INVESTIGATOR STUDY PLAN - REQUIRED

Title: AlPHA Follow Up: Assessing VisuaL Perception in High Anxiety

Sponsor: National Institute of Mental Health K01 MH117290 NCT04187326

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1. TITLE
Assessing Visual Perception in High Anxiety Follow Up

2. EXTERNAL IRB REVIEW HISTORY*
This submission represents the follow up portion of a study that was conducted at the University of Pittsburgh from 2019-2023. This study was approved by the University of Pittsburgh IRB in 2018. The study ID for that approval is STUDY19010289. The contact info for The University of Pittsburgh IRB is askirb@pitt.edu

3. PRIOR APPROVALS:
The broader study that includes this protocol was approved following scientific committee review at the University of Pittsburgh in 2018.

Conflict of Interest (COI):
No one involved in this research has any actual or potential COI.

Clinical Engineering Department:
N/A

Biohazardous Agents:
N/A

***Radiation**:*
N/A

***Students as Subjects**:*
N/A

Research Informatics Core:
N/A

UMCCTS Protocol Review Committee (PRC)
N/A

4. OBJECTIVES*
The purpose of this study is to characterize visual system function in individuals with high trait anxiety. The fMRI portion of this study has already been conducted elsewhere. The follow up portion of the study is designed to determine if fMRI data can be used to predict future quality of life and anxiety symptoms that will be assessed at follow up. We hypothesize that visual cortex functional coupling will explain more variance in quality of life and anxiety severity at six months post-scan than prefrontal-amygdala functional coupling.
A subset of individuals with high trait anxiety will also complete an emotional faces task (MicroExpressions Training Task, or METT) as well as a 12-month follow up visit. This is an exploratory aim of the study to determine feasibility of the METT. We also hypothesize that individuals who complete the METT will show more improvement in anxiety symptoms at 12-months post-scan than those who do not.
Previously, participants in this study consented to an assessment visit, an fMRI visit, and a six month follow up data collection conducted remotely. In this initial consent form, it was mentioned that a subset of qualifying participants would be asked to complete the METT and a 12-month post-scan survey. The Pitt IRB asked us to consent these people via a separate consent form when they completed their six-month follow-up data collection.

The present IRB would thus cover participants who have completed the consent process at Pitt, as well as a subset of participants who have been consented up through their six-month follow-up data collection, who will need to be additionally consented for their 12-month data collection and the METT. Because the METT is randomly assigned to either 6-months or 12-months post scan, these participants will have to be consented at 6-months, as some of them will be asked to complete the METT at that time.

5. BACKGROUND*

Individuals with high trait anxiety (HTA) have elevated fear responses to threatening situations and are more likely to react with nervousness or apprehension to a broad range of situations that may not be threatening. HTA is a stable individually differing feature and trans-diagnostic risk factor for the development of a range of chronic illnesses and conditions, most prominently mood and anxiety disorders. HTA is also associated with poor functional outcomes in psychiatric disorders, such as reduced quality of life (QoL). However, the neurobiological underpinnings of HTA remain unclear. Identification of modifiable mechanisms that underlie HTA is critical given that HTA is a behavioral marker that often precedes the onset of psychiatric disorders and is associated with significant illness burden and suffering.

HTA is characterized by heightened sensitivity to threat or potential threat. Because of the primacy of social visual information for humans, the anxiety literature emphasizes social stimuli such as novel faces (potential threat) and emotional faces. Individuals with anxiety disorders misattribute threat to neutral stimuli, overestimate threat, and identify faces as threatening at lower emotional expression intensities relative to individuals without HTA.

In the traditional, top-down anxiety model, this bias is believed to be due to incorrect stimulus contextualization, mediated by prefrontal cortex (PFC) projections to the amygdala. However, the role of both bottom-up and top-down processes in visual perception has long been recognized. Taken together, there is ample evidence for a reduced perceptual threshold in HTA that cannot be explained by the received top-down model. Rather, such findings suggest that misattribution of threat or "diminished threat selectivity" in HTA includes a bottom-up sensory mechanism.

Enhanced visual cortex activation in response to novel or emotional stimuli is not solely dependent on top-down processes. Enhanced amplitude of the earliest visual waveform components in response to novel or emotional stimuli is well-established. The dual processing model posits that both bottom-up, implicit visual perception, and top-down, effortful attention, contribute to stimulus perception. In top-down processing, stimuli are attended because of effortful control that is often goal-directed. This process is facilitated by PFC projections to the amygdala and parietal cortex. In contrast, bottom-up implicit perceptual processes, facilitated by sensory cortices and the amygdala, are preattentive.

Perceptual alterations in HTA occur in a variety of contexts, indicating a generalized early processing mechanism. Although the literature has focused almost exclusively on fearful and angry face perception, perceptual processing of positive stimuli is also heightened in HTA and correlates with visual cortex function. The neural correlates of viewing more subtle emotional expressions in HTA, however, have not been investigated. Social interactions in the real world require interpretation of subtle emotional cues. Studies of subtle expressions created via emotional expression morphs are more naturalistic and would probe for a neural mechanism for reduced threat attribution threshold in HTA. By assessing visual cortex response to social and nonsocial stimuli that vary in their novelty or emotional intensity, we will test our hypothesis that HTA is characterized by enhanced visual cortex activity and bottom-up functional coupling to the amygdala, and that this functional alteration persists in a variety of contexts. If individuals with HTA show enhanced responsiveness to nonsocial stimuli, this would indicate generalized alterations in visual processes. Implicit, preattentive visual processing is designed to detect potential threats or rewards and occurs at an earlier latency than top-down processing, which provides context for

stimuli. Thus, alterations in bottom-up processing would likely occur in response to a broad range of stimulus types. Observation of a generally elevated response would support the hypothesis that heightened reactivity in HTA is preattentive, implicit, and facilitated by an early bottom-up mechanism. Because the extant fMRI literature has focused nearly exclusively on threatening social stimuli, we are currently limited in our ability to answer questions about the function of the visual system in HTA and its relationship to processing in general as opposed to threat processing specifically.

6. INCLUSION AND EXCLUSION CRITERIA*
This portion of the study will be conducted on participants who have already been recruited, screened, and enrolled in the study at another site. The exclusion criteria for recruitment were:

1) estimated IQ<70, 2) contraindication to MRI (including metal implants or devices in the body, pregnancy, claustrophobia), 3) history of head trauma or loss of consciousness, 4) major medical or neurological illness 5) current psychiatric medication usage or use in the last three months, 6) alcohol/substance abuse or dependence and/or illicit substance use (excepting cannabis) in the last three months, determined by Structured Clinical Interview for DSM-IV (SCID), 7) history of mania or psychosis

This study does not include individuals who are not yet adults, as it was designed to assess visual system function in adults. Pregnancy was an exclusion criteria at the time of study enrollment because of MRI contraindications. No prisoners or adults lack capacity to consent are included in this study. No one who is a non-English speaker will be included, as all study instruments and instructions are in English and have not necessarily been validated in other languages.

Because this is the follow up portion of this study, it is possible that some participants may have become pregnant in the intervening months since they completed their fMRI scan. Because this is a phone and teleconference based follow up study that involves answering self-report questionnaires, there are no risks specifically associated with pregnancy. We will not be collecting information related to pregnancy status for the remainder of the study. Similarly, it is possible that participants may have begun taking psychiatric medication in the intervening months since they were first enrolled in the study. This is not an exclusion criterion for the follow up portion of this study, as this study was designed to be a naturalistic study of high trait anxiety. Therefore, participants were not instructed to change their behavior regarding treatment/seeking treatment while enrolled in this study.

7. STUDY-WIDE NUMBER OF SUBJECTS*
NA

8. STUDY-WIDE RECRUITMENT METHODS*
NA

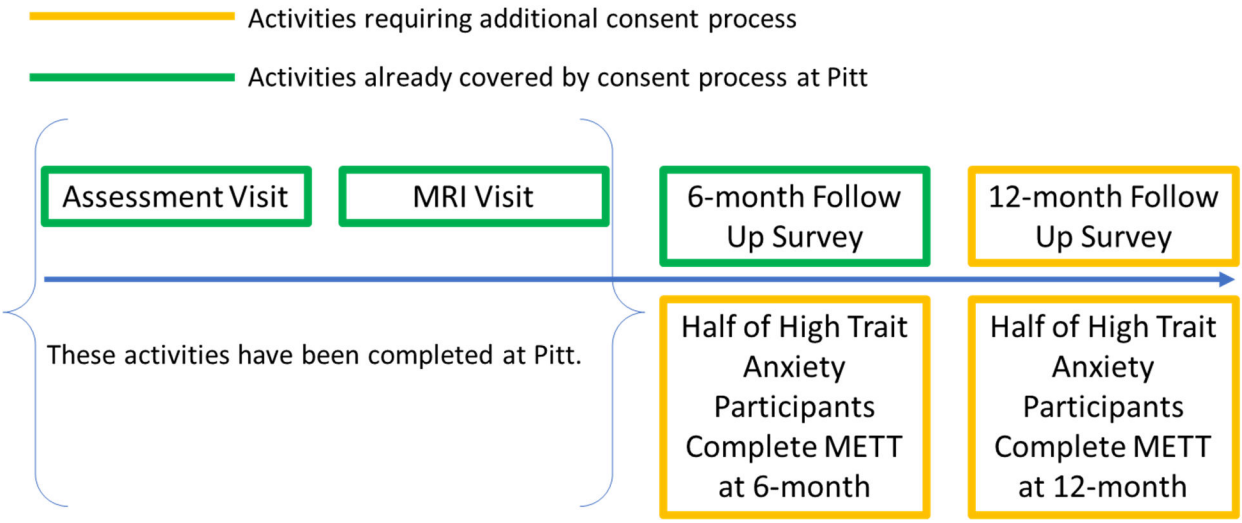
9. STUDY TIMELINES*
Participants will be enrolled in the study for approximately one year. All participants (n=16) are already enrolled in the study. The estimated date to complete the study data collection for this April 2024. Primary analyses are expected to be completed in September 2024.

10. STUDY ENDPOINTS*
The primary outcome measures will be 1) anxiety symptom severity, 2) self-reported quality of life (QLESQ form), 3) completion rate of the METT (feasibility)

11. PROCEDURES INVOLVED*

To assess the relative contributions of fMRI data to anxiety severity and QoL longitudinally, participants will repeat QoL and anxiety measures via online forms approximately six months post-scan visit. These self-report forms assess various facets of anxiety symptoms and quality of life. These measures include the Depression, Anxiety and Stress Scale (DASS), Mood Anxiety Symptoms Questionnaire (MASQ), Perceived Stress Scale (PSS), Sensory Over Responder Scale (SOR), Somatic Symptoms Scale (SSS), Spielberger State Trait Anxiety Inventory, STAI, Quality of Life Enjoyment and Satisfaction Questionnaire- Short Form (QLESQ), Profile of Mood State Questionnaire (POMS), and an update to their medication form in case there have been any changes to their medication usage.

As an Exploratory Aim designed to test the hypothesized mechanism for altered visual processing in HTA and its relation to future clinical and functional measures, individuals with HTA will be randomly assigned to complete a visual discrimination behavioral manipulation at either 6 months post scan or 12 months post scan. The behavioral manipulation is the Micro Expressions Training Tool (METT), a visual discrimination task that will be used to determine if the visual system is a tractable target for intervention. The METT presents images of micro expressions; participants receive real-time feedback following forced choice emotional identification. The METT includes a brief pre-test, training, and then a post-test. It takes approximately 75 minutes to complete. We will collect performance data, to include accuracy and rate of training. Emotional micro expressions are subtle, involuntary expressions that communicate emotion. Facial micro expression identification is trainable and associated with social behavior and psychological well-being. We will repeat collections of self-report data in the HTA participants approximately 12 months from the initial fMRI visit via online survey. This will allow us to assess possible intervention effects on anxiety symptom severity and QoL 12 months later.



12. DATA AND SPECIMEN BANKING*

NA

13. Data Analysis and Management*

With a maximum of five covariates (gender, age, socioeconomic status, fMRI motion parameters) of no interest and three needed terms, we will be 91% powered to detect moderate effects with f2 =0.15 and n=75 (30 LTA, 15 intermediate, 30 HTA, as defined by the STAI score at initial recruitment at Pittsburgh). All regression analyses will be conducted with STAI as a continuous variable, but STAI score

cutoffs will be used during recruitment to ensure an optimal distribution of trait anxiety. The Exploratory Aim is not designed to test for significant effects, but to provide pilot data for R01 submissions. Thus, outcome assessments will focus on effect size comparisons.
This submission is to complete the follow up data analyses on the outstanding 16 participants who have completed the first half of the study but not the follow up data collection. Therefore, no new participants are being recruited. Data quality will be monitored by the study PI to ensure that self-report measures are completed (unless a participant opts not to complete a measure, which is of course permissible), and that the METT is administered appropriately.

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*
Participants will be completing self-report measures of anxiety symptoms and quality of life, and some will also be completing a computerized task where they will be asked to look at emotional faces. Therefore, we do not anticipate any significant risks to the safety of participants. The data will be reviewed by the study PI, who has expertise in clinical research. This will be performed on an ongoing basis. As this study is remote, we will not be able to offer participants local resources for treatment. We will instead include a link to national resources provided by the CDC in our email communication.

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*
NA

16. RISKS TO SUBJECTS*
The most likely and common risk associated with study procedures is boredom. Participants may become bored while completing self-report forms or the METT. There is also an infrequent risk of breach of confidentiality. To minimize risk, participants will be reminded that they are free to terminate their participation at any time. Risk of breach of confidentiality will be minimized by staff training in proper procedures for handling confidential information. Furthermore, identifiable data will be kept in separate, password-protected digital files that are stored on a secure server. Self-report and METT data will be given a unique subject identifier, not identifiable information.

17. POTENTIAL DIRECT BENEFITS TO SUBJECTS*
NA

18. VULNERABLE POPULATIONS*
NA

19. MULTI-SITE RESEARCH*
NA

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*
NA

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*
We will not be sharing research results with participants.

22. SETTING

Research procedures will occur in the PI's lab space in the Medical School Building. Data collection will occur via secure online form, over the phone, and/or over Zoom. These activities will be conducted in private office space over the UMass secure network.

23. RESOURCES AVAILABLE

The PI for this study is a faculty member in the Department of Psychiatry. His responsibilities include study design, training and oversight of study staff, and review of data for quality assurance. He may also participate in data collection and analysis as needed.

A research coordinator for this project will be primarily responsible for scheduling and reminding participants of appointments, as well as data collection and data entry. This role requires training in the use of study measures and administration of the METT behavioral task, to be provided by the PI.

A research assistant for this project will be responsible for cleaning, managing, organizing, and analyzing data collected for this project. This role requires training in data management and analysis, to be provided by the PI.

The PI is responsible for ensuring that all staff involved in this research are adequately trained and informed regarding the protocol, procedures, and their roles. This includes ongoing training in data collection and storage to ensure compliance with the IRB. The PI typically meets with study staff on a weekly basis to review study progress, but also is available as needed. New staff will be trained in all protocols and procedures, then they will observe protocols and procedures performed by the PI, then they will perform protocols and procedures with supervision by the PI before they will collect data without the PI present. These steps may be repeated at the discretion of the PI to ensure fidelity with all procedures.

24. LOCAL RECRUITMENT METHODS

The participants for this study have already been recruited and enrolled; this protocol is solely for the follow up data collection that occurs at 6 months, and, for a subset of participants with high trait anxiety, at 12 months. There are 16 remaining participants with outstanding follow up data collection. Participants were recruited from the Pittsburgh, PA community via Pitt+Me, a University of Pittsburgh-based research recruitment site, as well as via community flyering. Identifiers were recorded only for the purpose of payment. Each participant was assigned a unique ID and the database containing these identifiers and that linked the unique ID to these identifiers is stored on a secure server and is password protected. Only staff involved in scheduling data collection have access to this database.

Payment for the six month data collection is $15. Participants who are eligible for the 12 month data collection receive an additional $20 for completion of surveys and an additional $15 for completion of the METT, for a possible total of up to $50.

The PI will work with UMass Chan Grant Accounting to compensate subjects during the period when BoA is being replaced.

A ($15-$50) card issued by a major bank will be given to each participant. To be eligible to receive the research stipend - the subject's name, address, phone number, and type of phone (mobile, landline) will be provided to the UMass Chan business office to procure the card. The card will be mailed directly to the subject. Once this information is provided to the business office – this identifying information will be destroyed by the PI.

25. LOCAL NUMBER OF SUBJECTS

There are 16 participants with outstanding follow up data collection.

26. CONFIDENTIALITY

Data will include METT outcomes (accuracy and completeness data) that will be recorded by study staff in a digital or paper format. Participant responses to survey data and medication form data will be digital. There is the potential that some data (METT outcomes, medication forms) may need to be collected in a hard copy format in case of computing difficulties. Regardless of format, all data will be coded with a unique subject ID and will not have direct identifiers.

Data will be collected primarily by the research coordinator but may also be collected by the PI if necessary for scheduling reasons. Data will be collected either via REDCap, or via secure servers housed at the University of Pittsburgh (we have a reliance agreement in progress for this purpose). Digital data will be stored on secure, password protected servers at UMass Chan or the University of Pittsburgh. Any hard copies will be stored in locked file cabinets in locked office space that is a part of the PI's lab space on the third floor of The Medical School Building.

The METT will be administered remotely via Zoom over the UMass network. This will occur with the use of a laptop and will not occur from locations outside of the PI's lab space.

Access will be limited to study staff or secondary investigators for related research questions. Data released to secondary investigators will be released in a de-identified format. Individuals not involved in data collection or scheduling will not have access to identifying information. Identifying information and its link to the unique subject ID will be stored in a password-protected database on a password-protected server.

Whenever feasible, identifiers will be removed from study-related information, and personally identifiable information is kept separate from actual data. Precautions are in place to ensure the data is secure by using passwords and encryption, etc. No identifiable data will be released to anyone without the signed consent of the participant and no identification of the subject as a participant will be made to outside sources without signed consent. We keep no detailed written narratives with private information.

This study was automatically assigned a certificate of confidentiality as it was funded by the NIH.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Data collection will occur via secure online form. The link to this form will be emailed to participants. Participants can complete this online form at their discretion. All participant reminders and scheduling phone calls will occur in a private office setting at the Medical School Building. The medication form is not a part of the secure online form, and therefore data from that form will be collected over the phone, again, in a private office setting at the Medical School Building. Participants who are eligible for the METT will be scheduled for a Zoom call that will be conducted over the secure UMass network. This call will also be conducted in a private office setting. Participants will be reminded that they can skip any survey questions they do not wish to answer. Only information necessary for conducting the research will be collected. Because this is a follow up data collection, participants will have previously completed survey measures at their initial visit when they were enrolled in the study.

The research team will not access protected health information for research purposes.

28. COMPENSATION FOR RESEARCH-RELATED INJURY
No funds have been set aside for compensation for research-related injury.

29. ECONOMIC BURDEN TO SUBJECTS
There will be no costs associated with participation in this research.

30. CONSENT PROCESS
All study staff will be trained in the informed consent process by the PI. This research constitutes the follow up portion of an existing study that was conducted at the University of Pittsburgh. For this study, all participants completed a baseline visit, an fMRI scan visit, and a 6 month survey. These three portions of the study were therefore included in a single consent form that was administered prior to any research procedures. However, a subset of participants (those with high trait anxiety) are asked to complete two additional procedures: a 12 month follow up survey, and the METT, which is administered with either the six month or the 12 month surveys. Of the participants with remaining follow up data collection, a small number of individuals with high trait anxiety still need to be consented for these procedures. All participants without high trait anxiety have already been consented for follow up, at the time of their enrollment.

We will consent the remaining high trait anxiety individuals for the follow up data collection remotely. It is not feasible to consent them in-person, given that they were recruited in Pittsburgh, PA. Therefore, the consent process will take place prior to follow-up data collection and will be conducted remotely, either over the phone or over Zoom. Participants will be given the opportunity to ask questions and to consider whether to continue their participation in the study.

31. PROCESS TO DOCUMENT CONSENT IN WRITING
We will document the consent process using RedCap. A link to the consent form will be sent to participants to review and sign.

32. DRUGS OR DEVICES
NA

INVESTIGATOR STUDY PLAN - REQUIRED

eIRB Attachments Upload Checklist

Upload the following items as applicable to your submission. This checklist is provided for your convenience and is not a requirement for review.

	Investigator Study Plan
	Sponsor protocol
	Research portion of the grant
	Human subjects portion of the grant
	Written approvals from ancillary reviews (Clinical Engineering, COI, IBC, RSC, etc.)
	Recruitment materials such as flyers, brochures, posters, scripts of radio ads, etc.
	Data collection sheets, case report forms, etc.
	Surveys, measures, instruments, etc.
	Measures to assess capacity to consent
	DMC or DSMB charter
	Data safety monitoring plan
	Adverse event log
	Investigator brochure or package insert for drugs
	Instructions for use or approved FDA labeling for devices
	Sponsor justification or FDA documentation for non-significant risk device study
	IND or IDE documentation
	Patient information sheet for Humanitarian Use Device
	Approval order for Humanitarian Use Device
	Product labeling for Humanitarian Use Device
	HIPAA waiver
	HIPAA authorization
	Authorization to contact form
	Consent form(s)
	Assent forms(s)
	Fact sheet(s)
	Multi-site communication plan
	Study staff training plan
	SOPs or Manuals of Operations
	Screening log
	Compensation log
	Certificates of translation or translator attestations
	Data use agreements, memoranda of understanding,
	Documentation of data/specimen anonymity (i.e., provider will never break the code)