UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

INSTITUTO DE PSIQUIATRIA

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TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO: ASPECTOS NEUROPSICOLÓGICOS E TERAPIA COGNITIVO-COMPORTAMENTAL PARA CATÁSTROFES NATURAIS

Rio de Janeiro

2016

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Transtorno de Estresse Pós-Traumático: Aspectos Neuropsicológicos e Terapia Cognitivo-comportamental Para Catástrofes Naturais

Dissertação de mestrado submetida à
Universidade Federal do Rio de Janeiro
visando à obtenção do título de
Mestre em Saúde Mental

Orientadora: Paula Rui Ventura
Professora Adjunta do Instituto de Psicologia e
do Programa de Pós graduação do Instituto de Psiquiatria da UFRJ

Rio de Janeiro
Março/2016

FICHA CATALOGRÁFICA

TM

043

L864 Lopes, Alessandra Pereira

Transtorno de Estresse Pós-Traumático: Aspectos Neuropsicológicos e Terapia Cognitivo-comportamental Para Catástrofes Naturais / Alessandra Pereira Lopes. Rio de Janeiro, 2016.

130f.: il.

Dissertação (Mestrado) – Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria / Programa de Pós-Graduação em Saúde Mental, 2016.

Orientadora: Paula Rui Ventura

1. Transtorno de Estresse Pós-traumático. 2. Neuropsicologia. 3. Terapia Cognitivo-comportamental I. Ventura, Paula Rui. II. Universidade Federal do Rio de Janeiro. Instituto de Psiquiatria.

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Dissertação de Mestrado apresentada ao 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 Mestre em Saúde Mental.

Aprovada em: Rio de Janeiro, _____ de março de 2016.

_____
Profª. Drª. Paula Rui Ventura – Presidente da banca
Professora Adjunta do Instituto de Psicologia e do
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AGRADECIMENTOS

Primeiramente agradeço a Deus por ter me iluminado durante os anos da faculdade, de experiência profissional e de mestranda. Se não perdi a cabeça durante vários momentos desses últimos três anos, acredito que foi por sua causa e iluminação, sim, o mestrado foi pesado.

A minha família que sempre me apoiou nos meus estudos e vontade de ser cientista, me apoiaram e me ajudaram a chegar até aqui. As primas Guigui, Lourdes e Tia Ermelinda pelo abrigo dado nesse período permitindo estar a algumas quadras do IPUB. Um agradecimento especial ao primo Beto, um dos poucos acadêmicos da família, por um apoio especial durante o mestrado, me incentivando, me mostrando o quanto é importante e que mesmo com os pesares que essa vida acadêmica trás, vale a pena continuar investindo nela. Ah, não podia faltar, a culpa é dele de me inserir nesse meio viciante de dar aula, afinal de contas isso que importa e é divertido num sábado inteiro né?

Aos meus amigos da faculdade, que mesmo no mestrado após quatro anos de formatura, continuaram sendo meus amigos, até competição para participar como controle da pesquisa teve! No Carnaval saíram da folia para me ajudar, participando das avaliações e arrumando participantes desesperadamente, ou com tanta inabilidade social como eu, afinal quem nunca perguntou no meio do Facebook a idade e escolaridade da pessoa né gente? Tantos compartilhamentos daquela simpática figurinha mostrando quais participantes ainda precisava que perdi a conta...soube que até no Whatsapp ela rodou.

As meninas do apê, Ludmilla e Marcione, que apesar do pouco tempo de convivência viram meu último ano do mestrado de perto, participaram da corrida dos controles, e pelas diversas experiências trocadas sobre bioestatística, quando e como fazer a dissertação e etc., afinal somos um apartamento de mestrandas e doutoranda.

Agradeço também ao Centro de Neuropsicologia Aplicada (CNA) e Instituto D´Or de Pesquisa e Ensino (IDOR) que participaram com dedicação desse projeto também, afinal alguns participantes dessa amostra que segue são funcionários daqui né? Um agradecimento especial ao Psicólogo Gabriel Coutinho que cedeu testes psicológicos para a minha pesquisa e que me ajudou a montar a bateria de avaliação de

uma maneira que ficasse o menos chato possível as três horas que os participantes passavam comigo com um único intervalo, intercalando testes verbais, não-verbais e computadorizados. Outro agradecimento especial vai ao meu chefe Dr Paulo Mattos, que apesar de não acreditar em TEPT, "não sei por que pesquisa isso, nem existe!" (piada interna, rs), entendeu e cedeu gentilmente o espaço de avaliação das salas do IDOR e CNA quando precisei avaliar participantes controles, ou quando precisei trocar meus horários de trabalho porque o participante só podia justamente no meu dia de pesquisa no IDOR, por último acho que já o deixei louco com tantas trocas de horários.

Às melhores sócias do mundo, Juliana e Marseylle, que entenderam perfeitamente a loucura que é fazer mestrado (Juliana já era calejada nisso, e Marseylle acho que tenho que explicar melhor, se quer embarcar nessa é porque não entendeu direito ainda...), e foram pacientes e compreensivas quando a frase que mais escutavam era "tô sem tempo para isso" e durante esse um ano de parceria que coincidiu com o mestrado entenderam perfeitamente que teria de deixar alguns projetos para trás.

A Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) que acreditou no meu projeto e minha habilidade e forneceu bolsa para tal projeto, permitindo o desenvolvimento do mesmo. E já no final do ano de 2015, mesmo vendo a crise econômica do Governo do Estado do Rio de Janeiro respeitou todos os seus bolsistas dando satisfações e entendendo que para muitos aquela bolsa era o que os mantinha aqui e no mundo acadêmico.

Quanto ao primeiro artigo, o agradecimento feito na monografia vale para aqui também, afinal a monografia virou um artigo! Então lá vai: "um agradecimento especial aos que foram responsáveis por proporcionar-me este tema e curiosidade de estudar e ajudar as pessoas que sofrem com desastres naturais, que faço questão de citar nominalmente: Andrea Goldani (por todo o apoio e empenho na Universidade Estácio de Sá – Friburgo, doando seu tempo, estagiários e espaço para o desenvolvimento do trabalho), Flávia e Cristiana (pelo auxílio na divulgação e realização do treinamento aos terapeutas da Região Serrana), Cleyton, Ana Carolina e Fernanda (os fiéis estagiários e psicólogos (as) da Profa. Andrea que foram muito prestativos, auxiliando em todo o processo da aplicação do projeto)."

Quanto ao estudo que foi o meu projeto de mestrado em si e que venho me dedicando nos últimos três anos (desde o probatório a coleta de dados já estava rolando)

a todos os 51 participantes da pesquisa, que doaram gentilmente um período de seu dia para participar da pesquisa, entendendo a importância do avanço da ciência, mesmo num país em que ainda é tão pouco valorizada. Vocês (51 participantes) que nos fazem acreditar que isso vale a pena...que pessoas acreditam no que fazemos!

Por último e não menos importante o agradecimento a galera do Laboratório Integrado de Pesquisa do Estresse (LINPES)!!!! Vamos a cada um para (tentar) não esquecer de ninguém.

Aos médicos psiquiatras e residentes do grupo que demonstraram tamanho entusiasmo com esse projeto, e me ajudaram muito conversando com os pacientes e solicitando a participação na pesquisa de neuropsicologia. Os residentes que eram mais entusiasmados a aprender neuropsicologia do que os psicólogos (rsrsrs) mesmo sabendo da impossibilidade de administrarem testes faziam questão de estar comigo durante as avaliações e aprender um pouco mais sobre esse campo. Um agradecimento especial ao Dr. Mauro Mendlowicz que além de aceitar o convite para compor a banca, também acreditou nesse projeto, fez a entrevista de todos os pacientes e de pronto me chamava para avaliá-los, tornamos as terças-feiras de alguns pacientes cansativas com entrevista pela manhã e avaliação à tarde. Outro agradecimento especial ao Dr. William Berger que até participar como controle da pesquisa quis, mas escolaridade de mais de 20 anos não dá né... Mas agradeço a prontidão em se envolver nesse projeto e pela revisão desta dissertação com uma característica perfeccionista de dar inveja (me ensina?). Por último, um agradecimento especial à alma feminina do ambulatório de TEPT, a Dra. Mariana da Luz, que além de aceitar o convite para compor a banca, dividiu comigo as reorganizações que o ambulatório passou nesses últimos 2 anos, e agradeço por sempre me lembrar que não sou polvo e não posso sair pegando várias coisas para fazer por aí (a melhor controladora de *Burnout*!).

Ao Dr. Ivan Figueira por todo o suporte nos artigos, pelas "achadas de *gap*" e pela experiência compartilhada. Ah e por entender meu apego pelos papéis e não pela tecnologia, afinal por que não aparecer nas reuniões com um monte de artigos no tablet e não impressos né? Ao Dr. Evandro Coutinho por todo o auxílio na estatística e nosso companheiro Stata.

Ao doutorando do LINPES, Carlos Eduardo Norte (ou Cadu mesmo como todos os chamam) que me incentivou e vibrou junto comigo com o projeto de

neuropsicologia, pelos almoços nos raros dias que coincidiram no IPUB e por ser mais um a me estimular e mostrar que a vida acadêmica vale a pena. A psicóloga Maria Pia, que já não está mais no grupo, mas também fez parte nesses dois anos de mestrado, dividiu comigo as triagens do ambulatório, e foi compreensiva como ninguém quando não podia fazer uma triagem para estar na outra sala avaliando algum participante, por mais que isso a deixa-se sobrecarregada.

A todos os estagiários, que mais do que ajudar nesse período, mais do que terem vontade de aprender e se tornarem ótimos psicólogos (as), durante essa jornada se tornaram amigos, um abraço imensurável a vocês.

As minhas duas estagiárias (melhores do mundoooooo) Raquel e Vivian, que além do interesse em comum pela neuropsicologia, dividimos também os trabalhos do projeto (tanto intelectuais quanto braçais), ideias e opiniões, monografias e artigos, e que com certeza tornaram esses três anos de coleta de dados mais divertidos. Ah claro e não podia deixar de lembrar que tornaram esse mestrado o mais produtivo da história! Afinal as duas grávidas ao mesmo tempo e com previsão de nascimento próximo a defesa foi um ótimo teste para controle da ansiedade e estresse de todas nós. Mas obrigada por me darem o privilégio de fazerem Olivia (carinhosamente apelidada de Alessandra Olivia) e Bruno (carinhosamente apelidado de O Goleiro), respectivamente, fazerem parte dessa história. Fica a dica aos próximos mestrandos e doutorandos de darem mais leituras e trabalhos aos seus estagiários para evitar tempo ocioso (né meninas?).

A todo o grupo de psicologia do LINPES que me acolhe desde 2009 e que me despeço com a defesa, muito obrigado.

Por último o agradecimento a quem fez isso acontecer, a Dra. Paula Rui Ventura, que me acompanha desde 2009 e viu vários ciclos meus se iniciarem e se fecharem, o de monitora, o de aluna de iniciação e hoje o de mestranda.

MUITO OBRIGADA!

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AC – Teste de Atenção Concentrada

AVC – Acidente Vascular Cerebral

BED – *Binge Eating Disorder*

CBT – *Cognitive Behavioral Therapy*

DSM – Manual Diagnóstico e Estatístico dos Transtornos Mentais

IGT – *Iowa Gambling Task*

IPUB – Instituto de Psiquiatria

LINPES – Laboratório Integrado de Pesquisa do Estresse

MINI – *Mini International Neuropsychiatric Interview*

PTSD – *Posttraumatic Stress Disorder*

ONU – Organizações das Nações Unidas

QI – Quociente de Inteligência

RAVLT – Lista de Aprendizagem Auditivo-verbal de Rey

RJ – Estado do Rio de Janeiro

SCID – *Structured Clinical Interview Diagnostic*

TCC - Terapia Cognitivo-comportamental

TCE – Traumatismo Crânio-encefálico

TEA – Transtorno de Estresse Agudo

TEPT – Transtorno de Estresse Pós-traumático

TOC – Transtorno Obsessivo-compulsivo

UFRJ – Universidade Federal do Rio de Janeiro

WAIS – III – Escala Wechsler de Inteligência para Adultos (3ª Edição)

WCST-64 – *Wisconsin Card Sorting Test 64 – Item version*

RESUMO

LOPES, Alessandra Pereira. Transtorno de Estresse Pós-Traumático: Aspectos Neuropsicológicos e Terapia Cognitivo-comportamental Para Catástrofes Naturais. Rio de Janeiro, 2016. Dissertação (Mestrado em Saúde Mental) – Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2016.

O Transtorno de Estresse Pós-traumático (TEPT) pode ocorrer após a pessoa ter vivenciado, testemunhado ou tido conhecimento de um evento traumático, que ofereceu risco de morte, sério ferimento ou ameaça à integridade física, e como resposta ao evento tenha sentido intenso medo, impotência ou horror. Os sintomas devem estar presentes pelo período mínimo de um mês para o diagnóstico e envolvem revivescência, evitação/entorpecimento emocional e hiperestimulação. A Terapia Cognitivo-comportamental (TCC) é o tratamento de primeira escolha para o transtorno e a farmacoterapia é também utilizada. Conduzimos uma revisão sistemática investigando a eficácia da TCC no TEPT causado por desastres naturais. A terapia se mostrou eficaz para o TEPT quando oriundo de terremotos. O resultado não pode ser generalizado para outros tipos de eventos naturais devido ao pequeno número de estudos encontrados na literatura envolvendo outros desastres naturais. Outro aspecto clínico do TEPT refere-se ao prejuízo do funcionamento cognitivo apresentado pelos pacientes. Há poucos estudos, com resultados inconclusivos e divergentes. No intuito de investigar as alterações cognitivas dos pacientes com esse transtorno, foi realizada avaliação neuropsicológica das funções cognitivas em vítimas de violência interpessoal. Observou-se que quando comparados ao grupo controle (participantes que passaram por trauma, porém não desenvolveram o transtorno), os pacientes com TEPT apresentaram interferência retroativa em tarefa de avaliação de memória verbal, prejuízos na memória visual, velocidade de processamento vocabulário e quociente de inteligência (QI). Os achados de ambos os estudos podem auxiliar na condução e melhoria dos tratamentos oferecidos aos pacientes com TEPT.

Palavras-chave: TEPT; Terapia cognitivo-comportamental; Neuropsicologia; Catástrofes naturais.

ABSTRACT

LOPES, Alessandra Pereira. Transtorno de Estresse Pós-Traumático: Aspectos Neuropsicológicos e Terapia Cognitivo-comportamental Para Catástrofes Naturais. Rio de Janeiro, 2016. Dissertação (Mestrado em Saúde Mental) – Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2016.

The Post-traumatic Stress Disorder (PTSD) can occur after a person has experienced, witnessed or been aware of a traumatic event, which offered risk of death, serious injury or threat to physical integrity. In response to the event he has felt intense fear, helplessness or horror. The symptoms must be present for a minimum of one month to the diagnosis and involve reviviscence, avoidance and hyperarousal. Cognitive-behavioral Therapy (CBT) is the first choice treatment for the disorder and pharmacotherapy is also used. We conducted a systematic review to investigate the efficacy of CBT on PTSD secondary to natural disasters. The therapy was effective when the trauma was related to earthquakes. The results could not be generalized to other types of natural events due to the small number of studies related to other natural disasters. Another clinical aspect of this disorder refers to the loss of cognitive functioning presented by the patients. There are few studies presenting inconclusive and conflicting results. In order to investigate the cognitive impairment of patients with this disorder, we conducted a neuropsychological assessment of cognitive functions in victims of urban violence. It was observed that, compared with the control group (participants who were victims of trauma but did not develop the disorder), patients with PTSD presented retroactive interference in verbal memory assessment, performed worse in visual memory, processing speed, vocabulary and Intelligence Quotient (IQ). The findings of both studies can assist in conducting and improving treatments offered to patients with PTSD.

Keywords: PTSD; Cognitive Behavioral Therapy; Neuropsychology; Natural Disasters.

SUMÁRIO

1 INTRODUÇÃO

1.1 DIAGNÓSTICO DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

O Transtorno de Estresse Pós-traumático (TEPT) recebeu esta denominação e reconhecimento pelos profissionais de saúde, na década de 1980, após a Guerra do Vietnã (KRISTENSEN, PARENTE & KASZNIAK, 2005), através do Manual Diagnóstico e Estatístico de Transtornos Mentais – 3ª Edição (DSM-III) (APA, 1980). Anteriormente à década de 80, este transtorno era denominado como "trauma emocional", "choque nervoso", "neurose traumática" e "neurose de guerra" (VENTURA *et. al*., 2011).

Hoje em dia, para o diagnóstico de TEPT, de acordo com a *American Psychiatric Association* (2000) – *foram usados para esta pesquisa os critérios diagnósticos do DSM-IV, pois a atualização do DSM-5 entrou em vigor com a pesquisa em andamento* -, é necessário que a pessoa tenha vivenciado, testemunhado ou tido conhecimento de um evento traumático, que ofereceu risco de morte, sério ferimento ou ameaça à integridade física (Critério A1), e como resposta ao evento tenha sentido intenso medo, impotência ou horror (Critério A2).

Os sintomas que ocorrem após a exposição ao trauma, envolvem: revivescência persistente através de *flashbacks* e pesadelos (Critério B); evitação de estímulos associados ao trauma, podendo ser objetos, lugares, pessoas e lembranças, além de embotamento da responsividade relacionada à perda de interesse em atividades antes prazerosas, sentimento de futuro abreviado e capacidade reduzida de sentir emoções (Critério C); hiperestimulação aumentada, observada através de respostas de sobressalto exageradas, hipervigilância, irritabilidade, dificuldade de se concentrar e insônia ou dificuldade de manter ou iniciar o sono (Critério D). Este quadro sintomático deve ter duração de no mínimo um mês do evento, antes disso o diagnóstico atribuído é de Transtorno de Estresse Agudo (TEA) (APA, 2000).

Apesar de os estudos que fazem parte desta dissertação utilizar a 4ª edição do DSM como base diagnóstica, faz-se importante traçar-se um comparativo do que mudou

da 4ª edição para a 5ª edição do Manual Diagnóstico. Dentre as principais alterações estão a retirada da necessidade de vivenciar o trauma com intenso medo ou horror, e alterações negativas da cognição e humor relacionadas ao evento traumático. No quadro a seguir pode ser observado o comparativo em ter as duas edições:

Critérios	DSM-IV	DSM-5
A	Exposição a um evento traumático vivenciado com intenso medo ou horror.	Exposição a um evento traumático vivenciado, testemunhado, conhecimento ou exposição repetida.
B	**Revivência por um ou mais desses exemplos:** Lembranças intrusivas; Pesadelos; *Flashbacks*; Reatividade fisiológica frente a estímulos relacionados ao trauma.	**Revivência por um ou mais desses exemplos:** Lembranças intrusivas; Pesadelos; *Flashbacks*; Reatividade fisiológica frente a estímulos relacionados ao trauma.
C	**Esquiva/Entorpecimento emocional por três ou mais desses exemplos:** Evita atividades, locais, pessoas ou lembranças relacionadas ao trauma; Redução do interesse nas atividades; Sensação de distanciamento perante outras pessoas; Restrição afetiva; Sentimento de futuro abreviado.	**Esquiva/Entorpecimento emocional por três ou mais desses exemplos:** Evita atividades, locais, pessoas ou lembranças relacionadas ao trauma; Redução do interesse nas atividades; Sensação de distanciamento perante outras pessoas; Restrição afetiva; Sentimento de futuro abreviado.
D	**Hiperestimulação autonômica por dois ou mais desses exemplos:** Insônia ou dificuldade de manter o sono; Irritabilidade; Dificuldade de concentração; Resposta de	**Alterações negativas de cognição e humor relacionados ao evento com dois ou mais dos exemplos:** Incapacidade de recordar aspectos importantes do evento; Crenças

Critérios	DSM-IV	DSM-5
	sobressalto exagerada.	negativas sobre si, os outros e o mundo; Cognições distorcidas sobre as causas e consequências do evento; Estado emocional negativo persistente; Diminuição do interesse; Sensação de distanciamento; Incapacidade de experienciar emoções positivas.
E	Os sintomas estão presentes há mais de um mês após o evento traumático.	**Hiperestimulação por dois ou mais desses exemplos:** Insônia ou dificuldade de manter o sono; Hipervigilância; Comportamento auto-destrutivo; Irritabilidade; Dificuldade de concentração; Resposta de sobressalto exagerada.
F	Os sintomas causam prejuízo e sofrimento significativos no funcionamento social ou ocupacional.	Os sintomas estão presentes há mais de um mês após o evento traumático.
G		Os sintomas causam prejuízo e sofrimento significativos no funcionamento social ou ocupacional.

Quadro 1 – Comparativo do diagnóstico de TEPT do DSM-IV e DSM-V

Quanto ao critério principal para o diagnóstico (Critério A1), os eventos traumáticos podem ser combate militar, agressão pessoal (ataque sexual, assalto à mão armada, roubo ou qualquer espécie de ataque físico ou ameaça à integridade física), sequestro, ataque terrorista, tortura, encarceramento e desastres provocados pelo homem ou pela natureza (APA, 2000).

Quanto aos especificadores do diagnóstico este pode ser dividido em agudo (a duração dos sintomas é inferior a três meses após o trauma), crônico (a duração dos sintomas é superior a três meses) e de início tardio (os sintomas manifestam-se seis meses ou mais após o trauma) (APA, 2000). É comum que a sintomatologia, caso não remita dentro de três meses, permaneça por cerca de 12 meses, necessitando de tratamento para remissão (VENTURA *et. al*., 2011).

O TEPT pode ocorrer na infância, juventude e fase adulta. Os sintomas podem surgir após três meses do trauma, apesar de haver alguns casos em que ocorre um lapso de seis meses até a manifestação dos primeiros sintomas, como no TEPT de início tardio (APA, 2000).

A prevalência do TEPT varia de acordo com a comunidade estudada, com índices que variam entre 1 e 14% (CABIZUCA, 2013; RIBEIRO *et. al*., 2013). Em populações de risco, como ex-combatentes, regiões com alto índice de criminalidade, ou na presença constante de desastres naturais, esse índice pode chegar a 50% (VENTURA *et. al*., 2011; KESSLER *et. al*., 1995). No que se refere à população urbana brasileira, cerca de 11% tem risco de desenvolvimento de TEPT, e as mulheres tem maior propensão de desenvolvimento do transtorno (LUZ, 2016).

Transtornos psiquiátricos comórbidos ao TEPT são encontrados em 80% dos casos, sendo os diagnósticos de depressão maior (48%), distimia (22%), transtorno de ansiedade generalizada (16%), fobia simples (30%) e abuso de substâncias (73%) os mais encontrados (VENTURA *et. al*., 2011; MARGIS, 2003).

1.2 TRATAMENTO DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

Diante do sofrimento que acomete os pacientes que desenvolvem este transtorno (Serafim & Mello, 2010), desenvolver e adaptar protocolos de tratamento para o TEPT pode ser considerado uma questão de saúde pública (STEIN *et. al*., 1997), o conhecimento das alterações nas funções cognitivas presentes em pacientes com TEPT, por sua vez, pode ajudar a tornar os tratamentos mais eficazes.

O indivíduo que desenvolve TEPT apresenta uma série de alterações neurobiológicas, cognitivas, afetivas e comportamentais com o intuito de se adaptar à nova ordem imposta pelo acontecimento traumático. Alterações funcionais acontecem, modificando estruturas cognitivas: crenças positivas a respeito de si mesmo e do mundo, que existiam anteriormente, podem ser confrontadas e transformadas em crenças disfuncionais; crenças negativas anteriormente existentes podem ser reforçadas de acordo com as interpretações distorcidas do acontecimento e das consequências. O padrão afetivo é também modificado, marcado pelo elevado nível de ansiedade, apatia, raiva, vergonha e culpa. Mudanças comportamentais são também presentes, com a esquiva de lugares e outros estímulos que foram pareados ao trauma. Dessa forma, além das alterações neuroquímicas, as alterações nos padrões normais das cognições, dos afetos e dos comportamentos, justificam a intervenção psicoterápica (VENTURA *et. al*., 2011).

O tratamento para o TEPT visa à redução dos sintomas, melhora da percepção de perigo do paciente e reestabelecimento dos sentimentos de confiança e segurança. Para alcançar esses objetivos o tratamento pode ser medicamentoso ou psicoterápico, sendo a Terapia Cognitivo-Comportamental (TCC) a intervenção de primeira escolha para o tratamento do TEPT, mais barata e que promove maior qualidade de vida quando comparada à farmacoterapia (LE *et. al*., 2014; VENTURA *et. al*., 2011; ECHEBURÚA, 2010). Apesar disso, nos casos graves aconselha-se que a TCC seja acompanhada de tratamento farmacológico (VENTURA *et. al*., 2011; ECHEBURÚA, 2010).

Em revisão realizada por Mendes *et. al*. (2008) a TCC mostrou-se mais eficaz quando comparada às outras modalidades psicoterapêuticas, no que se refere à remissão da sintomatologia do transtorno, e efeitos semelhantes quando comparada à terapia de exposição e terapia cognitiva isoladamente. Sendo assim, a TCC é considerada o tratamento de primeira linha para pacientes com TEPT (FORBES *et. al*., 2007; YEHUDA *et. al*., 2015; BRADLEY *et. al*., 2005).

Essa abordagem psicoterápica tem como característica geral ser estruturada, objetivando educar o paciente a respeito do seu problema e de como manejá-lo. Assim como, diretiva, trabalha com o aqui-e-agora, ou seja, é orientada para o problema apresentado. E exige a participação ativa tanto do paciente como do terapeuta (RANGÉ & BORBA, 2008; BECK, 1997).

É fundamental para o início do tratamento psicoterápico do TEPT que o indivíduo não esteja mais em contato direto com o agente estressor (SCHREINER, 2005). É necessária também a realização de uma entrevista clínica para entendimento do caso e coleta de dados sobre o evento traumático (VENTURA *et. al*., 2011).

Dentre as técnicas psicoterápicas utilizadas na TCC para o TEPT estão a psicoeducação, exposição (ao vivo e imaginária), manejo de ansiedade e reestruturação cognitiva (VENTURA *et. al*., 2011; MEDEIROS & KRISTENSEN, 2010; BISSON & ANDREW, 2006; KNAPP & CAMINHA, 2003; FOA & ROTHBAUM, 1998).

Técnicas Psicoterápicas	Descrição da Técnica
Psicoeducação	Consiste na informação ao paciente de como será o tratamento e sobre o transtorno que apresenta, possibilitando assim maior entendimento e normalização dos sintomas que apresenta. Esta técnica pode ser estendida a familiares para que saibam o que ocorrerá ao longo do tratamento e o porquê das reações de seu familiar relacionado aos sintomas do transtorno apresentado. Pode ser realizada através de textos, sessões em conjunto (paciente e familiar) explicativas, vídeos e etc.
Exposição (ao vivo)	Esta técnica consiste na exposição direta do paciente aos estímulos ou situações temidas e evitadas por serem desencadeadoras de ansiedade. A exposição é feita repetidamente e de forma gradual (anteriormente ao início da exposição é elaborada, junto ao paciente, a lista de estímulos e situações que passou a evitar e separadas por ordem de dificuldade). O tempo de exposição deve ser longo o bastante para permitir o aumento da ansiedade até um máximo, seguida de sua redução. Esse tempo de permanência do paciente exposto ao estímulo viabiliza os processos de habituação e extinção. A exposição situacional (*in vivo* / ao vivo) envolve a exposição segura a um estímulo externo inofensivo que pareça ou relembre o paciente do trauma. Os

	estímulos usados na exposição situacional incluem lugares, situações e objetos associados ao trauma.
Exposição (imaginária)	A exposição imaginária envolve a exposição sistemática, repetida e prolongada às memórias traumáticas, incluindo as memórias após o trauma, se estas também provocarem sofrimento. Este tipo de exposição reduz o sofrimento associado às memórias traumáticas e à revivência dos sintomas. A exposição imagística também ensina ao paciente que as memórias do trauma e as emoções associadas a ele não são perigosas. Pode ser feita através de uma descrição por escrito do evento ou gravação da narrativa do mesmo, em que o paciente relê ou escuta repetidamente, respectivamente, até a redução da ansiedade.
Manejo de Ansiedade	Visa ajudar o paciente a controlar os sintomas fisiológicos da ansiedade. Sendo duas técnicas mais usadas, a respiração diafragmática e o relaxamento muscular progressivo. A primeira auxilia o paciente a respirar profundamente, e não superficialmente e de maneira rápida como quando ansioso. A segunda auxilia o paciente a detectar os primeiros sinais de tensão muscular para logo assim descontrair, produzindo uma resposta contrária à de ansiedade. Ambas atuam na regulação do Sistema Nervoso Autônomo.
Reestruturação Cognitiva	Visa ajudar o paciente a identificar os pensamentos automáticos questionando-os através das evidências reais (via questionamento socrático ou experimentos comportamentais) e construir alternativas menos tendenciosas e padronizadas para um possível pensamento disfuncional.

Quadro 2 – Descrição das técnicas utilizadas na TCC para TEPT

A TCC em grupo para o TEPT utiliza as mesmas técnicas que o tratamento individual. O diferencial está na inserção da reintegração e apoio social, além de

facilitar a percepção do paciente de que não é o único a desenvolver e apresentar as dificuldades consequentes do transtorno. Dependendo do envolvimento do grupo, essa modalidade de intervenção pode auxiliar também na reestruturação cognitiva, em que os outros pacientes auxiliam o relator do pensamento ou crenças relacionadas ao trauma, através de suas experiências (SCHREINER, 2005).

O uso da realidade virtual como estratégia no tratamento cognitivo-comportamental para o TEPT é crescente. Esta estratégia surge como coadjuvante para auxiliar as técnicas de exposição, tendo em vista as dificuldades encontradas, como pouca adesão do paciente (contornada com a imersão proporcionada pela realidade virtual), impossibilidade de controle do ambiente externo para realização da exposição ao vivo (por mais que o paciente só seja encorajado a se expor em ambientes seguros). Diante dessas dificuldades os ambientes virtuais surgem como opção, com possibilidade de precisão e controle das exposições, através de cenários que simulam a situação traumática, assim como demais locais e situações evitados pelo paciente (VENTURA *et. al*., 2011; GONÇALVES *et. al*., 2012; MCLAY *et. al*., 2014; RIZZO *et. al*., 2015).

1.3 TERAPIA COGNITIVO-COMPORTAMENTAL PARA TEPT ORIUNDO DE CATÁSTROFES NATURAIS

Uma especificidade do tratamento psicoterápico para o TEPT é o tipo de trauma ao que o sujeito foi exposto, como por exemplo, os desastres naturais. Apesar da eficácia da TCC já ser conhecida para o transtorno (LE *et. al*., 2014; VENTURA *et. al*., 2011; ECHEBURÚA, 2010), pouco se sabe sobre a administração dela após catástrofes naturais, estando a maioria da literatura na área datada juntamente ao início do século XXI (KAR, 2011).

Diretrizes internacionais aconselham o uso da TCC poucas semanas após o desastre ou outro evento chocante para reduzir os sintomas de TEPT (TE BRAKE *et. al*., 2009). No entanto, apesar do aumento tanto no número e gravidade das catástrofes naturais (PIELKE, 2006) e o impacto significativo sobre a saúde, à literatura relacionada com o desastre em PTSD é surpreendentemente escassa no que se refere à avaliação da eficácia das intervenções para este tipo de transtorno (NICE, 2005).

1.4 NEUROPSICOLOGIA DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

Poucos estudos evidenciam as alterações cognitivas dos pacientes com TEPT (QURESHI *et. al.*, 2011). Pesquisas com pacientes que sofreram intoxicação ou Traumatismo Crânio-encefálico (TCE), no momento do trauma, mostram queixas cognitivas (PAGES *et. al.*, 2014), porém poucos estudos com vítimas de violência urbana investigaram as alterações e queixas cognitivas destes pacientes (QURESHI *et. al.*, 2011). A partir das queixas relatadas por pacientes ambulatoriais com o diagnóstico de TEPT, tem sido sugerida a avaliação neuropsicológica para maior entendimento dos déficits cognitivos.

Kristensen, Parente e Kaszniak (2006) e Menezes (2013) salientam a importância da avaliação das funções cognitivas no TEPT para além de questões diagnósticas, podendo auxiliar no planejamento terapêutico.

As investigações neuropsicológicas nestes pacientes iniciaram-se no pós-guerra tendo maior força na década de 80. Apesar de no início o foco maior do prejuízo cognitivo desses pacientes envolver a memória e seus circuitos. Em estudos posteriores, no início do século XXI, foram identificadas a atenção e as funções executivas como deficitárias nos paciente com diagnóstico de TEPT. Alterações estas respaldadas por modificações nas estruturas cerebrais e relato dos pacientes a respeito da funcionalidade antes e após o evento traumático (KRISTENSEN, PARENTE & KASZNIAK, 2006; BRESSAN *et. al*., 2009).

Em revisão realizada por Qureshi *et. al.* (2011) foram apresentados estudos que compararam as funções cognitivas de vítimas de trauma com e sem TEPT. Foi observado que quanto maior a gravidade do transtorno maior o comprometimento cognitivo. E como conclusão os autores apontaram a heterogeneidade deste campo de pesquisa, pois os estudos apresentavam resultados diferentes no que se refere ao déficit ou não da função observada, como por exemplo, a capacidade de aprendizado e atenção mostrou-se alterada em sete dos 13 estudos que avaliaram esta função. A mesma dificuldade foi observada quanto à função executiva, deficitária em nove de 16 estudos. Já a memória foi observada como deficitária em seis dos 18 artigos revisados. Tendo em vista os resultados divergentes, fazem-se necessários mais estudos na área controlando variáveis como comorbidades e uso de substâncias psicoativas.

1.5 OBJETIVOS

Nessa dissertação serão incluídos dois artigos (um de revisão e um artigo empírico), que tem por objetivos, respectivamente:

1) Revisar o cenário pouco explorado sobre uso da TCC para TEPT oriundo de catástrofes naturais.

2) Avaliação das funções cognitivas em pacientes do ambulatório do Laboratório Integrado de Pesquisa do Estresse do Instituto de Psiquiatria da UFRJ (LINPES-IPUB-UFRJ).

2. ARTIGO 1

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PLOS ONE

Systematic Review of the Efficacy of Cognitive-Behavior Therapy Related Treatments for Victims of Natural Disasters: A Worldwide Problem

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Abstract

Natural disasters can have devastating consequences. Each year, about 225 million people are victims of natural disasters worldwide, and up to 13,5 million of these people can develop post-traumatic stress disorder (PTSD) in the first or second year following the disaster. Cognitive-behavior therapy (CBT) is the first-choice treatment for this disorder. In order to evaluate the efficacy of psychotherapeutic treatment based on cognitive-behavior therapy for people who developed post traumatic stress disorder after natural disasters we conducted a systematic search of published studies. We used the terms reported below in the electronic databases ISI Web of Science, PsycINFO, PubMed, PILOTS and Scopus with no restrictions of language or publication date. Articles that described randomized controlled, non-randomized controlled and non controlled studies on the efficacy of cognitive-behavior therapy for individuals diagnosed with post-traumatic stress disorder after exposure to a natural disaster were eligible for inclusion. The studies were required to use a standardized measure of effectiveness before and after the intervention and have a group of patients who had used cognitive-behavior therapy as the only intervention. Our search identified 820 studies, and 11 were selected for this review. These 11 studies involved 742 subjects, 10 related to earthquakes and 1 to a hurricane. The cognitive-behavior therapy techniques used were various: 7 studies used exposure therapy, 2 studies used problem solving, and the only 2 studies with adolescents used techniques including reconstructions and reprocessing of the traumatic experience. As limitations, the search involved only five electronic databases, no experts in the field were consulted, and the heterogeneity of the findings made it impossible to perform a meta-analysis. The results suggest the efficacy of cognitive-behavior therapy, particularly exposure techniques, for the treatment of post-traumatic stress disorder after earthquakes. However, further studies with stronger methodologies, i.e. randomized-control trials and non-randomized controlled trials, are needed.

Citation: Lopes AP, Macedo TF, Coutinho ESF, Figueira I, Ventura PR (2014) Systematic Review of the Efficacy of Cognitive-Behavior Therapy Related Treatments for Victims of Natural Disasters: A Worldwide Problem. PLoS ONE 9(10): e109013. doi:10.1371/journal.pone.0109013

Editor: Linda Chao, University of California, San Francisco, United States of America

Received June 16, 2014; **Accepted** September 5, 2014; **Published** October 8, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

Funding: These authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

The consequences of natural disasters can be devastating, as they are large-scale, potentially traumatic events which affect a significant number of people [1]. Along with the increase of the world population between 1960 and 2005, an annual increase of 5% in the number of natural disasters and of 4% in the number of people affected by these disasters was observed [2].

About 225 million people worldwide are affected by natural disasters annually, i.e. 1/25 people in the world [3]. Of these, up to 13,5 million (3–6% of 225 million exposed to this kind of disaster) can develop post-traumatic stress disorder (PTSD) in the first or second year following the disaster [4].

Post-traumatic stress disorder (PTSD) can occur in people who have experienced, witnessed or known about a traumatic event that posed risk of death, serious harm or threat to physical integrity, and as a response to it have felt intense fear, helplessness or horror. The symptoms usually appear one month after the trauma and involve three clusters: re-experiencing, avoidance and hyperarousal [5].

For treatment of PTSD, first-choice interventions are cognitive-behavioral therapy (CBT) and drug therapy [6]. CBT includes exposure techniques, cognitive re-structuring and anxiety management [7–8]. The exposure technique is the most used and most successful technique for treating this disorder. It involves patients confronting their fears, either through imagination or in vivo. Anxiety management includes relaxation training, diaphragm breathing, social skills training, and distraction techniques. In a literature review, Foa and Meadows [7] showed that prolonged exposure and stress inoculation training are effective in reducing PTSD symptoms.

International guidelines advise using CBT a few weeks after a disaster or other shocking event to reduce PTSD symptoms [9]. However, despite the increase in both the number and severity of natural disasters [10] and the significant impact on health, the disaster-related literature on PTSD is surprisingly scanty as

regards the assessment of efficacy of interventions for this type of disorder [11]. The aim of this study is to evaluate the efficacy of psychotherapeutic treatment based on CBT for individuals who developed PTSD after natural disasters, through a systematic review. To the best of our knowledge there is no systematic review or meta-analyses about CBT efficacy for PTSD after natural disasters.

Methods

Search Strategy

We conducted systematic searches in the electronic databases ISI Web of Science, PsycINFO, PubMed, PILOTS and Scopus with no restrictions of language or publication date. The search occurred until April 03, 2013. We performed advance searches in all 5 databases using the following search terms:

- PTSD OR "stress disorder" OR "Post-traumatic Stress Disorder"
- earthquake OR "mass trauma" OR disaster OR flood OR tsunami OR cyclone OR hurricane OR whirlwind OR flaw OR "vortex typhoon" OR tornado OR "natural disaster*"
- "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*"

The terms indicated in each item were combined using "AND", a function which is available in all databases. In the ISI Web of Science the search was restricted to articles and notes, but in PsycINFO, PubMed, PILOTS and Scopus it was conducted in all fields.

Besides these searches in electronic databases, we also performed manual searches in the reference sections of published texts in the field as an additional guarantee that every eligible article for inclusion was indeed covered by the survey.

We then analyzed the abstracts of all studies identified and excluded papers that did not meet the selection criteria. If a given abstract met inclusion criteria for the study, the full text was analyzed [12]. The selection process is described in Figure 1.

For this research, a wide definition of CBT was considered, encompassing behavioral and/or cognitive strategies.

Criteria for including studies in this review

We selected articles that reported randomized controlled, non-randomized controlled or non controlled studies using CBT for individuals diagnosed with PTSD after exposure to a natural disaster, and which provided a standardized measure of effectiveness before and after the intervention. To distinguish non controlled studies from case studies, we followed the criterion that open trials should comprise 10 cases or more [13].

We excluded review articles, book chapters, dissertations and theses, as well as studies without a standardized measure of effectiveness before and after the intervention, case studies, studies without patients using CBT as the only intervention; studies of samples with diagnosis of PTSD resulting from trauma other than a natural disaster; studies with animal models; and studies without a formal diagnosis of PTSD.

Quality evaluation of the studies

After the search phase, we did an analysis of the methodological quality of the randomized controlled trials and the non-randomized studies selected based on an adaptation of the Cochrane Collaboration Tool for Assessing the Risk of Bias [14]. One author (A.L.) extracted study characteristics and another author (E.C.) assessed risk of bias (Table 1).

Results

Our survey identified 820 studies, from which 11 were selected for this review (Figure 1) according to the above-mentioned inclusion criteria: 3 randomized controlled, 3 non-randomized controlled and 5 non controlled trials. Two of these studies used the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders – Third Edition Revised) as a basis for diagnosing PTSD [15,16], while the other ones used the fourth edition. Table 2 shows the descriptions of the studies.

We excluded 165 duplicated studies that had been found in the electronic search in the five databases. After reading the abstract, 625 studies were excluded for the following reasons: 10 were case studies, 111 were reviews, 47 were book chapters, dissertations or theses, 2 did not have an intervention group that used only CBT, 146 did not focus on treatment response, 67 did not focus on PTSD, 237 did not focus on natural disasters, 3 did not use humans and 2 had the aim of validating instruments. From the remaining 30 studies, 18 were excluded after reading the full text for the following reasons: 5 were case studies, 3 used mixed samples, 3 were intervention projects (had no results), 2 did not focus on PTSD, 2 did not use CBT, 1 did not have an intervention group that used only CBT intervention, 1 did not focus on natural disasters, and 1 revised data from a previous study.

Of the 11 articles, 7 used exposure techniques (three randomized studies [17–19] and four non controlled studies [20–23]), and of these, 2 focused on exposure through narrative [19,23] and 2 used exposure with other cognitive and behavioral techniques, which were also the two studies with children [21,22]. Two other trials used problem solving techniques [24,25]. The only two studies with adolescents [15,16] used techniques encompassing reconstruction and reprocessing the traumatic experience, identification of traumatic memories and building up tolerance to related reactions, development of acceptance and adaptation to earthquake-related changes, mental reconstruction of deceased persons, and fostering of normal development.

Figures 2 and 3 summarize the different aspects concerning the methodological quality of the studies. Among the randomized clinical trials most of the methodological aspects were well covered. Only one study did not mention if the compared groups were balanced concerning age, gender and other potential confounders. One study did not mention if patients received other treatments besides the intervention and another one did not control for potential confounders. All non-randomized studies did not mention the use of blinding assessment.

Randomized Controlled Studies

Basoglu, Salcioglu, Livanou, Kalender and Acar [17] tested the effectiveness of a behavioral treatment session as compared to waiting list three years after the earthquake that hit Turkey in 1999. The intervention focused on reduction of fear and avoidance, habituation to anxiogenic stimulus, and increasing in the sense of control over traumatic stressors. The first stage of treatment involved the identification of problems like fear and avoidance of earthquakes, re-experiencing and hyperarousal. The second stage consisted of explaining the mechanism and logic of exposures. The final step in the session set up goals (stimuli related to the trauma) and instructions for self-exposure. No cognitive restructuring was conducted during the treatment. The study found that a single session of behavioral therapy was a cost-effective

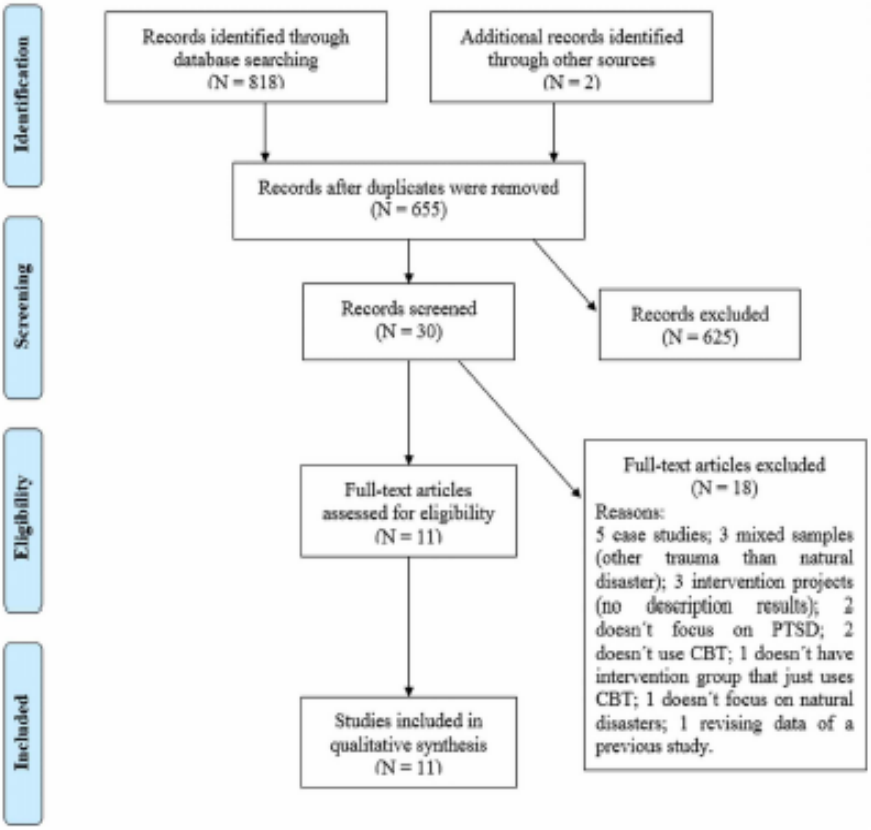

Figure 1. Flowchart of the process of identification and selection of studies.
doi:10.1371/journal.pone.0109013.g001

strategy for earthquake survivors with PTSD, particularly those of lower socioeconomic status (SES) and education.

Basoglu, Salcioglu and Livanou [18] examined the efficacy of a single exposure session in an earthquake simulator and self-exposure instructions in reducing PTSD symptoms as compared to a control group. The treatment was performed in two stages. The first aimed to explain the intervention, set up goals, and provide instructions for self-exposure. The second stage involved exposure in an earthquake simulator, explaining that this exposure was designed to increase the participant's sense of control. The simulator consisted of a small furnished house with a platform underneath that caused quakes of various intensities. Participants controlled the quaking (through a remote control) to initiate quakes and increase their intensity when they felt ready for that. If a participant's anxiety was more connected with the quakes, they were told to focus on the feeling, vision and sound of the movement. If anxiety was related to re-experiencing, they were encouraged to speak about the event as an imaginal exposure. The session with the simulator was finished when the participants felt in total control of their anxiety and fear. The mean duration of this second part of the intervention was 33 minutes. No sort of cognitive restructuring was used during the intervention. This treatment was found to be statistically significant and effective for the intervention group, despite the control group showing a 21% reduction in scores on the *Clinician-Administered PTSD Scale* (CAPS).

As compared to the previous study [17], the simulator exposure intervention with instructions for self-exposure was more effective in reducing PTSD symptoms than the intervention with instructions for self-exposure alone, with 79% and 59% of improvement, respectively, in treated groups. However, single-session interventions do not appear to be effective in cases of multiple co-morbidities [18].

Zang, Hunt and Cox [19] evaluated the efficacy of Narrative Exposure Therapy (NET) as a short-term treatment for PTSD in Chinese survivors from the Sichuan earthquake. Participants were stimulated to provide a chronological narrative of their lives focused on the trauma. This intervention is designed to help the cognitive process and habituation of emotional responses to the trauma. A comparison of pre-test, post-test and follow-up showed a statistically significant reduction of PTSD symptoms in the group receiving NET. Moreover, the treatment also offered benefits in co-morbidities, such as a reduction in depression and anxiety symptoms, gains which were maintained until two months after treatment. The authors concluded that NET was an effective treatment for earthquake survivors regarding reduction of PTSD symptoms and improvement of overall mental health.

Table 1. Description of variables in evaluation of methodological quality.

Criterion	Description	Evaluation
Random Sequence Generation	Evaluate the way the randomization sequence was generated	Low Risk of Bias: proper randomized way of generating randomization sequence; examples are sequences generated by computer programs
		Unclear Risk of Bias: Does not inform how the randomization sequence was generated
		High Risk of Bias: Non-randomized or inadequate way of generating randomization sequence
Allocation Concealment	Evaluate concealment of sequence, i.e. how difficult it was for participants or evaluators to predict to which group the next subjects would be assigned	Low Risk of Bias: The randomization sequence was generated so as to promote concealment of it
		Unclear Risk of Bias: Does not inform how randomization sequence and attempt of concealment was generated.
		High Risk of Bias: No attempt of concealment of randomization sequence
Single Blinding (rater)	Evaluate if the evaluator was "blind", i.e. when evaluating he/she was unaware of which group the subject belonged to (intervention or waiting list)	Low Risk of Bias: Evaluator did not know which group the subject belonged to while evaluating
		Unclear Risk of Bias: Does not inform if evaluator was aware of the group the subject belong to
		High Risk of Bias: Evaluator knew which group the subject was assigned to.
Incomplete Outcome Data	Evaluate information about loss of data at follow-up	Low Risk of Bias: There was little or no loss along the study, and this is mentioned by the author
		Unclear Risk of Bias: No losses were mentioned, when the numbers clearly pointed so
		High Risk of Bias: Great loss along the study
Selective Reporting (Reporting Bias)	Mention along the results all of the criteria, variables and measures described in the aim and methods of the study	Low Risk of Bias: Results of all the criteria, variables and measures mentioned
		Unclear Risk of Bias: No information about the criteria, variables and measures used, as well as their results.
		High Risk of Bias: Criteria, variables and measures were used that were not reported in the results section
Concomitant Treatment	Inform if there was treatment concomitant to the provided one	Low Risk of Bias: Absence of concomitant treatment
		Unclear Risk of Bias: No information about concomitant treatment
		High Risk of Bias: Presence of concomitant treatment to the one offered in the study
Description of Treatment	Describe activities performed during the treatment	Low Risk of Bias: Mentions how many sessions were held and activities were described by session
		Unclear Risk of Bias: Incomplete description about the treatment
		High Risk of Bias: Did not provide description of the number and content of sessions.
Description of Control Activity	Describe activities performed by the control group or waiting list	Low Risk of Bias: Mentions if control group performed any activities, and if so, which ones
		Unclear Risk of Bias: Incomplete description of activities performed by control group
		High Risk of Bias: No information on activities performed by control or waiting list group. Or performed some similar activity to the intervention group
Identification of Internal Comparability	Identify numerical or social demographic differences between intervention and control groups	Low Risk of Bias: No differences found between the groups and authors identified and highlighted such differences
		Unclear Risk of Bias: It was not possible to clearly evaluate the differences between groups
		High Risk of Bias: There were differences but authors do not mention it
Statistical Treatment for Internal Comparability	Use statistical treatment to control for differences observed between the groups (intervention X control)	Low Risk of Bias: There was difference between the groups and a statistical method was used to control for it

Table 1. Cont.

Criterion	Description	Evaluation
		Unclear Risk of Bias: Authors do not provide data for this evaluation
		High Risk of Bias: A difference was found, but no statistical treatment was used to control for it.

doi:10.1371/journal.pone.0109013.t001

Non-randomized Controlled Studies

Goenjian, Karayan, Pynoos, Minassian, Najarian et al [15] evaluated the efficacy of a number of sessions of brief trauma-focused psychotherapy after the earthquake that hit Armenia in 1988. The intervention was initiated one and a half years after the earthquake. Treatment was based on five areas: reconstructing and reprocessing traumatic experiences and associated emotions; identifying and enhancing tolerance of reminders and links to traumatic experiences; enhancing acceptance, adapting to changes and losses related to the earthquake; mental reconstruction of deceased persons in the disaster; and promotion of normal development. The intervention group showed a statistically significant reduction of PTSD symptoms (intrusion, avoidance and autonomic hyperarousal) as compared to the control group. The trauma-focused psychotherapy showed good results in reduction of PTSD symptoms and prevention or worsening of depressive symptoms.

Goenjian, Walling, Steinberg, Karayan, Najarian et al [16] determined the effectiveness of trauma-focused therapy in improving PTSD and depressive symptoms, comparing treated and untreated adolescents. The intervention took place in a school setting and comprised four 90-minute group sessions and two 1-hour individual sessions. The most symptomatic students received up to 4 individual sessions and sessions with the family when indicated. The intervention used CBT techniques and was based on five areas mentioned above in the Goenjian, Karayan, Pynoos, Minassian, Najarian et al [15] study. Before treatment (15 years after the earthquake), the groups did not differ significantly in PTSD symptoms. However, 5 years after the earthquake, PTSD symptom scores (re-experiencing, avoidance and autonomic hyperarousal) were significantly lower in treated than in untreated students. Although the scores decreased in both groups, the reduction was three times greater in treated students. There was also a significant reduction in depressive symptoms in students who received treatment and an increase in those who did not.

Ferdos and Seyed-Hosein [24] assessed the effectiveness of a problem solving program in survivors of an earthquake in Iran in 2003. Training sessions of 2 hours each were held three times a week for one month and conducted by a therapist and a co-therapist. The first session was aimed at providing information about the intervention program and group rules. At the next three sessions the patients were taught coping strategies and trained in problem solving. At the fifth session training strategies were reviewed. At the sixth session control of intrusive thoughts was introduced. From the seventh to the twelfth sessions participants gave some feedback on the strategies chosen to cope with the problems, how effective they felt they were, and were encouraged to discuss the positive and negative aspects of the chosen strategies, preparing individuals to make their choices for problem solving by themselves. The experimental groups showed a significant increase in coping strategies skills focused on problem solving rather than on emotion, i.e. more effective coping strategies.

Non Controlled Studies

Basoglu, Livanou, Salcioglu and Kalender [20] investigated with earthquake victims how brief a CBT intervention for PTSD could be, without undermining its effectiveness. The number of sessions for the intervention was not previously determined, the interval between sessions was about 16 days, and the treatment was finished when there was clinical improvement as observed by the therapist and patient. The treatment was conducted individually and in groups, and was divided in three steps. The first consisted in identifying the problems that emerged after the earthquake, such as avoidances, autonomic hyperarousal and re-experiencing symptoms. Pyschoeducation on the treatment came next. The third and last step of the treatment involved setting up goals and instructions for self-exposure to the avoidances raised in the first step. No cognitive restructuring was performed during treatment. The intervention was performed in a mean of 3-4 sessions. There was no difference between patients that were using or not using on psychiatric medication. A limitation of this study was the low number of participants in the follow-up evaluation, making it impossible to determine if the improvement in PTSD symptoms was maintained.

Giannopoulou, Dikaiakou and Yule [21] examined the effects of a cognitive-behavior intervention in a group of children with PTSD after the earthquake that hit Athens in 1999. Children that had another childhood-related comorbid psychopathology were not included in the study. The first session was a meeting with the parents to provide psychoeducation on the disorder and treatment. Children participated in six sessions, each including the session's agenda, a review of the previous week's and homework, psychoeducation and skill training, practice assisted by the therapist and setting homework for the next week. At the first session with the children (second session of the intervention), group rules were set up and PTSD symptoms were explained as a common reaction in those who undergo difficult or abnormal situations. At session two techniques for promoting a sense of control over trauma-related memories, nightmares and emotions were taught. The third session focused on symptoms of autonomic hyperarousal, and the children were taught how to identify reactions and to use progressive muscle relaxation and breathing techniques when they occur. At the fourth session avoidant behaviors were worked on by introducing the hierarchy of avoidances, and through the "fear thermometer" they could rank situations, places, people and memories they had been avoiding since the trauma. Sessions 5 and 6 were devoted to exposure, when the model of gradual exposure was explained and the participants were encouraged to perform imaginal exposure in the session. In vivo exposures were assigned as homework with the help of the parents. At the seventh session all that had been learned during the intervention as regards anxiety management and exposure was reinforced and summarized, with an emphasis on relapse prevention, as well as working on plans for the future. The intervention produced a statistically significant reduction in PTSD (intrusions, avoidances and autonomic hyperarousal) and depres-

Table 2. Description of studies.

Study	Sample	Trauma	Blinding	Type of Intervention	Number of Sessions	Assessment of PTSD Symptoms	Moments of evaluation	Results in PTSD symptoms
Randomized Controlled Studies								
Basoglu *et. al*, 2005	59 adults (31 to SSBT and 28 to WL)	Earthquake	Double Blinding (Assessments + Participants)	Behavioral Treatment/	1 session of 60 minutes	CAPS	Before and week 6, 12, 24 and 1, 2 year after treatment	Treatment was effective in reducing PTSD symptoms (P< .001). 71% of the sample had a reduction in PTSD symptoms 24 weeks after the intervention.
				Self-exposure				
Basoglu *et. al*, 2007	31 adults (16 to SSBT and 15 to RA)	Earthquake	Double Blinding (Assessments + Participants)	Behavioral Treatment/	1 session of 60 minutes	CAPS	Before and week 4, 8, 12, 24 and 1, 2 year after treatment	Treatment effects were significant (P<0.01), 80% of the sample had significant reduction in PTSD symptoms and fear 24 weeks after the intervention. Between-group comparisons were significant on all measures.
				Exposure				
Zang *et. al*, 2013	22 adults (11 to NET and 11 to WL)	Earthquake	Single Blinding (Assessment)	NET	4 sessions of 90 minutes	IES-R	Before and immediately after treatment and 2 weeks and 2 months after treatment	The participants that received NET showed significant (P< 0.01) reductions in PTSD symptoms immediately after the treatment.
Non-randomized Controlled Studies								
Goenjian *et. al*, 1997	64 adolescents (35 to group treatment and 29 to control group)	Earthquake	Not Available	Brief trauma/grief focused psychotherapy	4 group sessions of 30 minutes and two individual sessions of 60 minutes	CPTSD-RI	Before and after treatment	After intervention the adolescents that received treatment had a significant (P< 0.05) decrease in all three categories of PTSD (re-experiencing, avoidance and hyper arousal autonomic)
Goenjian *et. al*, 2005	63 adolescents (36 to group treatment and 27 to control group)	Earthquake	Not Available	Brief trauma/grief focused treatment	4 group sessions of 30 minutes and two individual sessions of 60 minutes	CPTSD-RI	Before and after treatment	Both groups had significantly decreased scores (P<0.001), but in the treated group all three categories (re-experiencing, avoidance and hyper arousal autonomic) decreased, whereas in the untreated group only re-experiencing symptom was reduced.

Table 2. Cont.

Study	Sample	Trauma	Blinding	Type of Intervention	Number of Sessions	Assessment of PTSD Symptoms	Moments of evaluation	Results in PTSD symptoms
Ferdos&Seyed-Hossein, 2007	160 adults (80 to experimental group and 80 to control group)	Earthquake	Not Available	Problem Solving	12 sessions of 2 hours	Mississippi PTSD Scale	Before and after treatment	There was significant (P = 0.001) reduction of PTSD symptoms compared to control groups. The experimental groups showed significantly (P<0.02) increased coping skills focused on problem solving.
Not Controlled Studies								
Basoglu *et. al*, 2003	167 adults	Earthquake	Not Applied	Behavioral Treatment/ Self-exposure	An average of 3 to 4 sessions	TSSC	Before and after treatment, and follow-up at 1 to 2, 2 to 3 and 3 to 9 months after the treatment	76% of participants had a reduction in PTSD symptoms with one session and 88% with two sessions, so the treatment had a significant (P<0.001) effect in reducing PTSD symptoms
Giannopoulou *et. al*, 2006	20 children	Earthquake	Not Applied	CBT	6 sessions of 2 hours with children and 1 session with parents	CRIES	Before and immediately after the treatment and 18 months and 4 years after the intervention	Treatment caused significant (P = 0.001) reduction in PTSD symptoms. Of 17 children who completed treatment, only two continued to meet PTSD diagnosis, i.e. the others showed remission of the disorder.
Ofraz *et. al*, 2008	14 adults	Earthquake	Not Applied	Psychoeducation and Problem Solving	6 sessions of 60 to 90 minutes	CAPS	Before and after the treatment	A significant (P = 0.001) reduction of PTSD symptoms was observed in psychoeducation and problem solving group.
Jaycox *et. al*, 2010	118 children (58 to CBITS and 60 to TF-CBT)	Hurricane	Not Applied	CBT	CBITS = 10 group sessions and 1 to 3 individual sessions	CPTSD-SS	Before and 5, 10 months after the treatment	Both groups showed significant reduction in PSTD symptoms (CBITS = P<0.001 and TF-CBT = P<0.01).
					TF-CBT = 12 individual or conjoint sessions (children and parents)			
Zhang *et. al*, 2011	24 persons (aged 6-80 years)	Earthquake	Not Applied	CBT	30 minutes of daily sessions for 1 week	Chinese version of IES-R	Before and after treatment	Participants that received CBT and CBT plus acupoint stimulation showed significant (P<0.01) reductions of PTSD symptoms after treatment.

The studies of Zhang et. al. (2011), Jaycox et. al. (2010) and Ofraz et. al. (2008) are originally randomized studies, but for the purposes of this review and analysis of their results they were used as open trials. Abbreviations: IES-R = Impact of Event Scale – Revised; CPTSD-RI = Child Posttraumatic Stress Disorder Reaction Index; CAPS = Clinician-Administered PTSD Scale; CPTSD-SS = Child PTSD Symptom Scale; CRIES = Children's Revised Impact of Event Scale; TSSC = Traumatic Stress Symptom Checklist; SSBT = Single Session Behavioral Treatment; WL = Waiting List; RA = Repeated Assessments; NET = Narrative Exposure Therapy; CBITS = Cognitive-Behavioral Intervention for Trauma in Schools; TF-CBT = Trauma-Focused Cognitive-Behavioral Therapy; CBT = Cognitive-Behavioral Therapy.

doi:10.1371/journal.pone.0109013.t002

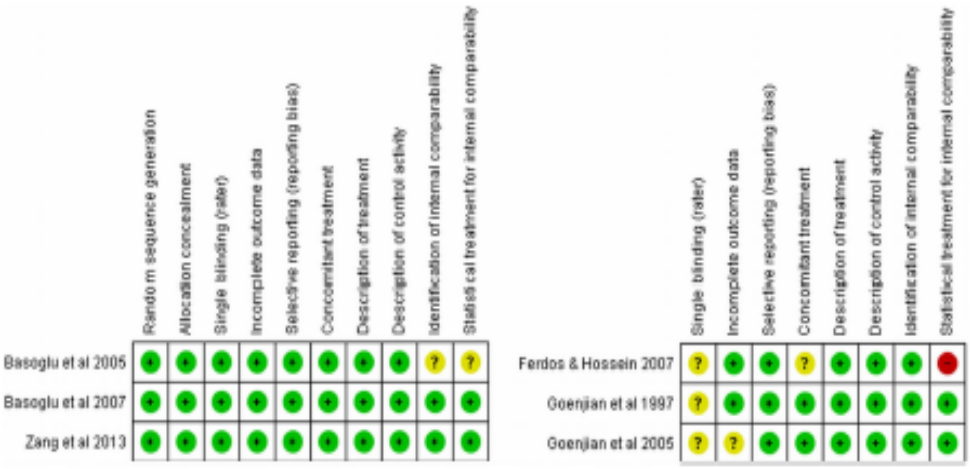

Figure 2. Methodological Analysis for Study.
dot:10.1371/journal.pone.0109013.g002

sive symptoms at the end of treatment and 18 months later. Of the 17 children who completed the treatment only 2 continued to meet the diagnosis of PTSD.

In the three studies described below we had to separate the intervention groups. The results of the studies were used separately, that is, each group was analyzed as if it were an intervention group. We did not include them in the randomized or non-randomized categories because they did not have a group with no intervention that could be used as a control group. Even though the two studies were randomized studies, for the present review they were classified as open trials/non controlled studies, because the results of the intervention for each group were used separately.

Oflaz, Hatipoglu and Aydin [25] assessed the effectiveness of a psychoeducational intervention, including problem solving and coping strategies, as compared to medication and medication with psychoeducation group, in reducing PTSD symptoms in Turkish earthquake survivors. At the first session participants were interviewed about their feelings and beliefs about the traumatic experience. The second session and third session were dedicated to psychoeducation about the disorder, giving details on the nature of posttraumatic reactions. At the fourth session problem solving was introduced. At the fifth session the patients set up goals and were stimulated to put them in practice, in the interval between sessions. The sixth session was devoted to a review of what had been done and learned during the intervention. A statistically significant reduction in PTSD symptoms was observed in the medication with psychoeducation only group.

Jaycox, Cohen, Mannarino, Walker, Langley et al [22] identified students with PTSD symptoms from three schools following hurricane Katrina and offered them two interventions (Cognitive-Behavioral Intervention for Trauma in Schools – CBITS and Trauma-Focused Cognitive-Behavioral Therapy – TF-CBT). Both interventions used cognitive-behavioral strategies, such as psychoeducation, relaxation techniques, management of emotions, cognitive restructuring, narration of trauma and exposures. TF-CBT was conducted in 12 joint sessions, with child and parents, and was used only in a clinical context, while CBITS

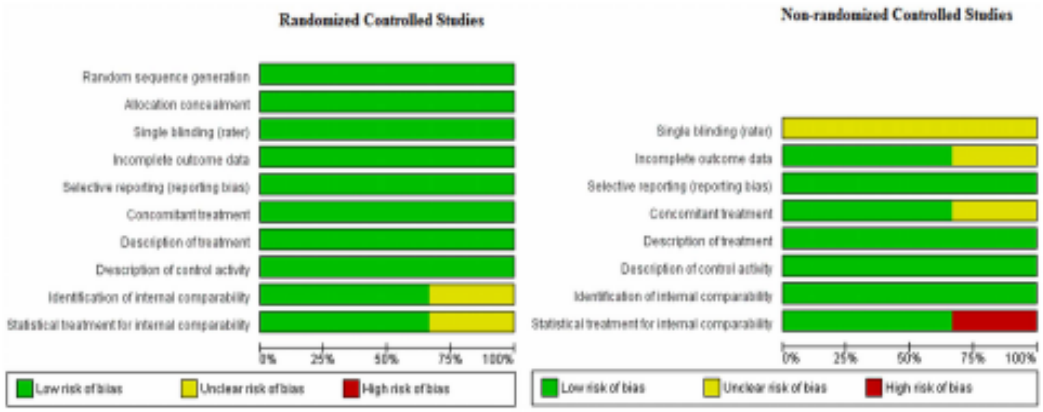

Figure 3. Methodological Analysis by Criteria.
dot:10.1371/journal.pone.0109013.g003

was delivered in groups in a school setting and only with the child, consisting of 10 group sessions and 1–3 individual sessions. Both groups had a statistically significant reduction in PTSD symptoms. Despite the reduction in PTSD symptoms, 37 children in the CBITS and one in the TF-CBT group still met the diagnostic criteria of PTSD at a 10-month follow-up. Family support was correlated with less impairment caused by the disorder.

Zhang, Feng, Xie, Xu and Chen [23] studied the curative effect of acupoint stimulation on the earthquake-caused PTSD in a group of patients. The subjects submitted to CBT were asked to describe the earthquake event (trauma) as they had experienced it, including the most horrifying scene, rescue of family members, pain sensation, and psychological and psychophysiological discomfort. As a result there were no dropouts, even though the patients suffered distress recalling the effects of the trauma. The authors conclude that CBT alone and CBT with acupoint stimulation are both effective in reducing PTSD symptoms, but suggest CBT in conjunction with acupoint stimulation be used in disaster-stricken areas, because it was found to be more effective than CBT alone.

Discussion

Main Findings

The efficacy of CBT for PTSD is well established as documented by systematic reviews [26,27] and meta-analyses [28,29]. The examination of the primary research on which reviews and meta-analyses are based, shows that samples from a diversity of traumas are used, particularly sex abuse, war and traffic accidents [30–33]. Few reviews attempt to focus on a specific trauma, such as Dossa and Hatem [29] on the use of CBT in adult women with PTSD who were victims of war violence, where 9 randomized studies were found. In the present review, in contrast, only 3 randomized studies were found. There are more randomized controlled trials.

As far as we know, this is the first systematic review focusing only on natural disasters. Of the 11 articles included here, all (3 randomized-control trials, 3 non-randomized controlled trials and 5 non controlled studies) reported a significant reduction of PTSD symptoms after treatment, suggesting efficacy of intervention. However, 10 of the 11 articles evaluated earthquake victims and only one evaluated victims of any other natural disaster, a hurricane, and no studies were found on landslides, forest fires, floods, volcanic eruptions, meteorite falls or tsunamis (for the latter, studies were found, but they did not meet the inclusion criteria of this review). Therefore, there is no evidence of the efficacy of CBT for victims of natural disasters other than earthquakes.

The restriction of samples to certain age groups precludes generalizing the claim of CBT efficacy in PTSD following natural disasters. Of the studies, 6 were with adults, 2 with adolescents and 2 with children, and one was with a mixed sample (ranging from 6 to 80 years). No study was found focusing solely on an elderly population, even though this is the group that is most vulnerable to post-disaster psychiatric morbidity [34]. Therefore, generalization of the efficacy outcome was partially precluded regarding age groups.

The randomized-controlled trials employed only the exposure technique as intervention and there was a significant reduction of PTSD symptoms in these studies. A number of independent groups of randomized-controlled trials around the world point to the efficacy of prolonged exposure therapy in the treatment of PTSD, with rapid change and maintenance of treatment gains over time [35]. The findings of the present review corroborate those of previous reviews [7,26,35], finding that exposure in its various forms (in vivo; quake platforms; narration of trauma) is effective in reducing PTSD symptoms.

Methodological Issues

Considering that 225 million people are annually exposed to natural disasters [3], the existence of only 6 controlled studies evaluating the efficacy of CBT in patients with PTSD following this type of trauma shows a huge gap in the evidence-based literature. The existing studies involved only 742 people with PTSD, indicating the need for more research in the area, particularly with stronger methodologies, including more follow-ups (only 3 of 11 articles evaluated participants after one year of intervention) and randomized controlled trials so as to guarantee the efficacy of this therapy for PTSD related to natural disasters. Other authors have already warned about this paucity, taking into account the fact that natural disasters are one of the most studied events as a cause of PTSD, without there having been an equal focus on treatment.

Limitations

One limitation of this review concerns the use of five electronic databases, even though they represent the main ones. No experts in the field, other than the authors of articles requested by e-mail, were consulted, leading to no information about non-published studies. Another limitation was the heterogeneity of studies, which made it impossible to perform a meta-analysis.

Future Directions

We recommend the development of additional randomized controlled trials to validate the findings of this review, as already highlighted elsewhere [21,27], as well as studies with more follow-ups, to investigate if the positive results reported for CBT use in reducing PTSD symptoms are maintained over time.

More studies with group interventions and using technological resources should be conducted, because natural disasters usually affect a large number of people. Of the studies covered in this review, four used group intervention [15,16,21,22] and only one used technological resources [18]. A technological resource that could be used to reach more people, and even reach inaccessible places, is the Internet (through computers, cell phones and other portable devices), evaluating beforehand the viability of this according to the country stricken and resources available to the population. None of the articles reviewed here used such a resource, even though this type of intervention for PTSD is already possible [36,37].

A large number of children develop PTSD after natural catastrophes [38–40]. It is crucial that these children be identified quickly and offered an effective treatment for the disorder [22]. However, there are few controlled studies about treatment for children and adolescents following disasters [15]. In this review we found only 2 non-randomized controlled studies and 3 open trials with children and adolescents in their samples.

Social and cultural adaptation of psychotherapy is particularly important as regards PTSD following natural disasters [27]. Most of the damage caused by natural disasters occurs in more populous regions, like Asia, with greater number of deaths and affected people [2]. The question of how to offer psychotherapy as developed in the West, with its proven efficacy, to a population

with different perceptions of stress and strategies to deal with it, may be a challenging one [8,34]? In order to adapt a typically Western treatment to an Eastern culture, we need to take into account the way they conceive mental health, and its services interventions should be adapted to local cultural and religious backgrounds. It is important that these populations do not view CBT as an imported approach, but as a proven technique that requires cultural adaptations for a better result [8]. Although this is already underway in recent studies [19,23,41], more studies should be conducted in order to get to know what is actually well accepted by the population (taking into account adherence and number of dropouts), as well as to evaluate if historical strategies of treatment of this population can also be beneficial in conjunction with CBT.

Another potential focus of studies in this area is the training of therapists to work in situations of natural disasters. Evidence-based treatments, including prolonged exposure therapy, are highly underutilized, resulting in unnecessary suffering, increased health costs, and work absenteeism [35]. Mclean and Foa [35] summarize the efforts, successes and challenges for disseminating prolonged exposure (PE) therapy. It was noted that permanent supervision of PE experts is a key element for successful treatment.

The results of this systematic review suggest the efficacy of CBT for treatment of PTSD following earthquakes, mainly with regard to the use of exposure techniques. However, in order for these results to be confirmed, we need further studies with more methodological rigor, and that include other types of natural disasters.

Supporting Information

Checklist S1 PRISMA Checklist used in this study.
(DOC)

Author Contributions

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

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3. ARTIGO 2 - FUNÇÕES NEUROPSICOLÓGICAS EM VÍTIMAS DE VIOLÊNCIA URBANA COM E SEM TEPT

Em produção

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RESUMO

Cerca de 11% da população urbana brasileira tem Transtorno de Estresse Pós-traumático (TEPT). Apesar da alta prevalência de eventos traumáticos em população urbana, os estudos neuropsicológicos focam mais a população militar do que civil. Além disso, os resultados de investigação das funções cognitivas no TEPT são heterogêneos e algumas destas funções pouco estudadas, como as funções executivas, aprendizado e reações emocionais. O presente estudo busca investigar as funções cognitivas de maneira ampla (memória – visual, verbal e operacional, atenção, funções executivas – flexibilidade cognitiva e tomada de decisão, aprendizado, inteligência e velocidade de processamento) alteradas em pacientes com TEPT que sofreram violência urbana. Foi realizada a avaliação de sujeitos com TEPT e controles (que sofreram trauma, mas não desenvolveram o transtorno). Foram avaliados 40 sujeitos (20 participantes com TEPT e 20 controles) pareados por sexo, idade e escolaridade. A média de idade dos participantes foi de 35 anos e de escolaridade 14 anos. Participaram do estudo 26 mulheres e 14 homens. Como resultado, observou-se que o grupo TEPT sofre mais interferência retroativa em teste de avaliação da memória verbal, apresenta comprometimento da memória visual, velocidade de processamento, conhecimento de palavras e quociente de inteligência.

Palavras-chave: TEPT; Neuropsicologia; Funções Cognitivas.

INTRODUÇÃO

As taxas de violência urbana no Brasil são alarmantes. Em 30 anos a taxa de homicídios aumentou 259%, cerca de 4,4% ao ano. Em 2003 a maior causa de mortes no Brasil era por agressões e acidentes de trânsito. Em 2005, 6,8% das internações hospitalares foi em decorrência de acidentes ou violência (WAISELFISZ, 2011; SOUZA & LIMA, 2006). Entre 1980 e 1995 a taxa de homicídios por arma de fogo no Brasil mais do que triplicou passando de 10/100.000 habitantes para 38,18 (ZALUAR & LEAL, 2001). De acordo com pesquisa da Organização das Nações Unidades (ONU), o continente americano tem os maiores índices de homicídio, estando o Brasil em 3º lugar dentre os maiores índices da América Latina, e 11 das 30 cidades mais violentas são brasileiras (ONU, 2013). Um estudo realizado em São Paulo e Rio de Janeiro (duas metrópoles brasileiras) mostrou que 63,06% dos participantes no Rio de Janeiro e 59,40% em São Paulo já passaram por eventos traumáticos ao longo da vida relacionados à violência urbana (RIBEIRO *et. al*., 2013), e 11% da população urbana brasileira tem risco condicional de desenvolver Transtorno de Estresse Pós-traumático (TEPT) após trauma (LUZ *et. al*., 2016). Traumas ao longo da vida são altamente prevalentes na população brasileira e o TEPT está entre as consequências psiquiátricas mais comuns da exposição traumática (BRESSAN *et. al*., 2009).

Apesar da alta prevalência de eventos traumáticos em população urbana, os estudos neuropsicológicos focam mais a população militar do que civil. Em revisão da literatura, o dobro dos estudos avaliam funções cognitivas no TEPT oriundo de traumas relacionados à guerra na fase adulta (QURESHI *et. al*., 2011). Cerca de 14 estudos (KOSO *et. al.*, 2012; PAVLÓVIC *et. al*., 2012; TIAN *et. al*., 2012; HART *et. al*, 2008; JOHNSEN *et. al*., 2008; GILBERTSON *et. al*., 2006; KOSO & HANSEN, 2006; SAMUELSON *et. al*., 2006; KIVILING-BODÉN & SUNDBOM, 2003; VASTERLING *et. al*., 2002; VASTERLING *et. al*., 1998; BARRETT *et. al*., 1996) são com participantes de traumas de guerra e apenas sete estudos (FLAKS *et. al*., 2014; WINGO, 2013; JENKINS *et. al*., 1998; STEIN *et. al*., 2002; JENKINS *et. al*., 2000; TWAMLEY *et. al.*, 2004; LESKIN *et. al*., 2007) são com população civil, ou seja, participantes que sofreram violência interpessoal em geral.

Além disso, os resultados de investigação das funções cognitivas no TEPT são heterogêneos (QURESHI *et. al.*, 2011) e algumas destas funções foram pouco estudadas, como por exemplo, as funções executivas, aprendizado e reações emocionais (BRESSAN *et. al*., 2009). Este foco em algumas funções cognitivas em detrimento de outras pode ser um problema de origem histórica, tendo em vista que as investigações neuropsicológicas no TEPT iniciaram-se na década de 80, com ênfase na investigação da memória. Apenas no século XXI que a atenção e funções executivas passaram a ser investigadas no transtorno e identificadas como deficitárias também (KRISTENSEN, PARENTE & KASZNIAK, 2006). Outro aspecto que pode ser responsável pela heterogeneidade dos resultados são as diferenças nas características da amostra, como uso/abuso de substâncias, comorbidades, doenças neurológicas, traumatismo craniano, dentre outras variáveis (STEIN *et. al*., 2002).

Além da relevância numérica apresentada, informações detalhadas sobre os sujeitos com TEPT podem auxiliar no delineamento do tratamento, com maior especificidade e eficácia (BRESSAN *et. al*., 2009; KRISTENSEN, PARENTE & KASZNIAK, 2006).

Tendo em vista os desencontros da literatura, a avaliação de domínios cognitivos de uma maneira restrita, a escassez de estudos com violência urbana e a possibilidade dos achados neuropsicológicos dos pacientes com TEPT auxiliarem na condução dos tratamentos oferecidos, o presente estudo objetiva investigar as funções cognitivas de maneira ampla em pacientes com TEPT causado por violência urbana.

METODOLOGIA

Participantes

A amostra consistiu de 43 adultos da cidade do Rio de Janeiro que passaram por traumas de violência urbana na fase adulta (não foram considerados nesse estudo traumas na infância). Como critério de inclusão os participantes tinham de ter 18 anos ou mais e menos de 60 anos. No caso dos participantes com TEPT ser paciente em

acompanhamento do Ambulatório do Laboratório Integrado de Pesquisa do Estresse do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (LINPES/IPUB/UFRJ) apresentando diagnóstico de TEPT como patologia primária. Foram excluídos participantes com risco de suicídio, gravidez, transtornos de personalidade *borderline* e anti-social, esquizofrenia, psicose, abuso ou dependência de substâncias psicoativas, participantes com diagnóstico de TEPT subclínico ou em remissão, e participantes com Quociente de Inteligência (QI) abaixo de 80 pontos (possibilitando controle das variáveis observadas, de modo que estas não estejam sofrendo influência da inteligência primariamente, e sim do transtorno estudado). Pacientes com diagnósticos de origem neurológica atual ou pretérita, como por exemplo, epilepsia, Traumatismo Crânio-encefálico (TCE) – decorrentes ou não do trauma e seguido ou não de ausência de consciência, Acidente Vascular Cerebral (AVC), demências, esclerose múltipla, problemas de pressão intracraniana, também foram excluídos. Participantes que tinham realizado avaliação neuropsicológica ou psicológica em menos de dois anos foram excluídos com a finalidade de evitar efeito de aprendizado dos testes. Para os participantes controles (sem TEPT e expostos a trauma) foi adicionado um critério de exclusão a mais, que era a inexistência de qualquer transtorno mental no momento da avaliação. Estes participantes foram recrutados pessoalmente pela primeira autora do estudo e foram voluntários na participação da pesquisa.

Medidas

As medidas neuropsicológicas foram escolhidas de maneira a avaliar o máximo de funções cognitivas possíveis de modo a não tornar a avaliação longa, o que poderia ser um fator desmotivador. A Escala Wechsler de Inteligência para Adultos (WAIS-III) (NASCIMENTO, 1998) não foi utilizada como um todo no intuito de poupar tempo da avaliação, sendo escolhidos os subtestes que avaliavam funções cognitivas mais avaliadas e comprometidas no TEPT (QURESHI, 2011).

Os testes neuropsicológicos foram administrados em todos os participantes por psicólogas treinadas, e serão descritos no quadro a seguir (Quadro 3). Velocidade de

processamento foi avaliada pelos subtestes Códigos e Procurar Símbolos da Escala Wechsler de Inteligência para Adultos 3ª Edição (WAIS-III) (NASCIMENTO, 1998). Atenção e memória de trabalho foram avaliadas através do subteste Dígitos da WAIS-III (NASCIMENTO, 1998), sendo a ordem direta e inversa endereçando cada função respectivamente. Atenção sustentada foi avaliada através do Teste de Atenção Concentrada (AC) (CAMBRAIA, 2009). Função executiva, no que se refere à flexibilidade cognitiva, foi avaliada através da versão computadorizada do *Wisconsin Card Sorting Test, 64-item version* (WCST-64) (KONGS *et. al.*, 2000). Função executiva, no que se refere à tomada de decisão, foi avaliada através do *Iowa Gambling Task* (IGT) (MALLOY-DINIZ *et. al.*, 2008). Inteligência foi avaliada por estimativa, através dos subtestes Vocabulário e Cubos da (WAIS-III) (NASCIMENTO, 1998). Visuoconstrução foi avaliada através do subteste Cubos da (WAIS-III) (NASCIMENTO, 1998). Memória visual foi avaliada através da Figura Complexa de Rey (OLIVEIRA *et. al*., 2004). Memória verbal e aprendizagem foram avaliados através da Lista de Aprendizagem Auditivo-verbal de Rey (RAVLT) (MALLOY-DINIZ *et. al*., 2000).

Teste	**Descrição do Teste**
Códigos (WAIS-III) (NASCIMENTO, 1998)	Consiste em preencher janelas em branco com o símbolo correspondente ao número, o mais rápido possível, dentro do tempo máximo de dois minutos.
Procurar Símbolos (WAIS-III) (NASCIMENTO, 1998)	Consiste em procurar dentro de uma linha com diversos símbolos um dos dois símbolos apresentados como modelo e depois marcar sim ou não de acordo com a existência dos símbolos modelos dentro da linha. Esta tarefa também deve ser feita o mais rápido possível no tempo máximo de dois minutos.
Dígitos (WAIS-III) (NASCIMENTO, 1998)	É solicitado ao participante que repita uma sequência de números na ordem mencionada. Em seguida é solicitado que repita sequências de números que ouviu (diferentes das primeiras) em

Teste	Descrição do Teste
	ordem contrária a que foi verbalizada pelo examinador (“de trás para frente”).
Teste de Atenção Concentrada (AC) (CAMBRAIA, 2009)	Consiste no avaliando conseguir identificar de maneira rápida e precisa 3 (três) modelos de setas apresentados dentre outros modelos, realizando o cancelamento dos 3 modelos solicitados.
Wisconsin Card Sorting Test 64-item version (WCST-64) (KONGS *et. al.*, 2000)	Consiste em apresentar ao participante uma carta por vez, do total de 64 e solicitar que combine cada uma com uma das quatro cartas modelo. Ao avaliando é informado apenas se a combinação foi feita de modo correto ou incorreto, possibilitando assim avaliar a flexibilidade cognitiva do mesmo em formular novas hipóteses e categorias de combinações.
Iowa Gambling Task (MALLOY-DINIZ *et. al.*, 2008)	Consiste em uma simulação de um jogo de cartas envolvendo perdas e ganhos de dinheiro fictício. Ao avaliando é solicitado que faça escolhas entre quarto baralhos (A, B, C, D). Cada vez que o participante vira uma crata recebe uma recompensa em dinheiro fictício, no entanto em algumas ocasiões, sem que possa prever quando, o examinando é punido com perda de dinheiro. O objetivo é ganhar o máximo de dinheiro que puder, levando em consideração que o jogo já começa com R$ 2000,00 em sua conta. Para isso o avaliando deve escolher as cartas dos montes com melhor custo/benefício de acordo com o objetivo do jogo, porém essa relação só pode ser analisada na medida em que as escolhas forem sendo realizadas.
Vocabulário (WAIS-III)	Consiste em apresentar palavras que o avaliando as defina tal como um dicionário ou dando sinônimos

Teste	Descrição do Teste
(NASCIMENTO, 1998)	ou exemplos.
Cubos (WAIS-III) (NASCIMENTO, 1998)	Consiste em montar figuras apresentadas como modelos com pequenos cubos no menor tempo possível.
Figura Complexa de Rey (OLIVEIRA *et. al*., 2004)	Consiste em mostrar uma figura e pedir que o participante reproduza a figura olhando para ela. Depois de terminada a cópia a figura é retirada da mesa. Passados 30 minutos o é requisitado ao participante a reprodução da figura com os elementos que lembrar sem ter acesso à figura modelo.
Lista Auditivo-verbal de Rey (RAVLT) (MALLOY-DINIZ *et. al*., 2000)	Consiste na repetição de uma lista de palavras por cinco vezes, em que o participante deve repetir todas as palavras que lembrar em cada uma das repetições da lista. Após é apresentada uma nova lista de palavras para que o paciente repita as que lembrar (lista distratora). Após a lista distratora, solicita-se ao participante que recite o que se lembra da primeira lista, sem o examinador repetir dessa vez. Após 20 minutos é solicitada a evocação das palavras que se lembra da primeira lista repetida.

Quadro 3 – Descrição dos testes neuropsicológicos

Procedimento

Os 43 participantes foram convidados a participar da pesquisa e foi dado o consentimento informado por escrito (Projeto aceito pela Plataforma Brasil em 21/11/2013 – Nº: 462889). Para fins de coleta de informações sobre o trauma, critérios de exclusão e uso de medicação, todos os participantes passaram por uma entrevista

semiestruturada. Para fins diagnósticos os participantes com TEPT responderam a SCID I (*Structured Clinical Interview Diagnostic*) (DEL-BEN *et al.*, 2001), administrada por um psiquiatra treinado (M.M.), em que foi realizado o diagnóstico de TEPT e comorbidades. Os participantes sem TEPT (controles) responderam a MINI (*Mini International Neuropsychiatric Interview*) (AMORIM, 2000), administrada por uma psicóloga treinada (A.P.L.), para fins de exclusão de quaisquer transtornos mentais. Para este estudo foram considerados os critérios diagnósticos do Manual Estatístico de Transtornos Mentais 4ª Edição (DSM – IV; APA, 2000), enquanto o estudo estava em andamento houve o lançamento da 5ª edição do DSM.

Uma bateria neuropsicológica com duração média de três horas foi administrada aos sujeitos. As avaliações foram realizadas por psicólogas treinadas (A.P.L. e R.A.K.A.). Todos os resultados neuropsicológicos foram verificados duas vezes pela primeira autora, através da recorreção dos testes, para evitar discrepâncias quanto à correção e pontuações. Os testes foram administrados na seguinte ordem (de maneira a não ter interferência de materiais nos testes de avaliação de memória) a todos os participantes:

Teste	**Função avaliada**
Lista Auditivo-verbal de Rey (RAVLT) (MALLOY-DINIZ *et. al*., 2000)	Aprendizado e Memória Verbal
Cubos (WAIS-III) (NASCIMENTO, 1998)	Visuoconstrução e Inteligência
Códigos (WAIS-III) (NASCIMENTO, 1998)	Velocidade de Processamento
Teste de Atenção Concentrada (AC) (CAMBRAIA, 2009)	Atenção Concentrada
Wisconsin Card Sorting Test 64-item version (WCST-64) (KONGS *et. al.*, 2000)	Flexibilidade Cognitiva
Procurar Símbolos (WAIS-III) (NASCIMENTO, 1998)	Velocidade de Processamento

Teste	Função avaliada
Figura Complexa de Rey (OLIVEIRA *et. al*., 2004)	Memória Visual
Vocabulário (WAIS-III) (NASCIMENTO, 1998)	Conhecimento de Palavras e Inteligência
Dígitos (WAIS-III) (NASCIMENTO, 1998)	Atenção e Memória Operacional
Iowa Gambling Task (MALLOY-DINIZ *et. al.*, 2008)	Tomada de Decisão

Quadro 4 – Descrição das ordens e funções dos testes neuropsicológicos utilizados

Os dados de três participantes não foram incluídos nas análises, devido a alguns critérios de exclusão: um sujeito teve TCE no momento do trauma (o próprio não soube referir em entrevista, e a equipe médica teve conhecimento após ser solicitado exame de imagem), outro participante tinha QI abaixo de 80, e a terceira participante tinha disfunção executiva (em entrevista os comportamentos como resultado da disfunção foram relatados como prévios ao trauma e ainda presentes no momento da avaliação). Assim, a amostra final foi de 40 sujeitos, sendo 20 com TEPT e 20 expostos a trauma sem TEPT.

O estudo foi realizado de maneira controlada, 20 pacientes com TEPT foram comparados a 20 vítimas de trauma interpessoal, sem TEPT ao longo da vida. Foram pareados a escolaridade e sexo dos participantes, sendo iguais, e a idade variando de +/- 5 anos tendo como referência o grupo TEPT.

			TEPT		**Controle**	
Par	**Sexo**	**Escolaridade**	**Idade**	**Trauma**	**Idade**	**Trauma**
1	F	12 anos	37	Assalto	37	Acidente com Familiar
2	F	12 anos	36	Assalto	40	Assassinato de familiar
3	F	9 anos	41	Assalto	35	Assalto
4	M	12 anos	30	Colisão de navios	29	Assalto

			TEPT		Controle	
Par	**Sexo**	**Escolaridade**	**Idade**	**Trauma**	**Idade**	**Trauma**
5	F	16 anos	21	Abuso sexual	24	Assalto
6	M	16 anos	46	Sequestro	48	Assalto e foi baleado
7	F	14 anos	22	Tentativa de abuso sexual	19	Sequestro
8	F	12 anos	29	Assalto	25	Assalto
9	F	17 anos	37	Ameaça de morte	38	Assalto
10	F	14 anos	27	Reconhecimento de corpo de familiar	24	Assalto
11	M	16 anos	41	Assalto	36	Ameaça de morte
12	M	12 anos	41	Sequestro	47	Assalto
13	M	16 anos	26	Sequestro	29	Presenciou assassinato
14	F	16 anos	27	Sequestro	27	Assalto
15	M	17 anos	45	Sequestro	43	Assalto
16	F	12 anos	38	Sequestro	37	Sequestro
17	M	16 anos	40	Assalto	37	Acidente automobilístico
18	F	16 anos	40	Assalto	41	Acidente automobilístico
19	F	12 anos	39	Assalto	39	Acidente automobilístico
20	F	16 anos	57	Assalto	52	Assalto

Quadro 5 – Descrição dos participantes pareados de acordo com sexo e escolaridade

Análise Estatística

Análises das medidas neuropsicológicas foram realizadas de maneira comparativa entre as médias dos grupos com TEPT e controles (expostos a trauma sem TEPT). Foi utilizado o teste não-paramétrico de Wilcoxon (Mann-Whitney) para realizar a comparação. Todas as análises foram realizadas através do programa Stata 12. Foram considerados estatisticamente significantes os P valores inferiores ou iguais a 0,05.

RESULTADOS

Características dos participantes

Para toda a amostra, a média de idade foi de 35 anos de idade e de escolaridade foi de 14 anos. Participaram do estudo 26 mulheres e 14 homens, constituindo 65% e 35% da amostra, respectivamente.

Os participantes que foram expostos a traumas, porém não desenvolveram TEPT não faziam uso de medicação psiquiátrica no momento da avaliação. Dos participantes com TEPT, um (5%) não fazia uso de medicação, quatro (20%) faziam uso de medicação há um mês, 11 (55%) faziam uso de medicação psiquiátrica entre um mês e um ano, um (5%) fazia uso de medicação há dois anos, um (5%) fazia uso de medicação há três anos, um (5%) fazia uso de medicação há cinco anos e um (5%) fazia uso de medicação há seis anos.

Os participantes do grupo TEPT, 95% (n = 19) apresentaram comorbidades, sendo que 60% (n = 12) apresentaram apenas um transtorno comórbido, 20% (n = 4) apresentaram dois transtornos, 10% (n = 2) apresentaram três transtornos e 5% (n = 1) apresentou cinco transtornos. Dentre os transtornos em comorbidade com TEPT na amostra, estão: Depressão maior (90%; n = 18), Transtorno do Pânico (20%; n = 4), Transtorno Obsessivo-Compulsivo (TOC) (15%; n = 3), Agorafobia (10%; n = 2), Fobia Específica (10%; n = 2); Transtorno de Descontrole Periódico (BED) (5%; n = 1).

Resultados neuropsicológicos

Através da análise estatística (comparação entre os grupos) observou-se que há diferença estatisticamente significativa na interferência retroativa (observada através da diferença em A6 e Reconhecimento das Listas A e B do teste RAVLT – p = 0,03; p = 0,04; p = 0,05, respectivamente), memória visual (p = 0,04), velocidade de processamento – avaliada pelo subteste Códigos (p = 0,007), QI (p = 0,02), e Vocabulário – que avalia o conhecimento de palavras e é usado como medida de inteligência pré-mórbida, e neste estudo compôs o QI estimado (p = 0,01) (LEZAK, 1995). Nessas funções o grupo TEPT teve desempenho inferior ao grupo controle.

Os grupos não apresentaram diferenças estatisticamente significativas (vide Tabela 1) em alguns aspectos da memória verbal, avaliado através da RAVLT como: aprendizado (p = 0,32), reconhecimento (p = 0,07) e evocação tardia (p = 0,35). Também não houve diferença no que se refere à atenção (p = 0,15) e memória operacional (p = 0,08), visuoconstrução (p = 0,08), atenção concentrada (p = 0,7), flexibilidade cognitiva (p = 0,07) e tomada de decisão (p = 0,09).

Tabela 1 – Comparação do grupo TEPT e controle no teste Lista Auditivo Verbal de Rey (RAVLT)

Variável	TEPT	Controle	P Valor
APRENDIZADO			
A1	6.30 (1.38)	6.75 (1.37)	0.22
A2	9.05 (1.66)	9.25 (1.97)	0.65
A3	10.65 (2.20)	11.25 (1.71)	0.34
A4	11.45 (2.30)	12.35 (1.81)	0.24
A5	12.30 (1.94)	12.70 (1.65)	0.64
B1	5.35 (1.34)	5.95 (1.73)	0.08
A6	9.50 (2.76)	11.05 (2.39)	**0.04**
MEMÓRIA			
A7	9.95 (2.92)	10.75 (2.35)	0.36
Acertos A	14.10 (1.37)	14.70 (0.73)	**0.05**

Variável	TEPT	Controle	P Valor
Acertos B	12.90 (2.14)	14.30 (1.26)	0.06
Demais Acertos	19.10 (1.33)	19.50 (0.68)	0.48
Reconhecimento	11.10 (3.99)	13.50 (2.06)	0.07
A1-A5	49.75 (8.14)	52.30 (6.65)	0.33

Tabela 2 – Comparação do grupo TEPT e controle no subteste Códigos (WAIS)

Variável	TEPT	Controle	P Valor
Escore	55.60 (17.58)	70.25 (13.16)	**>0.01**

Tabela 3 – Comparação do grupo TEPT e controle no teste Atenção Concentrada (AC)

Variável	TEPT	Controle	P Valor
Acertos	92.00 (24.44)	95.85 (18.39)	0.59
Erros	0.80 (1.05)	0.30 (0.47)	0.11
Omissões	7.85 (6.95)	9.75 (6.34)	0.28
Total	83.35 (26.90)	85.80 (19.58)	0.73

Tabela 4 – Comparação do grupo TEPT e controle no teste *Wisconsin Card Sorting Test*

Variável	TEPT	Controle	P Valor
FLEXIBILIDADE COGNITIVA			
Erros	25.75 (10.42)	21.55 (9.30)	0.18
Categorias Completas	1.95 (1.31)	2.65 (1.08)	0.08
Ensaios para 1ª categoria	13.95 (9.88)	17.00 (14.21)	0.75

Tabela 5 – Comparação do grupo TEPT e controle no subteste Procurar Símbolos (WAIS)

Variável	TEPT	Controle	P Valor
Escore	29.45 (9.47)	33.90 (6.47)	0.10

Tabela 6 – Comparação do grupo TEPT e controle no subteste Cubos (WAIS)

Variável	TEPT	Controle	P Valor
VISUOCONSTRUÇÃO			
Escore	32.55 (11.98)	40.15 (13.67)	0.09

Tabela 7 – Comparação do grupo TEPT e controle no subteste Vocabulário (WAIS)

Variável	TEPT	Controle	P Valor
CONHECIMENTO DE PALAVRAS			
Escore	33.45 (10.43)	41.35 (9.93)	**0.01**

Tabela 8 – Comparação do grupo TEPT e controle no QI Estimado

Variável	TEPT	Controle	P Valor
Valor	104.87 (12.23)	114.12 (12.62)	**0.02**

Tabela 9 – Comparação do grupo TEPT e controle no teste Figura Complexa de Rey

Variável	TEPT	Controle	P Valor
Cópia	34.55 (1.60)	35.30 (1.12)	0.13
Evocação (MEMÓRIA VISUAL)	17.32 (3.92)	20.65 (6.46)	**0.04**

Tabela 10 – Comparação do grupo TEPT e controle no subteste Dígitos (WAIS)

Variável	TEPT	Controle	P Valor
ATENÇÃO			
Escore Direta	8.10 (2.04)	9.30 (2.59)	0.12
Maior Sequência Direta	5.60 (1.27)	6.25 (1.55)	0.15
MEMÓRIA OPERACIONAL			
Escore Inversa	6.00 (1.86)	6.85 (2.32)	0.24
Maior Sequência Inversa	4.35 (1.03)	5.05 (1.31)	0.08
Escore Total	14.10 (3.62)	16.15 (4.48)	0.19

Tabela 11 – Comparação do grupo TEPT e controle no subteste Iowa Gambling Task

Variável	TEPT	Controle	P Valor
TOMADA DE DECISÃO			
Bloco 1	-4.30 (4.69)	-2.10 (4.32)	0.11
Bloco 2	0.50 (6.08)	-0.40 (3.76)	0.81
Bloco 3	1.10 (5.56)	1.20 (5.24)	0.99
Bloco 4	3.20 (6.90)	3.20 (5.99)	0.85
Bloco 5	2.50 (6.45)	0.80 (6.03)	0.57
Baralho A	20.15 (5.44)	21.85 (5.69)	0.50
Baralho B	28.75 (7.34)	26.80 (5.71)	0.41
Baralho C	21.55 (6.17)	23.50 (5.41)	0.24
Baralho D	29.55 (7.11)	27.85 (6.84)	0.53
Tendência Geral	2.20 (17.21)	2.7 (15.79)	0.91

DISCUSSÃO

Principais achados

Nossa investigação utilizou uma bateria neuropsicológica abrangente, investigando a maioria das funções cognitivas. As variáveis como idade, escolaridade, gênero, doenças neurológicas e abuso/dependência de substâncias psicoativas foram controladas. Comparando os grupos com e sem TEPT encontrou-se diferença estatisticamente significativa nas funções de inteligência, memória visual, velocidade de processamento e interferência retroativa.

Apesar do número de pesquisas serem duas vezes maiores em pesquisas com amostra de trauma de guerra observa-se como resultado desse e outros estudos (FLAKS *et. al.*, 2014; JENKINS *et. al*., 2000; JENKINS *et. al.*, 1998) que a população civil também apresenta comprometimentos cognitivos em decorrência do TEPT (VASTERLING & VERFAELLIE, 2009). Há menos resultados positivos quanto à alteração cognitiva no TEPT oriundo de trauma de violência urbana. O que pode ser em decorrência do menor número de estudos nesta população.

Hoje existe uma robusta base de estudos evidenciando que as alterações cognitivas não estão presentes apenas nos momentos em que o sujeito tem de lidar com estímulos que lembrem o trauma, mas de maneira contínua, respaldadas em alterações neuroquímicas e estruturais no cérebro desses pacientes (VASTERLING & VERFAELLIE, 2009; SAMUELSON, 2011; HULL, 2002).

De modo consistente com pesquisas anteriores, que examinaram memória visual (KOSO *et. al*., 2006), velocidade de processamento (SAMUELSON *et. al*., 2006; JENKINS *et. al*., 2000), interferência retroativa (YEHUDA *et. al*., 1995), conhecimento de palavras e QI (VASTERLING *et. al*., 2002) no presente estudo também foram encontrados comprometimentos nestas funções no grupo TEPT quando comparados ao grupo exposto a trauma sem TEPT.

Danckwerts & Leathern (2003) em revisão observaram que as alterações em memória visual parecem menos proeminentes do que as alterações de memória verbal.

No entanto observando-se a revisão de Qureshi *et. al.* (2011) dos 16 estudos semelhantes ao presente, ou seja, que avaliam adultos (até 60 anos) e com trauma na mesma fase (apenas na vida adulta) apenas seis avaliaram memória visual, sendo que apenas um apresentou comprometimento, enquanto 15 avaliaram memória verbal. Então não parece uma questão de menos alterações e sim de menos foco de estudo neste tipo de memória. Sendo este estudo o primeiro com amostra de trauma interpessoal em adultos a evidenciar déficits na memória visual quando comparado o grupo TEPT ao grupo controle. Além da alteração de memória associada ao TEPT, temos relatos de que a presença de déficit em memória visual prévia à exposição aos cenários de guerra confere risco adicional para o desenvolvimento de TEPT. (Marx *et. al.* 2009 apud VASTERLING & VERFAELLIE, 2009).

A velocidade de processamento apareceu como um dos domínios comprometidos no grupo TEPT, porém apenas através do subteste Códigos e não do Procurar Símbolos (NASCIMENTO, 1998), ambos avaliam a mesma função. Contesta-se que o subteste Códigos (NASCIMENTO, 1998) seja mais difícil para realização do que o subteste Procurar Símbolos (NASCIMENTO, 1998), e por isso teve relevância estatística, enquanto o subteste Procurar Símbolos teve p valor limítrofe (p=0,08). Com o aumento da amostra estudada pode-se conjecturar que essa diferença entre os subtestes diminuísse de modo que o desempenho em velocidade de processamento pudesse ser inferior no grupo TEPT como um todo. Resultados de alteração da velocidade de processamento também foram observados por Twanley *et. al.* (2009) e Jenkins *et. al.* (2000) em mulheres vítimas de violência do parceiro e vítimas de abuso, respectivamente. Ressalta-se ainda a possibilidade dessa alteração estar relacionada ao uso de antidepressivos (AMADO-BOCCARA *et. al*., 1995).

Nesse estudo foi observado um déficit de interferência retroativa no grupo TEPT, observado tanto pela diferença estatisticamente significativa no A6 da RAVLT, demonstrando que este grupo tem maior dificuldade de evocar o material aprendido (nota-se que não houve alteração na aprendizagem) após introdução de material distrator. Assim como observado pela dificuldade de discriminação no reconhecimento se o material solicitado para evocação era da Lista A ou B (lista distratora). Dificuldade semelhante foi observada por Vasterling *et. al.* (1998) em adultos sobreviventes da Guerra do Golfo. Sendo assim esse é o primeiro estudo com amostra civil a identificar este tipo de alteração nestes pacientes.

Quanto às alterações do QI observadas, parece estar intimamente ligadas à dificuldade no subteste Vocabulatório da WAIS – III (NASCIMENTO, 1998) observada no grupo TEPT. Este subteste é usado como estimativa de funcionamento intelectual pré-mórbido (LEZAK, 1995; VASTERLING *et. al*., 2002), ou seja, podemos inferir que a dificuldade observada no grupo TEPT quanto ao conhecimento de palavras é prévia ao desenvolvimento do transtorno, tendo em vista que toda a amostra passou por trauma e desenvolveu o transtorno na fase adulta. A alteração de QI já foi observada em outros estudos (MACKLIN *et. al*. 1998; MCNALLY & SHIN, 1995; VASTERLING *et. al*., 2002) em pessoas com diagnóstico de TEPT.

McNally & Shin (1995) e Macklin *et. al.* (1998) foram os primeiros a relatar que baixo QI poderia ser um fator de risco para o desenvolvimento de TEPT em sujeitos expostos a combate militar. No estudo desses autores foi observado que os recursos intelectuais pré-mórbidos estimados contribuitram significantemente e exclusivamente para a variância nos escores na escala de avaliação dos sintomas de TEPT. Outras associações realizadas sobre menos recuros intelectuais, nível pré-mórbido, inteligência e diagnóstico de TEPT em medidas indiretas, como aritmética e tarefas de raciocínio verbal, Teste de Qualificação das Forças Armadas, realização educacional e graduação militar foram relatadas por Vasterling *et. al.* (2002).

Com baixo QI os sujeitos que desenvolvem TEPT teriam capacidade reduzida e menos eficaz de lidar e processar o trauma (TWAMLEY *et. al*., 2004), funcionado como um fator de risco para o aumento da gravidade do transtorno e dificuldades no tratamento e manejo do mesmo.

Além das alterações estatisticamente significativas acima observadas, foram verificadas outras alterações que não tiveram p valor significativo, mas limítrofe. Essas funções são importantes para as atividades do dia a dia, tratamento e podem estar relacionadas com as queixas cognitivas destes pacientes. Os testes que avaliam as funções memória operacional ($p = 0,08$) (Dígitos da WAIS – III; NASCIMENTO, 1998), visuoconstrução ($p = 0,08$) (Cubos da WAIS – III; NASCIMENTO, 1998) e flexibilidade cognitiva ($p = 0,07$) (WCST-64; KONGS *et. al*., 2000), tiveram um p valor limítrofe. Com o aumento da amostra imagina-se que estas funções também se apresentariam como comprometidas com significância estatística. Como por exemplo, observado no estudo de Vasterling *et. al.* (2002) que com uma amostra um pouco maior

do que a desse estudo (TEPT = 26 e sem TEPT = 21) observou a memória operacional como deficitária no TEPT.

Implicações Clínicas

As alterações cognitivas associadas ao TEPT tem grande relevância clínica, tendo em vista que mesmo que o desempenho cognitivo apresente uma pequena piora após o desenvolvimento do transtorno, o paciente que o experimenta pode perceber isso como muito angustiante ou perturbador em comparação com o nível pré-morbido. Por isso faz-se importante a construção e validação de instrumento voltados à avaliação comparativa da queixa cognitiva antes e após o trauma, ficando mais claro para o paciente as suas alterações e para o clínico que o acompanha, podendo escolher o tratamento de maneira que amenize a queixa cognitiva (VASTERLING & VERFAELLIE, 2009).

Os déficits cognitivos podem influenciar drasticamente no processamento da memória traumática e no curso do transtorno, tendo-se em vista que os pacientes com dificuldades em memória e habilidades cognitivas mais integradas (como QI) podem apresentar mais dificuldade na recuperação da memória autobiográfica e no processamento da mesma, promovendo prejuízos na recuperação emocional. Da mesma forma, a integridade neurocognitiva pode influenciar como as pessoas lidam com o TEPT, alterando a sua capacidade de implantar recursos ambientais ou mecanismos de enfrentamento, tais como reavaliação adaptativa do evento traumático (VASTERLING & VERFAELLIE, 2009).

Limitações

As limitações do presente estudo devem ser observadas, quando se trabalha com avaliação neuropsicológica dos pacientes com TEPT muitas variáveis tem de ser observadas, como comorbidades, uso de medicações e fatores motivacionais no momento da avaliação.

Primeiro, as comorbidades não puderam ser controladas neste estudo, e 95% da amostra do grupo TEPT apresentou transtornos comórbidos. Os estudos são desencontrados quanto à possibilidade das comorbidades interferirem ou não na avaliação das funções cognitivas no TEPT (SAMUELSON, 2011). Stein *et. al.* (2002) enfatiza que o comprometimento de memória pode ser estar relacionado à presença de Depressão maior como comorbidade, que foi o transtorno identificado em 90% do grupo TEPT. Já no estudo de Vasterling *et. al.* (2002) veteranos do grupo TEPT com depressão como comorbidade (n = 13) tiveram mais erros por ação no teste de avaliação da atenção sustentada, escore relacionado à impulsividade e tiveram pior desempenho no teste de alternância da atenção do que os participantes com TEPT, porém sem depressão como comorbidade. No entanto não houve diferença quanto a variável intelectual, sugerindo-se que tal não esteja exclusivamente atribuída a comorbidade de depressão.

Comparando-se o resultado deste estudo com similares, o comprometimento de memória visual, interferência retroativa e velocidade de processamento podem estar relacionados à presença de comorbidades, porém não o resultado de QI e conhecimento de palavras.

Segundo, o uso de medicações foi objeto de estudo de Vasterling *et. al.* (2002) revelou que veteranos medicados tiveram um desempenho inferior num teste de avaliação de cálculo e memória operacional e cometeram mais erros por ação em teste de avaliação da sustentação da atenção do que os veteranos com TEPT, porém não medicados. Em nosso estudo não foi possível tal comparação, tendo em vista que apenas um dos participantes do grupo TEPT não fazia uso de medicação no momento da avaliação, por constar de uma amostra clínica (todos os participantes estavam em tratamento psiquiátrico e/ou psicológico no momento do estudo), sendo um dever ético oferecê-lo e não poder interrompê-lo. Novamente, os resultados referentes às medidas de inteligência parecem não ser alterados com o uso de medicação, conforme relatado pelo mesmo autor.

Terceiro, os resultados não podem ser generalizados para pessoas com diagnóstico de TEPT que não oriundo de violência urbana, e que não seja da população brasileira.

O último ponto de limitação observado é quanto à motivação para a realização da avaliação, como 90% do grupo TEPT apresentavam também depressão, naturalmente demonstravam-se menos motivados. A tentativa para controle deste aspecto foi realizar a bateria de avaliação intercalando testes verbais, não verbais e computadorizados, de maneira que as três horas de avaliação pudessem ser menos monótonas possíveis. Além disso, foi oferecido um intervalo de 10 a 20 minutos ao completar 1 hora e 30 minutos da avaliação.

Considerações para Estudos Futuros

Para futuros estudos na área, recomendam-se estudos longitudinais a fim de avaliar grandes populações de risco (por exemplo, populações de lugares expostos a constantes desastres naturais ou guerras) para averiguar se os déficits cognitivos observados surgem após a exposição ao trauma e consequente diagnóstico de TEPT ou se na verdade são fatores predisponentes para o desenvolvimento do transtorno, como realizado por Parslow & Jorm (2007).

Recomenda-se também a construção e validação de inventários ou entrevistas padronizadas para averiguar as queixas cognitivas dos participantes antes e após o trauma. Os estudos da área ficam voltados aos resultados dos testes neuropsicológicos e pouca ênfase é dada a queixa subjetiva do paciente, entendendo como eles percebem as alterações cognitivas em suas atividades de vida diária, que é de suma importância para o trabalho clínico com esses pacientes.

O TEPT é um transtorno que acomete todas as fases da vida, desde a infância até o envelhecimento (APA, 2000). No entanto, observa-se nesse campo de pesquisa material amplo com adultos (QURESHI *et. al.*, 2011) e idosos (SCHUITEVOERDER *et. al*., 2013), porém poucos estudos avaliam as funções cognitivas de crianças com TEPT.

Ainda no tema infância são necessários mais estudos investigando a relação de traumas ocorridos na infância e déficits cognitivos observados (independente da avaliação ter sido realizada com sujeitos adultos, crianças ou idosos), para melhor entender o desenvolvimento do cérebro e a relação com o TEPT.

De modo a exaurir as limitações dos estudos da área quanto à presença de comorbidades e uso de medicações, recomenda-se a realização de meta-análises sobre o tema, e a realização de mais estudos controlados com grupos TEPT com comorbidade *versus* TEPT sem comorbidade e TEPT medicado *versus* TEPT não medicado, respectivamente. Sugere-se que tal seja realizado em amostra não clínica tendo em vista a dificuldade de controle dessas variáveis em amostra clínica, como observado nesse estudo.

Tendo em vista que as alterações de funções cognitivas são relatadas em diversos estudos, apesar de divergentes quanto ao padrão, ou seja, quais mais comprometidas e quais menos (QUREISH *et. al*., 2011) recomenda-se estudos no intuito de examinar os efeitos de reabilitações e treinos cognitivos endereçando as funções cognitivas observadas como deficitárias aos pacientes com TEPT.

CONCLUSÃO

Este estudo controlado por pareamento identificou alterações na memória visual, interferência retroativa em tarefa de memória verbal, velocidade de processamento, conhecimento de palavras e inteligência (QI) em participantes com TEPT após passarem por traumas interpessoais. Observa-se que foi o primeiro estudo a relatar comprometimento em memória visual em uma amostra de civis. E de acordo com literatura prévia e conhecimento neuropsicológico de que o subteste Vocabulário (NASCIMENTO, 1998) é uma medida cristalizada e de alto valor pré-mórbido, o déficit observado quanto ao conhecimento de palavras e inteligência é provavelmente prévio ao trauma, e não resultado da exposição traumática e acometimento do transtorno.

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4. CONCLUSÕES

Ambos os estudos apresentam resultados que nos fazem repensar a prática clínica e pesquisas direcionadas ao TEPT.

No caso do primeiro estudo, fica comprovada a eficácia da TCC para TEPT oriundo de terremotos. Porém por escassez de estudos com outros tipos de desastres naturais e estudos com pouco rigor metodológico (dos 11 estudos incluídos na revisão, apenas três eram randomizados e três controlados) torna-se inviável a avaliação da eficácia dessa abordagem psicoterápica de uma maneira ampla no contexto de eventos traumáticos de origem natural.

As técnicas psicoterápicas utilizadas nos estudos são as mesmas utilizadas em TCC para TEPT de modo geral (VENTURA *et. al*., 2011; BISSON & ANDREW, 2006; KNAPP & CAMINHA, 2003; FOA & ROTHBAUM, 1998). Porém dos 11 estudos apenas dois não utilizaram técnicas de exposição.

Ainda sobre o tema de desastres naturais, na tentativa de entender melhor as populações afetadas por esse evento traumático e promover um atendimento clínico mais especializado, recomenda-se o estudo com população de idosos (dos 11 artigos apenas um envolveu amostra mista até 80 anos) que não foi abordada diretamente em nenhum estudo. Recomenda-se também, dentro do aspecto clínico, o foco em outras técnicas da TCC, como por exemplo, as técnicas cognitivas, de maneira a fornecer mais dados para comparação entre as técnicas psicoterápicas e definir o que é mais eficaz nesse contexto.

Por ser um evento que atinge a grande número de pessoas recomendam-se mais estudos com uso da tecnologia (podendo oferecer tratamento a locais que possam ter sido isolados em virtude do desastre, por exemplo) e com treinamento de terapeutas para esse tipo de atendimento (TCC após catástrofes naturais) de modo a multiplicar as possibilidades de oferta do tratamento.

Outro aspecto clínico muito importante salientado no estudo de catástrofes naturais é a necessidade de adaptação deste tipo de psicoterapia para população oriental, já que é uma psicoterapia de base ocidental. Recomenda-se então a condução de estudos que unam a TCC com práticas orientais como Yoga e meditação, de maneira a promover maior inserção e aceitação da população asiática, e oriental em geral, ao tratamento proposto.

Quanto ao segundo estudo, observa-se um prejuízo das funções cognitivas condizentes com as queixas desses pacientes relatadas no atendimento ambulatorial (queixas de atenção e memória após o evento traumático e surgimento dos sintomas). Tendo em vista os déficits de funções cognitivas evidenciados nos pacientes vítimas de trauma interpessoal, pode-se incentivar a pesquisa de medicamentos que não prejudiquem mais as funções deficitárias, como a memória e velocidade de processamento.

Em termos psicoterápicos, pode-se pensar em sessões com menos conteúdo, tendo em vista que esses pacientes sofrem com interferência retroativa, uma sessão com muito conteúdo novo pode atrapalhar e agir como fator confundidor para o para o paciente. Propostas de reabilitação cognitiva para esses pacientes podem ser coadjuvantes no tratamento psicoterápico, auxiliando no reestabelecimento das funções prejudicadas e consequente redução das queixas relatadas.

Quanto à pesquisa na área recomenda-se a condução de estudos longitudinais a fim de responder a questão de diversos estudos na área: seriam as alterações de funções cognitivas decorrentes do TEPT ou predisponentes ao diagnóstico? Recomenda-se também a condução de estudos neuropsicológicos com população infantil que desenvolve TEPT.

Apontada como limitação deste estudo e como proposta para estudos futuros na área de neuropsicologia do TEPT sugere-se a realização de pesquisas em população ainda não tratada a fim de obter maior controle sobre as variáveis confundidoras no resultado, como medicação e comorbidades.

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ANEXOS

ANEXO A – Termo de Consentimento Livre e Esclarecido

AVALIAÇÃO DAS FUNÇÕES COGNITIVAS EM PACIENTES DIAGNOSTICADOS COM TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO (TEPT)

Você está sendo convidado a participar desta pesquisa que visa entender as alterações das funções cognitivas (como por exemplo, atenção e memória) em pacientes que tem o diagnóstico de Transtorno do Estresse Pós-traumático (TEPT).

Este estudo está sendo realizado no ambulatório dos Transtornos Relacionados ao Estresse vinculado ao Laboratório Integrado de Pesquisa do Estresse (LINPES) sediado no campus da Praia Vermelha da Universidade Federal do Rio de Janeiro, e encontra-se sob orientação da professora Dra. Paula Ventura.

Você será submetido a uma avaliação neuropsicológica, que constará de entrevista e testes neuropsicológicos. Esta avaliação ocorrerá em sessão única com duração média de 3 horas.

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 o seu atendimento médico e psicológico não serão prejudicados.

Você não terá nenhuma despesa para participar da pesquisa e também nada será pago por sua participação. Após a realização da avaliação você receberá se assim desejar, uma entrevista de devolução para demonstração e explicação dos resultados obtidos na sua avaliação. Como benefícios, esta pesquisa pretende oferecer melhorias no tratamento psicoterápico e medicamentoso dos pacientes com TEPT, visando a integridade de suas funções cognitivas.

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. Caso em algum momento você não queira mais participar da pesquisa ou que seus dados sejam utilizados, basta informar aos pesquisadores responsáveis, e não ocorrerá nenhum prejuízo quanto aos seus tratamentos (psiquiátrico e psicológico) perante esta opção.

A sua participação é muito importante, já que os dados obtidos neste estudo possibilitarão o maior entendimento do transtorno (TEPT), que é um transtorno comum e que causa muitos prejuízos e sofrimento na vida das pessoas.

Caso precise ou tenha alguma dúvida que não foi elucidada pela leitura do termo, favor entrar em contato com:

Alessandra Lopes (CRP: 05/44267)

Celular: (21) 99503-6466

Telefone fixo: (21) 3873-5538

Declaro ter lido o texto acima e de forma livre e esclarecida concordo com os termos apresentados e com a minha participação nesta pesquisa.

Rio de Janeiro, _____ de _____ de 201___.

_____

Nome do (a) paciente

_____

Assinatura do (a) paciente

Alessandra Pereira Lopes

Pesquisadora Assistente

CRP 05/44267

Tel: (21) 99503-6466

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ANEXO B

OPEN ACCESS Freely available online

PLOS ONE

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 dose 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.

Citation: Rodrigues H, Figueira I, Lopes A, Gonçalves R, Mendlowicz MV, et al. (2014) Does D-Cycloserine Enhance Exposure Therapy for Anxiety Disorders in Humans? A Meta-Analysis. PLoS ONE 9(7): e93519. doi:10.1371/journal.pone.0093519

Editor: Andreas Reif, University of Wuerzburg, Germany

Received September 17, 2013; **Accepted** March 7, 2014; **Published** July 3, 2014

Funding: This work was partially supported by the National Council for Scientific and Technological Development (CNPq) and the Carlos Chagas Filho Foundation for Research Support in Rio de Janeiro (FAPERJ). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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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.

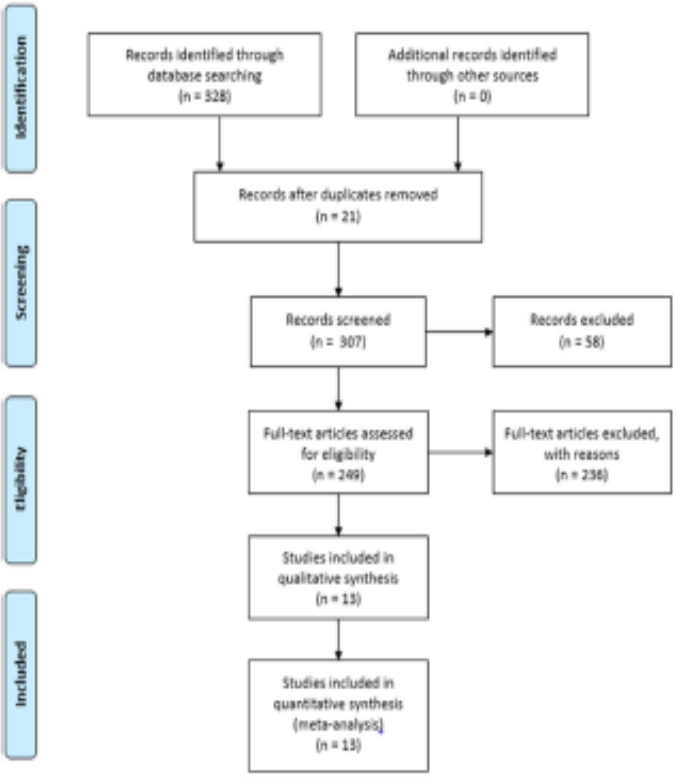

Figure 1. Flow Diagram.
doi:10.1371/journal.pone.0093519.g001

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
Kline 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.

doi:10.1371/journal.pone.0093519.t001

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

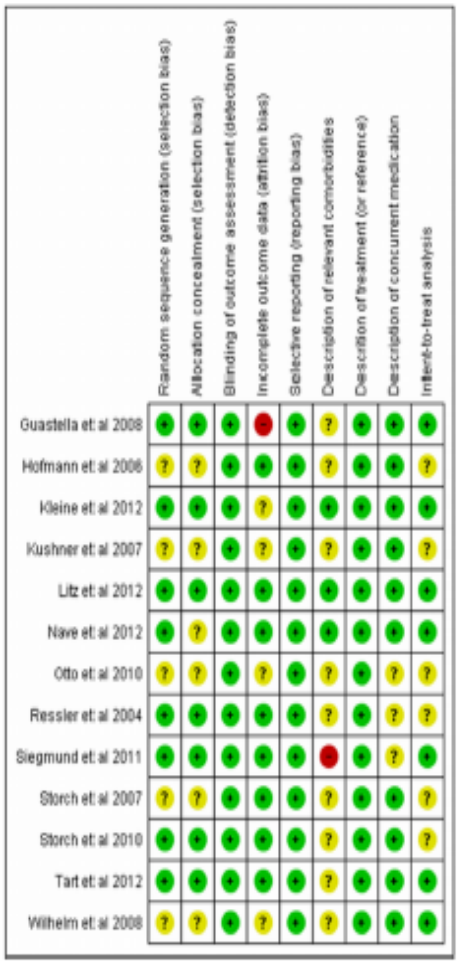

Figure 2. Methodological quality of the included studies (by study).
doi:10.1371/journal.pone.0093519.g002

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

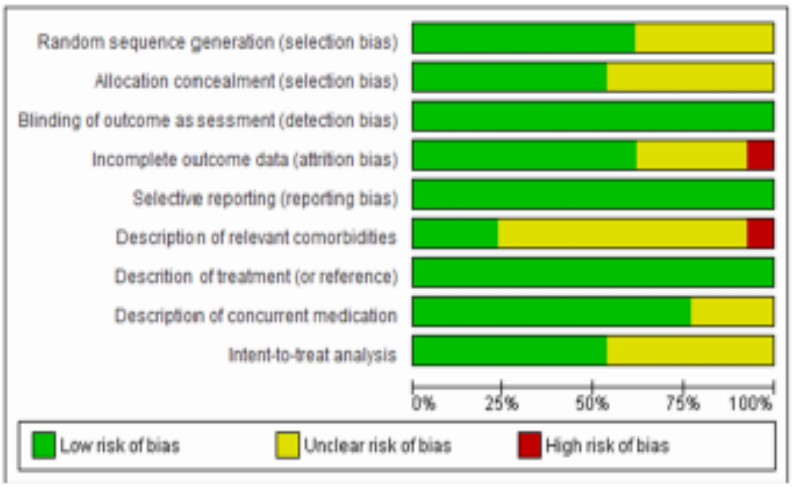

Figure 3. Methodological quality of the included studies (by domain).
doi:10.1371/journal.pone.0093519.g003

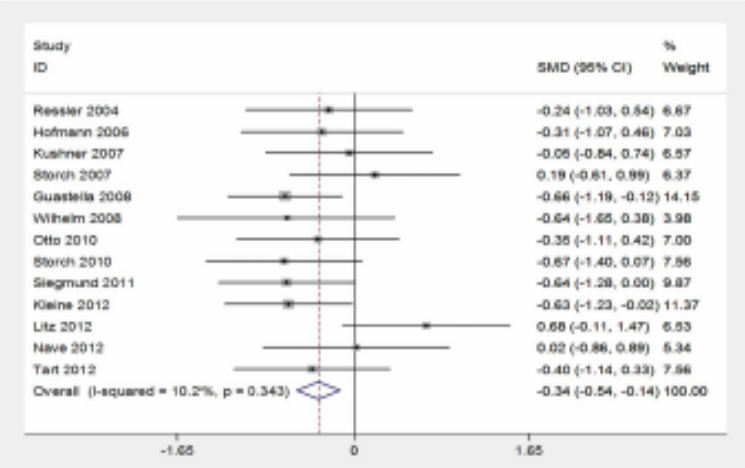

Figure 4. Forest-plot.
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disorder [54] indicated that the use of concomitant medication does not seem to have affected the results, and there is no contraindication for the use of other psychotropic medications with DCS. Another possible explanation 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 Klein 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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ANEXO C - Is the Traditional Cognitive Behavioural Therapy Effective on Reducing Anxiety in Cancer Patients? A Systematic Review and Meta-analysis of Randomized Controlled Trials

No prelo

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ABSTRACT

Objective: This meta-analysis aims to verify the efficacy of the traditional cognitive-behaviour therapy (CBT) on anxiety symptoms of cancer adult patients. Methods: Meta-analyses of randomised controlled trials (RCTs) have been conducted by searching the ISI Web of Knowledge, PsycINFO and Pubmed/Medline databases. Results: 14 studies were included, comprising 1,399 patients with different types and severity of cancer. Forty-two percent of the pooled sample involved breast cancer patients, not considering other major types of cancer such as lung cancer, which was addressed by only one study. The length of CBT varied from 1 to 10 one-hour sessions weekly. The traditional CBT was found to be moderately efficacy for anxiety (es=0.63; CI=95%, p= 0.02). Conclusions: The traditional CBT is related to short-term effects of reducing anxiety in cancer patients.

Key-words: Cancer; Anxiety, CBT; Cognitive Behaviour Therapy; Meta-analysis

BACKGROUND

Cancer is currently one of the most prevalent, deadly and challenging diseases. In 2012, there were about 32.6 million people living with cancer worldwide, of which 14.1 million represented new cases and 8.2 million died of cancer. It is expected that the number of new cases will increase from 14 to 22 million in the next two decades. The increase in both new cases and cancer-related deaths occurs worldwide, but it is greater in non-developed regions such as Africa, Asia and Central and South America [1].

The diagnosis of cancer causes great psychological distress on both patients and their families. Invasive treatments are often necessary despite the fact that no therapeutic success is warranted. Therefore, it is unsurprising that anxiety is among the most frequent psychological problems in cancer patients [2, 3, 4].

About 20% to 30% of the patients with breast cancer complain of anxiety, depression and low self-esteem at some point after diagnosis [5], which may affect the immune-neuroendocrine systems [6,7,8]. It is possible that intense, ongoing periods of discomfort and anxiety are associated with impairment of the functions of the immune system cells, which help preventing the occurrence of infectious diseases and metastasis [9], since patients with high levels of stress show decreased phagocytic cell activity [10]. In advanced cancer patients, the psychological distress is even more devastating. Thirty to forty percent of the patients show significant anxiety, which in turn exacerbates the physical symptoms and worsens their quality of life [11], mainly when the treatments fail, thus generating uncertainty of their survival.

Although the effectiveness of CBT is well established in controlling anxiety in adult patients [12, 13, 14], the meta-analyses [15, 16, 17, 18, 19] investigating this issue among cancer patients have some methodological limitations. First, they did not focus exclusively on

randomised trials [15]. Second, they included studies not submitted to peer review [15, 17, 19]. Third, they included techniques not directly related to CBT (e.g. alternative medicine [17] and music therapy [16]). Fourth, they used a very broad definition of CBT, including studies on expressive writing [15] and relaxation techniques [17]. In fact, very broad definitions do not allow adequate assessment because of the inclusion of diversified therapeutic ingredients [20].

Up to date, by analysing the peer-reviewed literature, it was observed that no meta-analysis had been conducted to investigate the efficacy of traditional CBT in reducing the anxiety of patients on cancer treatment. To fulfil this gap in the literature, we performed both systematic review and meta-analysis of randomised studies to verify the effectiveness of traditional CBT in adult cancer patients with anxiety symptoms. Furthermore, we also conducted an analysis of the methodological quality of each study for this review based on an adapted version of the Cochrane Collaboration Tool for Assessing the Risk of Bias [21].

METHODS

We searched ISI Web of Knowledge, PsycINFO and Pubmed/Medline electronic databases for studies published until October 2014, regardless of the language used. The following terms were used for the search on ISI Web of Knowledge ("Topic Search"), PsycINFO and Pubmed/Medline ("All Fields"):

- CBT OR "cognitive-behav*" OR "cognitive behav* therapy" OR "cognitive therapy" OR "behav* therapy"
- Cancer* OR tumor OR neoplasia OR metasta* OR carcino*
- Anxiety OR "autonomic symptoms"

The groups of terms indicated in each item were combined by using the booleans "AND" of the electronic databases. In addition to this search, we have also researched the bibliographic references of the selected studies and the reviews and meta-analyses found in our search.

We have included in our systematic review and meta-analysis of the literature studies with the following characteristics: 1) clinical randomised trials; 2) studies using traditional CBT, which was defined as being those therapies incorporating both cognitive and behavioural strategies in the same treatment modality. A definition identical to ours was used in a meta-analysis by Mitte [22]; 3) studies assessing anxiety symptoms by using standard psychometric instruments; and 4) samples of adult patients.

We have excluded studies which did not use validated psychometric scales for assessing anxiety in the study population, as well as those whose sample had subjects with anxiety disorders, since we aimed to evaluate anxiety symptoms on a continuous rather than on a categorical basis (i.e. by means of diagnoses). We have also excluded studies which did not use face-to-face interventions; samples of subjects younger than 18 years old or subjects who were no longer on cancer treatment; and animal-based studies. In addition, we opted to exclude texts not peer reviewed, such as textbook chapters, dissertations and theses, including those written in languages other than Portuguese, English or Spanish.

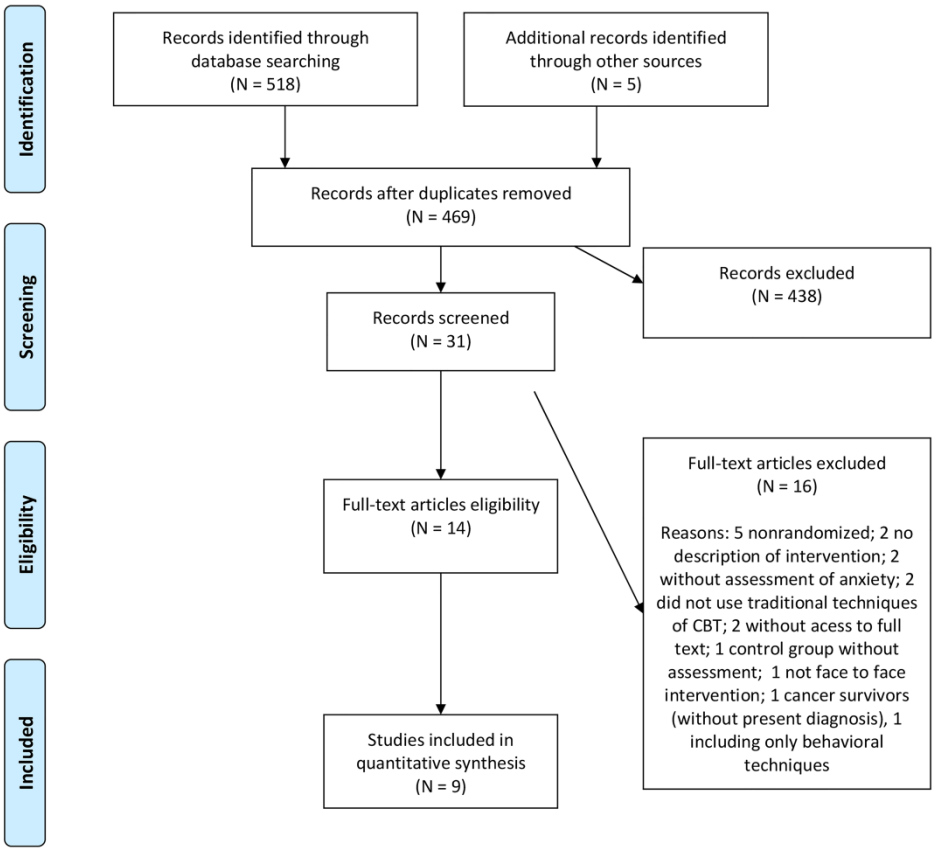
The selection process was carried out independently by two authors (MMFR & HCS). After the search phase, we have analysed the methodological quality of the selected studies based on an adapted version of the Cochrane Collaboration Tool for Assessing the Risk of Bias [41]. The quality assessment used a model adapted from that proposed by Higgiens & Altman [23], being conducted by two authors (MMFR & ESPC). The items included were the following: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of

outcome assessment, (iv) incomplete outcome data, (v) selective reporting, (vi) concomitant treatments, and (vii) description of the control activity (Table 1).

Two separate meta-analyses were carried out as some studies presented their findings by using endpoint outcomes and others used change from baseline. Random effect models were estimated because the findings showed a significant heterogeneity. This inconsistency was evaluated by chi-squared test for heterogeneity and I-squared statistic [24]. Standardised mean differences (SMD) were calculated as the studies assessed anxiety symptoms through different scales. This procedure was adopted because the studies used different scales for measuring anxiety symptoms. The SMD expresses the differences in standard deviations instead of the original values of the scales. Forest plots were used to present the meta-analyses graphically. The small number of studies in each analysis allowed neither the risk of publication bias to be assessed nor the possible sources of heterogeneity to be identified. All the analyses were carried out by using the Stata 12 software.

RESULTS

Fourteen studies have been included in the systematic review and nine had data necessary for inclusion in the meta-analysis.



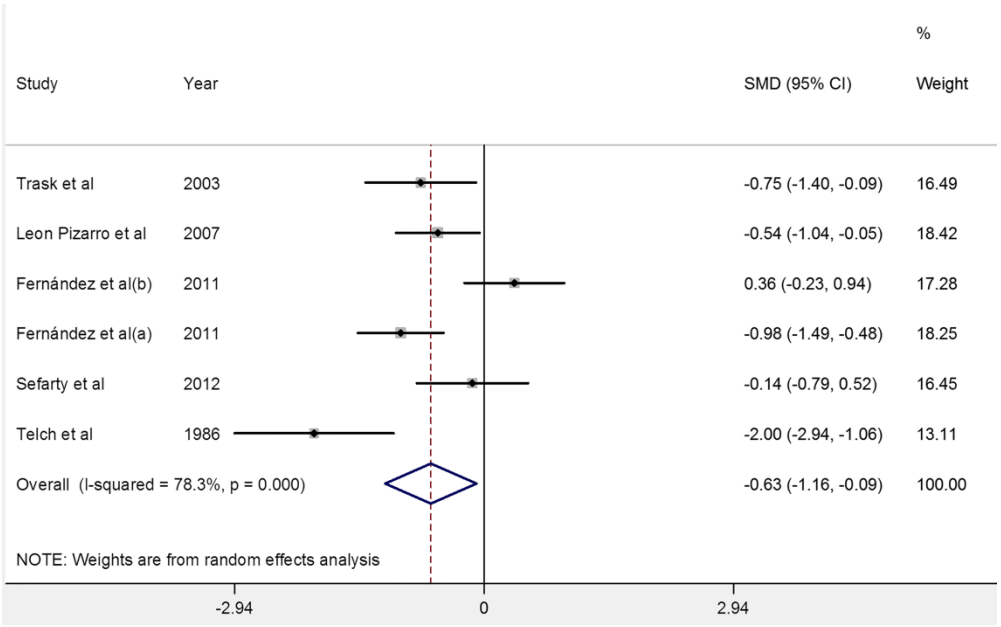
Of the 14 studies found, ten were carried out in the United States of America (USA) and the United Kingdom (UK). Many studies used samples of different types and severity of cancer, but the majority of them investigated breast cancer (42.8%). There was a predominance of female subjects in the total initial sample (77.6%). Other details were listed in Table 2.

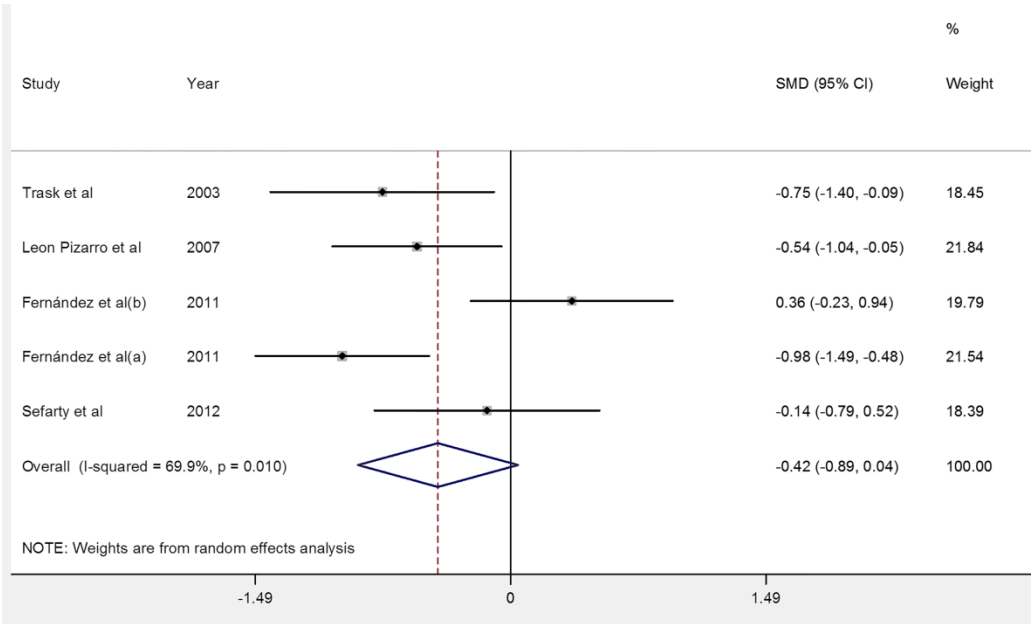
Two meta-analyses have been conducted, one assessing six studies by comparing final scores between two groups (endpoint), and other assessing three studies by comparing variation in the score (changes from baseline) between intervention and control groups.

Comparing the Final Scores between Two Groups

The final mean scores in the CBT group was 0.63 standard deviation lower than that observed in the control group. This difference is statistically significant (p= 0.02). However,

there is an important heterogeneity between the results of the studies (I^2 = 78%). The forest plot (Figure 1) shows that the study by Telch & Telch [25] differs regarding the magnitude of difference between the groups, although the pattern observed in the other studies had been kept. In order to investigate the impact of this study on the findings, we have conducted a sensitivity analysis (Figure 2).

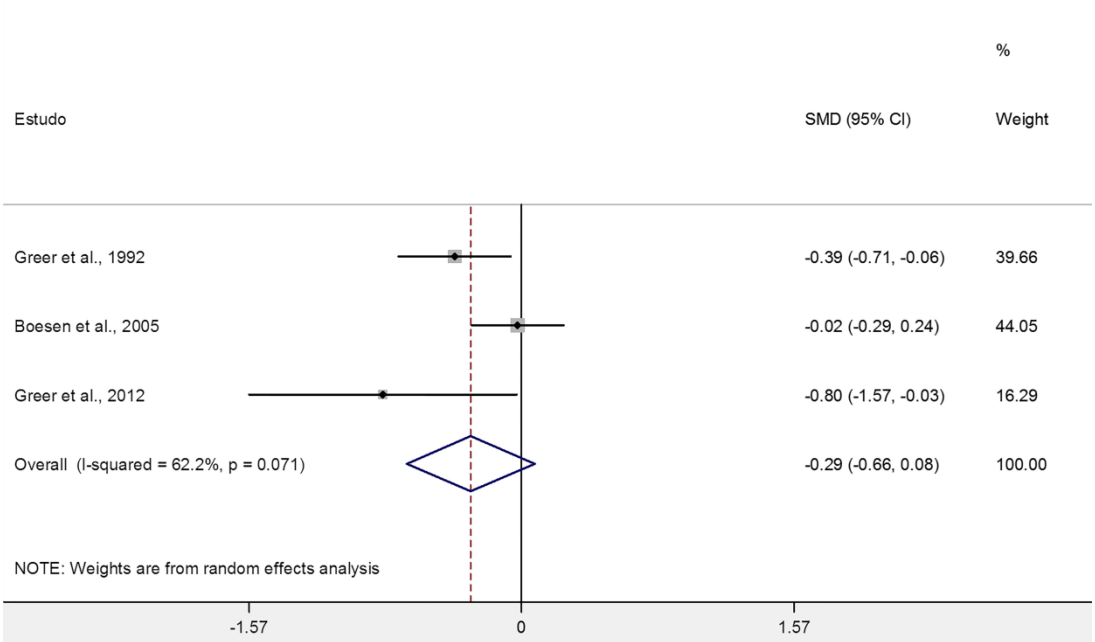




If the study by Telch & Telch [25] is not considered, one can observe a reduction in the magnitude of the effect found, that is, the difference between the final scores of CBT and control groups. Even so, the difference is still in favour of the CBT group, but at a borderline significance level (p= 0.07), which suggests the existence of an advantage for CBT. It should be emphasised that there is no reason for not considering the study by Telch & Telch [25] as it is in accordance with our inclusion criteria. The increase in p-value possibly reflects the reduction in the number of studies following removal of the study by Telch & Telch [25].

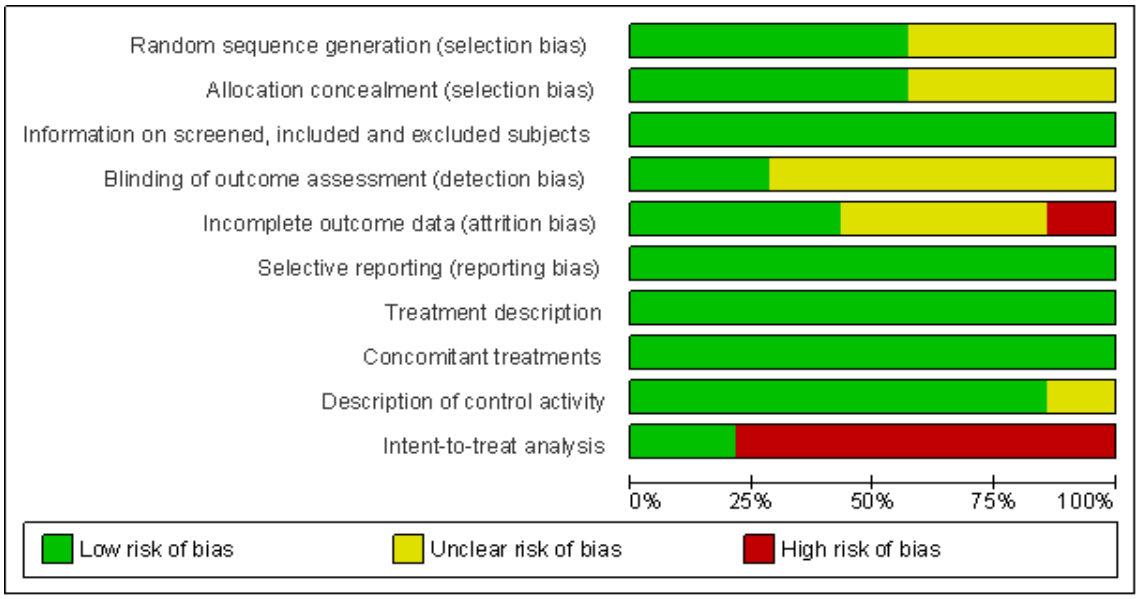
Comparing the Variation in the Scores between Two Groups

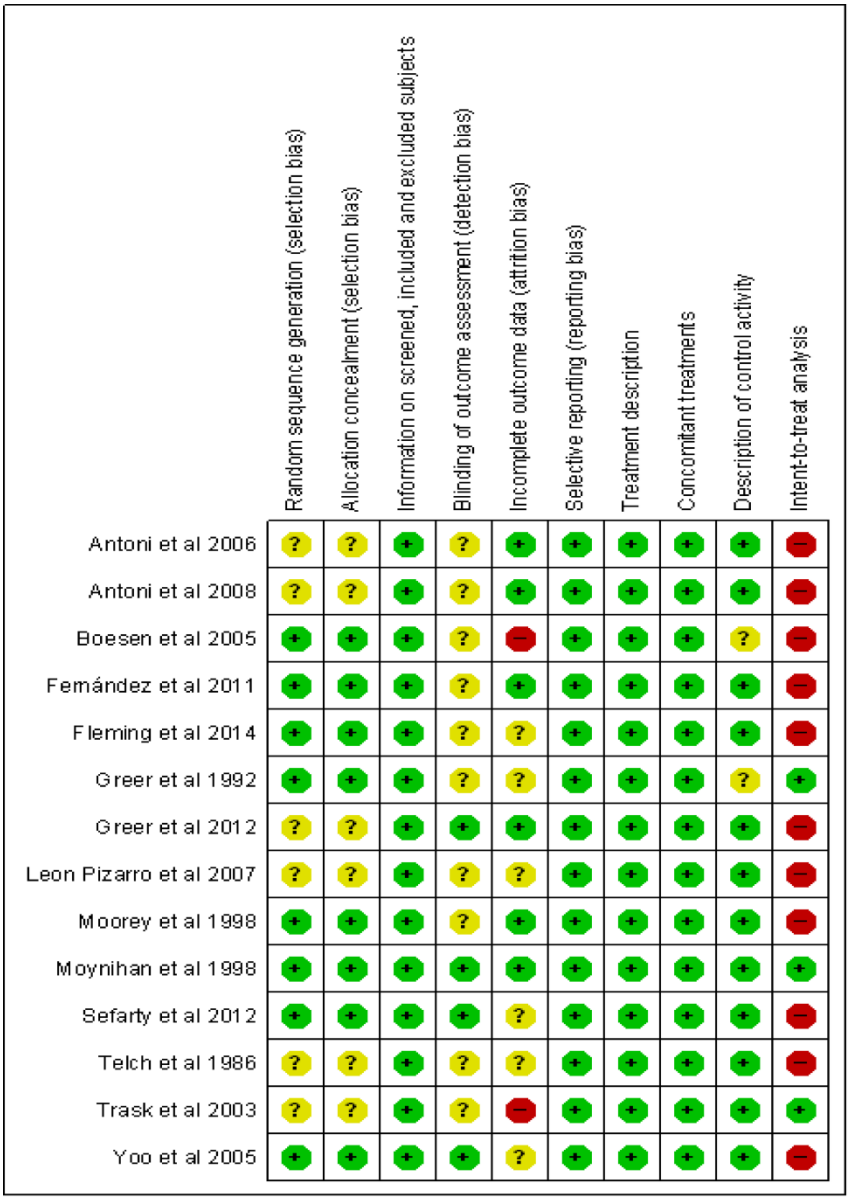
With regard to the three studies comparing the variation in the scores between intervention and control groups, the difference of 0.29 standard deviation did not reach statistical significance (p= 0.12), probably as a result of the small number of studies (i.e. type 2 error due to low sampling power). Here, heterogeneity was also high (62%) (Figure 3).



Quality Assessment of the Studies and Statistical Analysis

The different aspects of the methodological quality of the studies are listed in figures 4 and 5. One can note that 78.6% of the studies did not evaluate the intention to treat (ITT), whereas 57% provided no information on loss of outcome data (incomplete outcome data), i.e., more than a half of the studies did not assess the data loss, nor considered it for the results. Moreover, 42.8% of the studies provided no clear information on how randomisation and allocation concealment had been performed, which favours the possibility for both subjects and researchers to know in which group they will participate, thus weakening the methodological rigour of a randomised study. Finally, 71% of the studies provided no clear information on the blinding process performed by the researcher.





CONCLUSIONS

Main Findings

In the present study we have conducted two meta-analyses of randomised controlled trials on the effectiveness of traditional CBT in reducing anxiety symptoms, involving 1,399 adult cancer subjects. The first meta-analysis demonstrated the efficacy of CBT by comparing intervention and control groups in terms of reduction of anxiety symptoms. The

comparison of the final scores of the groups (endpoint) were used as parameter, which allowed us to rate the effect size as being moderate (*d* Cohen = -0.63). In the second meta-analysis, which assessed the change between intervention and control groups, the effect size was rated as being borderline (*d* Cohen = -0.29), but their small samples do not allow drawing clear conclusions. The main methodological weaknesses of the RCTs included in our meta-analyses were the following: ITT analyses, blinding, and incomplete outcome data.

Previous meta-analyses corroborate our finding [15, 16, 18], since they found positive results with CBT despite the variation in the magnitude of effect size. These variations are likely to be the result of the heterogeneity in the inclusion and exclusion criteria as well as in the definition of CBT. For example, some meta-analysis included non-randomised studies [15], theses and non-peer reviewed articles [15, 18, 19], whereas the present meta-analysis included peer-reviewed RCTs only.

Another important source of discrepancy between the studies is the scope of the definition of CBT. Previous meta-analyses [15, 16, 18] used broader definitions of CBT, whereas we have opted for a more narrow definition. For example, there are meta-analyses [17] which included studies using relaxation techniques only (behavioural component). In the present meta-analysis, such studies were not included as we have opted for a more traditional definition of CBT, that is, at least one cognitive and one behavioural technique.

Limitations of the Studies

The studies included in our meta-analysis had some limitations. First, six studies did not provide all the data necessary for statistical analysis. Due to that, only nine studies of the 14 (64.3%) identified in the systematic review were included in meta-analysis. This happened

because some studies had non-comparable outcomes, i.e., some of them presented scores of change between groups (change analysis) and others endpoint analysis.

Second, some studies did not provide data from missing patients and, despite the author's efforts to obtain it, only one responded our e-mails. This limitation reduced the sample of subjects and consequently the precision of the estimate of confidence interval.

Third, the studies included are heterogeneous in terms of type of cancer, stage of the disease, number of CBT sessions and type of radio and chemical therapies. In addition, despite we have used a narrow definition of CBT, the types of CBT techniques ranged among studies (e.g. training in muscle relaxation, described in a few articles, may include progressive muscle relaxation or specific breathing techniques). Another possible source of heterogeneity is that of gender: 77.6% of the samples consisted of women, which did not allow any gender generalisation.

Fourth, many studies did not limit the inclusion to patients with significant anxiety only, that is, those scoring above the minimum scores for some specific psychometric scales. Only six studies used significant anxiety as inclusion criterion [11, 25, 26, 27, 28, 29]. On the other hand, studies which found no significant results for anxiety raised the hypothesis that the levels of anxiety were already low prior to the beginning of treatment [30]. From this rationale, therefore, severe cancer patients showed more expressive results. This hypothesis is corroborated by Schneider [18], who conducted a meta-analysis and observed that effects on anxiety and depression are usually overlooked when distress before intervention is low, but prominent when it is high.

Methodological Analysis

With regard to the methodological quality, it was found a lack of information mainly on items regarding ITT analyses, blinding and incomplete outcome data. Of these, ITT analysis was the most deficient item, with 78.6% of the studies performing no such analysis. On the other hand, the most adequately reported items were description of treatment and information on screened, included and excludes subjects in all articles reviewed. Due to such a limitation, it is necessary to carry out more studies assessing information on missing data and its impact on the results reported.

Limitations of the Meta-Analysis

Among the limitations of the present work, the first one results from the fact that we have searched three databases only; however, these are the most important ones. The second limitation is that we did not make contact with experts in order to find additional studies. The third limitation was the language restriction (English, Portuguese and Spanish). We considered, however, that the two latter limitations probably would not be enough to affect our results.

Further Studies

We recommend that future studies should describe all quantitative data in detail according to checklists, such as the CONSORT checklist [31], which lists key items for reporting RCTs. Similarly, more specificity in describing stage of disease, type of cancer and type of treatment would make the results less heterogeneous.

The methodological analysis performed in the present work evidenced the need of a greater methodological rigour in the items ITT analyses, blinding and incomplete outcome data. ITT analysis deserves special attention because it was the most deficient item, being used in less than 25% of the studies. In the ITT approach the individuals are analysed depending on the group to which they are assigned rather than on the treatment they receive. The reason for that is to maintain the benefits of the randomisation [32]. Furthermore, the lack of information on dropouts through the item "incomplete outcome data" can lead to an attrition bias, which refers to systematic differences between groups due to withdrawals from a study [23]. Data on the reasons for dropouts might lead to strategies aimed to increase the participation rate among the target population [33]. By estimating the percentage of patients who benefit from treatments available and investigating the variables involved in the rates of dropout and relapse following psychotherapy, we can further develop more efficient and lasting treatments and strategies. Finally, the lack of blinding for assessment of the patient's evaluation increases the chance of bias in the classification, since knowing the group to which the patient belongs can influence the rater's perception.

The majority of the studies focus on breast cancer, as shown in the present meta-analyses (42.65%) as well as in data reported by Moyer et al. [33]. However, there are still many understudied areas. For example, although lung cancer is one of the most prevalent and severe cancers, affecting 1.82 million people and resulting in 1.6 million deaths [34], only one RCT included in the present work had investigated patients with this type of cancer.

The lack of follow-up data also becomes a major problem. In the present sample, only five of the 14 RCTs had included psychometric evaluation six months after treatment. Despite the well-documented efficacy of CBT, there is a scant of studies examining its long-term efficacy [35, 36], mainly after two years of follow-up. This gap is further evidenced in

cancer patients and becomes a challenge as this population has considerable rates of severity and mortality.

We have found no investigation on differences in efficacy between several CBT techniques, types of cancer, stages of the disease regarding benefits and optimal treatment duration. There is also a scant of studies on populations living in regions other than Europe and North America [33]. The use of positive psychology techniques may enhance the overall efficacy of the treatment, since the interventions are mainly focused on reducing the psychopathology [37]. The increase in positive affect, one of the strategies of the positive psychology, can be more efficient in cancer patients with anxiety symptoms.

Summarizing, the traditional CBT was shown to be efficient in controlling the anxiety of cancer patients. However, the existence of only 14 randomised CBT trials in this population shows that this important area has been understudied, since about 14 million people are diagnosed with cancer worldwide every year.

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Table 1 – Description of variables in evaluation of methodological quality

Criterion	Description	Evaluation
Random Sequence Generation	Evaluate the way the randomization sequence was generated	Low Risk of Bias: proper randomized way of generating randomization sequence; examples are sequences generated by computer programs Unclear Risk of Bias: Does not inform how the randomization sequence was generated High Risk of Bias: Non-randomized or inadequate way of generating randomization sequence
Allocation Concealment	Evaluate concealment of sequence, i.e. how difficult it was for participants or evaluators to predict to which group the next subjects would be assigned	Low Risk of Bias: The randomization sequence was generated so as to promote concealment of it Unclear Risk of Bias: Does not inform how randomization sequence and attempt of concealment was generated. High Risk of Bias: No attempt of concealment of randomization sequence
Blinding Outcome Assessment	Evaluate if the evaluator was "blind", i.e. when evaluating he/she was unaware of which group the subject belonged to (intervention or waiting list)	Low Risk of Bias: Evaluator did not know which group the subject belonged to while evaluating Unclear Risk of Bias: Does not inform if evaluator was aware of the group the subject belong to High Risk of Bias: Evaluator knew which group the subject was assigned to.
Incomplete Outcome Data	Evaluate information about loss of data at follow-up	Low Risk of Bias: There was little or no loss along the study, and this is mentioned by the author Unclear Risk of Bias: No losses were mentioned, when the numbers clearly pointed so High Risk of Bias: Great loss along the study
Selective Reporting (Reporting Bias)	Mention along the results all of the criteria, variables and measures described in the aim and methods of the study	Low Risk of Bias: Results of all the criteria, variables and measures mentioned Unclear Risk of Bias: No information about the criteria, variables and measures used, as well as their results. High Risk of Bias: Criteria,

		variables and measures were used that were not reported in the results section
Concomitant Treatment	Inform if there was treatment concomitant to the provided one	Low Risk of Bias: Absence of concomitant treatment Unclear Risk of Bias: No information about concomitant treatment High Risk of Bias: Presence of concomitant treatment to the one offered in the study
Description of Control Activity	Describe activities performed by the control group or waiting list	Low Risk of Bias: Mentions if control group performed any activities, and if so, which ones Unclear Risk of Bias: Incomplete description of activities performed by control group High Risk of Bias: No information on activities performed by control or waiting list group. Or performed some similar activity to the intervention group

Table 2 – Description of studies

Study	Sample	Cancer	Instruments	Intervention	Duration	Results
Fleming, 2014	CBT = 73 Control = 40	Any Type	HADS	Sleep schedule, cognitive approches, sleep hygiene and relaxation, psychoeducation.	5 sessions	No statiscally reduction on anxiety
Sefarty, 2012	CBT = 19 Control = 20	Any type	HADS, POMS-TMS	CBT techniques as described by Aaron Beck.	Up to 8 sessions delivered over 10 weeks	Significant improvements in POMS occurred with both interventions.
Greer, 2012	CBT =20 Control = 20	Any type	HAM-A, HADS	Goal setting, education about anxiety, relaxation training, coping with cancer fears, activity planning and pacing.	6 or 7 sessions	Significantly greater reductions in CBT group on HADS and HAM-A scores.
Fernández, 2011	Breast (29 control X 25 CBT), Lung (37 control X 47 CBT)	Breast and Lung	HADS	Self-observation and recording of behaviour, behavioural testing, management of situational contingencies, acceptance and detachment from emotions and thoughts and homework	4 to 6 sessions	When comparing the groups of lung cancer patients, CBT significantly reduced anxiety compared to the control group. Breast cancer patients did not show significantly differences between groups.
Antoni, 2008	CBT = 69 Control = 65	Breast	HAM-A	Progressive muscle relaxation, relaxing imagery, cognitive reestructuring, stress reduction techniques, coping strategies and interpersonal skills.	10 sessions	CBT group presented significantly lower anxiety in last HAM-A assessment, demonstrating efficacy in anxiety symptoms.

Leon Pizarro, 2007	CBT = 32 Control = 34	Breast and Gynecologic	HADS	Information about brachytherapy, training in relaxation and guided imagery	1 session and homework	Significant difference in the values of anxiety between control and study group (p=0.008), with statistically significant reduction in the study group.
Antoni, 2006	CBT = 92 , Control = 107	Breast	HAM-A	Muscle relaxation, guided imagery, cognitive restructuring, coping skills, and interpersonal skills with a supportive group of breast cancer patients at similar points in medical treatment	10 sessions	CBT had a smaller but significant effect on interviewer-rated assessments of general anxiety symptoms, causing a downward trajectory in anxiety ratings, whereas subjects in the control condition had no comparable decline over time.
Boesen, 2005	CBT = 112 Control = 129	Melanoma	POMS	Psychoeducation, consisting of health education, enhancement of problem-solving skills, stress management, and psychological support	6 group sessions	A significantly larger average decrease in the TMD score was observed in the intervention group compared with the control group at first follow-up, but no significant changes in anxiety; probably because patients have low scores for anxiety in baseline.

Yoo, 2005	CBT = 30 Control = 30	Breast	MAACL	Muscle relaxation, guided imagery	6 session and homework	Between group differences was significant in patients' anxiety, depression, and hostility variables, but only anxiety showed a significant session effect.
Trask, 2003	CBT = 25 Control = 23	Melanoma	STAI	Training in relaxation, problem solving and cognitive challenging	3 sessions	Significantly lower anxiety among CBT group at two and six months follow up.
Moynihan, 1998	CBT = 36 Control = 37	Testicular	HADS	Coping strategies directed at current problems, identification of patient's personal strengths, identification of negative automatic thoughts and how to challenge such thoughts, role play, progressive muscular relaxation and expression of feelings and open communication between patient and spouse	6 sessions	CBT did not seem to be effective, although the treatment group showed a marginal reduction in anxiety at two months

Moorey, 1998	CBT = 25 Control = 22	Any type	HADS, STAI	Coping strategies directed at current problems, identification of patient's personal strengths, identification of negative automatic thoughts and how to challenge such thoughts, role play, progressive muscular relaxation and expression of feelings and open communication between patient and spouse	8 sessions	Significant differences between the treatments. CBT produced greater change from baseline in anxiety, and this change persisted in 4 month follow up. There were no statistically significant differences between treatments at 1 year.
Greer, 1992	CBT = 72 Control = 84	Any type (except cerebral tumor and skin cancer different of melanoma)	HADS	Coping strategies directed at current problems, identification of patient's personal strengths, identification of negative automatic thoughts and how to challenge such thoughts, role play, progressive muscular relaxation and expression of feelings and open communication between patient and spouse	6 sessions	In the therapy group the proportion of severely anxious patients fell from 46% at baseline to 20% at eight weeks and 20% at four months; in the control group, there were only minor changes.
Telch, 1986	CBT = 13 Control = 14	Any type	POMS	Coping skills training, relaxation and stress management, assertive communication, cognitive restructuring and problem solving, feelings management, and pleasant activity	6 sessions	Consistent superiority of the CBT intervention over supportive group therapy and the no-treatment control.

				planning		

CBT = Cognitive Behaviour Therapy, HADS = Hamilton Anxiety and Depression Scale, STAI = State-Trait Anxiety Inventory, HAM-A = Hamilton Anxiety Scale, POMS = Profile of Mood States, POMS-TMS = Profile of Mood States – Total Mood Score, MAACL = The Multiple Affect Adjective Checklist.

ANEXO D - Quem aposta melhor? Avaliação da tomada de decisão no TEPT usando o *Iowa GamblingTask*

Em produção

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Resumo

Contexto: A tomada de decisão tem importante papel no comportamento humano, encontrando-se prejudicada em muitos transtornos psiquiátricos como no Transtorno de Estresse Pós-Traumático (TEPT). **Objetivo:** Comparar a tomada de decisão de sujeitos com e sem TEPT, mas com histórico de evento traumático, para avaliar o desempenho de ambos os grupos utilizando o *Iowa Gambling Task* (IGT), de maneira controlada e pareando os participantes. **Métodos:** Participaram da pesquisa 18 sujeitos, com idade entre 19 e 48 anos, divididos em dois grupos (TEPT e controle). O grupo TEPT foi submetido a Entrevista Clínica Estruturada para Transtornos do Eixo I do DSM-IV (SCID I). Os critérios de inclusão foram: o participante ter sido diagnosticado com o transtorno, não apresentar risco de suicídio, gravidez e sintomas psicóticos. Os controles responderam à Entrevista Neuropsiquiátrica Internacional (MINI) para descarte de outros diagnósticos de transtornos mentais. O instrumento utilizado para avaliação da tomada de decisão foi o IGT. **Resultados:** Os resultados não indicaram significância estatística relevante entre os grupos (p=0,56). **Conclusão:** Os gráficos apontam na direção de uma aprendizagem mais lenta para a tomada de decisão em indivíduos com TEPT, mas não há diferença estatisticamente significativa na tomada de decisão entre os dois grupos.

Palavras-chaves: Tomada de decisão; TEPT; IGT; Neuropsicologia

Introdução

Você sabe como toma as suas decisões? A tomada de decisão se refere a um complexo processo que envolve o raciocínio e o desenvolvimento de estratégias a fim de produzir inferências válidas para a situação (DAMÁSIO, 2012). Este processo é composto pelos procedimentos de avaliação e formação de preferências entre as opções de escolha; seleção, escolha e execução das ações; avaliação das consequências e resultados (ERNST & PAULUS, 2005; RUTZ, HAMDAN & LAMAR, 2013).

Tomar uma decisão vantajosa implica em pesar diferentes riscos e benefícios baseados em experiências prévias, tais como: características físicas das opções; resultados previstos, como valência (positivo/negativo), saliência (intensidade/magnitude), probabilidade e tempo; valores relativos e número de opções para selecionar; experiência anterior e resultados obtidos; e o contexto em que essas decisões são tomadas (ERNST & PAULUS, 2005). Este processo envolve circuitos cerebrais que são predominantemente regulados por regiões corticais, como o córtex pré-frontal dorsolateral (CPFDL) e ventromedial (CPFVM), córtex cingulado e amígdala (ERNST & PAULUS, 2005; DRETSCH, 2012).

Dentre várias teorias da tomada de decisão, a hipótese do marcador-somático (BECHARA *et. al*., 1994; DAMÁSIO, 2012; BECHARA, DAMÁSIO & DAMÁSIO, 2000; DAMÁSIO, 1996) propõe que os sentimentos gerados a partir das emoções secundárias foram ligados, pelo processo de aprendizagem, a resultados futuros previstos de determinadas situações. Dessa forma, os marcadores-somáticos atuam como um alarme automático da escolha a ser realizada, podendo soar como um sinal de alerta ajudando no processo de decisão, dando destaque a algumas opções, tanto adversas como favoráveis, e eliminando-as rapidamente da análise subsequente.

Estudos mostraram que os marcadores-somáticos estão localizados no córtex pré-frontal (BECHARA & DAMÁSIO, 2004), região interligada ao sistema de emoções secundárias. Essas emoções são geradas a partir da recordação de um evento pessoal ou hipotético, resultando em estados somáticos. As emoções primárias são estímulos inatos ou aprendidos que causam estados físicos agradáveis ou aversivos. Quando esta área é lesionada, este mecanismo passa a operar inapropriadamente e o sujeito passa a optar por escolhas que lhe proporcionam mais desvantagens do que vantagens (DAMÁSIO *et. al*., 1994).

O *Iowa Gambling Task* (IGT) é uma tarefa utilizada na avaliação da tomada de decisão emocional em condições de incerteza, penalidade e recompensa (será descrita na sessão de Métodos). Estudos iniciais comprovam a eficácia do IGT na avaliação da tomada de decisão com base nos resultados de pacientes lesionados no CPFVM (FUKUI *et. al*., 2004; BECHARA, TRANEL & DAMÁSIO, 2000) ou na amígdala (BECHARA *et. al.*, 1999), uma vez que demonstraram desempenho significativamente pior na tomada de decisão do que o grupo não lesionado. Além disso, evidências obtidas por ressonância magnética funcional de indivíduos saudáveis reforçam ainda mais o papel do CPFVM na tomada de decisão, avaliada através do IGT, além de outras regiões como o córtex orbitofrontal, ínsula, córtex somatossensorial secundário, estriado e giro do cíngulo. (LIN *et. al*., 2008; LI *et. al*., 2010; LAWRENCE *et. al*., 2008; WINDMANN *et. al*., 2006)

Diferentemente de outras tarefas em que toda informação necessária para a tomada de decisão está previamente disponível, o IGT está baseado em um processo de aprendizagem exploratório para avaliar a antecipação dos riscos na tomada de decisão (FUKUI *et. al*., 2004).

A tomada de decisão e seu comprometimento estão presentes em muitos distúrbios psiquiátricos (ERNST *et. al*., 2002), como no Transtorno de Estresse Pós-Traumático (TEPT). Estudos realizados demonstraram alterações neurobiológicas e funcionais no CPFVM de pacientes com TEPT, região esta também relacionada à tomada de decisão (KOENING & GRAFMAN, 2009; LANIUS *et. al*., 2006). Embora déficits na tomada de decisão não sejam um sintoma de TEPT, pacientes com este diagnóstico tem alterações cerebrais funcionais e estruturais, e prejuízos nas funções cognitivas que sugerem que a habilidade de tomar decisões está alterada (BRAND & STARCKE, 2012).

A literatura atual apresenta uma série de achados em que o TEPT está associado a comprometimentos nas funções cognitivas (QURESHI *et. al*., 2011; BRANDES *et. al*., 2002; VASTERLING *et. al*., 2002; YEHUDA *et. al*., 2005), mas poucos são os que avaliam a tomada de decisão em pacientes com este transtorno. Dretsch *et. al.* (2012) utilizando as versões *Standard* e *Variante* do IGT avaliaram a tomada de decisão de 46 combatentes de guerra, sendo 23 diagnosticados com TEPT conforme os critérios diagnósticos do DSM-IV-TR. Na versão *Standard*, os baralhos A e B são mais vantajosos nos ganhos imediatos, mas as perdas são muito maiores em longo prazo. Na versão *Variant*, os baralhos C e D foram invertidos para que os ganhos e perdas fossem mais desvantajosos, produzindo assim, pequenas perdas imediatas e menores ganhos em longo prazo. Ambos os grupos obtiveram aprendizado da tarefa, sendo o desempenho dos indivíduos com TEPT pior do que os

controles. Além disso, quando comparados os resultados dos grupos nas duas versões da tarefa, os soldados com TEPT apresentam prejuízo na tomada de decisão emocional, que parece ser devido à incapacidade de equilibrar punição e recompensa tardia. Isso foi evidenciado pelo desempenho normal na versão *Standard* do IGT, mas significativamente pior na versão *Variant*, em comparação com o grupo controle.

Sailer *et. al.* (2008) investigaram pacientes com TEPT e controles saudáveis em uma tarefa de tomada de decisão enquanto respostas neurais eram avaliadas por ressonância magnética e tarefas cognitivas. A tarefa consistiu de ganhos e perdas que se seguiram a um padrão de escolhas em que os participantes poderiam aprender por meio de feedback. Os pacientes se diferenciaram dos controles tanto no nível comportamental quanto neural. O grupo com TEPT aprendeu as respostas corretas mais lentamente do que o grupo controle. Funcionalmente, o grupo de TEPT e o grupo controle apresentaram diferenças nas respostas neurais para ganhos, mas não para perdas. Durante o processo de ganhos na última fase de aprendizado da tarefa, os pacientes com o transtorno mostraram menor ativação no núcleo accumbens e no córtex pré-frontal medial do que o grupo controle, sugerindo que indivíduos com o transtorno estão mais insensíveis à recompensa.

Além desses, outro estudo (ELMAN *et. al*., 2009) que não utiliza o IGT para avaliação da tomada de decisão, avaliou se o TEPT poderia estar associado a uma diminuição do circuito de recompensa neuronal. Para isso um grupo de pacientes com TEPT e um grupo controle foram submetidos a uma tarefa de perdas e ganhos monetários para que as fases de expectativa e resultados da atividade pudessem ser avaliadas. Os resultados mostraram que o grupo com TEPT apresentou menor ativação da região bilateral do estriado para ganhos e maior tendência para desativação dessa região para perdas, sugerindo que estas áreas estão prejudicadas no TEPT.

Apesar de a literatura indicar que a tomada de decisão pode estar deficitária em pessoas com esse diagnóstico (DRETSCH *et. al*., 2012; BRAND & STARCKE, 2012; SAILER *et. al*., 2008; LANIUS *et. al*., 2006), buscas realizadas mostraram que poucos são os estudos que avaliam a tomada de decisão em indivíduos com TEPT, assim como as considerações desses achados para tratamentos adequados. Deste modo, o objetivo da pesquisa foi comparar a tomada de decisão de sujeitos com TEPT com a de sujeitos sem TEPT, mas com histórico de evento traumático, para avaliar o desempenho de ambos os grupos.

Métodos

Sujeitos

O presente estudo é um recorte de um estudo maior envolvendo participantes que foram divididos em dois grupos com nove integrantes cada. O primeiro grupo é constituído por indivíduos com TEPT e o segundo é composto por sujeitos com histórico de evento traumático, que não desenvolveram o transtorno. Os grupos são compostos por sujeitos de ambos os sexos sendo 14 mulheres (77,78%) e 4 homens (22,22%), com idade entre 19 e 48 anos (μ = 31,61; *DP* = 8,59).

Tabela 1 - Descrição dos participantes

Procedimentos

Os indivíduos com TEPT foram avaliados por psiquiatras através da Entrevista Clínica Estruturada para Transtornos do Eixo I do DSM-IV (SCID I) (DEL-BEN *et. al*., 2001) que utiliza como critério diagnóstico o Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-IV-TR), sendo o critério de inclusão o participante ter sido diagnosticado com TEPT, não apresentar risco de suicídio, gravidez e sintomas psicóticos. Os sujeitos com histórico de trauma, mas que não desenvolveram TEPT foram entrevistados por uma psicóloga e responderam à Entrevista Neuropsiquiátrica Internacional (MINI) (AMORIM, 2000) para descarte de outros diagnósticos de transtornos mentais, considerado como critério de exclusão para o grupo a presença de qualquer transtorno mental atual. Os sujeitos com TEPT foram recrutados do Laboratório de Pesquisa Integrada do Estresse (LINPES) do Instituto de Psiquiatria da UFRJ (IPUB/UFRJ). Já os participantes sem TEPT foram selecionados de diferentes locais conforme as características dos indivíduos com o transtorno, sendo pareados de acordo com gênero, idade e escolaridade, de modo a minimizar as diferenças entre as amostras.

Os participantes não podiam ter qualquer desordem cerebral como epilepsia, Traumatismo Cranio-encefálico (TCE) e/ou Acidente Vascular Cerebral (AVC), meningite e problemas de pressão intracraniana atualmente ou ao longo da vida.

Os participantes foram recrutados e agendados individualmente para a avaliação neuropsicológica que ocorreu no Instituto de Psiquiatria da UFRJ (IPUB/UFRJ). Na data prevista para a avaliação, foi explicado o objetivo da pesquisa aos participantes e assinado o

termo de consentimento informado. Posteriormente foi feita uma entrevista inicial para coletar dados básicos dos pacientes.

Iowa Gambling Task

Os participantes foram submetidos à avaliação neuropsicológica, sendo administrado o IGT para a avaliação da tomada de decisão.

O teste consiste na simulação de um jogo de cartas envolvendo ganhos e perdas monetárias. É solicitado ao examinando que escolha uma carta dos quatro baralhos por vez (A, B, C, D) da forma que o paciente preferir. O teste consiste em 100 jogadas e só termina após todas elas serem realizadas. Para cada escolha, o participante recebe uma recompensa monetária, e às vezes é punido com a retirada de uma parcela do montante que recebeu durante a atividade. Após cada jogada realizada, os participantes recebem três tipos de feedback: (1) Duas mensagens indicando a quantia ganha ou perdida na jogada, (2) um rosto sorridente é apresentado após a revelação da quantia ganha e um rosto triste é apresentado após a revelação da quantia perdida, e (3) o tamanho da proporção das barras verde e vermelha que estão posicionadas no topo da tela, que indicam o total de dinheiro ganho ou perdido (redução da barra verde) após cada seleção. O esquema de recompensas e punição é pré-determinado. O teste começa com uma quantia de R$ 2.000,00, e o avaliado é instruído a ganhar a maior quantidade que conseguir, e que há baralhos que possuem melhor custo/benefício quando comparados com outros para atingir tal objetivo.

Análise estatística

Inicialmente foram obtidas as medidas de tendência central (média e mediana) e de dispersão (desvio-padrão) da variável tendência geral. Essas medidas foram calculadas separadamente, para os grupos TEPT e controle.

Em seguida, calcularam-se as médias de aprendizado ao longo dos cinco blocos, separadamente para cada um dos grupos. Por fim, estimou-se a média de escolhas para cada um dos quatro conjuntos de baralho, também de forma separada para aqueles com e sem TEPT.

A significância estatística das diferenças entre os grupos foi avaliada através do teste não paramétrico de Kruskal-Wallis, devido ao pequeno número da amostra e à grande dispersão dos dados. Todas as análises foram realizadas com o programa Stata 12.0.

Resultados

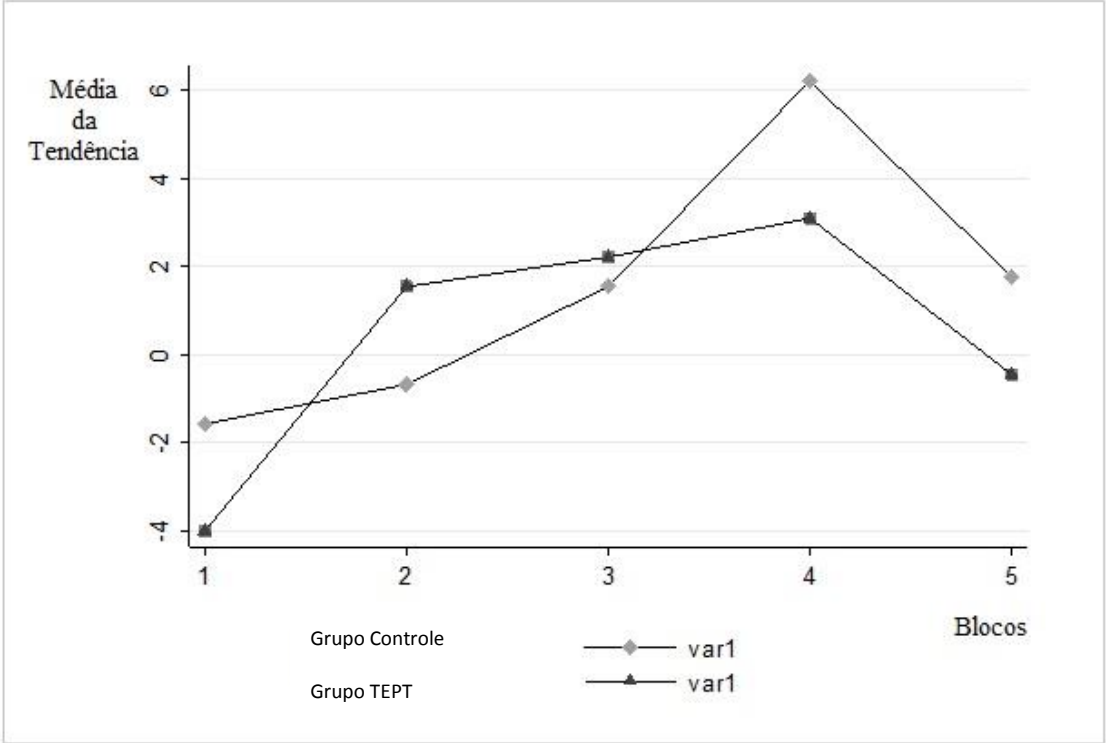
Inicialmente foram comparados os escores de tendência entre os indivíduos com e sem TEPT. A tabela 2 apresenta as médias, medianas e desvios-padrão para cada um dos grupos. Embora a média tenha sido mais elevada no grupo controle, a diferença não alcançou significância estatística (p=0,56).

Tabela 2 – Médias, medianas e desvio-padrão

Grupo	Média	Mediana	Desvio-padrão
TEPT	2,44	2	17,69
Controle	7,33	6	17,05

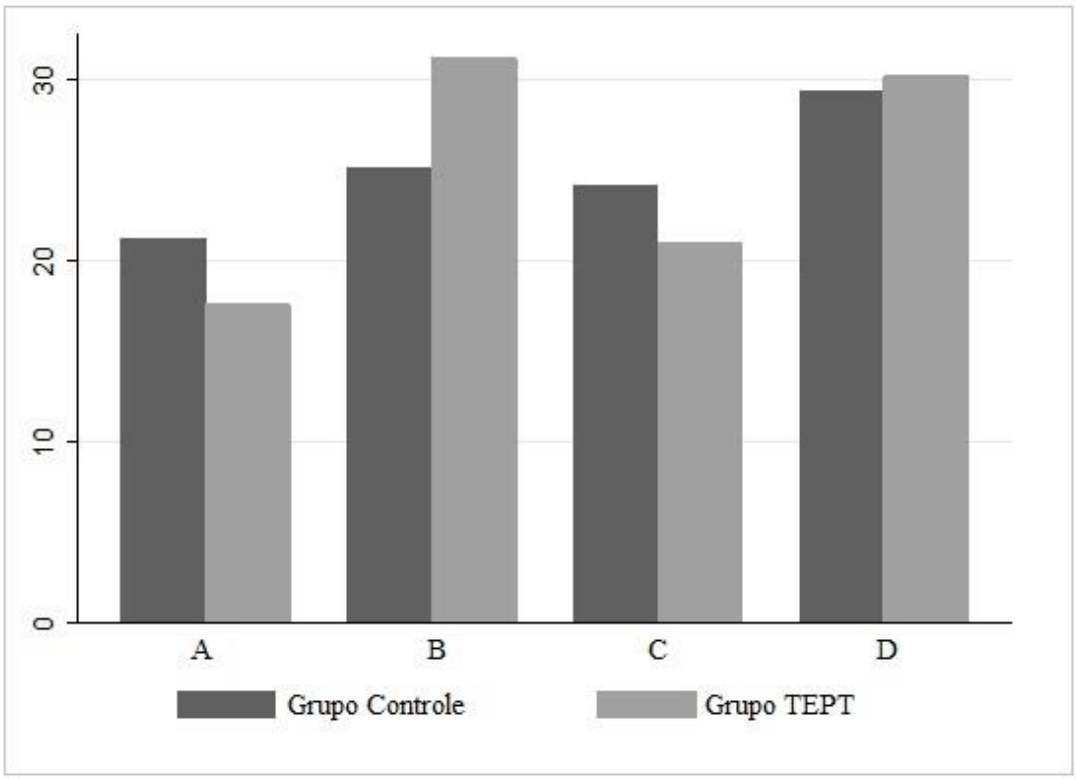
Quando analisamos o ganho de aprendizado entre os grupos ao longo dos cinco blocos de jogadas, o gráfico 1 sugere que o grupo controle tem um ganho de aprendizado mais rápido na primeira metade da tarefa. Observa-se ainda que, em ambos os grupos, existe um declínio desse aprendizado depois do quarto bloco.

Gráfico 1 - Curvas de aprendizado por grupo e blocos de jogada



O gráfico 2 apresenta o número médio de vezes em que cada conjunto de baralhos foi escolhido em cada um dos grupos. Nota-se que a maior diferença entre os grupos está no número de vezes em que o baralho B foi escolhido. Esse baralho é caracterizado por levar aos maiores ganhos, mas também às maiores perdas. Já no conjunto de baralho D, onde o ganho é menor e as perdas também, observa-se maior equilíbrio entre o número de vezes em que foi selecionado. Em todos os casos, o valor de p fornecido pelo teste de Kruskal-Wallis foi superior 20%, exceto no caso do baralho B, em que o valor de p foi de 0,11. A inspeção visual do gráfico de barras aponta na direção de mais escolhas por ganhos imediatos (baralho B) no grupo TEPT.

Gráfico 2 - Média de escolhas por baralho



Discussão

O presente estudo investigou a tomada de decisão de sujeitos com TEPT e sem TEPT, mas com histórico de evento traumático, para a comparação de ambos os grupos, utilizando o instrumento IGT. Os resultados obtidos estão de acordo com os achados da literatura internacional que aborda o tema.

A inspeção visual do gráfico curva de aprendizado indica que em ambos os grupos há aprendizagem da tarefa, mas com diferentes padrões. No grupo TEPT um padrão mais lento do aprendizado quando comparado ao grupo controle. Ainda sobre a inspeção do gráfico, o grupo TEPT apresentou ganho de aprendizado caracterizado pela preferência de escolha dos baralhos C e D em detrimento dos baralhos A e B. Posteriormente, o grupo continua a evoluir na tarefa, porém com baixo rendimento, seguido de queda no bloco 5. Esta queda no rendimento ao longo dos blocos 2, 3, e 4 pode estar relacionada ao aumento do número de escolhas dos baralhos A e B, como demonstrado no Gráfico 2.

O gráfico 2 mostra que no grupo com TEPT há a predominância de escolhas dos baralhos B e D ao longo de toda a tarefa. Porém, como este grupo apresentou ganho de aprendizado no primeiro bloco, deduz-se que houve preferência de escolha pelos baralhos C e

D. Contudo, tal preferência passa a ser apresentada pela escolha dos baralhos A e B nos demais blocos, diminuindo assim o rendimento do grupo.

Os resultados gerados pelo grupo de TEPT apontam na direção dos achados de Bechara *et. al.* (1994). Estudos com amostras maiores poderiam confirmar ou não a tendência encontrada em nossa amostra. Neste estudo foi comparado um grupo controle com indivíduos saudáveis com grupo de indivíduos com lesão no córtex ventromedial. Na comparação, foi evidenciado que os controles optam por escolhas vantajosas a longo prazo (baralhos C e D) enquanto que os pacientes persistem em escolher os baralhos A e B durante toda a tarefa. Os autores sugeriram que o processo de tomada de decisão desses pacientes foi motivado pela recompensa imediata, ou seja, uma incapacidade de antecipar as consequências de suas ações.

Além disso, uma hipótese para esta mudança de comportamento no decorrer da tarefa pode estar relacionada aos resultados que os estudos com neuroimagem obtiveram ao comparar pacientes com TEPT e controles, que realizaram tarefas que envolviam recompensa e punição. Conforme os artigos publicados por Elman *et. al.* (2009) e Sailer *et. al.* (2008), os pacientes com TEPT se diferenciaram dos controles tanto em níveis funcionais quanto estruturais. Em relação aos níveis funcionais, Sailer *et. al.* (2008) observaram menor motivação por parte dos participantes com TEPT para a realização e concretização da tarefa. Este dado pode ajudar a compreender o modo como os sujeitos escolhem as cartas do baralho a partir de um dado momento da tarefa, optando por escolhas aleatórias ao invés de ações baseadas em um processo de aprendizagem. Já no nível estrutural, em ambos os casos foi observado que regiões cerebrais envolvidas com o circuito de recompensa eram menos ativadas nos sujeitos com TEPT. Elman *et. al.* (2009) apontou que o grupo com TEPT apresentou menor ativação da região bilateral do estriado para ganhos e maior tendência para desativação desta região para perdas, o que poderia sugerir que o grupo com TEPT obtendo ganhos, a resposta emitida pode ser aquém do esperado devido a uma falha no sistema de monitoramento de recompensa.

O grupo controle começou a tarefa optando pelos baralhos mais vantajosos a longo prazo (média da tendência geral = 7,33), obtendo ganho gradual de aprendizagem da tarefa, atingindo o seu pico no bloco 4 e posterior declínio. Nota-se que, apesar de na primeira metade da tarefa o grupo controle apresentar ganho de aprendizagem em menor velocidade quando comparado com o grupo TEPT (vide Gráfico 1).

Os resultados brutos apontaram declínio na curva de aprendizado em ambos os grupos a partir do bloco 4. Uma hipótese para esta queda de desempenho pode estar relacionada à tendência do participante em arriscar mais a partir da segunda metade da tarefa (BECHARA,

2015). Durante a primeira parte da administração do teste, os participantes estão focados em compreender as regras do jogo, uma vez que desconhecem os baralhos e há a necessidade de experimentar cada um deles de forma aleatória, na tentativa de descobrir estratégias (BRAND *et. al*., 2007). Nessa fase, foi observado o aumento gradual do ganho de aprendizagem tanto no grupo de TEPT quanto no controle, embora os participantes ainda não tivessem o conhecimento dos esquemas de reforço e punição e tenham optado em muitos casos pelos baralhos mais desvantajosos, uma vez que estes se mostram mais atrativos.

Na segunda metade da administração do teste os participantes já adquiriram conhecimento do funcionamento de recompensa e punição do jogo e começam a arriscar mais em suas jogadas. Desse modo, observa-se uma mudança de postura frente ao teste quando comparados a primeira e segunda metade da tarefa, sendo a primeira caracterizada pela aprendizagem e desenvolvimento de estratégias de jogo, e a segunda, pelo gradual declínio deste processo em decorrência do aumento de risco assumido pelo indivíduo nas suas jogadas. Consequentemente, este risco reflete em ganhos adquiridos, mas também em maiores perdas (BECHARA, 2015).

No decorrer da tarefa, sujeitos normais tendem a ter um desempenho de escolhas que levam a ganhos em longo prazo. Porém pacientes com transtornos neuropsiquiátricos tendem a manter um padrão de escolhas imediatistas, caracterizada por ganhos maiores em curto prazo e um acúmulo sucessivo de prejuízos a longo prazo (CARDOSO *et. al.*, 2010).

Além disso, deficiências na impulsividade e processamento de recompensa foram identificadas em diferentes tipos de patologias que supostamente estão associadas a prejuízos no processo de tomada de decisão, como no caso de pacientes com transtorno obsessivo-compulsivo (CAVEDINE *et. al.*, 2002), indivíduos diagnosticados com transtorno de déficit de atenção com hiperatividade (TDAH) (MALLOY-DINIZ *et. al.*, 2008), dependentes químicos (BECHARA & DAMÁSIO, 2002), jogo patológico (LINNET *et. al*., 2010), dentre outros. Em se tratando de indivíduos com TEPT, foi observado que em muitos casos, sobreviventes de eventos traumáticos se envolvem em atividades que abarcam comportamentos de risco (JOSEPH *et. al*., 1996), na tentativa de lidar com o transtorno (WILSON & ZIGELBAUM, 1986 *apud* JOSEPH *et. al.*, 1996), além de apresentarem maiores índices de raiva e comportamento agressivo do que pessoas sem TEPT (CHEMTOB *et. al*., 1994).

Os resultados de um estudo realizado com pacientes diagnosticados com TEPT e elevados níveis de excitabilidade e comportamento impulsivo agressivo, demonstraram alterações no fluxo sanguíneo em diferentes regiões cerebrais, em especial na área dos

gânglios da base da região ventral, local onde se situa o núcleo accumbens (PAVIC, 2003). Por sua vez, o núcleo accumbens parece ser um receptor sensível de informações, de modo que uma das suas funções é a estimulação ou inibição de atividades em estruturas do cérebro relacionadas ao controle da tomada de decisão e iniciação de respostas motoras adaptativas. Deste modo, as alterações encontradas sugerem que há perturbação da realização das atividades desempenhadas pelo núcleo accumbens e de estruturas cerebrais relacionadas ao sistema límbico e os processos psicológicos por ele mediados. Consequentemente, os sintomas de irritabilidade, hiperexcitabilidade, hipersensibilidade e reações de emergência exageradas, podem estar associadas ao mau funcionamento adaptativo de resposta.

Ainda que o IGT não seja uma tarefa perigosa e que possa causar dano a integridade física, ela coloca os participantes em situação de incerteza e necessidade de assumir riscos na tomada de decisão para a realização do que é proposto. Assim, pode-se inferir que sujeitos com TEPT ao realizarem a tarefa do IGT, podem ter as funções relacionadas a tomada de decisão, recompensa e impulsividade prejudicadas devido a má regulação das áreas cerebrais envolvidas nesses processos.

Finalmente, os dados obtidos apontam que indivíduos com TEPT apresentam desempenho inferior para tomada de decisão quando comparados com indivíduos que passaram por evento traumático, mas não desenvolveram o transtorno. Contudo, ressalta-se a importância do desenvolvimento de novos estudos que avaliem esta função em sujeitos com TEPT, tanto utilizando o IGT quanto outras tarefas. Além disso, mais estudos com neuroimagem podem ser importantes fontes de esclarecimento acerca das áreas ativadas e inibidas durante o processo decisional em indivíduos com o transtorno.

O número de pessoas que buscam tratamento ainda é muito reduzido (SCHAEFER, LOBO & KRISTENSEN, 2012), o que contribui para uma das limitações deste estudo, que é o tamanho reduzido da amostra, levando-se em consideração que a captação dos participantes foi através do ambulatório, ou seja, uma amostra clínica. Consequentemente, a diversidade nos padrões de respostas apresentados pelos participantes está diretamente relacionado ao que foi elucidado pela análise estatística. Portanto, incentiva-se a realização de novas investigações com amostra ampliada a fim de comparar os resultados gerados com os do estudo atual, bem como os demais disponíveis na literatura, para se obter dados mais concisos, adquirir e ampliar novas informações.

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Tabela 1 – Descrição dos participantes

Participante	Idade	Escolaridade	Trauma	Comorbidades
Paciente				
V. O. T. M.	37 anos	Ensino Médio	Assalto	Agorafobia + TOC + Depressão + Fobia Social
R. C. C. G.	36 anos	Ensino Superior Incompleto	Assalto	Transtorno de Personalidade Obsessivo-compulsivo + Depressão + Transtorno de Pânico
S. F. T.	30 anos	Ensino Médio	Colisão de navios com possibilidade de explosão em trabalho na Marinha	Transtorno do Pânico
W. N. S.	46 anos	Ensino Superior	Sequestro	Depressão
S. A. A.	22 anos	Ensino Superior Incompleto	Tentativa de abuso e ameaça com faca	-
R. M. M.	29 anos	Ensino Superior Incompleto	Assalto	Depressão
L. J. T.	37 anos	Pós-graduação	Ameaça de morte por cliente do banco	Depressão
L. C. A.	27 anos	Ensino Superior Incompleto	Reconhecimento do corpo do pai no IML	Depressão
P. S. S.	21 anos	Ensino Superior	Abuso Sexual	Depressão
Controle				
S. F. A. D.	37 anos	Ensino Médio	Acidente do pai em hospital	-
K. C. P. C.	40 anos	Ensino Médio	Assassinato do tio	-
M. A. S. V.	29 anos	Ensino Médio	Assalto	-
A. A. S.	48 anos	Ensino Superior	Assalto em que levou um tiro no braço.	-
F. A. O. S.	19 anos	Ensino Superior Incompleto	Sequestro	-
N. L. P.	25 anos	Ensino Médio	Assalto em ônibus na Avenida Brasil	-
D. O. L.	38 anos	Pós-graduação	Assalto	-
A. C. S.	24 anos	Ensino Superior Incompleto	Assalto a mão armada	-
A. C. T. T.	24 anos	Ensino Superior	Assalto no ônibus	-