Treating Phobia With Multivoxel Neuro-reinforcement

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Protocol and Additional Information

The objective of this study is to use the novel approach of neuro-reinforcement based on decoded fMRI information to reduce fear responses to fearful stimuli (e.g., spiders, heights) in individuals with phobias, directly and unconsciously in the brain, without repeatedly exposing participants to their feared stimuli.

Specific Aims

(1) confirm that our method engages the neurobiological target (amygdala reactivity to images of a feared object) in a population of individuals with specific phobia; and (2) to determine dosage-response optimization.

The investigators aim to enroll a total of 30 patients. The investigators seek female and male participants in equal proportions. The age range of the subjects will be between 18 and 65. The investigators will work to achieve an ethnic and racial distribution that is consistent with the very diverse community found in the Los Angeles area and the UCLA campus: Hispanic/Latino 56.4%, African American 7.7%; Asian/Filipino/Pacific Islander 15.8%; White (non-Hispanic) 17.5% (California Health Interview Survey).

Potential research participants' eligibility will be confirmed at the beginning of the first session, but eligibility criteria will also be listed in recruitment materials. A research assistant or other personnel possessing current CITI and HIPAA certification will conduct an eligibility screening interview in a private room. Following onset of the study, subjects who are unable to attend to or respond to stimuli as required by the experimental protocol will be excluded.

Anxiety disorders, the most common group of mental disorders in the United States, represent a major mental health problem. Phobias, in which fear and anxiety are triggered by a specific stimulus or situation, are the largest category of anxiety disorders and affect 5 - 12% of the world's population. The treatment of anxiety disorders represents almost one third of mental health costs annually. Specific phobias and other anxiety disorders, such as PTSD, represent a significant driving force in seeking mental health-related treatment. These disorders present a major challenge, and researchers have previously explored various ways to address this challenge. One of the most effective psychotherapy methods for the treatment of phobias involves exposure, or repeated approach towards feared stimuli, often in a hierarchy of least to most anxiety-provoking distances or situations. Exposure-based therapies are effective in reducing symptoms, but their effectiveness depends on the individual's capacity or willingness to consciously confront their feared object. The associated distress can be so extreme that it prevents patients from seeking treatment, and contributes to attrition from exposure once treatment begins: estimated dropout rates can top 70%, with three out of five refusing to even begin treatment, meaning that as low as 12% of patients receive adequate treatment. Even other therapies that require conscious engagement with the aversive stimulus, such as cognitive therapies, show high dropout rates. As a result, there is an unmet need for treatment that minimizes attrition and subjective patient discomfort, especially for clinical populations for whom conventional exposure-based therapies are prohibitively aversive. This problem has led

some researchers to develop less aversive exposure-based therapies—for example, by showing the phobic stimulus very briefly, and immediately following it with a visual mask. However, in general, learning effects are weak and short-lasting when stimuli are fully masked because masking greatly reduces the signal strength of neural representation in the visual system. It would seem ideal if the investigators could capitalize on the potential benefits of fully unconscious presentation without sacrificing neural signal strength of the relevant visual representation.

In the R61 phase, the investigators will enroll 30 patients, who will be required to meet the DSM-5 criteria for specific phobias. Patients will be assessed by trained clinical personnel using the Anxiety and Related Disorders Interview Schedule (ADIS) for DSM-5 - Adult version, a structured clinical interview based on the DSM-5 criteria (Brown & Barlow 2014) and the Fear Survey Schedule (Wolpe & Lang 1964). Participants presenting with post-traumatic stress disorder (PTSD), Obsessive Compulsive Disorder, Substance Use Disorder, Current Major Depression, Bipolar Disorder, Psychosis, neurologic diagnoses or unstable serious medical conditions will be excluded. Participants will also be excluded if they are currently prescribed psychotropic medication.

Roles and Responsibilities Our study procedures and results will be monitored by the Principal Investigator Michelle Craske, the UCLA Institutional Review Board, and an independent Data Safety and Monitoring Board.

Dr Craske will monitor adherence to the confidentiality rules, the quality of the data, their timeliness, and the correctness of their entry into computer files. This is a routine part of their supervision of postdoctoral fellows, graduate students and assistants. Every two weeks, data safety will be reviewed.

Trial Safety Specific Events That Would Preclude a Participant from Continuing the Intervention A participant will be precluded from continuing the intervention in the event of an adverse event rated 3 -5 according to the scale in the Reporting Adverse Events section below. Such events could include an injury or other event resulting in hospitalization or a persistent or significant disability or incapacity, a life-threatening or disabling event, or a fatal event.

Potential Risks and Protections Against Risk (see Human Subjects for more details) There are no known physical, social, legal, or other adverse effects associated with participation in this study. The risks from this study to the subject are minimal. At all times, participants will be informed that they are welcome to stop any part of the procedures at any time without penalty and to discuss their concerns or ask questions of the research staff at any time. Subjects will be informed that they should contact the PIs if they experience a research-related injury.

It is possible that some participants may become uncomfortable revealing personal information when completing questionnaires and/or become fatigued and bored during the experimental procedures. Participants may become physically uncomfortable with the electrodes attached to their person and/or with sitting for long periods of time during the psychophysiological procedures. They also may become anxious when exposed to the psychophysiological equipment and procedures. It is possible that participants may experience emotional distress when presented

with feared stimuli at the outset of the study. All on-site study personnel will be clinicians who will be available to address participants' needs in this regard.

Clinical interviewing will be conducted by trained advanced clinical psychology PhD students or staff who are sensitive to the potential discomfort that participants may have while discussing personal matters. All diagnostic procedures will be conducted by staff members experienced in performance of similar clinical studies, with appropriate Human Subjects and HIPAA certifications. Interviews will be conducted in sound protected rooms. All of the procedures, including fear conditioning, have been used extensively in prior studies without adverse events. Our instrumentation for psychophysiological recordings meets all standards for non- invasive recordings, is well maintained, and has approval from the US Food and Drug Administration. Standard application procedures are observed to minimize risk of infection. Subjects will be protected by: a) respecting their right to refuse to attempt or continue any task, b) providing reassurance or intervention if needed, and c) terminating the experimental procedures for participants that become acutely distressed during a session. To minimize the risks of fatigue, all participants appearing fatigued during the procedures will be allowed to take a break.

There are no known significant side effects associated with MRI procedures. The magnetic fields, at the strengths used, are assumed to be without harm, as our MRI scanning procedures fall within the FDA guidelines for radiofrequency electromagnetic field exposure. The investigators feel these are safe levels and are less hazardous than a comparable X-ray computed tomography examination. Exceptions include if a person has electrically, magnetically, or mechanically activated implants (such as cardiac pacemakers), clips on blood vessels in his or her brain, or other metallic objects in his or her body such as shrapnel, bullets, buckshot, or metal fragments; subjects with such attributes will not be allowed to participate. Although there are no known risks of an MRI scan to the unborn fetus, the investigators will not permit anyone who is or is suspected to be pregnant to participate. Subjects will thus be given an MRI screening questionnaire prior to participation, and will be excluded from participating in brain imaging studies if they indicate any risk factors on this questionnaire. The most serious potential risks are related to the possibility of ferromagnetic objects in the vicinity of the high- field magnet in the scanner. These objects could conceivably become projectiles due to the powerful magnetic field. Therefore, subjects will be asked to place all metallic and magnetic objects in their possession (e.g., keys, jewelry, credit cards) in a locker outside the magnet room. Most people do not find magnetic resonance scans uncomfortable, although mild discomfort has been reported on some occasions: 1. Some subjects may experience claustrophobia (fear of enclosed spaces) as they will be lying on a table in a horizontal cylinder that is only slightly wider in all directions than their body, and extra movement will be minimized as their head is secured. They will be instructed to notify the researcher in charge of the scan beforehand if they are prone to claustrophobia. 2. The MR scanner makes loud knocking or beeping sounds during imaging; earplugs will be provided to help reduce this noise. 3. Due to the rapid rate of change in magnetic gradients during imaging, the possibility exists for peripheral nerve stimulation. If this happens, subjects may feel creeping or tingling sensations, typically along their arms or lower back. 4. Dizziness and nausea may occur if the subjects move their head quickly in the bore of the magnet. 5. Finally, there may be some heating from the radio frequency coils, the cables to the coils, or response and physiological monitoring devices. The machine will be calibrated so that this heating will be no more than one degree of body temperature. Subjects will be instructed to immediately notify the

investigators if they feel uncomfortable at any time, for whatever reason. Subjects will be able to contact the research staff at any point in the study via a microphone mounted on the MRI scanner. They will also be instructed on how to use the emergency handheld device to inform the operator if they wish to immediately stop scanning and be removed from the magnet. The MRI can be stopped at any time at their request.

There is no known radiological risk of MRI scanning. Subjects will be screened in a standard fashion for magnet sensitive substances (metal prosthesis, etc.), for claustrophobia, and for other medical and psychiatric conditions prior to the study. In addition, any participant who has been told he or she has cardiovascular disease, or who is pregnant or nursing will be excluded. Participants will also be screened for neurological, psychiatric and substance abuse problems and a history of other medical problems or medical treatment related to cerebral metabolism and blood flow. Because the magnetism of the fMRI machine attracts certain metals, people with these metals in them (specifically pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, or plates) will be excluded from the study. The "metal" in dental fillings is less susceptible to magnetism and is therefore allowed. Procedures that will minimize discomfort during the scanning include the option of an MRI simulation laboratory and for an initial familiarization session in the scanner. Also, the use of headphones and video systems will minimize the potential discomfort of the scanner environment. Participants will be encouraged to ask questions about the equipment and procedures. Experimental procedures will be terminated if participants become overly distressed. A protocol outlining the specific steps on how to act if patients become overly distressed during these tasks will be available to all staff members. To ensure safety during MRI sessions, every researcher in the lab will complete a safety training course, every year. Subjects will be carefully screened to make sure they do not have any metal before being taken into the room with the MRI scanner. Subjects will wear earplugs to protect their hearing while in the MRI scanner. Volunteers who exhibit contraindications for MRI exams, such as pacemakers, surgical aneurysm clips and known metal fragments embedded in the body including eyes, will be excluded. Women of childbearing age will not be included in this study if they are or think they might be pregnant. Subjects with suspected cerebrovascular or pulmonary disease or a history of such will be excluded. Subjects who have experienced claustrophobia, or who have a history of migraine, arterial hypertension, coronary heart disease, asthma, or anemia will be excluded. Based on our current ethics protocol approved by UCLA, in all MRI studies the investigators will also exclude subjects with any history of epilepsy or other neurological disorders. Subjects will be carefully screened for these conditions prior to scanning, using a standardized form/checklist. Subjects will also be instructed not to use any recreational drugs (e.g., marijuana, cocaine) within 48 hours before participating, nor consume more than 3 units of alcoholic beverages within 24 hours before taking part in the study. Subjects will receive these instructions a week before participating, and their compliance will be checked again on the day of the experiment.

Consent Procedures and Subject Privacy Signed consent will be obtained from each participant. Member(s) of the study staff will meet with the prospective participants in a private room to review the consent documents and/or provide an oral explanation of the study. Any experiments involving MRI scanning will be undertaken in compliance with the safety guidelines for MRI research, and prior to participating in the study, subjects will be informed of the risks and benefits of the study, and will fill out and sign the screening questionnaire and informed

consent form. Individuals will be given a chance to ask questions before making a considered decision about whether or not to participate in the study. Subjects will be given as long as necessary to decide whether they wish to participate in the study. The investigator or study team member(s) will confirm that subjects understand the information conveyed during the consent process. Study procedures and consent forms will be reviewed and approved by the UCLA Institutional Review Boards. Participants will be provided a copy of the consent form and the original will be maintained in laboratory files.

Trial Stopping Rules Please see the procedures described in the Reporting Adverse Events section below.

Management of Incidental Findings Dr. Craske will follow a detailed, written action plan if the participant discloses suicidal intent/plan.

There is a small chance that the MRI scan will discover a brain injury, such as a brain tumor. In that case, the investigators will send the participant's scan to a radiologist, who will check the scan. If the finding is confirmed to be a clinically relevant abnormality that can be treated, this information is passed on to the participant's general practitioner. Each participant will be required to provide the name and address of his or her general practitioner.

Data Security Please see the data security measures described in the Data Management, Analysis, and Quality Assurance section below.

Reporting Adverse Events Per UCLA IRB requirements, the investigators will report any Adverse Events (including Serious Adverse Events) that meet the definition of an Unanticipated Problem to the IRB within 10 working days of PI/Co-PI awareness, with the exception of unexpected internal (on-site) death, which would be reported within 3 working days. The investigators will comply with the NIMH Reportable Events Policy.

In addition to Unanticipated Problems Involving Risks to Subjects or Others, the following adverse events will be monitored: deaths, suicide attempts, study dropout, psychiatric hospitalizations, and clinical deterioration, defined as emergent suicidal ideation or suicidal plan, development of serious substance abuse, or emergence of a new psychiatric or medical diagnosis or behavior posing significant risk to the subjects of others.

The following grading system will be used to assess the seriousness of any adverse events:

0 No adverse event or within normal limits

Mild adverse event
Moderate adverse event
Severe adverse event resulting in hospitalization or a persistent or significant disability/incapacity
Life-threatening or disabling adverse event
Fatal adverse event The Ph.D. level project coordinator will be trained in what events to look for and to report any such events to Dr Craske. If the event is graded 2-4, Dr. Craske, a licensed

clinical psychologist, will interview the participant and take the appropriate action. The UCLA IRB and NIH will be notified within 24 hours of any serious adverse events (SAEs), in the 3-5 range. All SAEs will be reported to the DSMB within 2 days of their occurrence. Within a week of any SAEs, the DSMB together with Dr Craske will determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or consent form (at Risks and Inconveniences) are required. Furthermore, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.
Dr Craske will conduct a review of all non-serious adverse events at least quarterly. They will evaluate the types, frequency, and severity of the adverse events and determine if modifications to the protocol or consent form are required. A summary of the non-serious adverse events will be reported to the IRB and DSMB periodically or, at minimum, when yearly re-approval of the IRB protocol is sought. The summary will include number of Participants enrolled, treatment retention and reasons for drop-out, and a description of graded adverse events to date. Dr or Craske or the IRB has the authority to stop or modify the study.

Data Management, Analysis and Quality Assurance All data will be specifically obtained for research purposes during individual test sessions. Sources of material obtained from participants will include amygdala reactivity, skin conductance response (SCR), and subjective fear ratings in both the R61 and R33 phases. In the R33 phase the investigators will also assess spontaneous recovery with the Behavioral Approach Test (BAT) and Anxiety and Related Disorders Interview Schedule (ADIS). The identifying information that will be collected from study participants includes all information required to create a GUID: sex, first name, last name, middle name, date of birth, and city/municipality of birth. The investigators will also collect email addresses.

A member of the research team with current CITI and HIPAA certification will assign a code number to each data file. The key pairing each code number with each participant's name and other identifying information will be stored separately from the data files themselves, in a locked filing cabinet to which only declared research personnel have access. All of the interviews and study procedures will be conducted in private, locked room where only the experimenter and participant are present in order to protect each participant's privacy. The data collected will be used only for this study. Upon completion of the study, all data files will be stripped of personal identifiers and/or the key to the code destroyed. The investigators agree to follow the OHRPP Data Security in Research guidance and procedures.

The investigators will recruit subjects through community outreach. Patients meeting the DSM-5 criteria for specific phobias will be recruited through the UCLA Anxiety and Depression Research Center and advertising in the local community. In order to maximize the fidelity and reliability of the between-subjects decoder for fearful objects, it is necessary to establish a pool of hyper-realigned brain activity patterns from control subjects matching the demographics of the patient population. Therefore, the investigators will attempt to achieve a high level of diversity in our sample by placement of advertisements and flyers in local community recreational centers and religious centers in areas more densely populated by Asians, Hispanics, and African Americans as well as through Internet-based advertisements. Every month, the investigators will monitor the ethnic and racial distributions in the recruited sample. If the investigators observe

that the investigators are not reaching the targeted level of diversity, the investigators will make further outreach efforts.