Examining Changes in Microbiota Over the Course of PTSD Treatment Protocol

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The overall goals of this project are to evaluate the use of 5-day intensively-delivered Cognitive Processing Therapy to treat PTSD and to determine the associations between the microbiome, salivary cytokines, and the presence of and recovery from PTSD. Specifically, this study is designed to 1) determine whether individual Cognitive Processing Therapy (CPT) delivered twice per day over 5 consecutive days (CPT-5) is tolerable, acceptable, and effective in reducing PTSD symptoms, 2) determine the microbial signatures associated with PTSD, 3) evaluate whether the abundance and composition of microbiota and salivary cytokine levels change over the course of PTSD treatment, and 4) examine whether changes in microbial signatures are associated with changes in cytokine levels.

Scientific Review:

Cognitive Processing Therapy (CPT) is an evidence-based psychotherapy for posttraumatic stress disorder (PTSD; Resick, Monson, & Chard, 2016) that has demonstrated efficacy and effectiveness in a large range of settings and a variety of populations (Monson et al., 2006; Resick et al., 2017; Resick, Nishith, Weaver, Astin, & Feuer, 2002; Resick, Williams, Suvak, Monson, & Gradus, 2012). Clinical outcome data from the Road Home Program Intensive Outpatient Program (IOP), which offers CPT daily over the course of three weeks to treat veterans with PTSD, show that participation in the IOP produces large PTSD and depression symptom reductions. This suggests that patients are able to safely and effectively work on their trauma on a daily basis with CPT and that the daily delivery of CPT may also be acceptable and effective.

While existing evidence-based interventions for PTSD, such as CPT, have been shown to be effective for the treatment of the disorder, it has also been suggested that underlying biology may contribute to treatment refractory PTSD. The microbiome has received increased attention and been proposed as an important factor that impacts brain function and mental health through what is referred to as the gut-brain-axis (Carabotti et al., 2015; Collins et al., 2014; Heijtz et al., 2011). However, it has yet to be determined what role microbiota play in PTSD and whether the abundance of various microbiota changes over the course of evidence-based PTSD treatment.

The proposed project will address these questions by examining microbial signatures of individuals with PTSD to establish whether previously identified microbial signatures (cf. Hemmings et al., 2017) can be found in another sample and whether those signatures can be found in oral microbiota in addition to fecal microbiota. The project will also examine whether microbial signatures change over the course of PTSD treatment to determine whether symptom improvement and changes in inflammatory marker levels are associated with changes in microbiota.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Individuals are eligible for the current study if they:

1. Are 18 years or older
2. Are fluent in English
3. Have experienced a Criterion A traumatic event during their lifetime
4. Have a PTSD diagnosis verified by the Clinician Administered PTSD Scale for DSM-5
5. Are interested in receiving evidence-based treatment (CPT) for PTSD and able to attend 10 therapy sessions over the course of one week (5 days)
6. Are willing and interested to complete self-report measures and clinician-rated assessments at multiple time points over the course of the study

Exclusion Criteria:

Individuals are excluded from the current study if:

1. The traumatic event occurred in the past month
2. They are currently suicidal or homicidal
3. They have a history of psychosis or mania
4. They have not been on a stable dose of medication for at least one month
5. They made changes to the diet in the past month or are planning to make changes over the course of therapy
6. They have completed an evidence-based PTSD treatment in the past 3 months or are currently receiving an evidence-based PTSD treatment
7. They have mental retardation or significant cognitive impairment that would prevent them from engaging in CPT
8. They have a serious or unstable medical illness or instability for which hospitalization may be likely within the next year
9. They have an active substance use disorder (within the past 3 months)
10. They are involved with current legal actions related to the traumatic event that is anticipated to be targeted during treatment
11. They have a history (within the past year) or presence of an eating disorder
12. They are currently taking or have taken an antibiotic in the past 30 days
13. They are currently taking a corticosteroid
14. They have had part of the digestive tract removed or altered within the past year
15. They have had any surgery or procedure within the past 30 days that has required fasting for more than 12 hours or bowel preparation beforehand
16. They have a visual or auditory impairment that would prevent them from fully participating in study activities

Research Plan:

Study Population:

Trauma-exposed individuals will be recruited from the Rush Department of Psychiatry, Department of Behavioral Sciences, the Rush newsletters, the Rush website, Road Home Program: Center for Veterans and their Families, other Rush clinics, and postings to Rush/Road Home Program social media pages and website. Local first responders will also be recruited. Recruitment flyers will be posted in waiting areas in the Rush Departments of Psychiatry and

Behavioral Sciences. Approximately 200 individuals will be screened, anticipating that 40% of those screening positive on the phone and expressing interest in the study will be eligible and willing to participate (~40% of 200 screened = 80 participants). We plan to enroll at least 80 trauma-exposed individuals who meet the diagnostic criteria for PTSD, as assessed by a gold standard clinician-administered PTSD assessment, for the single-arm, open-label trial.

Study Activities:

Eligibility Phone Screening:

Individuals who are interested in participating in the proposed study will call in response to study recruitment flyers or will be called by the study staff once they have been referred, and they will then be screened via phone by a member of the study staff to be examined for eligibility. Individuals who meet exclusion criteria or who choose not to participate will be referred for other treatment as indicated. Potentially eligible and interested individuals will be scheduled for an in-person intake session, which may be conducted in 1-2 sessions based on the participant's scheduling availability. Informed consent will be obtained and signed at the beginning of the in-person assessment, prior to the conduct of any study activities. Alternatively, potentially eligible and interested individuals may schedule a telephone/video intake session. All telephone/video sessions will be conducted via a HIPAA compliant platform. Individuals who schedule telephone/video intakes will be sent a link to an electronic version of the consent form via REDCap prior to the conduct of any study activities.

Intake Assessment:

The intake assessment will be used to confirm the fit for the proposed project. Clinical interviewers with a minimum of a Master's degree in Psychology who are not providing the treatment will administer structured diagnostic interviews (e.g. CAPS and DIAMOND). Study staff will administer brief computerized assessments (e.g. Stroop task) and a full self-report assessment battery via Qualtrics. Participants will also be emailed a link to an internet-based dietary assessment. If participants consent to providing biosamples, study staff will also collect microbiota, salivary cytokine samples, and human DNA extracted from whole saliva. Completion of the intake assessment may take up to 4 hours and may take place over 1-2 days, depending on the participant's availability. Telephone/video intake assessments will include the administration of a brief computerized assessment and the provision of fecal samples but will not include the provision of saliva samples. Study staff will securely email the full self-report assessment battery to telephone/video intake participants via Qualtrics. Study staff will also securely email participants a link to the brief computerized assessment. All intake assessments will be audio recorded to establish diagnostic reliability. Intake assessments may also be audio and/or video recorded for research purposes.

Intensive Week-Long Cognitive Processing Therapy (CPT):

The eligible individuals will undergo a course of 1-week-long Cognitive Processing Therapy (CPT-5). CPT-5 will be delivered twice per day over the course of five business days (Monday through Friday; 10 sessions total) at approved study sites or via the HIPAA compliant platform.

Each 50 minute session will closely follow the CPT protocol and will be conducted by either Dr. Held, other doctoral-level psychologists, postdoctoral fellows, or other Master's level (or higher) clinicians who have received the official two-day CPT training and who are not involved in study assessments. All CPT sessions will be audio and/or video recorded and an independent fidelity rater with experience in the treatment will randomly select and review 20% of all therapy audio recordings to ensure that the intervention is provided with fidelity, which will be defined as 80% or more of the maximum possible score on the official CPT fidelity rating scales. CPT worksheets and homework assignments may be collected and copied for research purposes. Individuals with telephone/video sessions will have the option to complete electronic versions of CPT worksheets and to upload them to a secure folder accessible only by the individual and study staff.

Changes in PTSD severity and other relevant symptoms will be assessed before, during, and after the course of CPT using well-validated clinician-administered, self-report, and computerized assessments. Completion of assessments may take between 20 minutes for self-report measures and 90 minutes for combined self-report, computer-based, and clinician-administered assessments. Fecal- and oral-derived microbiota as well as salivary cytokines will also be assessed at various pre-treatment, post-treatment, and follow-up time points to determine whether the microbiome and cytokine levels change over the course of CPT. Participants will have the option to opt out of providing these biological samples and still receive CPT-5. Participants completing telephone/video sessions can provide optional fecal samples and will complete brief computerized assessments, but will not provide saliva samples.

Booster Sessions:

Following their completion of the course of CPT, participants will be given the option to schedule up to three in-person or telephone/video booster sessions of CPT with their study therapist. If a participant decides to use any booster sessions, they must be used by the date of the participant's 3-month follow-up visit. All booster sessions will be audio and/or video recorded. CPT worksheets and homework assignments may be collected and copied for research purposes. Participants will complete self-report measures at each booster session they choose to use.

Measures:

Self-report measures, clinician-rated assessments, a computerized task, and biological sample collection will be used during the study. The assessment schedule below details the different assessment time points for each measure. Measures may also be administered as needed at clinically relevant intervals.

Measure	Time Point									
	Intake	1 Week Interim	CPT-5 Day 1	Daily	CPT-5 Day 3	1 Week Post	2 Week Post	1 Month Follow-Up	3 Month Follow-Up	Optional Booster Sessions
Demographics Form	X									
Screening Questionnaire	X									
CAPS-5	X					X		X	X	
C-SSRS	X					X		X	X	
DIAMOND	X									
Ohio TBI Screen	X									
PCL-5	X			X		X	X	X	X	X
PHQ-9	X			X		X	X	X	X	X
GAD-7	X					X	X	X	X	
PTCI	X				X	X	X	X	X	
ADL	X									
AUDIT-C	X					X	X	X	X	
DAST-10	X						X			
CD-RISC-10	X					X	X	X	X	
PROMIS-SF-8	X					X	X	X	X	
PROMIS-SD-SF	X					X	X	X	X	
PROMIS-SRI-SF	X					X	X	X	X	
RAND-12+	X					X	X	X	X	
FFQ	X								X	
Diet Changes			X			X			X	
Emotional Stroop Test	X					X		X	X	
Oral-Derived Microbiota Samples+	X		X			X		X	X	
Salivary Cytokine Samples+	X		X			X		X	X	
Human DNA from Whole Saliva Samples+	X									
Fecal-Derived Microbiota Samples*	X		X			X		X	X	

Note:

CAPS-5 = Clinician Administered PTSD Scale for DSM-5; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **DIAMOND** = Structured Diagnostic Interview for Anxiety, Mood, OCD and related Neuropsychiatric Disorders; **Ohio TBI Screen** = Ohio Traumatic Brain Injury Screen; **PCL-5** = PTSD Checklist- Identified Patient Version; **PHQ-9** = Patient Health Questionnaire; **GAD-7** = Generalized Anxiety Disorder – 7-item; **PTCI** = Post-Traumatic Cognitions Inventory; **ADL** = Activities of Daily Living; **AUDIT-C** = Alcohol Use Disorders Identification Test; **DAST-10** = Drug Abuse Screening Test; **CD-RISC-10** = Connor-Davidson Resilience Scale – 10 items; **PROMIS-SF-8** = Patient-Reported Outcomes Measurement Information System Satisfaction with Participation in Social Roles Short Form; **PROMIS-SD-SF** = Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form; **PROMIS-SRI-SF** = Patient-Reported Outcomes Measurement Information System

Sleep-Related Impairment Short Form; **RAND-12+** = The Veterans Rand 12-Item Health Survey; **FFQ** = VioScreen Food Frequency Questionnaire

*Fecal collection will take place within one day of the assessment and prior to the following assessment. The CPT-5 Day 1 sample should ideally be collected on Sunday, one day before the first session, or as soon as possible after. For participants who did not complete the intensive CPT, follow-up intervals will follow the same schedule as for individuals who complete treatment.
+These assessments will not be administered to participants who opt to participate via telephone/video.
Biological sample collection will involve the collection of fecal- and oral-derived microbiota, salivary cytokines, and human DNA from whole saliva. Fecal samples will be collected by participants using a home collection kit. Participants will be provided instructions and all necessary equipment for sample collection and storage by a member of the study staff and will bring samples to their next treatment session. For participants completing telephone/video session, a home fecal sample collection kit as well as sample collection instructions, storage instructions and pre-paid return mailing information will be shipped to them. Salivary samples will be collected by study staff during study visits. Participants will be instructed to drink water prior to the session to ensure hydration and to rinse their mouth with water 10 minutes before the testing session with no other food or drink after. Participants will be instructed to refrain from the following activities prior to the saliva testing sessions: visiting the dentist within 48 hours, drinking alcohol and taking over-the-counter medications within 24 hours, drinking caffeine, smoking, and engaging in vigorous exercise within 2 hours, eating a major meal within 1 hour, and eating or drinking products with dairy, high levels of sugar, or high acidity within 20 minutes. Salivary cytokines and oral microbiota samples and human DNA from whole saliva will be collected by a member of the study staff during the study visit.

Biosample Analysis:

To assess whether microbial signatures change over the course of PTSD treatment and are different with regards to diversity and total abundance for trauma-exposed individuals with PTSD, total microbial DNA will be extracted from oral saliva and colonic fecal samples and processed using high-throughput 16S ribosomal RNA gene Illumina amplicon sequencing followed with bioinformatics analysis at RUMC. Human DNA will also be extracted from whole saliva and processed. De-identified samples may be transferred to a qualified external laboratory upon the completion of the study solely for the purposes of processing and analysis.

Risks:

The risks associated with this study are no greater than those associated with standard evidence-based treatment for PTSD. This study uses CPT, an existing evidence-based treatment for PTSD that has been shown to be both effective and safe. To date, no adverse events have been associated with intensive CPT, suggesting that intensively-delivered treatment is tolerable.

It is possible that participants may experience distress during CPT treatment. Participants' suicidality will be assessed by the treating clinicians on an ongoing basis and assessed formally

at the intake, 1-week post-treatment, 1-month follow-up, and 3-months follow-up assessment points using the Columbia Suicide Severity Rating Scale (C-SSRS). If a participant indicates having "Thoughts that [they] would be better off dead or of hurting [themselves] in some way" more than half the days (2) or nearly every day (3), the study clinician will conduct a safety assessment. If any participant becomes actively suicidal with intent, the study clinician will refer the participant to a higher level of care (i.e., psychiatric, medical, or emergency services). All sessions will take place during regular business hours, and clinical staff will be present and available to assist in the case of a crisis during an in-person session. In the case of a crisis during a telephone/video session, the study clinician will be available to assist or will instruct the participant to call 911 or go to their nearest emergency room. Prior to the start of any telephone/video session, the provider will inquire about the current location to have this information in case of an emergency. Individuals will no longer be able to continue this course of CPT if they are actively suicidal, but may be able to enroll at a later time after reaching stability per eligibility requirements.

While risk is minimal, a loss of confidentiality is possible, although unlikely. All study staff will work diligently to ensure that all data is stored securely and that study-related files are password protected so that only members of the study staff will have access to identifiable data. To protect confidentiality, each subject is assigned a unique code. Only study personnel will be able to link patient name to the identification number. All telephone/video sessions will be conducted using HIPAA compliant platforms. In addition, a Certificate of Confidentiality will be obtained. No identifiable data will ever be disclosed to any outside parties. De-identified data may be reported in aggregate for internal clinical use, publications, or other presentations.

Benefits:

Participants in this study may experience direct benefits. Given that CPT is an effective evidence- based treatment for PTSD, it is likely that participants may experience a significant reduction in their PTSD and depression symptoms by the end of treatment. The reduction in symptoms may enable participants to re-engage in daily functions. Participants may help advance our understanding of PTSD treatment and its biological effects on the body. Findings from this study may allow researchers to learn more about the physiological biomarkers associated with PTSD and how they are impacted by the current clinical practices that are used to treat individuals with PTSD.

Data Storage:

Specify the site at which the data will be stored and how it will be stored:

Audio recordings, video recordings, copies/scans of CPT session materials, and all electronic data collected through computerized tasks, the internet-based assessment, and Qualtrics-delivered self-report assessments will be de-identified, password-protected, and stored in a restricted folder within the RUMC secure network infrastructure. Audio recordings will be uploaded to the secure server within one business day and will be deleted from the recording device immediately upon upload. Telephone/video visit audio and video recordings from the HIPAA compliant telephone/video platform will be uploaded to the secure server within one

business day and will be deleted from the platform immediately upon upload. CPT worksheets electronically uploaded to the secure folder accessible only to the participant and study staff will be deleted from this folder following the participant's final study visit. Copies of the worksheets will be saved to a separate restricted study folder on the RUMC network infrastructure. When personally identifying data cannot be removed (as may be the case with audio or video files), they will be provided with a unique de-identified code and stored in a separate and secure network location.

Saliva and fecal samples will be stored in a -80 degree freezer in the locked laboratory of the Department of Psychiatry and Behavioral Sciences at RUMC until analyzed. No biological data sources will contain information that will personally identify subjects. To protect confidentiality, each subject is assigned a unique code for these specimens. Only study personnel will be able to link patient name to the identification number. All information and data related to the biological specimens collected in the study will be kept in a password protected computer file on the Department of Psychiatry and Behavioral Sciences secure server or in a secure locked cabinet in the Department of Psychiatry and Behavioral Sciences.

How long will the data be maintained and/or stored?

All biological and electronic data collected will be stored for least 5 years. Once the necessary analyses have been conducted after at least 5 years, all data will be securely deleted from the secure, password-protected file and system. Saliva and fecal specimens will be destroyed once necessary analyses have been conducted.

Who, other than the specified study team, will have access to the study records or data? Specify their name, role, and affiliation.
The principal investigator will monitor all access to data. Only study staff listed on and approved by the IRB will have access to the data for research purposes. Audio and/or video recordings may be shared with approved external collaborators for analysis through encrypted software shared on a secure web-based storage site. Participants in audio and/or video recordings will be identified by coded subject IDs. Upon completion of data collection, de-identified samples may be transferred to a qualified external laboratory solely for the purposes of conducting laboratory assays to generate necessary data for the study team. This laboratory will not utilize data generated from specimens for research purposes.

In line with the NIH Guidance on Consent for Future Research Use and Broad Sharing of Human Genomic and Phenotypic Data Subject to the NIH Genomic Data Sharing Policy (https://osp.od.nih.gov/wpcontent/uploads/NIH_guidance_elements_consent_under_gds_policy.pdf), some de-identified study data, including data generated from biospecimens may be placed into one or more scientific databases or shared with other researchers. Only approved researchers will be given access to these databases.

Justify your needs to collect PHI in this study:

PHI will be collected in order to characterize the participant sample and to maintain contact with participants throughout the study, deliver assessments, and document the treatment progress. The

internet-based measure (FFQ) requires the collection of PHI to identify respondents. The FFQ is an online measure delivered by VioScreen. All PHI collected from this measure will be converted to coded subject IDs before storage in the secure RUMC network infrastructure, and no PHI collected from this measure will be used for research purposes. Audio and video recordings may also contain PHI that can potentially identify respondents. As PHI cannot be removed from audio and video files, these files will be provided with de-identified codes and stored in a separate and secure network location.

Describe how and where PHI will be destroyed following the completion of the study:

Not applicable. No identifiable data will ever be shared by the study team with personnel outside of the approved study staff. Any data shared with external laboratories or other researchers will be de-identified. All the findings in this study will be de-identified or reported at a group level or in aggregate with no risk of identifying individual participants.

Will subjects be able to request that their information be removed from the data bank?

Yes. However, it may not be possible to withdraw or delete materials or data in the event that they have already been shared with other researchers.

Costs:

There will be no direct cost to participants to participate in this study. All clinical, professional, diagnostic and laboratory services related to the study will be provided at no cost to participants. However, participants will be responsible for their phone service provider's standard charges as they apply to any study-related phone calls.

Compensation:

	Intake	**CPT Day 1**	**1- Week Post**	**2- Week Post**	**1- Month Post**	**3- Month Post**	**Total**
Completion of Measures & Provision of Saliva Samples*	$20	N/A	$40	$15	$40	$50	**$165**
Provision of Optional Fecal Sample	$10	$ 10	$10	N/A	$10	$10	**$50**
Completion of Optional Semi-Structured Interview			$15				$15
Total Compensation Possible	$30	$10	$65	$15	$50	$60	**$230**

* Provision of saliva samples not available to participants who opt to participate via telephone/video.