# Child Characteristics, Neuromarkers, and Intervention Components Impacting Treatment Outcome: CCT, TF-CBT, TAU

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## 1. PURPOSE OF THE STUDY

### a. Brief Summary

This study is designed to examine three treatment conditions for traumatized youth: Cue-Centered Treatment (CCT), Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT), and Treatment as Usual (TAU) to determine which treatment works most effectively for which youth. We would like to determine feasibility of training on the treatment interventions. In addition, this study aims to inform development of systems of care for chronically traumatized youth.

### Objectives

We hope to determine whether 1) TF-CBT and CCT will have better outcomes than TAU, 2) Child characteristics predict better outcome in either TF-CBT or CCT and to identify which phases of treatment are most effective, and 3) Imaging findings will be predictors of improved outcome. This research is important because while there are many existing trauma interventions for youth, little is known about what is most essential in those interventions. This study will shed light on what components of treatment are most effective. Furthermore, there are minimal guidelines on how to select the most appropriate intervention for a particular child. This study will contribute to that knowledge by informing which interventions are suited best for which youth.

### b. Rationale for Research in Humans

This project will allow the investigation of three existing treatment interventions for children with post-traumatic stress disorder. The purpose is to inform treatment selection based on most effective treatment components and child characteristics.

## 2. STUDY PROCEDURES

### a. Procedures

The children will be referred from Stanford Youth Solutions and UCSF CAS. UCSF has approved recruitment at their site and they have provided their own consent forms. Some children may also be self-referred from the community as a response to a flyer that may have been distributed to them in a public forum, from a community organization, from a physician/pediatrician, or a hospital setting.

School staff will speak with parents of children they have identified as potential study candidates and with verbal consent will submit parent's name and phone number so that the research coordinator can make contact directly to conduct phone screening. School staff may also obtain verbal consent for a Stanford research team member to come to the school site and do informed consent process and screening at school for any participants that may have

transportation barriers.

Caregivers will undergo a telephone or in-person screening according to the inclusion and exclusion criteria. Written consent for participation will be obtained from participants, parents and/or legal guardians. Participants will be randomly assigned to one of three treatment conditions: TF-CBT, CCT, or TAU. Assessments will be administered at 4 time points: 1) pre-treatment, 2) mid-therapy, 3)post-treatment, and 4) three month follow-up. A medical/developmental history form will be completed only pre-treatment. The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI-II) will be administered only pre-treatment to rule out potential confounds for neuroimaging. The UCLA PTSD Reaction Index (PTSD-RI) parent and child versions will be used to assess exposure to traumatic events and posttraumatic stress symptoms. Given that trauma has high comorbidity with depression and anxiety disorders these symptoms will be assessed using the Multidimensional Anxiety Scale for Children (MASC), Children's Depression Inventory (CDI), and Trauma Symptom Checklist for Children (TSCC) or Trauma Symptom Checklist for Young Children (TSCYC). Executive functioning will be assessed by both child and parent report using the Behavioral Rating Inventory of Executive Function (BRIEF) and the Brief Impairment Scale (BIS) for the parent. A post-treatment services form will be completed only at the three month follow up appointment.

In addition, functional near-infrared spectroscopy (fNIRs) will be conducted at each of these time points to assess tasks of working memory, response inhibition, and facial recognition. We will be using the NIRScout which is a portable NIRS recording unit. NIRS technology uses specific wave lengths of light, introduced at the scalp, to enable the noninvasive measurement of changes in the relative ratios of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) in the capillary beds during brain activity.

The collaborating institutions roles will be for Judy Cohen of Drexel University to provide weekly case consultation via phone for the TF-CBT therapists as well as evaluate audio recordings for fidelity. Carl Weems of Iowa State University will serve as a consultant for statistical analyses. Susana Rivera of Serving Children and Adults in Need, Inc. will evaluate Spanish audio recordings for fidelity.

### b. Procedure Risks

The current research design poses minimal risk to the participants. All participants will be closely monitored for any adverse events that may arise from the study. All participants will be assisted in obtaining further treatment if needed.

### c. Use of Deception in the Study

N/A

### d. Use of Audio and Video Recordings

Audio recordings will be made of every treatment session for each of the three study interventions for the purposes of intra and inter rater reliability, if consent is given. These recordings will be identified only by subject number, will be kept in a locked file cabinet, and in a locked office. Only research staff on this project will have access to this data. Anonymity of all participants will be maintained throughout. If caregiver consent is provided, the audio recordings may be used in scientific meetings. The recordings will be destroyed after completion of the study.

Audio for participants at SYS will be recorded using encrypted, password protected recording devices owned by Stanford University. Recording devices at SYS have already been approved for use since the launch of the study. New iPads are being introduced to be used to audio record therapy sessions at the UCSF site. Stanford has purchased 3 iPads for their use. These iPads have gone through the attestation process and are fully compliant to be used with PHI by Stanford University. All devices and iPads are kept locked, are secure and password-protected. All audio files are uploaded and stored in MedBox, and then deleted from the devices.

### e. Alternative Procedures or Courses of Treatment

Other forms of psychotherapy or psychopharmacology may be advantageous to participants. However, there is no strong evidence to suggest that these treatments are necessarily better than the interventions that participants will be receiving.

### f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes.

### g. Study Endpoint(s)

The study is scheduled to end by July 2020. On average, each individual will actively participate for three to four months. If one study intervention clearly proves to be more effective than another during the course of the study then the study will be terminated before the projected total number of participants has been enrolled and we will make that intervention available to all participants.

## 3. BACKGROUND

### a. Past Experimental and/or Clinical Findings

A previous RCT of CCT (Carrion et al., 2013), sought to examine the efficacy of the intervention as a short-term, manual-based intervention for youth in the school setting with interpersonal violence exposure undergoing concurrent and chronic environmental adversity. The study findings, published in the Journal of Traumatic Stress (Carrion et al., 2013), utilized hierarchal linear modeling analyses to show that compared to the waitlist group, the cue-centered treatment group had greater reductions in PTSD symptoms both by caregiver and child report, as well as caregiver anxiety. Cue-centered treatment, a hybrid trauma intervention merging diverse theoretical approaches, demonstrated feasibility, adherence, and efficacy in treating youth with a history of interpersonal violence.

The previous RCT proved the efficacy of CCT compared to a waitlist group. The next step therefore, is to compare CCT to an active treatment which we chose to be TF-CBT due to the numerous RCTs proving the efficacy of TF-CBT in reducing trauma and associated symptoms. However, about 20-30% of youth do not respond to cognitive-behavioral therapies.

### b. Findings from Past Animal Experiments

N/A

## 4. DEVICES USED IN THE STUDY

### a. Investigational Devices (Including Commercial Devices Used Off-Label)

| **Investigational Device 1** | |
|---|---|
| Name: | N/A |

### b. IDE-Exempt Devices

| **IND-Exempt Device 1** | |
|---|---|
| Name: | NIRScout |
| Description: | The device is a portable NIRS recording unit. NIRS technology uses specific wavelengths of light, introduced at the scalp to enable the non-invasive measurement of changes in the relative ratios of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) in the capillary beds during brain activity. |

## 5. PARTICIPANT POPULATION

### a. Planned Enrollment

135 participants between 7 and 18 years of age and 135 caregivers (one caregiver for each participant). Participants will be enrolled at SYS in Sacramento (not Stanford-affiliated) and at UCSF CAS in San Francisco (not Stanford-affiliated). These will be trauma exposed youth presenting with posttraumatic stress symptoms and their caregivers as this is the target population for CCT and TF-CBT.

### b. Age, Gender, and Ethnic Background

Youth ages 7-18 will be recruited for the study of all genders and ethnic backgrounds.

### c. Vulnerable Populations

This study involves vulnerable subjects as we aim to study the effectiveness of several interventions for traumatized youth. 135 youth will be under treatment with therapists trained in assessment and treatment of traumatized youth. They will evaluate participants to determine if they need additional resources. We will provide referrals to those resources and work closely with SYS and UCSF CAS to ensure they are provided and SYS and UCSF CAS also have additional supportive services to which participants may be referred. For those youth that are community-referred, our research staff and therapist will provide the participants with any appropriate resources necessary.

### d. Rationale for Exclusion of Certain Populations

N/A

### e. Stanford Populations

N/A

### f. Healthy Volunteers

N/A

### g. Recruitment Details

Potential participants will be identified by the therapists at SYS and by staff at UCSF CAS. A designated contact person at each site will verify that potential participants agree to be contacted for screening by the research coordinator/UCSF designated staff. The study coordinator/UCSF designated staff will only then conduct a phone or in-person interview with potential participants' legal guardians to assess inclusion/exclusion criteria. If qualified participants and their legal guardians consent, they will be enrolled in the study.

Potential participants may also be identified via responses to flyers posted in community centers and public forums. Additionally, flyers, letters, and supplemental informational guides will be sent to physicians/pediatricians, schools, and community organizations to distribute to any patients or students that may be identified as potential participants.

School staff will speak with parents of children they have identified as potential study candidates and with verbal consent will submit parent’s name and phone number so that the Stanford University research coordinator can make contact directly to conduct phone screening. School staff may also obtain verbal consent for a Stanford research team member to come to the school site and do informed consent process and screening at school for any participants that may have transportation barriers.

### h. Eligibility Criteria

#### i. Inclusion Criteria

1) Report exposure to at least one traumatic event and endorse any symptoms on the UCLA PTSD Reaction Index
2) Ages 7-18
3) Willingness to participate in therapy and fNIRs imaging
4) Caregiver willing to participate in the study
5) Perpetrator of the traumatic event is not living in the home with the child

#### ii. Exclusion Criteria

1) Low cognitive functioning (IQ less than 70)
2) Substance dependence as defined by DSM criteria
3) Autism/Schizophrenia
4) Clinically significant medical illness

### i. Screening Procedures

Participants will be referred by therapists at SYS and by a designated staff member at UCSF CAS to be recruited for the study. 135 participants will be enrolled by Stanford research staff. The research coordinator/designated UCSF staff will contact caregivers of potential participants to conduct a phone or in-person screening to go over inclusion/exclusion criteria. Participants and their caregivers that qualify and provide consent will be enrolled in the study.

A letter will also be sent to physicians, pediatricians, and other clinicians in hospitals and clinics asking them to refer any patients that may be potential participants. Flyers will also be distributed in community organizations, youth centers, schools, and other community public spaces.

School staff will speak with parents of children they have identified as potential study candidates and with verbal consent will submit parent's name and phone number so that the research coordinator can make contact directly to conduct phone screening. School staff may also obtain verbal consent for a Stanford research team member to come to the school site and do informed consent process and screening at school for any participants that may have transportation barriers.

### j. Participation in Multiple Protocols

We will ask participants if they are enrolled in other studies. Participants may enroll in more than one study.

### k. Payments to Participants

Participants who complete all behavioral assessments and fNIRs at each time phase will receive a $25 gift card (a total of $100) which will incentivize participants to complete the assessments.

### l. Costs to Participants

There are no costs to the participant.

### m. Planned Duration of the Study

The entire duration of the study will be 4.5 years ending in July 2020.
(i) 10-15 minutes for screening of participants
(ii) 15-18 weekly 45-minute treatment sessions over the duration of 3 months. There will be completion of 3 hour behavioral assessments over 4 time points (pre-, mid-, post-treatment and six month follow-up). Participants will also do 45-60 minutes of fNIRs imaging at each of the time points.
(iii) Participant data will be processed and analyzed per participant, but mostly in bulk. Participant data will be analyzed periodically throughout the length of the study. After data acquisition, data will be checked for quality and will be double-entered. Analysis will be within and between groups.

## 6. RISKS

### a. Potential Risks

i. Investigational devices

N/A

ii. Investigational drugs

N/A

iii. Commercially available drugs, biologics, reagents or chemicals

N/A

iv. Procedures

None.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

None.

vii. Psychological well-being

The therapy sessions may cause uncomfortable feelings such as anxiety. However, in our experience participants appreciate the opportunity to talk about the traumatic experience and how it has impacted them and their families. The treatment can be stopped upon the parent or child's request. Previous published studies of cognitive-behavioral treatments for children with trauma have been effective at lessening depression, anxiety, and psychosocial dysfunction symptoms.

Other potential risk may be that in the course of treatment, other medical/psychological issues may be discovered that the child/caregiver was previously unaware of which may increase psychological distress. In this event, participants will be provided with appropriate referrals.

In the event that a participant endorses suicidal ideation, a system will be put in place in which non-clinician research staff will be provided with a list of questions to assess risk including specific thoughts of suicide, presence of a plan, means to carry out the plan, history of prior suicide attempts, availability of family and community support, and family history of suicide. The research staff will then contact a designated licensed research clinician (Dr. Carrion or Dr. Kletter) who will be available by phone within an hour. The clinician will review the information and guide the research staff on which safety procedure to follow which may include creation of a safety contract, referral to community resources, or contacting 911 for transport to the nearest emergency room if there is imminent danger. The study therapists are all clinicians trained in suicide assessment and will be able to assess risk and respond according to clinical judgment should ideation be expressed during the course of treatment.

viii. Economic well-being

None.

ix. Social well-being

Both CCT and TF-CBT have components of enhancing the relationship between caregiver and child, and strengthening the child's social support.

x. Overall evaluation of risk

**Low** - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

### b. International Research Risk Procedures

N/A

### c. Procedures to Minimize Risk

Confidentiality will be maintained by using designated therapy rooms at SYS (including for community-referred youth) and UCSF CAS and assigning participants a coded number by which all their data will be identified.

For school-referred youth, therapy may be provided at their respective school site in designated rooms for confidential therapy sessions. These rooms are already being used by school psychologists and social workers and will be made available for us to minimize any potential transportation barriers for participants.

Evaluation of the participants will occur at three time points during the treatment and if any hazards are detected such as co-morbid psychological symptoms, the study therapists will provide appropriate referrals to community resources.

### d. Study Conclusion

The study will terminate in July 2020, after all 135 participants have completed treatment.

Regular evaluations during four time points (pre-, mid-, post- treatment, and 3 month follow-up) will facilitate identification of any adverse effects. If participants have clinically significant worsening of PTSD, anxiety, or depressive symptoms, suicidal or violent behaviors, or substance dependence therapy will be discontinued. The study therapists, all masters level clinicians, will be able to make community referrals if they determine further intervention is warranted. Adverse effects and specific stopping triggers will be reported to the IRB.

### e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

N/A

ii. Person(s) responsible for Data and Safety Monitoring

N/A

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

N/A

v. DSMB Reporting

N/A

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes.

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No.

### f. Risks to Special Populations

Research not involving greater than minimal risk. The research must present no greater than minimal risk to children and adequate provisions must be made for soliciting the assent of the children and the permission of their parents or guardians. Please provide rationale for the above statement.

## 7. BENEFITS

The study interventions may reduce participants PTSD, anxiety, and depressive symptoms. Furthermore, the study hopes to elucidate which interventions are most appropriate for which youth and what child characteristics impact treatment outcome, which may result in improved treatment selection and more individually tailored treatment in the future.

## 8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.