [15] also suggests that narrowing the definition of positive adaptation only to the absence of PTSD can lead to erroneously classifying people as resilient who may in fact suffer from a disorder other than PTSD [17,18].

Despite the complexity of the construct, several scales have been developed to measure "resilience", and they actually appear to measure individual, social or family characteristics which can facilitate the process of resilience. In order to assess resilience in children and adolescents, some early studies used scales examining specific resilient characteristics and risk factors, such as locus of control [16]. Several studies have used scales to examine competence or coping skills, two qualities that may be related to resilience [13]. In a methodological review of resilience measurement scales [19], all of the measures had missing information regarding the psychometric properties. The scales that received the best ratings were the Connor-Davidson Resilience Scale, the Resilience Scale for Adults and the Brief Resilience Scale. Hoge et al. [13] argue whether resilience can be measured by a set of questions at a single point in time, as opposed to observing the subject during a stressful experience and then determining how well the person returns to normal functioning. In this scenario, resilience scales would measure an individual's reaction to an experimental paradigm or stressful life event overtime. Hoge et al. [13] also indicate that resilience scales should be used and observed in a trauma-exposed control group without PTSD, because these would probably be the individuals most likely to be truly resilient. However, studies assessing resilience in such groups are not available.

The promotion of resilience has potential implications for the prevention of mental disorders in professionals who are constantly exposed to risks, such as rescue workers and members of armed forces. Rescue workers, for instance, have high exposure to traumatic events and the pooled current worldwide prevalence of PTSD in this group of professionals is 10% [20]. The military is another group deserving greater attention regarding prevention strategies in order to reduce the health, social and economic burdens of mental disorders. The National Vietnam Veterans Readjustment Study (NVVRS) reported a life-time prevalence of warzone-related PTSD of 30.9% among the 3.1 million men and women who served during the Vietnam War [21]. Hoge et al. [22] assessed 2,530 men and women in US combat infantry units, before deployment to Iraq, and 3,671 after return from Iraq and Afghanistan. Rates of PTSD, major depression and generalized anxiety disorder ranged from 15.6 to 17.1% after deployment in Iraq and 11.2% after deployment in Afghanistan. Suicide rates have increased exponentially among American soldiers since the beginning of the wars in Iraq and Afghanistan [23]. The number of suicides committed after mission in Afghanistan has already exceeded the total number of U.S. military personnel who have died in combat in the same country [24]. To deal with this scenario, increasing research targeting secondary and tertiary prevention as well as treatment of mental disorders has been undertaken. However, there is a dearth of investigations targeting primary, pretrauma prevention of mental disorders in health samples in risk professions. Therefore, the development of evidence-based and research-informed resilience-building interventions have been considered essential to the success of primary mental disorders prevention programs [25].

Indeed, the great variability of the stress responses suggests the hypothesis that protective factors may prevent, weaken or attenuate the effects of stress, avoiding the development of mental disorders [26,27]. The existence of these protective factors increases the possibility of developing strategies for preventing psychiatric disorders and reducing the negative effects of adversity on individuals' mental health, i.e., the possibility of promoting resilience. Following this line of prevention, there are

several studies being published [28-40]. However, syntheses of the current knowledge about the efficacy or inefficacy of resilience-promoting programs are highly relevant, as these programs are already being widely implemented on a large scale. For example, the US Army, aiming at preventing or reducing the adverse psychological effects of combat, is submitting more than 900,000 soldiers and veterans to the Comprehensive Soldier Fitness (CSF) program with a cost of approximately 125 million dollars [41]. The CSF is based on the Penn Resiliency Program (PRP), typically a school-based program designed for youths in late childhood and early adolescence, although it has been evaluated in other settings, including primary care clinics and juvenile detention centers [42]. This massive training and research program has been criticized for being released without pilot testing to assess the effectiveness of such training in a military environment [43].

To the best of our knowledge, there are no systematic reviews or meta-analysis studies focusing on non-clinical adult samples. Thus, the purpose of this article is to systematically review studies that evaluate the effectiveness of resilience promotion in adults, where the intervention has focused on encouraging emotional resilience (or related constructs), in order to strengthen the individual against future stressors or adverse situations.

Method

Electronic searches were performed in the ISI, PsycINFO and PubMed databases, including every language and every year until January 20, 2013. The terms used in the individual search were the following:

ISI (advanced search):

- TS = ("behavi* therapy" OR "cognitive therapy" OR "cognitive behavio* therapy" OR CBT OR "cognitive reest*" OR "positive psychology" OR "well being therapy" OR "anxiety manage*" OR relaxation OR "stress control training" OR "stress inoculation training" OR "stress inoculation" OR "progressive relaxation" OR "diaphragmatic breathing" OR "social abilit* training" OR "social skills training" OR psychotherap*)
- TS = ("resilienc*" OR "Subjective well-being" OR "positive psychology" OR "health promotion" OR "cognitive flexibility" OR "post-traumatic growth" OR "stress-related growth" OR hardiness)
- TS = (protocol OR program OR treatment OR promotion)

All databases were activated and the survey included only "articles" and "notes". The results of each individual search were combined with "and".

In PsycINFO/PsychLit, we searched directly in "Any Field" and limited the search by including only "Journal Article" and excluding "Chapter", "Dissertation" or "Book Review". The same search terms were used in the ISI database. As in the ISI, the results of each individual search were combined.

In PubMed, we performed the search in "All Fields", and the groups of terms used and combined between each other were as follows:

- ("cognitive therapy" OR CBT OR "positive psychology" OR relaxation OR "stress inoculation training" OR "stress inoculation" OR "progressive relaxation" OR "diaphragmatic breathing" OR "social skills training" OR psychotherap*)
- (resilience OR resiliency OR "positive psychology" OR "health promotion" OR "cognitive flexibility" OR "post-traumatic growth" OR "stress-related growth" OR "hardiness")
- (protocol OR program OR treatment OR promotion)

In addition to searches in online databases, manual searches were performed in the reference list of selected articles and times cited lists (ISI database).

The criteria for including the studies in the review were: 1) evaluation of efficacy through studies with randomized controlled designs, non-randomized controlled trials, or open-ended trials of resilience training programs; 2) the purpose of the training program was to strengthen resilience, in order to prepare the individual to cope with future adverse events. Constructs directly related to resilience, such as hardiness or stress inoculation, were also considered valid; 3) the studies were conducted with non-clinical adult samples.

The exclusion criteria used for considering the studies for the review were: 1) studies which were not primarily designed to promote resilience, such as those with a focus on increased well-being or positive emotions; 2) theoretical articles or reviews, book chapters, theses or dissertations; 3) studies which focused on children or adolescents; 4) research that focused on strengthening resilience in physically and/or mentally ill individuals or with a primary focus on assessing resilience in the aftermath of exposure to specific traumatic events (e.g. resilience training after natural disaster); 5) case reports or case series (not open trial); for this instance, we used the definition of Pincus et al. (1993) stating that open trials should include 10 cases or more; 6) studies without a standardized efficacy measure before and after the intervention; 7) studies which performed baseline evaluation without intervention; 8) studies in which the resilience concept was related to another area of study (e.g., physics or mathematics); 9) studies which evaluated the effects of physical activity or yoga, rather than

psychological programs to promote resilience; 10) animal studies.

After the search phase, we performed an analysis of the methodological quality of each article selected for this review, based on an adapted version of the Cochrane Collaboration Tool for Assessing the Risk of Bias [44]. This tool suggests items through which it is possible to assess the risk of bias in each study. We selected seven items that would represent risk of bias consistent with randomized studies (random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, description of concurrent treatment and intent-to-treat analysis) and four risk items consistent with non-randomized studies (blinding of outcome assessment, incomplete outcome data, selective reporting and description of concurrent treatment).

Results

The results of our search can be seen in the flowchart (Figure 1).

Thus, a final set of 13 studies [28-40] were selected for this review (5 of these studies through electronic databases and 8 of them through searches in references or times cited lists). Out of these, 7 were randomized controlled trials, 5 were non-randomized controlled trials, and 1 was an open-ended trial. An additional table file shows each of the selected studies [see Additional file 1].

Of the seven randomized controlled trials considered for this review, three used "resilience scales," one measured the hardiness construct, and three used, as resilience surrogates, scales that assess process and factors related to this construct (such as coping, self-esteem, locus of control, social support and positive affect). The three studies which measured resilience through validated construct-measuring scales found statistically significant change, proving the effectiveness of the intervention. Of the three studies which used as resilience surrogates scales that assess process and factors, two of them found significant changes in the administered scales. The study which assessed hardiness obtained a significantly more positive result. Thus, six out of the seven randomized controlled trials suggested efficacy.

Among the five non-randomized controlled studies, one of them used the concept of hardiness, and four of them used the concept of resilience. The study which measured hardiness found significant change in relation to the control group after the intervention. Among the four studies which investigated resilience, only one controlled study employed a "resilience scale", showing a significant increase of resilience. The other three studies used as resilience surrogates scales that assess process

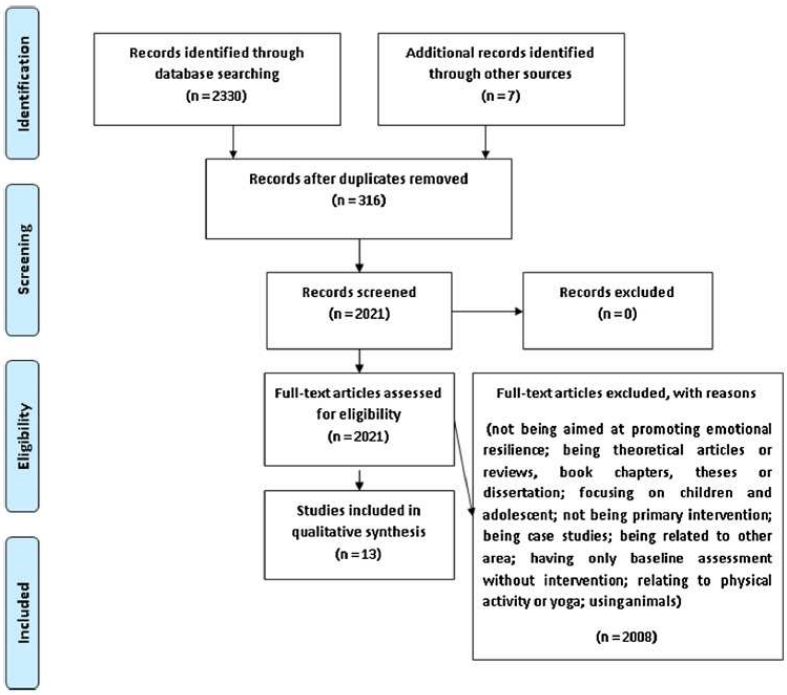

Figure 1 Flowchart of the process of identifying and selecting studies.

and factors related to this construct and found significant changes regarding only some of the factors. Therefore, the non-randomized studies were less consistent than the randomized ones with regard to the efficacy of the intervention.

The samples investigated were composed of employees of companies [29,35], bank employees [38], employees of a university [40], industrial workers [32], customer service professionals [36], managers [28,33], students [31,37], soldiers [30,39] and physicians [34].

The intervention programs used different approaches (positive psychology techniques, CBT, transformational coping, acceptance and commitment therapy, mindfulness, interpersonal therapy, attention and interpretation therapy, relaxation and diaphragmatic breathing).

As for the format of the interventions, four studies used online interventions [32,33,35,36], eight studies used group interventions, and in one study the intervention was based on face-to-face therapy [34]. The number and duration of the sessions varied as well. The shortest intervention had a total of 80 minutes [30] while the longest lasted hours [29]. Some studies did not specify the exact duration of their interventions [38,39]. Since there are only a few studies in total, it is not possible to determine which techniques, approaches, formats, and durations of intervention are most effective in promoting resilience.

Only three of the seven randomized controlled trials had follow-up data (10 weeks [29,33] and 23 days [30]). Among the five non-randomized controlled studies, three had follow-up data (6 months [35,36,39]).

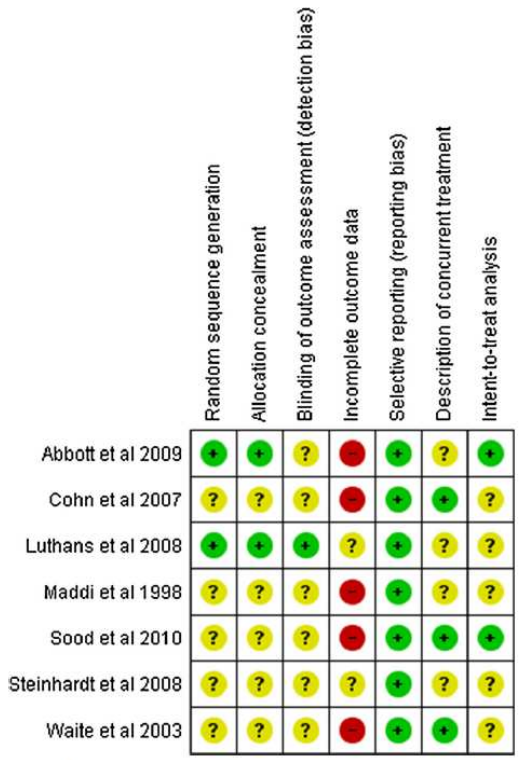

Figure 2 Methodological analysis of randomized controlled trials; + low risk of bias; - high risk of bias; ? Unclear risk of bias.

Assessment of methodological quality

Figures 2 and 3 summarize the different aspects concerning the methodological quality of the randomized and non-randomized studies. Only two out of the seven randomized studies provided information about the random sequence generation and allocation concealment, and thereby ensuring that there was no selection bias in the participants for each group. Only one study reported the existence of blinding of outcome assessment. Regarding incomplete outcome data, none of the randomized studies included complete data about all subjects (including the number of dropouts) in the final analysis, as two of them did not provide any information at all about data loss, and five had a high dropout rate. All of the studies provided data from all of the questionnaires administered at the beginning and end of the research, not omitting possible negative results. Three studies prevented participants from being subjected to other psychotherapeutic treatment at the time of the study, while four did not provide this data. Finally, only two studies performed intention-to-treat analysis.

None of the five non-randomized studies reported whether the assessors were blind to the condition of the participant, only one of these studies included data from all participants in the final analysis, while two of them did not provide this piece of information and did not include data from all participants. Finally, no study reported whether the subjects were undergoing other psychotherapeutic interventions at the same time.

Discussion

This systematic review is aimed at investigating the effectiveness of resilience-promoting programs, which are designed to strengthen individuals, in order for them to cope with future adversity. As far as we know, there has only been one previous systematic review/meta-analysis summarizing the evidence for the effectiveness of these programs. Brunwasser et al. [42] performed a meta-analysis to assess the effectiveness of the PRP, which showed no evidence of it being superior to active control conditions. The program had modest and inconsistent effects [43]. One major difference between the Brunwasser et al. [42] study and our research is that the first focused more on seeking to determine whether PRP was effective in targeting depressive symptoms, whereas our study attempted to assess the effectiveness of promoting

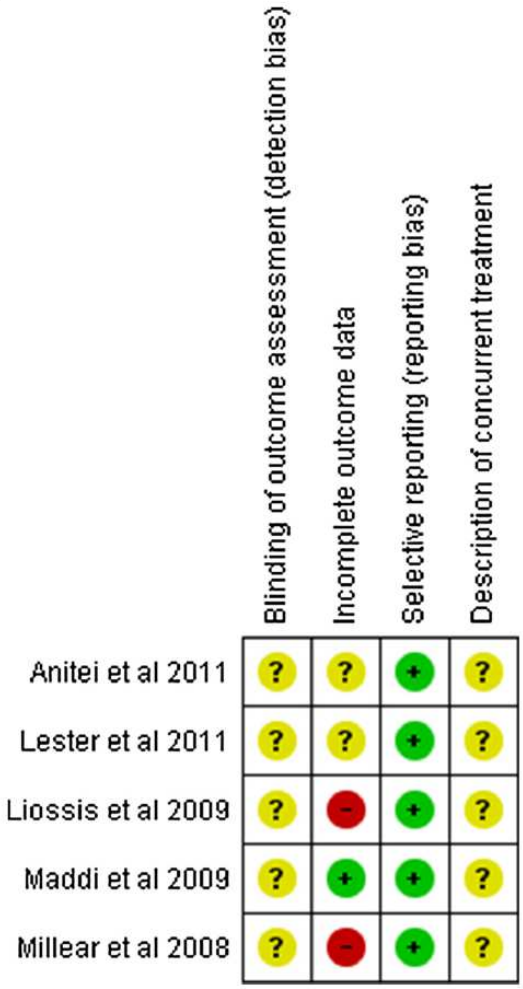

Figure 3 Methodological analysis of non-randomized controlled trials; + low risk of bias; - high risk of bias; ? Unclear risk of bias.

resilience in order to cope with adversity in general. In addition, there is a great difference between the samples of the two studies: Brunwasser et al. [42] focused on children and adolescents, while this systematic review focused on nonclinical adult samples.

Limitations of the studies

The selected studies had several limitations. The main one is concerning the lack of standardization of the resilience concept across the different studies included in this review. While this is common in emerging fields, unification of the concept is needed, so that the evaluation of the intervention effectiveness can be more objective. This is expressed, for example, in the variety of scales used by the authors.

As noted, few studies reported on follow-up data. Since adverse situations are random and unpredictable, it is important that resilience acquired after the intervention is maintained long term. However, we cannot say that the individual who received the intervention will be able to use the acquired skills if adversity occurs in the medium to long term.

Furthermore, no study has investigated the occurrence of adverse situations after intervention. That is, in all of the studies, the improvement in resilience was detected through a change in scores in "resilience scales" or of resilience-related factors. According to Masten & Coatsworth [45], for resilience to be identified, there needs to be a significant threat to the individual and, when facing such threat, the quality of adaptation or development needs to be good. Individuals who have never suffered significant threat cannot be considered resilient. Therefore, we cannot conclude that individuals who showed increased scale scores after the intervention will be effectively resilient after a traumatic event.

Furthermore, the selected studies assessed only the potential benefits of the interventions. No study has considered the possibility of the intervention posing some risk to the participants, nor reported data of adverse effects or the possibility of worsening after preventive action. Bonanno et al. [1] warned, for example, about suicide and eating disorder prevention programs that had negative effects on a portion of participants.

Assessment of methodological quality

Analysis of the methodological quality of the selected studies was greatly hampered by the poor reporting of the studies. Among the randomized clinical trials, information on five of the seven quality items was missing in more than half the studies. It is important to point out that the large majority of these trials were published after the CONSORT Statement of 2001, an expert consensus that listed the items deemed fundamental to reporting standards for a randomized clinical trial, had appeared in three very prestigious medical journals [46,47].

Concerning the included non-randomized studies, none of them provided information on blinding of outcome assessment and description of current treatment. It is also important to stress that all the included non-randomized papers were published after the STROBE statement[53] appeared in 2007 in several medical journals. The Strobe represents for observational studies what Consort is for randomized controlled trials.

So, for the reasons stated above, the evaluation of the methodological quality of the individual studies was compromised by the large amount of missing information. As a consequence, the interpretation of the findings was affected by the poor reporting in several studies.

Limitations of this review

Our study has some limitations. The first is related to the scope of our search, which was conducted using only three databases, albeit the three key databases. Another limitation concerns the bias related to the publication of positive results. We did not contact experts in the field to identify unpublished studies (the so-called "gray literature"). Unfortunately, given the large heterogeneity of studies, it was not possible to obtain a summarizing measure of the results to quantify the effect of the interventions.

Recommendations for future studies

Future studies should be reported according to the guidelines for controlled studies (e.g., CONSORT [46,47]) and non-randomized controlled studies (e.g., Strobe Statement [48]), thus avoiding the lack of crucial information for assessing the quality of these investigations. In addition, validated resilience scales should be used to assess the results. There is a need for improvement in the design of randomized observational trials, with an emphasis on randomized studies, as they are the gold standard for evaluating efficacy. Studies should also investigate factors which may mediate the effects of the intervention, yielding a certainty about the relative contribution of nonspecific factors in the outcome and identifying which specific program components can account for positive effects. The authors of the studies should state the characteristics of responders and non-responders or even of those who are adversely affected by the intervention.

Studies should also include follow-up data, and this should take place over a longer period after the intervention. Longitudinal samples of hazardous occupations such as police officers, soldiers and firefighters, are ideal for this type of study, as it is possible to evaluate the subjects on a baseline before they are exposed to hazardous situations. Moreover, resilience can be measured after the occurrence of dangerous situations.

Conclusion

Most of the studies included reported some degree of improvement in resilience-like variables among those subjects exposed to resilience-promoting programs. This finding was more frequent among randomized controlled trials than in other study designs, which were included in this systematic review. Although comparing the number of studies with positive versus negative findings ("vote-counting") has several limitations, poor operationalization of the constructs and the large heterogeneity in study designs and measurements prevented us from carrying out a meta-analysis. Nevertheless, it is worth noting that positive findings were more consistent among studies which used randomized designs, usually regarded as being less biased to evaluate interventions. These results, albeit fragile, point to the need to continue the investigation of the effectiveness of such intervention programs. It is imperative to design and conduct studies with a better methodology and better reporting (e.g., adherence to Prisma [49]) and to look for better evidence of the actual impact of resilience-promoting programs. Additional efforts should be made to determine the actual effects of the interventions, as this is crucial for the cost-effectiveness calculation of resilience-promoting strategies.

Additional file

Additional file 1: Description of selected studies.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TM conceived of and conducted the study. LW contributed by reviewing the literature and writing this paper. RG assisted in drafting the manuscript. EC supervised statistical analysis and helped interpret the results. LV critically commented on the draft manuscript. IF participated in coordination, assisted in drafting the study and consulted on the study methodology. PV coordinated and helped to draft the final version of the manuscript. All authors read and approved the final manuscript.

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A VIRTUAL REALITY EXPOSURE THERAPY FOR PTSD PATIENTS CONTROLLED BY A FUZZY LOGIC SYSTEM

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Abstract: This paper describes the main characteristics of two integrated systems that explore Virtual Reality technology and Fuzzy Logic to support and to control the assessment of people with Post-Traumatic Stress Disorder during the Virtual Reality Exposure Therapy. The integration of different technologies, the development methodology and the test procedures are described throughout the paper.

Keywords: Virtual Reality, Post-Traumatic Stress Disorder, Exposure Therapy, Fuzzy Logic.

Introduction

Nowadays, the increasing production exploring the Virtual Reality technologies is undeniable, particularly in the area of Medical Science. Although the three-dimensional (3-D) virtual environments have been frequently used in the neuropsychological area, the use of intelligent strategies for monitoring the patients' activities is rare. In general, the three-dimensional (3-D) environments open new possibilities to create environments suitable for simulations in the rehabilitation processes of

cognitive functions loss caused by traumas and injuries. These environments allow the simulation of real situations integrated with psychological evaluations, proposing tasks "with low risks to the patient". These characteristics stimulate the growing interest in the Virtual Reality Exposure Therapy (VRET) applications.

Many people suffer different traumatic events, but only 10% to 60% of men and 50% of women develop lifelong Posttraumatic Stress Disorder (PTSD) (Masci and Range, 2001). PTSD involves a constant sense of fear generated by the improper consolidation of trauma in the autobiographical memory (Brewin, Dalgleish and Joseph, 1996). Foa and Kozak (1986) argued that some exposure strategies to feared situations are common in psychotherapies for anxiety and that confrontation is an effective treatment for the anxiety disorder. However, for some patients it is difficult to immerse themselves in a scene due to avoidance traumatic symptoms. Thus, the use of new technologies could facilitate the treatment of these patients. In this sense, virtual reality has been used as a tool for exposure and it has achieved positive results in the treatment of several anxiety disorders, including Specific Phobias, Social Phobia, Panic Disorder and PTSD (Meyerbröker and Emmelkamp, 2010).

This paper presents two integrated environments for PTSD treatment: the ARVET (Virtual Environment Exposure to Trauma), a 3-D virtual environment to stimulate the memory of the patient with PTSD and the SAPTEPT (Evaluation System to Patients with Posttraumatic Stress Disorder), which explores the Fuzzy Logic to support the patients evaluation submitted to the ARVET. The ARVET presents some scenes that incorporate stimulus to the emotional processing, allowing an increase or decrease of the emotional answer. The SAPTEPT combines the perceived anxiety, indicated by the patient and the cardiac rate to classify the patient's level of anxiety as mild, moderate or severe. This classification will help the therapist to control the stimulus level provided by the ARVET environment.

This work is organized into 4 sections. Section 2 describes the main concepts related to the proposed systems; section 3 details the environment and presents the expected interaction results between the systems. Section 4 concludes the work and presents future research directions.

Methodology

This section will present the concepts essential for understanding the software development process: the Post-Traumatic Stress Disorder treatment, the Virtual Reality technology and some aspects about the Fuzzy Logic systems.

PTSD Treatment

PSTD involves a constant sense of fear generated by the improper consolidation of autobiographical memory of the trauma (Brewin, Dalgleish & Joseph, 1996). People with PTSD can not adapt back to their usual life. Thus, a re-reading of the environment they live in will be fundamental to reorganize the experienced situations.

In recent years, different theoretical and practical approaches have been explored to assess and rehabilitate cognitive processes such as visual perception, attention and memory, as well as training the motor skills (Ready, Pollack & Rothbaum, 2006). The Cognitive-Behavioral Therapy (CBT) is considered a good option for Post-traumatic Stress Disorder (PTSD) treatment. In general, it is performed by exploring techniques that include Psycho Education, Cognitive Restructuring Techniques, Anxiety Management, Imaginary Exposure and Live Exposure. Its aim is to break the cycle of symptoms leading to a habituation of stimuli. Moreover, it attempts to develop relaxation skills, enabling the patients' control of their emotional and physiological response in order to decrease their reaction when faced with stressful situations.

Virtual Reality

The Virtual Reality technology has been widely used in the cognitive stimulation, providing opportunities to offer some situations closer to the real world. Burdea and Coiffet (2003) defines the applications of Virtual Reality as a three-dimensional virtual environments that presents real-time graphics rendered by a computer, in which the user, via body position sensors or user-input devices, controls the viewpoint or the orientation of displayed objects.

In the last years virtual reality exposure therapy (VRET) has become a viable alternative for exposure in vivo, the gold standard for the treatment of anxiety disorders (Meyerbröker and Emmelkamp, 2010). In spite of exposure therapy, some patients find it difficult to imagine themselves in the scene due to avoidance symptoms, leading some of them to abandon treatment. In some studies, dropouts and non-response rates can reach 50% of cases (Schottenbauer, Glass, Arnkoff & Gray, 2008). Therefore, the use of new technologies could smooth the progress of exposure to avoidant patients. In this sense, virtual reality has been used as a tool for exposure and it has achieved positive results for treatment of several anxiety disorders, including Specific Phobias, Social Phobia, Panic Disorder and PTSD (Meyerbröker and Emmelkamp, 2010).

The Virtual Reality Exposure Therapy (VRET) facilitates the emotional engagement of patients with PTSD during exhibitions, outlining the avoidance symptoms, and therefore facilitates the therapist control (Ready, 2006). According to Rothbaum and Mellman (2001), the sense of presence induced by the virtual environment, which is rich in sensory stimuli, helps processing the emotional memories related to trauma. This technological device allows gradual exposure to the feared environment, according to patient needs. In this sense, some experiments have been done worldwide. Torres and Nunes (2011) used three-dimensional virtual environments with characteristics of "Serious Games" to simulate situations aimed at training and therapy. These games allow the simulation of real-world situations, providing training activities that stimulate cognitive functions and

psychomotor skills. The study conducted by McLay, Wood and Webb-Murphy (2011) evaluates the effectiveness of the VRET in the treatment of PTSD patients on the spot to combat in Iraq. According to these authors, three-dimensional virtual environments can be used to simulate situations aimed at training and therapy. In general, there is no automated control that gives the therapist results from the integration of different biofeedback variables obtained during the VRET. As an alternative, the inclusion of intelligent techniques, as Fuzzy Logic, can help to alleviate this problem by reducing the need of therapist decisions.

Fuzzy Logic

According to Zadeh (Zadeh, 2009) Fuzzy logic adds to bivalent logic an important capability: to reason precisely using imperfect information. Imperfect information is information which in one or more dimensions is imprecise, uncertain, incomplete, unreliable, vague or partially true. Fuzzy Logic uses the formal principles of approximate reasoning and searching to model imprecise reasoning that are usual in the human decisions. It has been a powerful tool, which is able to capture inaccurate information described in natural language and translate them to a qualitative and quantitative form, allowing the position of super categories.

Traditionally, a logical position has two extremes: "true" or "false". However, in fuzzy logic, a premise varies in degree of truth or relevance in the range 0-1, which leads to concepts of partly true or partly false. The control performed by the fuzzy logic mimics behavior-based rules, rather than a control explicitly restricted to deterministic models. The goal of Fuzzy Logic is to generate a logic output from a set of non-precise inputs, noisy, incomplete or even absent ones. According to Braga, Barreto and Machado (1995), "Fuzzy Math is an attempt to bring together the characteristic precision of mathematics and the inherent imprecision of the real world, born from the deep desire to better understand the mental processes of reasoning".

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Figure 1: The ARVET environment: general scenes views

The exposure to virtual environments can generate reactions and perceptions, which are difficult to be assessed jointly by the therapist. Aiming to integrate these data and classify the patient in real time during the VRET process, we developed an application that explores the techniques of Fuzzy Logic - the SAPTEPT - System of the Evaluation of the Patients with Posttraumatic Stress Disorder.

The LINPES researchers distinguish the groups of Psychometric and Psycho-physiological variables, whose values are collected during evaluations. Psychometric scales are established by filling in forms of self-report and Psycho-physiological data are obtained through the Biopac (Physiological data acquisition system).

Figure 2: An example of a scene of an accident: a person was hit by a bus

The scale used to measure the patient level of anxiety is the SUDS - Subjective Units of Disturbance Scale that assesses the degree of anxiety during the trauma stimulation. The SUDS is a range of integer values

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Figure 2: An example of a scene of an accident: a person was hit by a bus

The scale used to measure the patient level of anxiety is the SUDS - Subjective Units of Disturbance Scale that assesses the degree of anxiety during the trauma stimulation. The SUDS is a range of integer values

between 0 and 10 that measures the intensity of disturbance or distress experienced by an individual when subjected to trauma. For example, the individual perceives their level of anxiety at the time of exposure to the trauma, ranging from "no anxiety" to "high anxiety".

A meta-analysis conducted by Pole (2007) identified the Heart Rate as a Psycho-physiological group variable that changes when PTSD patients are exposed to a traumatic stimulus. Thus, the heart rate level confirms or not, the patient's anxiety. In this case, we consider the level of anxiety reported by the patient and the heart rate.

The Fuzzy Logic used in SAPTEPT captures inaccurate information, described them in natural language and converts them in qualitative information. The Fuzzy Logic can control the behavior of a system by changing the inputs according to a set of inference rules. These behavior-based rules model the system operations. The method, from the viewpoint of Fuzzy Logic, allows us to recognize patterns of anxiety gradual scale (Mild, Moderate, and Severe) in real-time measurements, when the psychometric scales (anxiety) and psycho-physiological (heart rate) are performed (Figure 3). Pattern recognition is one of the oldest and most obvious applications in the area of Fuzzy Theory.

This system classifies the patient's degree of anxiety while they are navigating in the ARVET. It indicates the difficult level changes that must be performed in the ARVET scenario. All tasks, scenes and the patient classification in the Fuzzy System were proposed by a group of psychologists, which are responsible to test these systems with their patients.

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Table1. This table describes the fuzzy inference results from the heart rate X anxiety variables. For example, when the heart rate is moderate and the patient say that his level of anxiety is mild, the system will classify that the patient level is moderate.

	Heart Rate		
Anxiety level	Mild heart rate	Moderate heart rate	Severe heart rate
Mild	*MILD*	*MODERATE*	*SEVERE*
Moderate	*MODERATE*	*MODERATE*	*SEVERE*
Severe	*MILD*	*SEVERE*	*SEVERE*

The SAPTEPT was developed in Python programming language and shows the classification of the patient every five minutes from the start of the evaluation. The results form the SAPTEPT system must be monitored by a therapist.

After the patient is classified in a new level, the therapist will ask him to open a door and enter in a new scene (Figure 4) that will present situations according to the patient classification.

Figure 4. The doors where the patient must enter to change the level of stimulation

A pipeline of the system use is presented in Figure 5.

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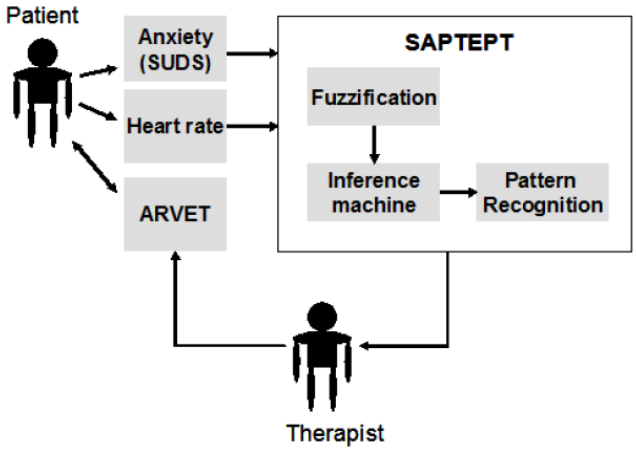
Figure 5. The pipeline of the system use.



Discussions

Aiming at analyzing some aspects of the prototype, we developed an evaluation experiment with two psychologists. This evaluation considered some usability aspects as: navigation facility; learning facility; response time; realism of scenes; pleasantness of the scenes; adequacy of objects in the tasks and matching colours.

The initial results of this experiment indicated that the 3-D environment has a high level of usability, but some aspects must be changed: some colors, some architectural details and the speed of buses and cars. At the other side, the Fuzzy system must have its interface slightly modified in order to facilitate responses from users about their anxiety level.

After those steps, the system will be used by a group of people with Posttraumatic Stress Disorder to measure its efficacy in control the level of tasks according to the patient evolution.

The prototype can be used in the first instance for cases of patients diagnosed with PTSD due to hits or car accidents (very common in large urban centers).

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Conclusions

In Brazil, there is a growing interest in the Virtual Reality technology to support health care procedures. In this sense, we need new software and new treatment strategies, where patients may have unrestricted access to the exercises with therapists precisely monitoring the results. Thus, in this case, the virtual environment must have some mechanisms to control user navigation and generate automatic reports to the therapist.

However, the development of such software depends on the integration of different technologies and expertise. In this context the Fuzzy Logic offers wide possibilities to control the user answers and support the therapist decisions.

This paper presented some results of a project that has two objectives. The first one is associated with the technical questions related to the intelligent strategies to support decisions and the second deals the integration of the intelligent modules with specific virtual three-dimensional environments. The next step of this research is to integrate the SAPTEPT with the ARVET.

Some therapists (psychologists) tested the system and proposed some changes that were considered in a new version of the system. The system is currently being tested with a group of people with PSTD associated to car accidents.

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Vivência de situações traumáticas

Paula Ventura e Raquel Menezes Gonçalves

O ser humano vive frequentemente se deparando com situações traumáticas, que ameaçam sua integridade física e/ou mental. Situações como guerras, catástrofes naturais, assaltos, acidentes, estupros idealmente não deveriam existir. Não teríamos, portanto, que lidar com as consequências danosas desses eventos. Mas, infelizmente elas fazem parte da existência humana e precisamos aprender formas de prevenir o adoecimento depois da vivência dos referidos eventos, bem como fortalecer aqueles que tenham que enfrentá-los cotidianamente, de modo a diminuir a probabilidade de que eles venham a desenvolver transtornos mentais.

O nosso organismo possui uma tendência natural para manter-se em equilíbrio. Esse equilíbrio é chamado pelos especialistas de *homeostase*. Quando passamos por algum evento traumático, é natural reagirmos a esse evento ficando constantemente com medo e sentindo muita ansiedade e tristeza, o que muitas vezes nos impede de cumprir obrigações ou de praticar atividades que antes nos proporcionavam prazer, como sair de casa ou trabalhar.

Para que o nosso corpo continue saudável, é interessante que ele volte a funcionar de maneira equilibrada. Isso acontece uma vez que o evento estressante acaba ou que conseguimos nos adaptar a esse evento. Dessa forma, voltamos a nos comportar como antes, diminuindo a ansiedade e tristeza relacionadas ao trauma e retomando as atividades de trabalho e lazer. No nosso corpo, as funções que foram alteradas anteriormente voltam ao seu estado normal. Se não houvesse esse retorno ao equilíbrio, nosso corpo sofreria as conseqüências do esforço excessivo, tornando-nos mais propensos a desenvolver doenças no futuro, como problemas cardíacos, por exemplo. Esse retorno ao equilíbrio é, portanto, muito importante pois dessa maneira é mais provável que consigamos manter o corpo saudável e o bem-estar.

A maioria das pessoas sofre alterações na maneira de ver o mundo, no comportamento e nos sentimentos após passar por um evento traumático. Um assalto, por exemplo, pode levar alguém a ver o mundo como perigoso, a sentir medo constante em simplesmente sair de

casa e, consequentemente, a sair só quando extremamente necessário. Entretanto, com o tempo o trauma é processado e a pessoa consegue modificar esse pensamento radical para um mais adaptativo, como “o mundo não é totalmente seguro, mas também não é totalmente perigoso”, e consequentemente diminuir seu grau de ansiedade e retomar suas atividades diárias que antes estavam sendo evitadas. Contudo, às vezes o evento pelo qual passamos é tão estressante e causa tanto sofrimento que algumas pessoas passam a ficar constantemente com medo, sentindo muita ansiedade e angústia, o que muitas vezes as impede, mesmo depois de muito tempo, de processar adequadamente a situação vivida. Dessa forma, é difícil voltar a trabalhar, a sair de casa ou até mesmo ficar com a família.

Nos últimos tempos, vimos a violência crescer de forma desmedida nos grandes centros urbanos. Como antes mencionado, não estamos livres da possibilidade de sofrermos acidentes, de presenciarmos ou sermos vítimas de violência tanto física quanto psíquica, de acontecerem desastres naturais, recebermos ou vermos alguém próximo receber o diagnóstico de alguma doença grave ou de presenciar outros eventos perturbadores. Dessa maneira, muitas pessoas estão constantemente sendo submetidas a situações traumáticas. Mesmo assim, a maioria das pessoas que passa por alguma dessas situações traumáticas não desenvolve nenhum transtorno psiquiátrico. Muitas vezes diante de situações extremamente difíceis uma pessoa consegue se recuperar bastante bem e levar a vida normalmente, mesmo ficando inicialmente abalada. Já em outros casos o indivíduo pode vir a desenvolver uma série de transtornos psiquiátricos, dentre eles a depressão, transtornos de ansiedade ou transtornos alimentares, por exemplo. Um dos desafios atuais dos especialistas no assunto é descobrir o que leva algumas pessoas a desenvolver essas doenças e outras, não. Seria o tipo de evento traumático? Seriam fatores biológicos que tornariam algumas pessoas mais vulneráveis a esses transtornos? Será que existem características individuais que ajudem algumas pessoas a se proteger de uma eventual patologia?

Transtornos relacionados a eventos traumáticos:

Um transtorno que está diretamente relacionado a um evento traumático é o *Transtorno de Estresse Pós-Traumático.* Para simplificar, chamaremos esse transtorno de TEPT. Uma pessoa desenvolve TEPT somente após sofrer ou testemunhar a ocorrência de um evento traumático. A probabilidade de desenvolvimento do transtorno aumenta se aumentar a “dose” de exposição a situações nocivas, ou seja, a intensidade, gravidade ou número de vezes a que a pessoa é exposta. Para ilustrar podemos mencionar o caso de um

cobrador de ônibus que é exposto a dez assaltos à mão armada. O grande número de vezes a que foi exposto a uma situação de risco aumenta a probabilidade de desenvolvimento de transtornos psiquiátricos. Para que o TEPT seja diagnosticado, o indivíduo tem que ter vivenciado ou testemunhado um ou mais eventos envolvendo morte ou ameaça à integridade física própria ou de outros e ele deve reagir a isso com intenso medo, impotência ou horror. Não caem nessa categoria, portanto, problemas conjugais ou brigas com o chefe, já que, na grande maioria das vezes eles não envolvem risco de morte. No desenvolvimento do TEPT, três grupos de sintomas devem ocorrer:

- No primeiro grupo são incluídos sintomas de *revivescência*. O trauma é constantemente revivido pelo indivíduo acometido através de lembranças intrusivas (imagens do evento, pensamentos ou percepções), pesadelos envolvendo o evento traumático, *flashbacks* que envolvem a sensação de o evento estar ocorrendo novamente e grande sofrimento psíquico quando o indivíduo é defrontado com estímulos que lembrem o trauma.
- O segundo grupo de sintomas envolve *reatividade fisiológica* provocada por estímulos relacionados ao trauma. Neste grupo de sintomas, o indivíduo sente-se irritável ou passa a ter explosões de raiva, fica vigilante todo o tempo, fica facilmente sobressaltado e com dificuldade de se concentrar em atividades rotineiras.
- Finalmente, no terceiro grupo de sintomas observa-se *esquiva* persistente desses estímulos e *entorpecimento emocional*, que podem ocorrer da seguinte forma: esforços para evitar pensamentos e sentimentos associados com o trauma, esforços para evitar atividades, locais ou pessoas associadas com o trauma, redução do interesse nas atividades, sensação de distanciamento em relação a outras pessoas, sentir-se emocionalmente entorpecido ou incapaz de ter sentimentos amorosos pelas pessoas que lhe são mais próximas e falta de expectativa positiva em relação ao futuro.

O TEPT é diagnosticado se esses sintomas persistirem por 4 semanas após o trauma e ocasionarem comprometimento na vida social e relacionada ao trabalho. A esquiva fóbica, ou seja, a evitação de estímulos que lembrem o trauma, em geral interfere nos relacionamentos interpessoais, o que pode levar a pessoa a se envolver em conflitos conjugais, divórcio ou perda do emprego, pois o medo constante a impede de realizar atividades no trabalho ou com

o cônjuge. Sintomas associados podem ocorrer, principalmente se o estressor for interpessoal, como abuso sexual, violência física, assalto e outros. Além disso, pode ocorrer prejuízo na modulação do afeto (o indivíduo pode apresentar afeto inadequado, como chorar em situações alegres ou rir nas tristes), comportamento autodestrutivo e impulsivo (que inclui uso abusivo de álcool e drogas), sintomas chamados dissociativos (sentir-se como estando num sonho ou fora de si, por exemplo), queixas físicas (como dores de cabeça, dores musculares, etc.), sensações de se inútil, vergonha, desespero ou desamparo, sensação de dano permanente, mudança na maneira de ver a si, o mundo e o futuro, hostilidade, retraimento social, sensação de constante ameaça, prejuízo no relacionamento com outros, ou uma mudança no jeito de ser do indivíduo.

Acredita-se que no Transtorno de Estresse Pós-traumático o indivíduo apresente dificuldade de processar o acontecimento do trauma em conjunto com as outras informações que mantém arquivadas em sua memória. As situações por nós vividas são registradas na nossa *memória autobiográfica*, que tem um contexto espaço-temporal específico, ou seja, lembramos quando e onde aconteceram. Por exemplo, as pessoas em geral se lembram de dias especiais como o nascimento de um filho, o casamento ou o primeiro emprego. São capazes de descrever a situação por elas vividas, quem estava presente, o local em que ocorreu e em que data, muitas vezes. Apesar de ser agradável lembrar-se de eventos prazerosos por nós vividos, tendemos, por outro lado, a não querer evocar lembranças desagradáveis. Eventos traumáticos são, por definição, desagradáveis. Apesar disso, pessoas que passaram por alguma situação traumática e não desenvolvem o TEPT têm condições, caso queiram, de verbalizar o que aconteceu com elas de forma detalhada, seguindo a ordem dos acontecimentos. Contudo, acredita-se que pessoas com TEPT apresentem dificuldade de arquivar as informações do trauma junto com outras memórias autobiográficas, havendo um armazenamento diferente do que as pessoas costumam fazer. Existe um outro tipo de memória que denominamos *memória implícita*. Esta engloba, dentre outros aspectos, aquelas relacionadas a hábitos ou emoções. Quando andamos de bicicleta ou dirigimos, não é comum descrevermos cada passo do que estamos fazendo (liguei o carro, pisei na embreagem, passei a primeira marcha, etc.). Se você tentar fazer isso, perceberá que é difícil falar dessa memória de maneira fluente, como se estivesse contando como foi o seu último aniversário. Você simplesmente faz sem precisar descrever, porque essa é uma memória automática, ativada sem que tenhamos que fazer esforço para evocá-la. A memória de um evento traumático, por não ser um hábito, e sim uma situação que foi vivida, deveria ser arquivada junto às outras memórias autobiográficas, mas indivíduos acometidos com TEPT teriam dificuldade de

integrar a memória traumática no sistema de memória autobiográfica e tenderiam a manter as informações no sistema de memória relacionado à memória implícita. As informações sensoriais vividas durante um evento traumático, tais como a voz do assaltante, a cor da roupa que ele usava, o cheiro do ambiente, tendem a ficar armazenadas em um sistema de memória implícita, sem serem corretamente integradas pelo sistema de memória autobiográfica. A não integração levaria à dificuldade de verbalização do trauma e de controle emocional facilitando a ocorrência de pesadelos e *flashbacks* acerca do evento traumático. É como se os sintomas de revivescência fossem uma tentativa do cérebro de processar adequadamente essa memória, ou seja, de arquivá-la onde ela deveria estar arquivada. É interessante notar que pessoas com TEPT, ao fazerem o relato da experiência traumática, tendem a verbalizá-la de maneira não tão fluente quanto verbalizariam outros eventos. A fala é marcada por breves pausas, que não estão presentes durante o relato de outras situações vividas. Seria como se eles estivessem descrevendo cada passo de como levaram um carro de um ponto a outro. Contar o evento traumático, em detalhes, tolerando o desconforto auxilia na incorporação do evento à memória autobiográfica, melhorando os sintomas de medo a ele associados. Se o indivíduo não conseguir fazê-lo, a terapia pode ser de grande valia neste sentido. O terapeuta, respeitando o ritmo do paciente, pode ajudá-lo a entrar em contato com memórias que, por serem muito desagradáveis, são por ele evitadas.

Essa regra vale para qualquer evitação que o indivíduo esteja fazendo após vivenciar um trauma. Assim como a evitação da memória do trauma, ocorre a evitação de estímulos relacionados a ele, como pegar ônibus se você foi assaltado em um, passar em frente a um hospital no qual você tenha ficado internado após um acidente, conversar com pessoas que estavam presentes no momento do trauma, etc. Mais uma vez, a melhor solução para diminuir a ansiedade relacionada a esses estímulos e enfrentá-los, e não evita-los como instintivamente fazemos. O enfrentamento de situações que passamos a associar a um perigo, mas que na realidade não são perigosas, auxilia na habituação àquele estímulo. Imagine que você gosta muito de uma música, e, portanto, passa a ouvi-la várias vezes ao dia. Dentre de pouco tempo você terá enjoado daquela música e ela não provocará a alegria que provocava antes, pois você se habituou a ela. Da mesma forma funciona o enfrentamento de estímulos que provocam ansiedade. Falar sobre o trauma e enfrentar situações, mesmo sendo difícil num primeiro momento, favorece a habituação.

Outra patologia que comumente acomete pessoas que passaram por eventos traumáticos é a depressão. Muitas pessoas que desenvolvem TEPT acabam desenvolvendo também depressão. É comum acreditarmos que depressão é o simples fato de ficarmos tristes,

mas na verdade existem muitos outros sintomas por trás desse transtorno. Depressão é uma doença grave que pode comprometer enormemente a vida do indivíduo acometido, inclusive podendo levar ao suicídio. A boa notícia é que, assim como o TEPT, a depressão tem tratamento comprovadamente eficaz, e quanto mais cedo ele é iniciado, maiores as chances de recuperação. Alguns sintomas que acompanham a depressão são: humor triste ou deprimido, perda de prazer em atividades que antes eram prazerosas, insônia ou hipersonia (dificuldade para dormir ou manter o sono ou dormir por muito mais tempo do que era de costume), alteração no apetite (comer mais ou bem menos do que de costume), cansaço constante, dificuldade de prestar atenção ou de lembrar fatos que antes se costumava lembrar, dentre outros. Uma pessoa deprimida costuma interpretar as situações de maneira negativa, mesmo quando não o são. Tende a ter uma visão negativa de si, do mundo e do futuro, valorizando mais os "contras" de uma situação do que os seus prós. Essa é uma tendência natural da depressão, e o indivíduo acometido não consegue, a princípio, ter controle sobre isso. A interpretação negativa das situações está relacionada ao surgimento de sentimentos negativos, como tristeza, por ex., e a comportamentos desadaptativos, como a tendência a isolar-se, o que estimula ainda mais a ruminação de pensamentos negativos, virando um ciclo vicioso:

Pensamentos negativos → sentimentos negativos (tristeza) → comportamentos desadaptativos (isolamento) → pensamentos negativos

Enfrentar a depressão exige esforço. É importante driblar a falta de vontade de realizar atividades e ficar isolado na cama, ruminando pensamentos negativos. Mas é possível quebrar o ciclo vicioso que mantém a depressão lidando tanto com os pensamentos quando com os comportamentos desadaptativos. Formular novas maneiras de interpretar as situações pode levar a sentimentos e comportamentos mais positivos. Você já reparou que pessoas que passam por situações parecidas ou até mesmo pela mesma situação tendem a vê-la de maneiras diferentes? Ver a situação de outros ângulos pode não ser fácil, mas é possível com algum treino e ajuda de profissionais. Além disso, alterar o comportamento também pode quebrar o ciclo vicioso da depressão. Ao invés de ficar em casa, isolado, fazer um plano de atividades a serem cumpridas durante a semana também pode influenciar a mudança de sentimentos e pensamentos negativos.

Mas lembre-se de que para que quaisquer destes diagnósticos sejam dados e tratados corretamente, é importante que a pessoa vá a um especialista (psiquiatra ou psicólogo).

Fatores de proteção: como se prevenir contra o desenvolvimento desses transtornos?

Existe alguma maneira de nos prevenirmos de patologias como o TEPT? Alguns pesquisadores da área vêm chegando a conclusões interessantes. Eles percebem que algumas características da personalidade podem auxiliar na recuperação mais rápida das consequências de um evento traumático, funcionando como fatores de proteção contra o desenvolvimento de doenças. Em um estudo realizado em 1994, dois autores americanos chamados Garmezy e Masten concluíram que existem três grandes fatores de proteção em crianças e adolescentes que vivem em situações adversas: o primeiro deles se refere a traços individuais, como inteligência, auto-estima, capacidade de resolver problemas e competência social. Num outro grupo de fatores estaria o apoio social proporcionado pela família. No terceiro grupo estaria o apoio social externo, ou seja, aquele proporcionado por grupos fora do ambiente familiar, como escola, grupos de igreja, etc. Embora o estudo desses autores identifique essas características em crianças e adolescentes, acredita-se que o mesmo ocorra em adultos. Podemos imaginar que adultos com essas características também sejam menos susceptíveis a desenvolver patologias em decorrência de traumas. Selecionamos, então, duas importantes características citadas por autores da área que funcionam como fatores de proteção contra as conseqüências danosas ocasionadas por um evento estressor. Existem outras características consideradas importantes. Contudo, para os propósitos deste livro, consideramos as características descritas abaixo mais interessantes.

A primeira delas é a chamada *resiliência.* Uma pessoa resiliente é aquela que consegue adaptar-se às adversidades, tendo alta capacidade de superação. É aquela pessoa que tem mais facilidade em lidar com as adversidades, ou na linguagem popular, “sacudir a poeira e dar a volta por cima”. A literatura mostra que pessoas mais resilientes são comumente mais extrovertidas, otimistas, têm laços afetivos mais fortes e tendem a contar com mais apoio social (que será descrito abaixo) do que pessoas menos resilientes. Essas pessoas estão menos propensas a desenvolver patologias, e importa menos o tipo de trauma pelo qual elas passaram, mas sim a maneira como a pessoa lida com o que aconteceu. Mesmo sendo uma situação muito grave, a maneira de olhar o que aconteceu pode ajudar a superar as conseqüências indesejáveis do trauma. Existem pessoas que surpreendentemente melhoram a qualidade de vida após passar por um trauma, pois passam a aproveitar mais o dia-a-dia e a valorizar cada momento que passam com as pessoas queridas.

Mas uma pessoa que não é resiliente está fadada a ser mais vulnerável a essas patologias? Felizmente não, já que podemos desenvolver a capacidade de resiliência. Uma

pessoa que não é, a princípio, resiliente, pode desenvolver alguns traços quando aprende a ver a situação de outros ângulos. Isso é visto na prática em pacientes que desenvolveram TEPT após uma situação traumática e conseguiram superar a doença após tratamento psicológico. Alguns estudos realizados com essas pessoas concluíram que, após o tratamento, elas mostravam mais traços de resiliência do que no início dele, indicando que esse aspecto foi desenvolvido em maior ou menor grau durante o tratamento.

O segundo fator que nos ajuda a lidar com eventos traumáticos é o *apoio social*. Apoio social refere-se ao contato com pessoas, como familiares, amigos ou profissionais de saúde, que nos auxiliem em atividades práticas e nos proporcionem apoio emocional. Atualmente, existem evidências científicas de que o apoio social pode atuar na prevenção de consequências maléficas de um trauma, sendo considerado outro importante fator de proteção contra o TEPT ou um fator de risco naquelas pessoas que não contam com apoio social após o trauma.

Podemos identificar essa característica levando em conta o número de pessoas com quem nos sentimos à vontade e podemos falar sobre quase tudo (incluindo parentes e amigos), nossa participação em atividades em grupo, como esportes ou cursos, por exemplo, o número de pessoas com quem podemos contar quando ficamos doentes, quando precisamos desafabar ou ouvir conselhos, em momentos de diversão, pessoas que demonstrem afeto por nós e nos façam sentir queridos.

Nosso corpo também responde ao apoio social de maneira benéfica à saúde. É sabido que ele reduz a carga alostática - padrão de resposta do organismo que ocorre quando não é possível se adaptar ao estímulo estressor, o que gera um desequilíbrio da homeostase – protegendo, assim, o organismo de doenças relacionadas ao trauma, como doenças cardiovasculares, por exemplo. Portanto, a importância do apoio social pode ser percebida tanto na saúde mental quanto na saúde física.

Outro fator que funciona como protetor contra o desenvolvimento de patologias após a ocorrência de um evento traumático é a capacidade percebida pelo indivíduo de ter controle sobre a situação, ou a chamada *auto-eficácia*. Bandura, autor que inicialmente descreveu a auto-eficácia, a define como a crença nas habilidades individuais de organizar e pôr em prática os recursos para administrar situações futuras. Uma pessoa que apresenta alta auto-eficácia tende a ter sucesso em atividades realizadas. Se alguém acredita que é capaz de lidar com um trauma da melhor maneira possível, a chance de sair-se bem nesse objetivo aumenta.

É possível também desenvolver essa característica. Um fator que pode aumentar o senso de controle é a previsibilidade da situação. Se estamos de certa forma acostumados ou

sabemos o que pode acontecer, é mais fácil manter o controle numa situação. Dessa forma, alguns profissionais que normalmente são expostos a situações traumáticas (como policiais ou bombeiros) podem desenvolver maior senso de controle antes mesmo de presenciar uma situação traumática caso recebam treinamento voltado para isso.

Outra forma de aumentar o senso de controle é focar a atenção em aspectos menos drásticos de evento traumático. Tirar a atenção de aspectos amedrontadores, como o sofrimento intenso de alguma vítima, pensamentos de desamparo e de iminência de morte podem funcionar como estratégias válidas de proteção.

Finalmente, aumentar a previsibilidade de fatores internos também pode funcionar. Não estamos acostumados a ter reações orgânicas extremas, como sentir os músculos paralisados, falta de ar, sentir o coração batendo rápido demais, tonteira, náuseas. Sentir tudo isso de uma vez pode ser extremamente assustador e certamente contribuem para a sensação de falta de controle. Contudo, essas sensações corporais podem ser provocadas em ambiente seguro, promovendo a habituação e aumentando o senso de controle quando elas ocorrerem em situações realmente perigosas. A utilização dessa estratégia no treinamento de profissões de risco pode auxiliar no preparo desses profissionais, funcionando como um fator de proteção contra o desenvolvimento de patologias decorrentes de um trauma.

Resumo

Portanto, seguir os passos expostos nesse capítulo pode ser de grande valia para lidar de maneira mais saudável com a vivência de situações traumáticas. Esses passos estão resumidos abaixo:

Modificar a maneira de vermos a situação, monitorando nossos pensamentos e modificando-os caso estejam distorcidos. Isso ajuda a desenvolver nossa capacidade de superação (a resiliência).

Enfrentar a memória do trauma e estímulos relacionados a ele, promovendo, assim, a habituação.

Aumentar o senso de controle da situação, ou trabalhar nossa auto-eficácia.

Buscar nossa rede de apoio social, ou seja, estar com amigos, familiares, grupos de atividades, enfim, estar com pessoas com quem se possa contar num momento de dificuldade.

Procurar ajuda especializada, caso lidar com o trauma seja mais doloroso do que pensaríamos que fosse.

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TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO RESISTENTE AO TRATAMENTO FARMACOLÓGICO: RELATO DE CASO

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INTRODUÇÃO

O tratamento cognitivo-comportamental para o Transtorno de Estresse Pós-traumático (TEPT) é considerado eficaz. Inúmeros estudos publicados na literatura científica testaram com sucesso protocolos de tratamento com esta base teórica em pacientes com histórico de eventos traumáticos diversos, de diferentes idades, em quadros agudos ou crônicos e em diferentes culturas, tanto com tratamento individual quanto em grupo (Cahill, Rothbaum, Resick & Follette, 2009).

O modelo cognitivo do TEPT entende que um evento traumático pode reforçar crenças relacionadas à vulnerabilidade previamente existentes ou contrastar com crenças muito rígidas de segurança a tal ponto que o processamento da memória do trauma fica prejudicado. Dessa forma, interpretações distorcidas levam a um senso constante de medo, ansiedade, vergonha, raiva, etc., e a comportamentos desadaptativos, como evitações. Caso um estímulo qualquer ative alguma lembrança do evento traumático, experimentam-se sintomas de revivescência, que ativam sentimentos mencionados acima citados e levam o indivíduo a tentar estratégias para evitar que esses sintomas sejam ativados novamente. Ocorre que essas estratégias, ao invés de protegê-lo dos sintomas, têm o efeito de reforçá-los, mantendo o quadro de TEPT (Ehlers & Clark, 2000).

Portanto, o tratamento com TCC envolve flexibilizar essas interpretações rígidas e distorcidas, ao mesmo tempo em que as estratégias comportamentais que mantém o TEPT são alteradas. Para isso, conta com técnicas tais como reestruturação cognitiva, exposições *in vivo* e imaginária e técnicas de manejo da ansiedade.

Será exposto neste capítulo o tratamento de um caso de TEPT a fim de ilustrar de que maneira a TCC pode promover a melhora de casos graves e resistentes à medicação. A paciente, doravante denominada A. procurou atendimento no Laboratório Integrado de Pesquisas sobre Estresse (LINPES), localizado no Instituto de Psiquiatria da UFRJ (IPUB) em março de 2007 apresentando sintomas de TEPT relacionados a um acidente de trabalhado ocorrido em novembro de 2005. Antes disso, havia passado por inúmeras emergências de hospitais com crises de ansiedade e submeteu-se, sem sucesso, a um tratamento psicoterápico por dois meses.

IDENTIFICAÇÃO

Os dados a seguir foram divulgados após a assinatura do termo de consentimento livre e esclarecido pela paciente.

Na época de sua chegada ao LINPES, A. tinha 46 anos, vivia em casa própria separada de seu marido, com quem tinha dois filhos. A. nasceu no Rio de Janeiro, tinha primeiro grau completo, frequentava uma igreja evangélica e trabalhava como cobradora de ônibus até o acidente de trabalho. Seu círculo familiar é composto por alguns irmãos e sobrinhos que moravam próximos a ela, seus dois filhos (19 e 23 anos) e seu namorado. Relatava boa relação com sua família, ótima convivência com os vizinhos, embora tenha se afastado de muitas ocasiões sociais antes de buscar tratamento devido aos sintomas. Antes do acidente, era descrita como uma pessoa bem humorada e forte, que era procurada sempre que alguém de sua convivência tinha problemas, pois era considerada boa conselheira e solucionadora de problemas por seus próximos. Tinha vida religiosa pouco ativa, embora relatasse vontade de ser mais presente em sua igreja. A paciente tinha laço afetivo mais estreito com a filha, pessoa que se encontrava quase diariamente ao seu lado.

SÚMULA PSICOPATOLÓGICA

A paciente chegou ao LINPES vestida adequadamente e com boas condições de higiene pessoal. Sua atitude foi cooperativa com a entrevistadora. Apresentou consciência clara e boa orientação autopsíquica (em relação a si própria), mas se mostrou desorientada alopsiquicamente (em relação ao tempo e espaço) em alguns momentos. Mostrou-se normotenaz (capaz de manter atenção na terapeuta), mas hipervigil (alto grau de atenção a estímulos externos). Memória e inteligência aparentemente não apresentavam alteração. Apresentava-se normoprosódica (volume da fala adequado). Sensopercepção alterada, relatando alucinação auditiva. Pensamento sem alteração de forma, curso e conteúdo. Humor triste e ansioso. Afetividade preservada. Apresentou-se hipobúlica (atividade voluntária diminuída). Psicomotricidade alterada, com lentificação psicomotora. Consciência do eu sem alterações e consciência de morbidade presente.

HISTÓRICO DE TRAUMAS

A. já havia passado por algumas situações traumáticas antes do acidente que levou ao desenvolvimento de TEPT: quando seu filho tinha sete anos, foi acometido por uma grave pneumonia e, após seu tratamento, parou de andar devido a uma infecção hospitalar, tendo ficado internado durante quatro meses. Também relata que a morte de sua mãe, por câncer, foi fonte de grande sofrimento. Além disso, um de seus irmãos era soro positivo e morreu devido a uma pneumonia, e A. só tomou conhecimento da doença de seu irmão após sua morte. Mesmo após passar por todos esses eventos, A. mantinha uma postura resiliente e se mostrou apenas temporariamente abatida por esses acontecimentos.

HISTÓRIA PATOLÓGICA PREGRESSA

A paciente não apresentou histórico que revelasse patologias.

EVENTO TRAUMÁTICO

O evento traumático que levou ao desenvolvimento de TEPT ocorreu durante o seu trabalho. A. estava realizando seu segundo trajeto do dia como cobradora da linha de ônibus pela qual trabalhava. O tempo estava bastante chuvoso, dificultando a visibilidade do motorista e deixando a pista escorregadia. Em dado momento do trajeto, o motorista do ônibus tentou ultrapassar uma van enquanto fazia uma curva. Neste momento a roda do ônibus virou e o veículo tombou. A. ficou presa na cadeira de cobrador com seus movimentos temporariamente limitados. Enquanto isso, ajudou a tirar algumas crianças pela janela do ônibus e juntou alguns pertences de passageiros que estavam próximos a ela. Em seguida, conseguiu se desprender e travar a roleta do ônibus. Saiu do veículo sem dor e ajudou a acalmar os passageiros que queriam agredir o motorista.

No dia anterior, A. havia avisado a sua filha a que horas passaria pelo ponto próximo ao local em que ela se encontraria, e combinaram que ela pegaria o mesmo ônibus no qual a paciente estava. Com medo de que ela visse o acidente, parou vários ônibus e perguntou aos motoristas se eles encontraram sua filha, sem pensar que a filha da paciente era uma desconhecida para eles. Depois, conseguiu levar o motorista até o carro da polícia para que ele não fosse agredido, e nesse momento ele a advertiu sobre seus ferimentos na perna e na cabeça. A partir de então, começou a sentir dor e foi levada a uma ambulância que se dirigiu a um hospital próximo, onde ficou internada por dois dias.

DIAGNÓSTICO NOSOLÓGICO

Transtorno de estresse pós-traumático

Episódio depressivo grave

CONDUTA FARMACOLÓGICA

Foi iniciado tratamento psiquiátrico em março de 2007, quando lhe foi prescrito flunitrazepan 1mg, paroxetina 30mg, trazodona 100mg. Em janeiro de 2008, sua medicação se encontrava estável há um mês (paroxetina 50mg e clorpromazina 100mg).

SINTOMAS DE TEPT

O tratamento foi focado no trauma relacionado ao acidente de trabalho, visto que este era o evento considerado mais ansiogênico para a paciente no momento. No início do tratamento com TCC, em quinze de janeiro de 2008, a medicação pouco havia ajudado na melhora dos sintomas, e A. apresentava, além dos sintomas de TEPT, desânimo, tristeza intensa e alterações do sono e apetite. O diagnóstico de TEPT foi dado de acordo com os critérios propostos pelo Manual Estatístico e Diagnóstico dos Transtornos Mentais, quarta edição revisada (DSM-IV-R) a partir da administração da entrevista estruturada (SCID-I - *Structured Clinical Interview for DSM Disorders*) (Del-Bem, Vilela, Crippa, Hallak, Labate & Zuardi, 2001), por uma psiquiatra do LINPES).

Além de haver presença de evento traumático (critério A), A. apresentava revivescências, *flashbacks*, pesadelos relacionados ao trauma (critério B), evitações como andar de ônibus, dirigir carro, ver notícias de acidente, ter contato com pessoas do trabalho, família e amigos, sair de casa, principalmente em dias de chuva, ouvir barulho de ambulância, além de sensação de congelamento e entorpecimento emocional (critério C) e dificuldade de concentração, irritabilidade, resposta de sobressalto exagerada. Esses sintomas causavam prejuízo significativo na vida de A. (critério D) e não eram explicados por outro transtorno (critério E). Apresentava também Depressão Maior secundária ao TEPT, com sintomas que incluíam humor triste, desânimo, ideação suicida, crises de choro frequentes, desesperança. Não conseguia sentir prazer nas atividades que gostava antes do trauma, como cozinhar, cuidar de sua casa, dentre outras, e por esse motivo saía cada vez menos de casa.

Esses sintomas se mantinham na medida em que A. evitava qualquer estímulo que a lembrasse do trauma. A simples menção a essas situações relacionadas ao trauma provocava fortes dores de cabeça e sensação de estar novamente no momento do acidente, o que representa um sintoma dissociativo (desrealização). Era comum a paciente dissociar frente a qualquer estímulo que lhe lembrasse o trauma, inclusive nas sessões de terapia e de exposição. Quando era inevitável a exposição a alguma dessas situações, fazia de tudo para fugir, o que muitas vezes acabava colocando-a em riscos reais.

A paciente mostrou-se bastante colaborativa, apesar de, na fase da terapia de exposição, ter desejado desistir do tratamento devido à alta ansiedade que sentia enquanto se expunha.

CONCEITUALIZAÇÃO COGNITIVA

Dados relevantes

Sempre foi considerada forte, “inatingível”

Geralmente era a pessoa consultada quando seus familiares, vizinhos e amigos tinham algum problema

História de traumas diversos

Acidente de ônibus

Crença Central

“Sou vulnerável”

“Nada dá certo na minha vida”

“Estou em perigo o tempo todo”

Crenças Condicionais

“Se eu me expuser a qualquer risco, outro acidente vai acontecer”

Estratégias Comportamentais Evitar qualquer situação na qual se perceba em risco Evitar saber dos problemas de outras pessoas (telefonemas, noticiários)		
Situação 1 Indo para o IPUB	Situação 2 Familiar foi internada e pediu que ela a acompanhasse na ambulância	Situação 3 Ao tentar dirigir
Pensamentos Automáticos “Vai acontecer um acidente”	Pensamentos Automáticos “Não irei tolerar o desconforto de estar novamente em uma ambulância”	Pensamentos Automáticos “Vou me acidentar novamente”
Significado “Estou em perigo”	Significado “Sou vulnerável”	Significado “Estou em perigo”
Emoção Ansiedade	Emoção Ansiedade	Emoção Ansiedade
Comportamento Desceu do ônibus	Comportamento Recusou o pedido	Comportamento Parou o carro no meio da avenida

PROTOCOLO DE TRATAMENTO COM TERAPIA COGNITIVO-COMPORTAMENTAL

O protocolo de tratamento de TCC para o TEPT desenvolvido por Edna Foa e colaboradores (Foa & Rothbaum, 1998) foi adaptado pela equipe de Psicologia do LINPES (Pedrozo, 2009) e utilizado com pacientes do ambulatório.

Consiste em 16 sessões de terapia (semanais) com 90 minutos de duração, intercaladas com 45 sessões de co-terapia (três vezes por semana). Definimos a co-terapia como a participação de estudantes de graduação de psicologia na implementação das técnicas cognitivo-comportamentais no período entre as sessões. Já as sessões de terapia foram conduzidas por uma psicóloga graduada pela UFRJ. Foram realizadas exposições imaginária (ao relato do evento gravado em fita) e *in vivo*, para a qual foi elaborada uma hierarquia de enfrentamento com as situações evitadas pela paciente, além de reestruturação cognitiva e técnicas de manejo da ansiedade, como respiração diafragmática, respiração polarizada e relaxamento muscular progressivo.

TRATAMENTO COGNITIVO-COMPORTAMENTAL

Reestruturação cognitiva: foram identificadas cognições relacionadas à vulnerabilidade, tais como: “Nada dá certo na minha vida”, “Se o acidente aconteceu, significa que acontecerá novamente”. A paciente trazia situações ocorridas durante a semana que alteravam seu humor. Os pensamentos associados eram identificados, avaliados quanto à sua acurácia e, caso fossem distorcidos, fazia-se a reestruturação desses pensamentos. A reestruturação destas cognições foi efetiva na flexibilização da maneira rígida e extrema de pensar da paciente. Consequentemente, observaram-se diminuição da ansiedade e aquisição de repertório comportamental mais adaptativo.

Técnicas de manejo da ansiedade: A. optou pela respiração diafragmática. A respiração diafragmática consiste em praticar a respiração mais profunda, expandindo o diafragma. Essa respiração controlada é praticada pela inspiração contando lentamente até 3 e expiração lenta contando até 3 (Greenberger e Padesky, 1999). Já o relaxamento muscular progressivo promove um relaxamento profundo, eficaz para pessoas cuja ansiedade é fortemente associada com a tensão muscular. No protocolo foi utilizado o relaxamento muscular de Jacboson (Jacobson, 1993). A sessão de relaxamento foi gravada para que a paciente pudesse praticá-lo em casa.

Durante o relaxamento a paciente relatava sensação de calma e melhora de suas dores musculares. Foi retirado o exercício nos músculos da face, pois A. sentia tontura. Ao invés disso, foi solicitado que ela imaginasse que estava contraindo e relaxando esse grupo muscular.

Exposição *in vivo*: foi realizado o enfrentamento gradual dos estímulos provocadores de ansiedade condicionados ao trauma. Esta parte do tratamento foi realizada com o auxílio de um co-terapeuta. Montou-se uma hierarquia de situações evitadas pela paciente, que foram enfrentadas desde a menos ansiogênica até a mais ansiogênica, sendo que só se passava para o próximo enfrentamento quando ela não sentia mais ansiedade no último item combinado. Quando a ansiedade era alta, realizava-se treino de relaxamento muscular progressivo e/ ou respiração diafragmática pela co-terapeuta, de modo que houvesse um manejo da ansiedade.

Escala hierárquica:

Grau de ansiedade:	Pré TCC	Pós TCC
1.___Andar de ônibus prestando atenção no trânsito	70%	0%
2.___Passar em viadutos no ônibus	70%	0%
3.___Contato com colegas do trabalho	80%	0%
4.___Andar em ônibus cheio	80%	0%
5.___Andar de ônibus em dias chuvosos	80%	0%
6.___Sentar do lado esquerdo do ônibus	90%	0%
7.___Andar em ônibus com alta velocidade	90%	0%
8.___Ler notícias sobre acidente de ônibus	100%	0%
9.___Som de ambulância	100%	0%
9. ___ Passar em frente à empresa de ônibus na qual trabalhava	100%	0%
10.__Fazer trajeto da linha de ônibus em que trabalhava	100%	0%

Ao final do tratamento, enfrentou algumas situações da escala hierárquica sem o auxílio do co-terapeuta.

Exposição imaginária: foi realizado o enfrentamento falado do evento traumático com o máximo de detalhes possível. A. era orientada a falar no tempo presente, com “um pé no consultório e outro no momento do acidente”. Depois, ouvia repetidamente o seu relato do trauma gravado em fita até que se habituasse completamente a ele e houvesse o reprocessamento da memória traumática. Inicialmente, como A. sentia fortes dores de cabeça ao tentar fazer a exposição imaginária e tinha sintomas de desrealização em vários momentos, ela foi estimulada a fazer o relato com os olhos abertos. Quando foi observada diminuição da ansiedade, ela foi

encorajada a fechar os olhos e só abri-los nos piores momentos (*hot spots*). Quando A. dissociava durante a exposição, era interrompida temporariamente e realizava-se o procedimento para que a dissociação fosse revertida, no qual ela deveria dizer o nome da terapeuta, quem ela era, o nome do local onde estava, juntamente com a observação visual do local. Só foi observada alguma diminuição da ansiedade máxima, pela primeira vez, na 34ª sessão de co-terapia.

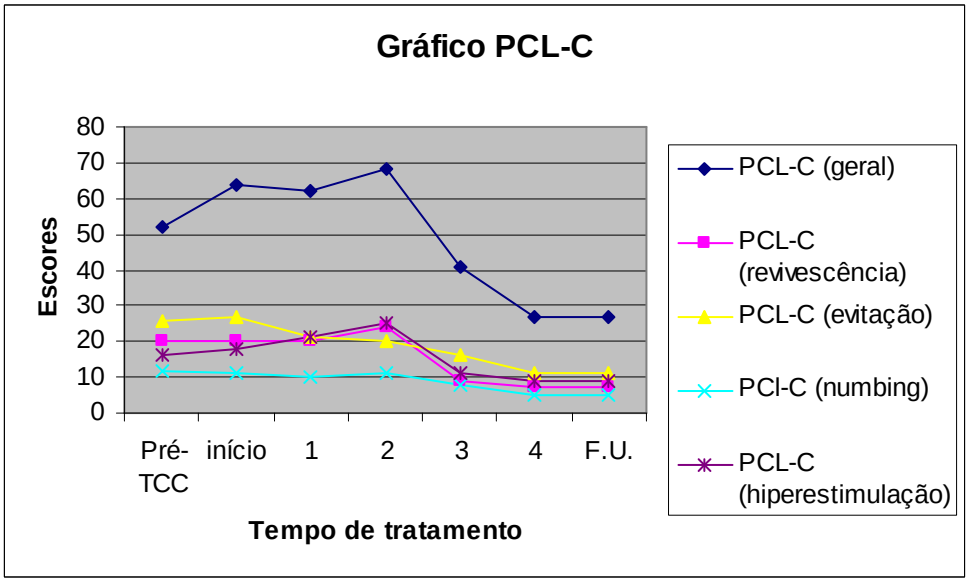
Nas primeiras sessões de exposição, a paciente pensou em abandonar o tratamento. Nessa fase, houve aumento da freqüência de pensamentos intrusivos, dos pesadelos e da ansiedade no dia-a-dia.

RESULTADO

Ao final do tratamento, a paciente não experimentava sensações físicas relacionadas à ansiedade, como sudorese na palma das mãos e dor no peito e conseguia reestruturar os pensamentos distorcidos sem a ajuda da terapeuta. Passou a fazer viagens de ônibus, nas quais muitas vezes adormecia, iniciou um novo trabalho como vendedora de coco e biscoitos, voltou a se relacionar com pessoas de sua convivência antes do acidente, sendo inclusive chamada de "sorriso" pelos vizinhos, apelido que lhe foi dado antes do acidente e havia parado se ser utilizado após o desenvolvimento de TEPT, e passou a cuidar mais da aparência. Meses depois, passou a participar ativamente do grupo do coro de senhoras da igreja perto de sua casa, indo a encontros três vezes por semana e fazendo visitas a outras igrejas. Tem feito algumas viagens com uma de suas irmãs sem relatar ansiedade alguma por ficar muito tempo dentro no ônibus. Passou a não apresentar revivescências, pesadelos, *flashbacks* ou pensamentos e lembranças intrusivos relacionados ao trauma.

Durante todo o tratamento a filha de A. a apoiou, ajudou a reavaliar certas situações, como por exemplo, no momento em que ela tentou abandonar o tratamento psicoterápico. Também foi importante ao reforçar positivamente os enfrentamentos que sua mãe realizava. Ao final do tratamento, sua filha escreveu uma carta de agradecimento à equipe pelo trabalho realizado.

O gráfico com o resultado da administração do *Post traumatic stress disorder scale civilian version- PCL-C)* (Berger, et al., 2004) encontra-se abaixo. Trata-se de uma escala de auto-relato que mede sintomas de TEPT, sendo que o diagnóstico pode ser dado caso a pontuação total seja igual ou maior que 50. No gráfico temos tanto o escore total do PCL-C, quando os escores dos subgrupos de sintomas, em cores diferentes.



FOLLOW UP DE 1 MÊS

A melhora se manteve. Contudo, continuava tendo pesadelos com outros eventos traumáticos que não foram trabalhados no tratamento. Alguns sintomas de depressão permaneceram, mas A. não relatava relação deles com o TEPT, mas com problemas relacionados ao ex-marido que não puderam ser trabalhados em terapia.

Algum tempo depois da terapia, recebeu alta do tratamento farmacológico, sendo liberado do uso de medicamentos psicotrópicos e retomando completamente a sua vida como era antes do acidente.

CONCLUSÕES

Mesmo sendo uma paciente dissociativa, o que a princípio vem acompanhado de maior gravidade e pior prognóstico (Ozer et al, 2003), A. teve excelente resposta ao tratamento convencional com TCC, com remissão da ansiedade na presença de estímulos considerados extremamente ansiogênicos antes do tratamento e reestruturações de crenças relacionadas à vulnerabilidade, o que é uma demonstração de que esse tipo de tratamento pode ser eficiente mesmo em casos mais difíceis.

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Neurociências e Terapia Cognitivo-comportamental

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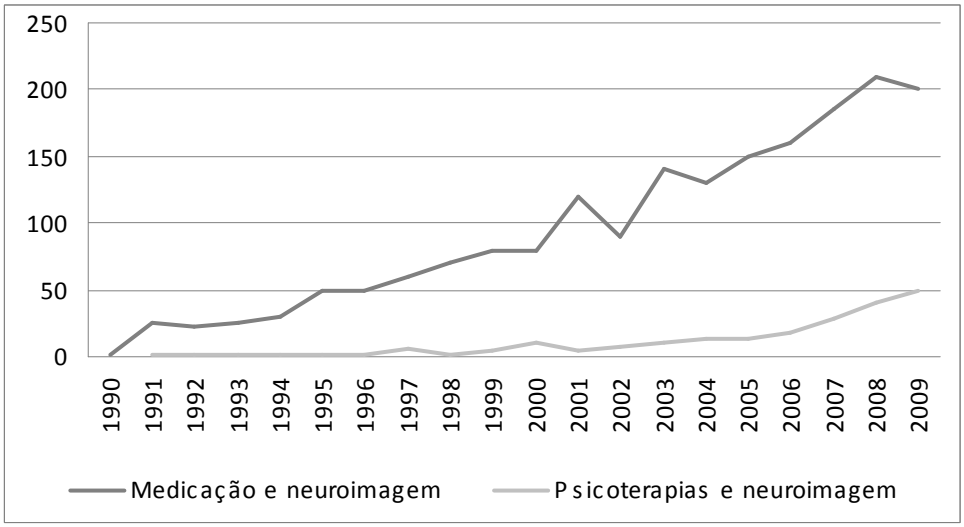
1 Introdução

A interseção da psicologia com outras áreas do conhecimento é uma tendência crescente. Até que os primeiros trabalhos que serviram de base para a teoria behaviorista fossem formulados, os modelos oriundos da psicologia não podiam ser replicados, generalizados para outras situações que não a experimental e sua verificação era contestável. Portanto, a metodologia utilizada até então pouco contribuía para a produção de conhecimento científico. Com o rigor experimental alcançado pelo behaviorismo, observou-se a inversão deste quadro. A partir de então, a aplicação da metodologia científica às teorias psicológicas começou a ser valorizada (Rangé, 1995). A terapia cognitivo-comportamental (TCC), que tem no behaviorismo suas bases filosóficas, também segue o preceito de que é necessário que uma área do conhecimento tenha suporte empírico e experimental para que produza conhecimento científico.

Ao longo do tempo, os estudiosos se dedicaram mais a clarificar as bases biológicas que estariam envolvidas com respostas medicamentosas. No entanto, especificar se ocorrem e quais são as mudanças cerebrais envolvidas com o tratamento psicológico bem sucedido é de grande importância. A literatura evidencia a discrepância entre o número de estudos publicados avaliando mudanças neurobiológicas devido a intervenções com medicação *versus* o número de estudos em psicoterapia, sendo o número de estudos com medicação significativamente maior (Roffman J. et al, 2005). O gráfico abaixo ilustra essa discrepância:



Medicação e neuroimagem versus psicoterapias e neuroimagem

Uma busca realizada na Base ISI/Thompson Reuters indicou mais de 200 artigos por ano publicados a partir de 2008 relacionando medicação e neuroimagem, ao passo que o número de artigos com diferentes psicoterapias e neuroimagem não passou de 50. Possivelmente essa disparidade está relacionada à visão de ciências que estudam mente e cérebro como instâncias separadas. Dessa forma a medicação estaria envolvida com intervenções biológicas relacionadas ao cérebro enquanto as psicoterapias estariam vinculadas às intervenções complexas relacionadas à subjetividade logo, com a mente. Podemos considerar que mente e cérebro são integrados e interdependentes. Os processos mentais exercem influência na plasticidade cerebral em vários níveis como celular, molecular e em circuitos neurais (Beauregard, 2007; Kumari, 2006). Para ilustrar essa relação Beauregard (2007) cita que pensamentos que induzem medo aumentam a secreção de adrenalina, enquanto pensamentos relacionados à felicidade aumentam a secreção de endorfina. Os processos neurais estão envolvidos com outros processos fisiológicos como o imune e endócrino que por sua vez estão associados à comunicação entre os processos mentais e cerebrais.

A neurociência tem desenvolvido vários métodos para analisar a função cognitiva e potencializar a compreensão do funcionamento mental de indivíduos saudáveis e com Transtornos Psiquiátricos. Os avanços recentes nas técnicas de neuroimagem têm ajudado a aumentar o entendimento dos correlatos neuronais dos transtornos mentais. A utilização de técnicas de neuroimagem tem sido uma área de contínuo interesse nas pesquisas psiquiátricas. Algumas técnicas utilizadas incluem Tomografia por Emissão de Pósitron

(PET), a Ressonância Nuclear Magnética Funcional (RNMF) e a Tomografia por Emissão de Fóton Único (SPECT).

A melhor compreensão dos mecanismos biológicos subjacentes à terapia pode promover melhoras nas intervenções terapêuticas, assim como ampliar o conhecimento sobre a formação e manutenção dos sintomas, auxiliando, no futuro, na escolha do tratamento mais indicado para determinado paciente (Hyman, 2007; Kumari, 2006; Linden, 2006). Descobrir de que maneira a TCC atua do ponto de vista fisiológico pode contribuir também para aumentar a adesão ao tratamento com TCC, já que se sabe que a parcela de sujeitos que não responde ou desiste do tratamento convencional com TCC pode chegar a 50 % dos indivíduos selecionados para o tratamento (Schottenbauer et al., 2008). Além disso, a identificação de alguns "biomarcadores-chave" em determinados indivíduos pode facilitar a prevenção do desenvolvimento de psicopatologias (Beauchaine et al., 2008).

A TCC oferece uma perspectiva interessante para a integração com o campo da neurociência, uma vez que, qualquer intervenção está vinculada a um suporte de pesquisa experimental e empírico. Essa abordagem psicoterápica se propõe a tratar vários transtornos mentais com índices elevados de eficácia (Beck, A, 2005; Beck, J, 2007; Foa, 2006). No entanto, o que ocorre no corpo de um paciente que responde ao tratamento? A TCC é capaz de promover alterações biológicas? Qual é a natureza do(s) problema (s) que estamos tratando? Será que a atividade metabólica de regiões previamente associadas aos Transtornos Mentais poderiam predizer a resposta à TCC? Será que pacientes com modelos particulares de metabolismo cerebral podem responder preferencialmente a um determinado tipo de tratamento? Com intuito de incitar a reflexão sobre estas questões este capítulo tem como objetivo apresentar resultados de estudos de neuroimagem e TCC nos Transtornos de Ansiedade.

2. Mudanças neurobiológicas relacionadas com TCC e Neuroimagem

2.1. Marcadores de eficácia da TCC

2.1. 1. Estudos com Fobia de Aranha

Indivíduos com Fobia de aranha experimentam medo persistente e intenso e desenvolvem comportamentos evitativos a todos os contextos relacionados a esse animal.

A TCC tem se mostrado eficaz na redução de sintomas de Fobia Específica (Öst, 1996; Paquette, et al,2003; Straube, Glauer, Dilger, Mentzel, Miltner, 2006). Quais as mudanças cerebrais subjacentes ao tratamento bem sucedido com TCC na Fobia de aranhas?

O funcionamento neuroanatômico associado com os sintomas de Fobia de aranha ainda não está claro. Os estudos publicados até o presente momento avaliam a redução do medo utilizando metodologia de provocação de sintomas, ou seja, o cérebro dos participantes da pesquisa é monitorado enquanto visualizam fotos contendo o estímulo fóbico.

Os resultados dos estudos indicam os seguintes achados: Paquette et al (2003) apontaram a participação do córtex pré-frontal dorsolateral e giro parahipocampal no processamento do medo fóbico, de maneira que,, após o tratamento com TCC, não houve ativação significativa dessas áreas. Straube et al (2006) demonstraram em seu estudo que o processamento de ameaça fóbica está associado ao aumento da ativação da ínsula e córtex cingulado anterior em sujeitos com fobia específica. Os sujeitos que responderam a TCC apresentaram redução da hiperatividade nessas regiões. Goossens et al. (2007) observaram redução da hiperativação da amígdala, do córtex cingulado anterior e ínsula após o tratamento; Finalmente, Schienle et al. (2009) observaram aumento da ativação do córtex orbitofrontal medial após o tratamento. Essa discrepância entre os achados requer pesquisas futuras.

O modelo do medo proposto por LeDoux (1998), no qual o processamento do medo se daria após o aumento da ativação de áreas pré-frontais que inibiriam a hiperativação da amígdala frente ao estímulo fóbico foi evidenciada no estudo de Schienle (et al. 2009). Os estudos de Straube (et al, 2006) e Goossens et al. (2007) revelaram redução da ativação do córtex cingulado anterior. A redução da ativação da amígdala, por sua vez, só foi observada nos estudo conduzido por Goossens et al. (2007). A participação da ínsula nos estudos de Straube (et al, 2006) e Goossens (et al, 2007), mostrou-se coerente com achados anteriores que indicam seu envolvimento no processamento de emoções negativas. Embora os diferentes estudos tenham encontrado resultados distintos quanto às áreas cerebrais envolvidas antes do tratamento, em ambos a TCC mostrou-se capaz de reduzir os sintomas e modificar os circuitos neuronais disfuncionais após o tratamento.

2.1.2 Estudo com Fobia Social

Segundo o DSM-IV, a Fobia Social tem como característica principal medo acentuado e persistente de situações sociais ou de desempenho nas quais o indivíduo pode se sentir embaraçado.

A TCC é um tratamento eficaz para a Fobia Social (Falcone & Figueira, 2001). No entanto, o que ocorre no cérebro do paciente após o tratamento? As mudanças neurofuncionais associadas com a redução da ansiedade social em pacientes submetidos ao tratamento com TCC e citalopram foram investigadas por Furmark (et al, 2002) através de PET. O estudo também teve como objetivo explorar se a mudança cerebral estava associada com os resultados a longo-prazo do tratamento. A TCC em grupo utilizou técnicas de exposição, reestruturação cognitiva e tarefa de casa.

O estudo conclui (Furmark et al, 2002) que os sítios neurais de ativação para o tratamento com citalopram e a TCC na Ansiedade Social convergem para amígdala, hipocampo e áreas corticais adjacentes, representando possivelmente um caminho comum no tratamento bem sucedido da ansiedade. A atenuação da atividade na região amígdalar e límbica com o tratamento foi associada com resultado favorável a longo-prazo e pode ser um requisito prévio para a melhora clínica. O estudo também revelou que o grau de redução da resposta límbica com o tratamento mostrou-se associado com o resultado clínico a longo-prazo. A diminuição da resposta do fluxo sanguíneo cerebral na amígdala, área cinzenta periaquedutal e tálamo esquerdo pode indicar quais pacientes apresentaram melhora maior em um intervalo de 1 ano. Assim, resultados favoráveis no *follow-up* de 1 ano estavam associados com maior atenuação da resposta do fluxo sanguíneo subcortical ao falar em público.

Furmark (et al, 2002) em sua discussão apresenta que a amígdala e o hipocampo são estruturas relacionadas ao condicionamento de estímulos aversivos em indivíduos com Fobia Social. Essas estruturas junto com as áreas rhinal, parahipocampal, periamigdaloide formam um sistema de alarme que pode ser ativado por estímulos ameaçadores. A redução da atividade na região da amígdala, do hipocampo e córtex adjacente pode ser um importante mecanismo através do qual ambos os tratamentos farmacológico e psicoterápico poderiam exercer efeito ansiolítico. A técnica de exposição da TCC pode atuar permitindo habituação sistemática da atividade neural nessas estruturas cerebrais. Um estudo conduzido por Leichsenring et al. (2008) confirmou esses achados, apontando normalização da ativação da amígdala e do hipocampo após o tratamento.

2.1.3 Estudo com Transtorno de Estresse Pós-Traumático

O TEPT é um transtorno precipitado por um trauma. Em decorrência do evento traumático, o indivíduo passa a re-experimentar do evento traumático, a evitar de estímulos a ele associados e a apresentar sintomas de hiperestimulação autonômica.

A TCC é indicada para o tratamento de pacientes com TEPT (Bisson, Shepherd, Joy, Newcombe, 2004; Caminha, 2005; Foa, 2006; Schreiner, 2005; Soares & Lima, 2003). Soares e Lima (2003) apresentam em seu estudo as modalidades de tratamento do TEPT amparadas em evidências, e apontam que as técnicas cognitivo-comportamentais mostram uma taxa de melhora em torno de 90% ao fim do tratamento e 85% em seis meses.

Felmingham et al. (2007) monitoraram oito indivíduos com TEPT por MRI antes e após o tratamento com TCC. Durante a visualização de expressões de medo e neutras, os autores observaram que nos pacientes que responderam ao tratamento houve aumento na ativação do córtex cingulado anterior e diminuição da atividade da amígdala. Os autores concluíram que tanto o córtex cingulado anterior quanto a amígdala estão envolvidos no processamento do medo, o que corrobora a hipótese do modelo clássico do medo, no qual há uma hiperativação da amígdala e hipoativação de regiões frontais, que se normalizam após o processamento adequado do medo.

2.1.4 Estudos com Transtorno Obsessivo-Compulsivo

As características principais do TOC são obsessões ou compulsões recorrentes que causam sofrimento acentuado, consomem tempo e interferem na rotina do indivíduo. Quais os efeitos neurobiológicos da TCC em pacientes com TOC? Foram identificados cinco estudos de neuroimagem com intuito de responder esta questão.

Baxter et al (1992) investigaram as mudanças no metabolismo cerebral decorrentes do tratamento com Terapia Comportamental e fluoxetina no TOC através do FDG-PET. A Terapia Comportamental consistia de técnicas de exposição com prevenção de resposta que foi individualizada para cada paciente, e realização de tarefas de casa.

Baxter et al (1992) concluíram que o metabolismo de glicose da cabeça do núcleo caudado direito mudou nos pacientes tratados com sucesso tanto com a Terapia Comportamental quanto com fluoxetina. Houve correlação significativa da atividade do córtex orbital com o núcleo caudado e o tálamo antes do tratamento em sujeitos que responderam. Essa correlação desapareceu depois do sucesso do tratamento.

Em estudo posterior, o mesmo grupo de pesquisa (Schwartz et al, 1996) investigou através de PET mudanças neurobiológicas em pacientes com TOC antes e depois da Terapia Comportamental. O objetivo deste estudo era replicar os achados anteriores com uma amostra independente e aumentar a amostra de sujeitos cujos resultados poderiam ser combinados com aqueles tratados com Terapia Comportamental no primeiro estudo (Baxter et al, 1992).

O Tratamento com Terapia Comportamental foi semelhante ao estudo anterior de Baxter (et al, 1992).

Os resultados do estudo anterior (Baxter et al, 1992) corroboram com a idéia que os pensamentos fixos e repetitivos e os comportamentos ritualizados observados no TOC seriam resultado da atividade patológica do circuito cortico-estriado-talâmico .

Schwartz (et al, 1996) concluiu que os resultados deste estudo replicavam os do estudo anterior (Baxter et al, 1992) apresentando mudança significativa na atividade metabólica do caudado direito que foi normalizada depois da Terapia Comportamental efetiva. Essa mudança não foi observada nos pacientes que não responderam ao tratamento. Quando a amostra do estudo anterior foi combinada com a desse estudo, foi possível demonstrar correlação pré-tratamento estatisticamente significativa entre o giro orbital direito, a cabeça do núcleo caudado e do tálamo que diminui depois do tratamento efetivo. No estudo anterior, resultados semelhantes foram encontrados com uma amostra tratada com Terapia Comportamental ou fluoxetina. A constatação de que esses efeitos podem ser demonstrados depois do tratamento efetivo apenas com Terapia Comportamental e que a correlação entre essas regiões não é observada em controles normais sugere que a articulação da atividade entre elementos do circuito cortico-estriado-talamico pode estar relacionada com a expressão dos sintomas de TOC.

Nakao (et al, 2005) para compreender a fisiopatologia do TOC avaliou as mudanças regionais cerebrais através da RNMF antes e depois do tratamento com Terapia Comportamental e medicação. Os autores tinham como hipótese que pacientes com TOC poderiam apresentar ativação anormal nas áreas frontais, especialmente no cingulado anterior, o que poderia influenciar nas tarefas cognitivas. Assim, os sintomas do TOC comprometeriam a função de monitorar o próprio comportamento, mas, para os autores, com o tratamento essa função seria recuperada.

O estudo concluiu que a hiperativação dos circuitos envolvidos na expressão sintomática do TOC, sendo eles córtex órbito frontal, giro cingulado anterior e núcleos da base podem diminuir com a melhora dos sintomas. No entanto, é importante ressaltar uma limitação do estudo referente à análise da mudança cerebral. Devido ao pequeno número de participantes não foi possível analisar separadamente os padrões de ativação cerebral decorrentes da intervenção com Terapia Comportamental ou com a fluvoxamina.

Em estudo recente utilizando PET, Saxena et al. (2009) observaram após o término do tratamento redução da ativação no tálamo e aumento na ativação do córtex cingulado anterior direito dorsal, o que demonstra que a TCC pode promover efeitos na atividade cerebral de

forma mais rápida do que se havia pensado anteriormente, pois o tratamento teve duração de apenas 4 semanas. Além disso, o efeito observado no córtex cingulado anterior indica uma via diferente de atuação da TCC em comparação com o tratamento farmacológico, já que o aumento da ativação nessa área é observado em resposta à TCC em outros transtornos, como na Depressão Maior (Goldapple et al., 2004).

No mesmo ano, Yamanishi et al. (2009) observaram através de SPECT que pacientes resistentes aos Inibidores Seletivos de Recaptação de Serotonina que responderam ao tratamento com TCC reduziram a ativação do córtex pré-frontal medial esquerdo (Área de Brodmann 10) e giro frontal medial bilateral (Área de Brodmann 10). Além disso, maior ativação do córtex orbitofrontal bilateralmente esteve associado à melhora dos sintomas de TOC nos pacientes respondentes.

É importante ressaltar que em todos os estudos os pacientes que responderam a TCC apresentaram mudanças cerebrais, embora um modelo de ativação ainda não esteja definido. Regiões relacionadas à sintomatologia do TOC, como córtex órbito frontal, giro cingulado anterior e caudado direito, apresentaram suas ativações regularizadas com o tratamento.

2.1.5 Estudos com Transtorno de Pânico.

Segundo o DSM-IV, o Transtorno de Pânico se caracteriza pela presença de ataques de pânico recorrentes e inesperados, seguidos por preocupação persistente acerca de ter outro ataque de pânico, preocupação sobre as possíveis implicações ou conseqüência dos ataques de pânico, ou mudança comportamental relevante relacionada aos ataques.

A TCC é eficaz no tratamento do Transtorno do Pânico (Rangé & Bernik, 2001; Ventura, 2005). Entretanto, há mudanças cerebrais quando o paciente responde a TCC? Foram identificados dois estudos de neuroimagem com PET investigando os substratos neurobiológicos da TCC em pacientes com pânico (Prasko et al, 2004; Sakai et al, 2006).

Prasko e al (2004) utilizando FDG-PET avaliaram as mudanças no metabolismo cerebral regional decorrentes do tratamento com TCC ou antidepressivo. Os sujeitos foram submetidos ao exame de PET antes e depois dos tratamentos. Prasko et al (2004) concluíram que ambos os tratamentos foram eficazes no manejo dos sintomas de pânico. As mudanças no metabolismo cerebral nas regiões corticais foram semelhantes para ambos os tratamentos. Houve aumento da atividade do metabolismo cerebral no hemisfério esquerdo principalmente nas regiões pré-frontal, temporoparietal e occipital e cingulado posterior. A diminuição foi predominante na região frontal do hemisfério esquerdo, e na região frontal, temporal e

parietal do hemisfério direito. Não foram encontradas mudanças na atividade metabólica de áreas subcorticais.

Os resultados do estudo apontam que tanto o tratamento com TCC quanto com antidepressivos podem ativar o processamento temporal cortical. Prasko et al (2004) em sua discussão apresentam que essa área paralímbica faz parte do sistema de alarme que informa sobre perigo externo, pois está envolvida com o processamento de emoções, avaliando estímulos exteroceptivos e classificando-os como emocionalmente significativos.

Sakai et al (2006) também utilizaram o FDG-PET para investigar as mudanças na utilização de glicose cerebral regional associada com redução da ansiedade após o tratamento com TCC. Os achados de neuroimagem após a TCC revelaram diminuição do metabolismo no hipocampo direito, córtex cingulado anterior ventral esquerdo, úvula e pirâmide do cerebelo esquerdo e ponte. O aumento do metabolismo de glicose cerebral regional foi encontrado na região pré-frontal medial bilateralmente. Os achados são compatíveis com a hipótese que regiões acima da amígdala podem ser moduladas adaptativamente nos pacientes que respondem a TCC.

3. Predição de Resposta

É possível que a atividade metabólica de regiões previamente associadas aos Transtornos Mentais possa predizer a resposta à TCC? Podemos presumir que pacientes com modelos particulares de metabolismo cerebral podem responder preferencialmente a um determinado tipo de tratamento? A predição de resposta de tratamento é de grande importância clínica, pois o conhecimento do metabolismo cerebral pré-tratamento poderá no futuro auxiliar na escolha da intervenção mais indicada para determinado paciente.

Brody et al (1998) utilizaram o FDG-PET para investigar se a atividade metabólica de regiões previamente associadas aos sintomas do TOC poderiam predizer a resposta à Terapia Comportamental. O estudo concluiu que um metabolismo pré-tratamento mais alto no córtex órbito frontal esquerdo estava associado com melhor resposta ao tratamento com Terapia Comportamental. Ao contrário, uma atividade metabólica mais baixa no córtex órbito frontal esquerdo estava associada com melhor resposta ao tratamento com fluoxetina.

Os resultados de ambos os grupos de Terapia Comportamental e medicação sugerem que pacientes com TOC com modelos particulares de metabolismo cerebral podem responder preferencialmente a um determinado tipo de tratamento. Brody et al (1998) discutem que uma possível explicação para os resultados do grupo de medicação é que o metabolismo do córtex órbito frontal esquerdo antes do tratamento mostrou tendência para uma correlação positiva

com gravidade dos sintomas iniciais na Y-BOCS. Esse dado pode indicar que a medicação é menos efetiva em sujeitos com o transtorno mais grave.

Brody et al (1998), em sua discussão, apontam que as funções atribuídas ao córtex órbito frontal poderiam explicar porque um metabolismo mais alto nesta região prediz resposta melhor à Terapia Comportamental. Dentre as funções do córtex órbito frontal são destacadas duas que poderiam estar relacionadas aos achados de seu estudo. Primeiro, o córtex órbito frontal é importante para mediar respostas comportamentais em situações nas quais o valor afetivo do estímulo muda, e em segundo, essa área parece ter importante papel na mediação da extinção. No tratamento bem sucedido com Terapia Comportamental, os pacientes experimentam mudança no valor afetivo que eles atribuíam ao estímulo e assim extinguem as compulsões. Conseqüentemente, para Brody et al. os sujeitos com metabolismo mais alto pré-tratamento no córtex órbito frontal teriam maior capacidade para mudar a atribuição do valor afetivo do estímulo e logo seriam mais capazes de extinguir as respostas compulsivas. Dessa forma, essas habilidades possibilitariam melhor resposta à Terapia Comportamental.

Bryant et al. (2008a) utilizaram ressonância magnética funcional para verificar se o cérebro de indivíduos com TEPT que respondem ao tratamento com TCC é ativado de maneira diferente ao cérebro dos que continuam preenchendo critério para o transtorno após o tratamento. Esses indivíduos foram monitorados durante a visualização de expressões de medo e neutras. Apesar de não ter havido grupo-controle, os autores observaram que os não respondentes ao tratamento apresentavam maior ativação da amígdala bilateral e do córtex cingulado anterior direito ventral durante a apresentação dos estímulos antes do tratamento. Os autores concluíram que, se o processamento do medo realizado pela amígdala é excessivo, pode ser mais difícil regularizar a ansiedade durante a TCC, dificultando o sucesso terapêutico. Contudo, a ativação aumentada do córtex cingulado anterior direito predizer má resposta ao tratamento não era esperada, já que a ativação desta região está envolvida no processamento adequado do medo. Uma possível explicação para esse achado e que, como os sujeitos foram monitorados durante a visualização de expressões de medo e neutras e essas imagens eram apresentadas de forma rápida e não consciente, pode não ter havido tempo suficiente para regiões mais frontais responderem a esses estímulos.

Não só a ativação, mas também o tamanho de determinadas regiões cerebrais podem estar envolvidas na resposta ao tratamento com TCC. Bryant et al. (2008b) observaram que pacientes com TEPT respondentes ao tratamento tinham maior volume do córtex cingulado anterior rostral do que os pacientes que não obtiveram melhora dos sintomas. Na medida em

que o volume dessa região é maior, esses indivíduos parecem estar mais aptos a regular o medo, processando-o de maneira mais adequada ao longo da TCC.

4. Conclusões

A TCC tem se mostrado eficaz no tratamento de vários transtornos mentais, embora os efeitos neurobiológicos de sua atuação ainda sejam pouco conhecidos. A TCC favorece a reestruturação dos pensamentos, a modificação dos sentimentos e comportamentos e promove novos aprendizados. Consequentemente envolve mudanças sinápticas (Moraes, K, 2006). Este capítulo teve como objetivo apresentar resultados de estudos de neuroimagam e TCC nos Transtornos de Ansiedade a fim de esclarecer se a TCC pode promover alterações neurobiológicas. Segundo os estudos apresentados, a TCC é capaz de modificar a atividade neural disfuncional relacionada aos transtornos de ansiedade nos pacientes que responderam ao tratamento. Cabe também ressaltar a importância dos estudos de predição de resposta ao tratamento. Até o momento, estudos envolvendo TOC e TEPT demonstram haver relação entre o tamanho e a ativação de áreas cerebrais anteriores ao tratamento e a resposta à TCC, ou seja, características neurais tanto morfológicas quanto funcionais podem indicar previamente ao tratamento se há mais chance de resposta terapêutica.

Outro aspecto particularmente interessante diz respeito aos achados de neuroimagem decorrentes do tratamento com TCC *versus* medicação, revelando um caminho comum de modificação cerebral. Esses achados sugerem, portanto, que a psicoterapia com TCC e a farmacoterapia, em alguns casos, podem ter sítios de atuação semelhantes (Furmark et al 2002; Baxter at al,1992; Prasko et al, 2004)

Os estudos publicados até o momento apontaram em seus achados de neuroimagem estruturas que participam tanto dos circuitos cerebrais envolvidos com a extinção quanto com a regulação cognitiva da emoção. Os resultados mostraram que a TCC regularizou especialmente os circuitos neurais disfuncionais envolvidos com a regulação de emoções negativas e extinção. No entanto, esses achados não foram homogêneos, havendo necessidade de pesquisas futuras.

A literatura aponta que muitos transtornos mentais estão envolvidos com a incapacidade de controlar o medo (LeDoux, 1998; Liggan & Kay, 1999) e dificuldade em regular emoções negativas (Mocaiber, 2005; Ochsner & Gross, 2005). Esses dados sugerem que o condicionamento de medo e a dificuldade em regular emoções tem importante papel na formação e manutenção especialmente dos transtornos de ansiedade. Mocaiber (2005) ressalta que a pesquisa sobre os circuitos neurais da extinção tem importante implicação clínica. Isto porque os transtornos de ansiedade são em parte caracterizados pela resistência à

extinção de reações emocionais aprendidas a estímulos ansiogênicos e por comportamentos de evitação.

É importante ressaltar que o tratamento com TCC abrange técnicas específicas que permitem tanto a extinção do medo condicionado quanto a regulação cognitiva de emoções. Podemos mencionar para ilustrar as técnicas de exposição, distração e reestruturação cognitiva.

A reestruturação cognitiva possibilita ao paciente questionar os fundamentos de seus pensamentos, promovendo alteração na emoção do paciente (Beck, J.,2007). Esta técnica pode ser considerada como estratégias de regulação cognitiva da emoção (Erk, Abler e Walter, 2006; Ochesner & Gross, 2005).

A técnica de distração utilizada no tratamento com TCC favorece que o paciente mude o fluxo de seu pensamento. A distração leva à redução dos sintomas de ansiedade, uma vez que auxilia o paciente a focalizar a atenção em outros estímulos, que não estejam causando desconforto físico (Ventura, 2005). Os estudos de regulação da emoção fortalecem a proposta terapêutica da TCC de que a diminuição da alocação dos recursos atencionais nos estímulos emocionais pode reduzir o impacto deste no indivíduo, uma vez que os transtornos de ansiedade podem ser parcialmente explicados pela facilidade em engajar ou desengajar a atenção nos estímulos ou situações negativas. (Mocaiber, 2005; Ochsner e Gross, 2005).

A técnica de exposição favorece a extinção do medo condicionado. Durante as exposições o paciente fortalece seu senso de controle reduzindo expectativas futuras de dano e aumenta seu senso de auto-eficácia. A exposição favorece o teste da realidade e por meio da constatação real de que as conseqüências catastróficas não vão ocorrer o indivíduo apresenta redução da ansiedade e deixa de emitir as respostas evitação. No entanto, é importante ressaltar que a extinção não se deve à perda de um aprendizado, mas sim à formação de um novo que se superpõe ao anterior e que inibe a resposta deste (Bayon et al, 2006; Hermans et al, 2006; Izquierdo, 2004; LeDoux, 1998; Quirk et al, 2006). A memória do medo, uma vez estabelecida, é relativamente permanente (LeDoux, 1998). Assim, a terapia através da exposição favorece a ativação de áreas que estariam relacionadas ao controle da reação de medo, promovendo a extinção.

Concluímos, portanto, que a TCC é capaz de promover mudanças neurobiológicas associadas aos benefícios terapêuticos já amplamente demonstrados.

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