Title: Protocol: Measurement and Modification of Threat Interpretation Bias in Neurodegenerative Movement Disorders (Aims 2 & 3)

NCT#: NCT05126862

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PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

Answer/Response: [REDACTED] Anxiety symptoms are experienced by up to 71% of persons with Huntington's disease (PwHD), causing significant burden for patients and caregivers [2, 3]. [REDACTED] Further, there have been no randomized controlled trials (RCTs) to evaluate efficacy of a specific psychological intervention for anxiety symptoms in PwHD. [REDACTED] Our long-term goal is to develop effective, accessible non-pharmacological interventions to reduce neuropsychiatric symptoms in patients with neurodegenerative movement disorders (e.g., HD, Parkinson's disease [PD]). With this overarching purpose in mind, our next step is to evaluate a cognitive bias modification for interpretation bias (CBM-I) intervention for reducing anxiety symptoms in PwHD. [REDACTED] For the current proposal, **we will** [REDACTED] **pilot an existing web-based CBM-I intervention (MindTrails) in PwHD**. MindTrails (PI: Teachman) is a free, multi-session, internet-delivered CBM-I training intervention to reduce anxious thinking. Participants complete five, weekly 20-minute modules designed to encourage cognitive flexibility through repeated practice assigning benign resolutions to ambiguous, anxiety-provoking situations. Launched in 2016, it has been completed by thousands of individuals and has been found to reduce interpretation bias and anxiety symptoms in a community sample with high trait anxiety [13].

PD sub-study:

As in HD, anxiety is very common in people with Parkinson's disease (PD). In keeping with our long-term goal to develop effective, accessible non-pharmacological interventions to reduce neuropsychiatric symptoms in patients with neurodegenerative movement disorders (e.g., HD, PD), we will [REDACTED] pilot an existing web-based CBM-I intervention (MindTrails) in PwPD.

[REDACTED] Objectives/Hypothesis

Answer/Response:

Main study:

[REDACTED] **Aim 2: To assess feasibility and preliminary efficacy of a web-based CBM-I intervention (MindTrails) for reducing interpretation bias and anxiety symptoms in PwHD**

Hypothesis 2: MindTrails will be feasible and will demonstrate preliminary efficacy for reducing interpretation bias and anxiety symptoms in PwHD.

N=20 PwHD will enroll in a pilot open trial of the existing MindTrails protocol. Mixed effects models will be used to evaluate preliminary effects of the intervention on interpretation bias and anxiety symptom change.

Aim 3: To conduct a qualitative evaluation of the MindTrails program in HD

Hypothesis 3: Qualitative data will reveal overall satisfaction with MindTrails and recommendations for future trials.

Participants in the Aim 2 open trial will be invited to complete qualitative interviews regarding their experiences with the MindTrails intervention (invite n=20 to obtain a minimum of n=10

interviews). Data will be used to develop a subsequent RCT of MindTrails specifically adapted for PwHD.

PD sub-study:
[REDACTED] **Aim 2: To assess feasibility and preliminary efficacy of a web-based CBM-I intervention (MindTrails) for reducing interpretation bias and anxiety symptoms in PwPD**
Hypothesis 2: MindTrails will be feasible and will demonstrate preliminary efficacy for reducing interpretation bias and anxiety symptoms in PwPD.
N=20 PwPD will enroll in a pilot open trial of the existing MindTrails protocol. Mixed effects models will be used to evaluate preliminary effects of the intervention on interpretation bias and anxiety symptom change.
Aim 3: To conduct a qualitative evaluation of the MindTrails program in PD
Hypothesis 3: Qualitative data will reveal overall satisfaction with MindTrails and recommendations for future trials.
Participants in the Aim 2 open trial will be invited to complete qualitative interviews regarding their experiences with the MindTrails intervention (invite n=20 to obtain a minimum of n=10 interviews). Data will be used to develop a subsequent RCT of MindTrails specifically adapted for PwPD.

[REDACTED]

Study Design: Biomedical

1. Will controls be used?
Answer/Response: No
►**IF YES, explain the kind of controls to be used.**
Answer/Response:

2. What is the study design?
Answer/Response: Other
[REDACTED] Aim 2: Single-group feasibility open trial
Aim 3: Cross-sectional qualitative interview

PD sub-study: same as above

3. [REDACTED] **Does the study involve a placebo?**
Answer/Response: No
►**IF YES, provide a justification for the use of a placebo**
Answer/Response:

Human Participants

Ages: **≥21 years old**
Sex: **Any**
Race: **Any**

Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

   Answer/Response: [REDACTED]
   Main study: [REDACTED] 20 [REDACTED]
   PD sub-study: [REDACTED] 20 [REDACTED]
   [REDACTED]

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

   Answer/Response: Main study: [REDACTED]
   For Aim 2, we anticipate 40% dropout as attrition can be quite high for online mental health interventions and CBT-based HD studies.
   For Aim 3, we do not anticipate dropout.
   PD sub-study: [REDACTED] For Aim 2, we anticipate 40% dropout as attrition can be quite high for online mental health interventions and CBT-based HD studies.
   For Aim 3, we do not anticipate dropout.

[REDACTED] **3. How many subjects will be enrolled at all sites?**

   Answer/Response: [REDACTED]

4. **How many subjects will sign a consent form under this UVA protocol?**

Answer/Response: Main study: [REDACTED] 20 of these will sign an additional consent for Aims 2 & 3[REDACTED] PD sub-study: [REDACTED] 20 of these will sign an additional consent for Aims 2 & 3. [REDACTED] [REDACTED] Inclusion/Exclusion Criteria

Main study:

AIM #1 and instrument feedback

1. **List the criteria for inclusion**

Answer/Response:

- Diagnosis of Huntington's disease
- Age 21 or older

2. **List the criteria for exclusion**

Answer/Response:

- Unable to read and understand English
- Previously diagnosed with dementia
- Not located in the USA

AIM #2 and 3

Inclusion Criteria-

Participated in Aim 1

Has anxiety symptoms (NeuroQoL-Anxiety > 12) (based on Aim 1 responses)

Exclusion Criteria-
None

PD substudy:
AIM #1 and instrument feedback
1. List the criteria for inclusion
Answer/Response:

- Diagnosis of Parkinson's disease
- Age 21 or older

2. List the criteria for exclusion
Answer/Response:

- Unable to read and understand English
- Previously diagnosed with dementia
- Not located in the USA

AIM #2 and 3
Inclusion Criteria-
Participated in Aim 1
Has anxiety symptoms (NeuroQoL-Anxiety > 12) (based on Aim 1 responses)

Exclusion Criteria-
None

[REDACTED]
3. List any restrictions on use of other drugs or treatments.
Answer/Response: None

Statistical Considerations

1. Is stratification/randomization involved?
Answer/Response: No
►**IF YES, describe the stratification/ randomization scheme.**
►**IF YES, who will generate the randomization scheme?**
_____ Sponsor
_____ UVA Statistician. Answer/Response:
_____ UVA Investigational Drug Service (IDS)
_____ Other*:* Answer/Response:

2. What are the statistical considerations for the protocol?
Answer/Response:
Main study:

[REDACTED]

Aim 2: To assess feasibility and preliminary efficacy of a web-based CBM-I intervention (MindTrails) for reducing interpretation bias and anxiety symptoms in PwHD

Subjects (N=20) will complete five, 20-minute MindTrails training sessions over five weeks, consistent with the existing MindTrails protocol which has been found to modify negative interpretations and reduce anxiety [13]. In addition, they will complete assessments included in the established MindTrails measures, which measure **anxiety symptoms** (Depression, Anxiety, Stress Scales-Short Form [DASS]: Anxiety Subscale (DASS AS)[23]), **depressive symptoms** (DASS: Depression Subscale [23]), **interpretation bias** (BBSIQ [14]), a **mental health history and treatment questionnaire**, and **user experience survey**. These assessments will be completed at baseline, after training sessions in weeks 3 and 5, and 2 months following the last (week 5) training session to assess durability of the effects. We will also collect **HD-specific demographic data** via **Demographic HD History Interpret** (e.g., CAG repeat length on the HD-affected allele) at baseline **and HD-related measures** (NeuroQoL-Anxiety, NeuroQoL-Depression [20, 21], and our novel MDIB measure) that are not included in the established MindTrails protocol.

Aim 3: To conduct a qualitative evaluation of the MindTrails program in HD

Subjects will complete a semi-structured interview that about their experiences with MindTrails and anxiety. Dr. Gibson or study staff will also administer the **Total Functional Capacity** [24] scale to classify participants by stage of HD and the Montreal Cognitive Assessment (5 minute/telephone).

PD sub-study:

[REDACTED] **Aim 2: To assess feasibility and preliminary efficacy of a web-based CBM-I intervention (MindTrails) for reducing interpretation bias and anxiety symptoms in PwPD**

Subjects (N=20) will complete five, 20-minute MindTrails training sessions over five weeks, consistent with the existing MindTrails protocol which has been found to modify negative interpretations and reduce anxiety [13]. In addition, they will complete assessments included in the established MindTrails measures, which measure **anxiety symptoms** (Depression, Anxiety, Stress Scales-Short Form [DASS]: Anxiety Subscale (DASS AS)[23]), **depressive symptoms** (DASS: Depression Subscale [23]), **interpretation bias** (BBSIQ [14]), a **mental health history and treatment questionnaire**, and **user experience survey**. These assessments will be completed at baseline, after training sessions in weeks 3 and 5, and 2 months following the last (week 5) training session to assess durability of the effects. We will also collect **PD-specific demographic data** via **Demographic PD History Interpret** (e.g., age of diagnosis) at baseline **and PD-related measures** (NeuroQoL-Anxiety, NeuroQoL-Depression [20, 21], and our novel MDIB measure) that are not included in the established MindTrails protocol.

Aim 3: To conduct a qualitative evaluation of the MindTrails program in PD

Subjects will complete a semi-structured interview that about their experiences with MindTrails and anxiety. Dr. Gibson or study staff will also administer the Montreal Cognitive Assessment (5 minute/telephone).

[REDACTED]

3. Provide a justification for the sample size used in this protocol.

Answer/Response:

Main study:

[REDACTED]

Aims 2 and 3 include a feasibility study and qualitative interviews. We will include 20 participants in the feasibility study, which will be sufficient to gather preliminary data in preparation for a future RCT. We will recruit all 20 participants in the feasibility study to complete qualitative interviews. All 20 subjects may not want to complete interviews, and we expect that a sample of 10 participants will be sufficient to reach data saturation on qualitative analysis based on Dr. Gibson's prior experience conducting and analyzing qualitative interviews in HD.

PD sub-study:

[REDACTED]

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[REDACTED]

4. What is your plan for primary variable analysis?

Answer/Response:

Main study:

[REDACTED]

5. What is your plan for secondary variable analysis?

Answer/Response:

Main Study:

Aim 2: Descriptive statistics will be used to summarize patient demographic, health history, and user experience variables. Because attrition can be quite high for online mental health interventions and CBT-based HD studies [6, 26], we will consider the intervention feasible in PwHD if 50% of participants complete at least 50% of the sessions. We will also compare demographic and clinical variables between adherers (>50% completers) and non-adherers to provide insight into which patients may require targeted retention efforts in a follow-up study (this will be done descriptively given small sample size). To evaluate target engagement and preliminary efficacy of MindTrails, we will use linear mixed-effects models to assess changes in interpretation bias and anxiety symptoms over the course of the intervention, including age, gender, and CAG repeat length as fixed effects. In the case that MDIB is not a valid and reliable

measure of interpretation bias in HD (Aim 1), we will use only BBSIQ, and not MDIB, in our analysis of interpretation bias for this aim. Because prior studies have shown potential for CBM-I to be effective in depressed samples [12], an exploratory mixed effects model will also be used to evaluate potential effects of the intervention on depressive symptoms, using the same fixed effects. (Note: Analyses for this aim are limited by the small, pilot sample, but Dr. Gibson will use this feasibility study to develop data analysis skills for this data as well as data for a future large RCT. We will focus our interpretation on effect size estimates given the small sample size limits power for significance testing; specifically, effect sizes will be reported as standardized β estimates.)

Aim 3: We will perform qualitative descriptive content analysis of answers, including iterative, line-by-line coding by multiple coders, and organization of findings into categories or themes. Qualitative interviews will continue until data saturation is reached, and no new themes are identified. Participant responses between disease stage groups will be qualitatively compared. This will help us to determine whether MindTrails is best suited for early-stage (1-2) HD patients as compared to those in later stages (3-4). The feedback will be used to modify the program in an iterative fashion and inform protocol development for a follow-up RCT.

PD sub-study:
Aim 2: Descriptive statistics will be used to summarize patient demographic, health history, and user experience variables. Because attrition can be quite high for online mental health interventions and CBT-based studies in neurodegenerative populations [6, 26], we will consider the intervention feasible in PwPD if 50% of participants complete at least 50% of the sessions. We will also compare demographic and clinical variables between adherers (>50% completers) and non-adherers to provide insight into which patients may require targeted retention efforts in a follow-up study (this will be done descriptively given small sample size). To evaluate target engagement and preliminary efficacy of MindTrails, we will use linear mixed-effects models to assess changes in interpretation bias and anxiety symptoms over the course of the intervention, including age, gender, and CAG repeat length as fixed effects. In the case that MDIB is not a valid and reliable measure of interpretation bias in PD (Aim 1), we will use only BBSIQ, and not MDIB, in our analysis of interpretation bias for this aim. Because prior studies have shown potential for CBM-I to be effective in depressed samples [12], an exploratory mixed effects model will also be used to evaluate potential effects of the intervention on depressive symptoms, using the same fixed effects. (Note: Analyses for this aim are limited by the small, pilot sample, but Dr. Gibson will use this feasibility study to develop data analysis skills for this data as well as data for a future large RCT. We will focus our interpretation on effect size estimates given the small sample size limits power for significance testing; specifically, effect sizes will be reported as standardized β estimates.)

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MindTrails-Movement Development substudy: n/a

6. Have you been working with a statistician in designing this protocol?
Answer/Response: Yes

IF YES, what is their name?
Answer/Response: [REDACTED]

7. Will data from multiple sites be combined during analysis?
Answer/Response: No

7(a). Does the study involve randomization?
Answer/Response:

IF YES, will randomization be done at each site or among sites?
Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?
Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?
Answer/Response:

7(d). Is there a common protocol used in all sites?
Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?
Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?
Answer/Response:

Main study:

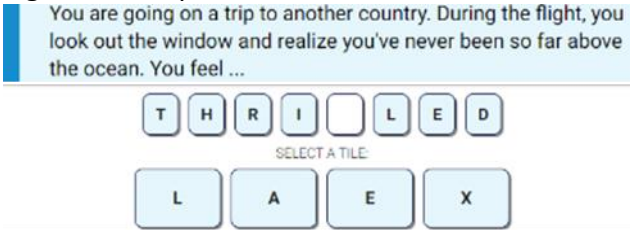
[REDACTED]

Aim 2: We will conduct a pilot open trial of MindTrails in 20 PwHD. MindTrails (https://mindtrails.virginia.edu/calm/public/researchSupport) is based on Mathews and

Mackintosh's Ambiguous Scenario Training design, a CBM-I protocol with established efficacy in trait anxious samples, which trains participants to assign more benign interpretations to ambiguous, anxiety-relevant situations [7, 9].

In each session, participants will read and resolve a series of 40 ambiguous scenarios (from a pool of 200 scenarios, see Figure 1 and demo training session: http://mt.sartography.com/demo/#/training/1). Participants will be asked to imagine themselves in each scenario, as previous work has highlighted the strengthening effect of imagery on interpretation training [27]. Ninety percent of scenarios will end with a word fragment that resolves the ambiguity of the scenario in a benign (anxiety-incongruent) manner. Once participants correctly complete a word fragment, they will answer a comprehension question, which ensures that they read the scenario and reinforces the positive interpretation of the scenario. They will then move on to the next scenario. Later sessions will make the task slightly more challenging by having word fragments missing 2 letters, rather than only 1 [16].

Figure 1. Sample MindTrails Scenario



Subjects will complete five, 20-minute MindTrails training sessions over five weeks consistent with the existing MindTrails protocol which has been found to modify negative interpretations and reduce anxiety [13]. In addition, they will complete assessments (see statistical considerations section above) at baseline, after training sessions in weeks 3 and 5, and 2 months following the last (week 5) training session to assess durability of the effects. MindTrails assessments are as follows:

- MindTrails Measures.pdf

Additional HD-specific assessments include:

- MDIB_samplequestion
- MDIB_REDCap.pdf
- NeuroQOLSF-Anxiety.pdf
- NeuroQOLSF-Depression.pdf

At baseline, participants will also complete ContactInfo.pdf.

For participants whose training sessions or assessments are incomplete, a member of the study team will contact these participants via phone and/or email as needed to

request completion of training sessions and/or assessments and to answer any study-related questions.

Aim 3: We will gather feedback from MindTrails PwHD participants, using semi-structured interviews. The 20 participants who participate in the MindTrails pilot (Aim 2) will also complete telephone interviews. Each participant will complete a semi-structured interview (~30 minutes) to query perceived benefits and limitations of MindTrails, specifically, web-based self-management interventions in general, as well as anxiety symptoms and social difficulties. Interview questions will be refined based on results of Aim 2. Sample interview questions are as follows:

1. What was your overall impression of the MindTrails program?
    a. In what ways was the program helpful for you?
    b. In what ways could the program be improved to help people with HD, specifically?
2. What barriers do you think might prevent someone with HD from completing the MindTrails program?

Subjects will also answer questions to complete the Total Functional Capacity (TFC.docx) scale and Montreal Cognitive Assessment 5 minute/telephone (MoCA 5 min-T – Version 2.1 English test.pdf)[28] during their telephone interview session.

PD sub-study:

[REDACTED]

Aim 2: We will conduct a pilot open trial of MindTrails in 20 PwPD. MindTrails (https://mindtrails.virginia.edu/calm/public/researchSupport) is based on Mathews and Mackintosh's Ambiguous Scenario Training design, a CBM-I protocol with established efficacy in trait anxious samples, which trains participants to assign more benign interpretations to ambiguous, anxiety-relevant situations [7, 9].

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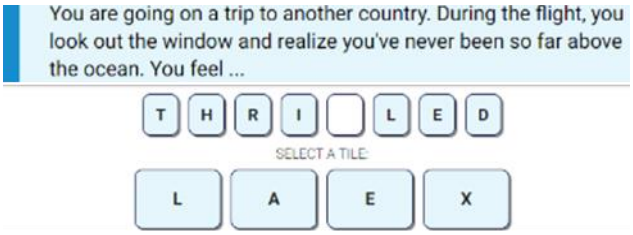

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For participants whose training sessions or assessments are incomplete, a member of the study team will contact these participants via phone and/or email as needed to request completion of training sessions and/or assessments and to answer any study-related questions.

<u>Aim 3</u>: We will gather feedback from MindTrails PwPD participants, using semi-structured interviews. The 20 participants who participate in the MindTrails pilot (Aim 2) will also complete telephone interviews. Each participant will complete a semi-structured interview (~30 minutes) to query perceived benefits and limitations of MindTrails, specifically, web-based self-management interventions in general, as well as anxiety symptoms and social difficulties. Interview questions will be refined based on results of Aim 2. Sample interview questions are as follows:

3. What was your overall impression of the MindTrails program?
    a. In what ways was the program helpful for you?
    b. In what ways could the program be improved to help people with PD, specifically?
4. What barriers do you think might prevent someone with PD from completing the MindTrails program?

Subjects will also complete Montreal Cognitive Assessment 5 minute/telephone (MoCA 5 min-T – Version 2.1 English test.pdf)[28] during their telephone interview session.

[REDACTED]

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.

Answer/Response: N/A

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