Cover Page for ClinicalTrials.gov

Official Title of the Study:

Attention-Bias Modification Treatment for PTSD

NCT Number:

NCT01888653.

Principal Investigator:

Yuval Neria, PhD

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646-774-8041

Date of Document:

March 5, 2019

New York State Psychiatric Institute

Institutional Review Board

March 5, 2019

To: Dr. Yuval Neria

From: Dr. Edward Nunes, Co-Chair

Dr. Agnes Whitaker, Co-Chair

Subject: Approval Notice: Continuation Expedited per 45CFR46.110(b)(1)(f)Category 8(c)

Your protocol #**6688** entitled: **NEURAL AND BEHAVIORAL MARKERS OF ATTENTION-BIAS MODIFICATION TREATMENT IN PTSD** Protocol version date 03/05/2019 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **April 1, 2019 to March 31, 2020.**

Consent requirements:

√ Not applicable: Data Analysis Only

☐ 45CFR46.116 (d) waiver of consent for secondary data analysis

☐ Signature by the person(s) obtaining consent is required to document the consent process

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.

✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.

✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.

✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

EN/AW/kpz4alw

Signed copy on file at IRB

Protocol Title:
Neural and Behavioral Markers of Attention-Bias Modification Treatment in PTSD

Version Date:
03/05/2019

Protocol Number:
6688

Clinic:
Anxiety Disorders Clinic

First Approval:
05/09/2013

Expiration Date:
03/31/2020

Contact Principal Investigator:
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Franklin Schneier, MD
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Research Chief:
Helen Simpson, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Dept of of Psychiatry, Theraputic Div
Within the division/department, what Center or group are you affiliated with, if any?
Anxiety Disorders Clinic

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York

State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
To date we have enrolled 51 subjects with Posttraumatic Stress Disorder (31 female, 20 male). Study procedures have been well tolerated. There have not been any study findings, recent literature, or untoward events occurring here or at other sites in the past year which might affect the analysis of the safety, risks, or benefits of the study.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes

Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
60
Total number of participants enrolled to date
51
Number of participants who have completed the study to date
41
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
PTSD
Total number of participants enrolled from this population to date
51
Gender, Racial and Ethnic Breakdown

39% Male
61% Female

Racial and Ethnic Breakdown:
44% White
34% African American
10% Asian/Pacific Islander
12% Other

78% Hispanic
22% Non-Hispanic

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?

No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Use of Placebo or Sham Treatment
✓ Psychotherapy Trial

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
The study is funded by a gift account that is administered through RFMH.
Is the project externally funded or is external funding planned?
No

Study Location

Indicate if the research is/will be conducted at any of the following

✓ NYSPI

This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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The present pilot study is a double blind trial that seeks to examine feasibility, acceptability, safety, efficacy, and risk/benefit ratio of ABMT in individuals with PTSD. This pilot study also seeks to identify specific

genes associated with anxiety disorders and to examine whether these can predict the success of the ABMT. In addition, pilot data assessing pattern separation (refers to the ability to encode inputs with some degree of overlapping information into distinctive representations) will be collected in subjects with PTSD via a brief memory task, named the Behavioral Pattern Separation Task—Object Version (BPS-O) (see Study Procedures section (4.A.8.) for a full description of the task).

Research Design: This pilot study aims: (1) to examine feasibility and acceptability of attention-bias-modification treatment (ABMT) in PTSD. The sample will include individuals with PTSD (n=**60**) with attention bias *towards and/or away from* threat (documented by dot probe task), which will undergo a 4-week (8-sessions) course of ABMT or an inactive Comparison Training Program (CTP).

Methods: The sample (n=**60**) will be randomized equally into two groups: Group 1 will receive a 4-week (8-sessions) course of inactive CTP; and group 2 will receive a 4-week (8-sessions) course of ABMT. The randomization will be stratified by age [<40 vs. ≥40] and gender [M/F]. All subjects will repeat the Dot-Probe Task after the four weeks of treatment to reassess attention bias.

Background, Significance and Rationale

Background, Significance and Rationale

Emerging research implicates biased attention to threat in the pathophysiology of anxiety disorders[1-4]. Recent findings demonstrate significant associations between attention bias and stress vulnerability[5, 6]. This work has motivated the development of a novel therapy, attention-bias-modification treatment (ABMT). ABMT is designed to implicitly modify patients' biased threat attendance via computerized training protocols. Emerging evidence indicates that ABMT is effective in modifying threat-related attention biases and in ameliorating anxiety symptoms[7,8,9,10]. However, it is unclear whether ABMT is efficacious for Posttraumatic stress disorder (PTSD). The present pilot study is a double blind trial that seeks to examine feasibility, acceptability, safety, efficacy, and risk/benefit ratio of ABMT in individuals with PTSD. In addition this pilot study seeks to identify specific genes associated with anxiety disorders and to examine whether these can predict the success of the ABMT. In addition, pilot data assessing pattern separation (refers to the ability to encode inputs with some degree of overlapping information into distinctive representations) will be collected in subjects with PTSD via a brief memory task, named the Behavioral Pattern Separation Task—Object Version (BPS-O) (see Study Procedures section (4.A.8.) for a full description of the task). Evidence suggests that impaired pattern separation, which is a deficiency in the ability to differentiate similar stimuli, underlies fear overgeneralization and may be highly associated with

attention bias to threat commonly seen in different anxiety disorders. Thus, we ask to collect pilot data assessing pattern separation for a potential grant that will assessed the putative association between – attention bias, impaired pattern separation and fear overgeneralization in PTSD.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

This pilot study aims to examine feasibility and acceptability of attention-bias-modification treatment (ABMT) in PTSD.

Hypothesis 1: (1) ABMT will diminish attention bias at post-treatment assessment (Dot-Probe) compared to CTP. (2) ABMT will produce greater symptomatic response (defined as >30% reduction on CAPS) than the CTP.

Description of Subject Population

Sample #1

Specify subject population
patients with DSM-IV Diagnosis of PTSD
Number of completers required to accomplish study aims
50
Projected number of subjects who will be enrolled to obtain required number of completers
60
Age range of subject population

18-60

Gender, Racial and Ethnic Breakdown

Population Sex:

- Females - ~60%
- Males - 40%

Population Ethnicity:

- African-American- 30%
- Hispanic- 15%
- Caucasian- 45%
- Asian/Pacific Islander - 10%

Description of subject population

We expect greater proportion of females than males due to the higher prevalence of PTSD among women in the US population. The ethnic distribution, represents the typical ethnic breakdown of the anxiety disorders clinic population, moderated by the ethnic breakdown of the current subject population.

Recruitment Procedures

Describe settings where recruitment will occur
Anxiety Disorders Clinic

How and by whom will subjects be approached and/or recruited?

Patients will respond to an advertisement (see below "study advertised/ publicized"). Patient will call the clinic and after verbal consent the research assistant (RA) will conduct a preliminary screening. If the patient will be eligible for the study the RA will invite him for further screening at the clinic.

How will the study be advertised/publicized?

Patients will be informed of the study through: (a) word-of-mouth referrals from former patients, (b) referral from area medical and mental health professionals, (c) publicity about the study, including articles in local newspapers and magazines, our IRB approved website (www.columbiatrauma.org), IRB approved flyers, appearances on local radio and television shows, etc., leading to self-referral of prospective patients, and (d) advertisements placed in local media and on the Internet (e) recruitme

Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
No

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

Name the subject group/sub sample
PTSD
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion criteria:	**Method of Ascertainment:**
1. Males or females between the ages of 18 and 60.	History
2. Current DSM-IV PTSD	SCID
3. Score equal or greater than 50 on the CAPS.	CAPS administration
4. Fluent in English and willing and able to give informed written consent and participate responsibly in the protocol.	Clinical interview
5. threat bias (i.e., ≥8ms mean decrease or increase in reaction time to threat faces vs. neutral faces on dot-probe task) at baseline.	Dot-probe attention bias task administration

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion criteria:	**Method of Ascertainment:**
1. Current DSM-IV Axis I disorder other than	SCID, HAM-D and clinical evaluation

PTSD. Patients with comorbid (i.e., secondary diagnosis of) major depressive disorder (MDD) will be allowed for enrollment if their HAM-D score doesn't exceed 25.	
2. Prior or current diagnosis of schizophrenia, schizoaffective disorder, organic mental disorder, bipolar disorder, or antisocial, schizotypal, and schizoid personality disorders.	SCID and clinical evaluation
3.Suicidal ideation or behavior that poses a significant danger to the subject. Unstable clinical condition such that participation in a controlled trial would pose a significant danger.	Psychiatric history; score $\geq$ 2 on item 3 of the Hamilton Rating Scale for Depression (HRSD-21-item), and the BDI suicide item
4. Prior participation in attention bias modification treatment (ABMT).	Psychiatric interview
5. Current or past history of seizure disorder (except febrile seizure in childhood).	Clinical evaluation
6. Currently on psychotropic medication. (excluding the use of hypnotics)	Clinical Interview regarding current medication treatment history.
7. Currently participating in formal psychotherapy. This includes: psychodynamic, cognitive behavioral and interpersonal therapies.	History
8. Current unstable or untreated medical illness.	Clinical interview, Medical history
10. Vision loss.	Preliminary screening, Clinical evaluation

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No

Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process

Potential subjects will be screened by telephone by a research assistant after obtaining oral consent **(IRB# 7094R, previously IRB # 6112R)**.
Psychiatric Diagnostic Evaluation: Patients deemed study eligible following preliminary screening will sign the Anxiety Disorders Clinic informed written consent for the psychiatric screening evaluation (IRB# 7094R, previously IRB # 6112R). An experienced psychiatrist will evaluate presenting symptoms, psychiatric history, treatment history, medical history, trauma history, social and family history, and current medical status. A Clinician-Administered PTSD scale (CAPS), Hamilton Depression Scale (HAM-D) as well as the Attention bias testing (Dot-Probe Task) to determine further eligibility for the study.

If the subject is eligible and if s/he consents for it, s/he will give DNA sample via saliva (~2 cc total) and will fill out the Ancestry Questionnaire. This questionnaire is very short and asks participant's to provide details of the country of birth and ancestry of their four grandparents. If the subject is not eligible, participation in the study will end and they will be referred to other studies or given the appropriate referrals. Subjects who are not eligible will not be asked to provide a saliva sample.

Describe Study Consent Procedures

Patient will meet face to face with the person that authorizes to discuss and document consent (see "person designed to discuss and document consent"). After patient reads the consent the clinician will go over the consent with the patient and answer all the patient's questions. After answering all the patient's questions by the clinician patient will sign the study consent. Throughout this process, the patient's will be told that they are free to refuse and that participation or non- participation in research has no effect on their ability to continue to receive clinical care or services.

Indicate which of the following are employed as a part of screening or main study consent procedures

✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Lazarov, Amit
Lowell, Ari
Neria, Yuval, PHD
Suarez-Jimenez, Benjamin
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

The study consists of the following procedures:

1) eligibility and baseline assessment
2) treatment visits (ABMT or CTP)
3) post treatment assessment for both ABMT and CTP group

Preliminary Screening: Potential subjects will be screened by telephone by a research assistant after obtaining oral consent. Psychiatric Diagnostic Evaluation: Patients deemed study eligible following preliminary screening will sign the Anxiety Disorders Clinic informed written consent for the psychiatric screening evaluation (IRB # 6112R). An experienced psychiatrist will evaluate presenting symptoms, psychiatric history, treatment history, medical history, trauma history, social and family history, and current medical status. A Clinician-Administered PTSD scale (CAPS), Hamilton Depression Scale (HAM-D) as well as the Attention bias testing (Dot-Probe Task) to determine further eligibility for the study.

If the subject is eligible and if s/he consents for it, s/he will give DNA sample via saliva (~2 cc total) and will fill out the Ancestry Questionnaire. This questionnaire is very short and asks participant's to provide details of the country of birth and ancestry of their four grandparents. If the subject is not eligible, participation in the study will end and they will be referred to other studies or given the appropriate referrals. Subjects who are not eligible will not ask to provide a saliva sample.

Selection of Participants Based on the Existence of Baseline Threat Bias: To ensure attentional bias in participants enrolled in the study, before they begin treatment and after they have signed study consent, their threat related attentional bias will be assessed through a simple computerized task. If they do not have attentional bias ***towards or away from*** threat at baseline, their participation in the study will end and they will be referred to other studies or given the appropriate referrals. The basic target for ABMT is pre-existing (pre-treatment) threat bias; hence the absence of such bias (not uncommon amongst anxious patients) might render ABMT ineffective[11].

Assessment of Attention Bias: the Dot-Probe Task: The dot-probe task version will be used for the attention bias assessment at baseline to establish eligibility at treatment, and on post-treatment assessment. A trained research assistant will administer these tasks.

The stimuli for the dot-probe task will be derived from pairs of face stimuli with angry and neutral expressions used by Bar-Haim and colleagues13. Two sets of faces will be used in the study (set A and set B). One set will be used for assessment and the other set will be used for training, allowing us to infer generalization. The faces-based dot-probe task will follow the protocol of the TAU-NIMH ABMT Initiative (Drs. Pine and Bar-Haim: PIs). The face stimuli are photographs of 20 different individuals (10 female) taken from the NimStim stimulus set, except for one female taken from the Matsumoto and Ekman set. Images of individuals will be randomly divided into two sets (A and B) – set A will be used for all subjects in the present study. The face display consists of pairs of angry-neutral or neutral-neutral faces of the same individual. The pre- and post-ABM/Comparison measurement protocol consists of 120 trials (80 angry-neutral and 40 neutral-neutral presentations). For both word-based and faces-based tasks, the target-probe display consists of an arrowhead pointing either left or right ("<" or ">"). The target appears at the location previously occupied by one of the stimuli, with a small, random jitter around the center of the stimuli. In each trial the participant is presented with the fixation cross (500ms), followed by the stimulus pair display (500ms), followed by the target display (1000ms). Response is followed by an inter-trial interval (average 500ms). In addition, fixation trials are included to be able to deconvolve the hemodynamic response function. Across trials, angry-face location, probe location, probe type, and actor are fully counterbalanced in presentation. If the subject performs with less than 70% accuracy on the first 10 trials, the program will display a warning and the experiment will be aborted. This warning provides an opportunity to re-brief the subject and initiate data collection again.

DNA Collection, Extraction and Analysis: The protocol to be used for collecting DNA samples will be identical to that which was previously used by Dr. Thalia Eley, Institute of Psychiatry, London, and Dr. Yair Bar-Haim, Tel-Aviv University, Israel. After the Eligibility assessment and consent, a saliva sample (~2 cc total) will be collected from each subject to be used for analyses of genomic DNA. Deindentified samples will be sent via secure air courier and with the appropriate documentation to Institute of Psychiatry (IoP) at King's College London for extraction of DNA using well-established protocols. After extraction, the original sample is destroyed and the extracted DNA is stored securely in IoP's laboratory system using a unique alpha-numeric code only. IoP will then genotype the samples with the aim of identifying genetic markers for ABMT efficacy. The primary candidate marker is the serotonin transporter polymorphism (5*HTTLPR*), which has been linked to performance on the dot-probe task and also treatment response. The lab will also investigate a limited number of other candidate markers based on the current understanding of the mechanisms involved in etiology and treatment response.

Treatment. Method of Assuring Double Blindness (ABMT and CTP): Participants will be randomly assigned to one of two conditions: ABMT or CTP. A research coordinator will place the randomly assigned

condition number in an envelope in each participant's file at the beginning of the study. Prior to each training session, another experimenter blind to the studies' aims and protocols will enter the number in the file into the computer to automatically begin the appropriate program. Participants will not know which condition the number represents. Thus, participants and experimenters will remain blind to the participant's condition until all post-ABMT or post-CTP assessments are conducted. To assess whether participants remained blind to their respective experimental condition, we will ask them at post-assessment whether they thought they had received the active versus comparison intervention. A trained research assistant will administer the computer-based ABMT and CTP sessions.

Attention-Bias Modification Treatment (ABMT): During each session, 240 trials (80 neutral-neutral pairs, 160 threat-neutral pairs) will be presented. On trials where participants see one neutral **face** and one angry face the probe will always follow the neutral face location. Thus, although there is no specific instruction to direct attention away from angry faces, on 66% of all trials (and 100% of the threat-neutral trials) the position of the neutral faces will indicate the position of the target probe.

Comparison-Training-Program (CTP): The comparison condition is identical to the ABMT protocol except that during the presentation of the trials where a angry face is presented, the probe will appear with equal frequency in the position of the threat and neutral face. Thus, neither threat nor neutral faces provide information regarding the position of the target probe, and there is no contingency between the position of either threat or neutral faces and the position of the probes.

Behavioral Pattern Separation-Task Object Version (BPS-O): The BPS-O is a well-established and reliable task[19] that was developed in order to characterize the behavioral outcomes of neural pattern separation. The task consists of two phases; a study phase and a test phase. In the study phase, participants engage in an indoor/outdoor judgment of pictures of everyday objects. In the test phase, immediately following the study phase, participants are given instructions regarding a surprise recognition memory test in which they have to identify each item as either "old", "similar", or "new". One-third of the images in the test phase are exact repetitions of images presented in the study phase (targets); one-third of the images are new images not previously seen (foils); and one-third of the images are perceptually similar to those seen during the study phase, but not identical (lures). We are particularly interested in the responses to these lure trials and the rates at which participants correctly identify these as "similar", avoiding the propensity to identify these as "old". Identifying these lure trials as "old" (i.e., over generalization) is likely driven by impaired pattern separation processes. The task takes 20 minutes.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

The PI and study psychiatrist will review at least weekly all currently enrolled patients in the ABMT and CTP treatment, and will withdraw a person from the study if the participant:

1. Requests to be withdrawn from the study.
2. A single CGI-I score of 6 or more will trigger evaluation of a participant whose condition seems to be worsening, and prompt an immediate visit within the next few days. The CGI will be administered to consider PTSD, and depression symptomatology.
3. Reports significant suicidal ideation, as assessed by the clinician and/or by the BDI-II- suicide item.
4. Shows clear-cut deterioration in social or occupational functioning.
5. Is non-compliant with protocol requirements.
6. Manifests a new or inter-current illness that prevents the patient from complying with the protocol.

Withdrawal from this protocol prior to the second Dot-Probe assessment will not affect the treatment to which all patients enrolling in the study are entitled.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

SCID (90 minutes at screening)

Beck Depression Inventory (10 minutes)

Clinical Global Impression – Severity Scale (CGI-S) (5 minutes)

Clinician Administered PTSD Scale (CAPS) (30 Minutes)

Hamilton Rating Scale for Depression (Ham-D) (10 minutes)

Spielberger State-Trait Anxiety Inventory (5 minutes)

The Life Events Checklist (LEC) (5 minutes)

The Dot-Probe- Tasks (10 minutes for both tasks)

Ancestry Questionnaire (5 minutes)
Behavioral Pattern Separation-Task Object Version (BPS-O) (20 minutes)

Please attach copies, unless standard instruments are used

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment

The maximum delay in provision of treatment will be 2 weeks for participants randomized to ABMT, and 6 weeks for participants randomized to CTP. The study treatment, ABMT, has appeared effective for some anxiety disorders, but is not an established treatment for PTSD.

Maximum duration of delay to standard care or treatment of known efficacy

The maximum delay in provision of active treatment will be 6 weeks (2 weeks for baseline assessments and 4 weeks for study treatments) from initial in-person psychiatric intake evaluation.

Treatment to be provided at the end of the study
Patients will be offered 3 months of medication and/or psychotherapy treatment in the ADC until they are remitted or referred to treatment elsewhere.

Clinical Treatment Alternatives

Clinical treatment alternatives

> Patients will be offered 3 months of medication and/or psychotherapy treatment in the ADC until they are remitted or referred to treatment elsewhere.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Interviews/assessments: Some subjects may find the interviews and assessments to be anxiety provoking or upsetting. Subjects will be informed that they may choose not to answer specific questions, and may stop the interview at any time if they are feeling uncomfortable. Every effort will be made to ensure patients' comfort.

Risks Associated with Treatment Procedures: To date, there are no known risks associated with ABMT. The procedures involve repeated exposures to photographs of faces. As the procedures involved in these tasks are similar to those encountered in daily life, no adverse events are anticipated. Participants may become fatigued when completing the computer sessions. Breaks will be offered frequently. Every effort will be made to ensure patients' comfort during treatment, and patients will be withdrawn if needed. *Non improvement and/or worsening*: There is the risk that some patients will not improve clinically or will experience worsening of their symptoms during the course of the treatment. A single CGI-I score of 6 or more will trigger evaluation of a participant, and prompt an immediate visit within the next few days. Patients who receive two consecutive CGI improvement ratings of 6 or 7 will be removed from the study and begin open treatment.

Saliva-sample: The main risk is that participants might find it uncomfortable to not eat or drink for an hour prior to giving the sample. Participant that will choose not to participate will not loss any of the benefit to which he is otherwise entitled.

Behavioral Pattern Separation-Task Object Version (BPS-O): there is no known risk that is associated with this task.

Describe procedures for minimizing risks
a. Careful medical and psychiatric screening will be used to identify subjects whose risk for potential adverse effects from treatment is elevated. Such subjects will be excluded from the study. For example, an actively suicidal patient would be excluded from study participation in order to provide immediate and appropriate clinical treatment.

b. Assessment of safety during first 4 weeks: All patients will have a clinical safety assessment completed by the study clinician during baseline and every week after that, including Clinician-rated CGI change scale and inquiry as to whether the participant is experiencing any worsening social anxiety, depression or other symptoms, or any suicidal ideation. (Patients answering affirmatively to any of these queries will be further evaluated for the safety of continuation in the study, including completion of QIDS-C. Significant worsening on the clinician-rated CGI change scale (score of 6 or more) or clinically significant suicidal ideation score > 2 on item 12 of (QIDS-C) are two examples of conditions that would require termination of study treatment and will prompt an immediate visit within the next few days.

c. Patients will be instructed to contact study personnel at any point in the study in the event of worsening of symptoms or relapse. Patients deemed to have clinically significant deterioration, relapse, who develop other symptoms such as suicidal ideation that interfere with safe participation, or who ask to discontinue research participation will be removed from the study and given appropriate clinical care.

d. At the end of the treatment, all patients will be provided with appropriate standard clinical care. The exact nature of "appropriate standard clinical care" will be determined by the judgment of clinicians familiar with the specific patient and may include medication, CBT treatment, or other modalities.

e. As in any type of treatment or clinical research program, patients' confidentiality will be carefully guarded and respected. All data with identifying information will be stored in locked file cabinets or password-protected computer files. Data being analyzed will be identified by subject codes and identifying information will be removed. The identity of patients will not be revealed in the presentation or publication of any results from the project. All assistants and others working on the project will be educated about the importance of strictly respecting patients' rights to confidentiality and will have received training in HIPAA and Good Clinical Practices.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

> All data collected will be kept confidential and used for research purposes only. Patients' charts will be kept in locked file cabinets identified by number. Access to research records is restricted to research staff and Federal, State, and Institutional regulatory authorities. We have obtained a Certificate of Confidentiality from the National Institutes of Health. Electronic data will be protected by password access.

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

This study is not designed to directly benefit the participants. Participants may or may not benefit from the treatment administered in this study

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

All subjects will receive $50 for each of the assessment sessions (pre-treatment and post-treatment Dot-Probe task); therefore participants completing both assessments will receive a total of $100. The compensation will be mailed to the subject in the form of a check within 4-6 weeks of the completion of each assessment.

References

References

1. Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IMH. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychol Bull. Jan 2007;133(1):1-24.

2. Pine DS, Fyer A, Grun J, et al. Methods for developmental studies of fear conditioning circuitry. Biological psychiatry. Aug 1 2001;50(3):225-228.

3. Pine DS, Helfinstein SM, Bar-Haim Y, Nelson E, Fox NA. Challenges in developing novel treatments for childhood disorders: lessons from research on anxiety. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. Jan 2009;34(1):213-228.

4. Shechner T, Britton JC, Perez-Edgar K, et al. Attention biases, anxiety, and development: toward or away from threats or rewards? Depression and anxiety. Apr 2012;29(4):282-294.

5. MacLeod C, Rutherford E, Campbell L, Ebsworthy G, Holker L. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. J Abnorm Psychol. Feb 2002;111(1):107-123.

6. Eldar S, Ricon T, Bar-Haim Y. Plasticity in attention: implications for stress response in children. Behav Res Ther. Apr 2008;46(4):450-461.

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Data Analysis

Independent samples t-tests were used to compare between-groups descriptive characteristics at pre-treatment, with a chi-square test for gender distribution. Treatment effects were tested using Generalized Estimating Equations (GEE; Zeger and Liang, 1986, Zeger *et al.*, 1988), as recommended for RCTs (Vens and Ziegler, 2012). GEE accounts for correlated repeated-measurements and accommodates missing data under the missing-at-random assumption, by computing estimated marginal means, thus serving as an intention-to-treat analysis strategy which includes data from all randomized participants who provided at least one data point. To represent within-subject dependencies in the models, we specified an unstructured covariance matrix. Overall effects of ACT relative to BC-ABM on clinician-rated (CAPS, HRSD) and self-reported (PCL-C, BDI-II) PTSD and depression symptoms were estimated using models containing main effects of group and time, and their interaction. The time-by-group interaction terms reflects the outcomes of interest in an intention-to-treat analysis (Badura-Brack *et al.*, 2015) and tests the treatment effect hypothesis of greater improvement (decrease) in symptoms over time for one group relative to the other. A Chi-square test was used to compare groups on CSC.

Effects of training on attention indices (AB and ABV) were examined per condition, as conditions diverged in training method and goal. Specifically, training-related changes in attention bias were examined in the BC-ABM group, while changes in ABV were examined in the ACT group.

All statistical tests were 2-sided, using $\alpha \leq .05$. Effect sizes are reported using Cohen's *d* when appropriate.