STUDY PROTOCOL

STUDY TITLE: Mind over Mood

R61 PHASE: Social Cognitive Training to Enhance the Efficacy of CBT for Depression in Youth: A Developmental Approach

STUDY IRB NUMBER # 190077

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1.0 BACKGROUND

Depression is a recurrent and persistent disorder associated with impairment in multiple domains and increased risk for substance use disorders and suicide (e.g., Costello, Erkanli, & Angold, 2006; Reinecke & Curry, 2008). Therefore, finding efficacious treatments for depression in adolescents is critical. Medications can reduce depression in youth, but they also can have undesirable side effects (Vitiello & Swedo 2004). Psychotherapies have been shown to successfully reduce depression in children and adolescents, although the overall effect sizes have been modest (e.g., ES=.34; Weisz, McCarty, & Valeri, 2006). A review of 52 RCTs testing the efficacy of psychotherapies for children and adolescents with depression, found that both Interpersonal Psychotherapy [IPT (ES = .56)] and Cognitive Behavioral Therapy [CBT (ES = .46)] were significantly more beneficial than most control conditions at post-treatment and at follow-up (Zhou et al., 2015). Thus, efficacious treatments for youth depression exist, but there is still room to improve upon these treatments. There remains a critical need to improve upon these therapies to reach even more youths with depression.

One variable hypothesized to affect children's interpersonal relationships is their level of social cognitive development on abilities particularly relevant to social functioning (e.g., social perspective taking). This study will test whether an intervention that aims to increase social cognitive (SC) abilities will improve these skills in youth with depression. We focus on the particular social cognitive abilities of perspective taking/theory of mind (ToM), because impairment in these skills has been associated with greater difficulties in interpersonal relationships and with depression (e.g., Bora & Burk, 2016; Nestor, Sutherland, & Garber, 2022). Social perspective taking ability also has a clear link to the skill of cognitive reappraisal, which is taught in CBT (Garber et al., 2016). The Social Cognitive abilities that are the focus of this intervention include recognition that other people may not see things the same way one does, which helps people have a better understanding of others' thoughts and feelings. This is particularly important when a person is experiencing disappointment or anger about what another person did or did not do. By taking the other person's perspective, the aim is for the person to see that their belief about the situation might not be what is going on.

Youths (ages 12-17) with depression diagnoses or clinical levels of depressive symptoms (CDRS-R $\geq$35) will be randomly assigned to either the social cognitive training enhanced CBT (CBT+SCT) or to CBT only. Pre- and post-treatment evaluations will assess social cognitions and depression. If the CBT+SCT intervention significantly improves children's SC abilities and decreases their depressive symptoms, then this will substantially improve clinical care.

2.0 SPECIFIC AIMS

This randomized controlled trial (RCT) aims to treat youths ages 12- to 17-years-old who have a current diagnosis of a depressive disorder or high levels of depressive symptoms (CDRS-R $\geq$35). The aim is to test the effects of CBT+SCT for (1) increasing children's social cognitive (SC) abilities. We also will examine the effects of the treatments on reducing depressive symptoms.

Hypothesis: Adolescents receiving CBT+SCT will show significantly higher levels of SC abilities at post-intervention, controlling for pre-intervention levels, as compared to youth in CBT alone.

Exploratory Hypothesis: Youth in CBT+SCT will show significantly lower levels of depressive symptoms at post-intervention, controlling for baseline levels, as compared to youth in CBT only.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Participants ages 12-17 years at the time of enrollment
2. Participants with a current diagnosis of a depressive disorder (Major Depression, Pervasive Depressive Disorder, Depression not otherwise specified) as defined by the Diagnostic and Statistical Manual of mental disorders (DSM-5) or clinical levels of depressive symptoms (CDRS-R $\geq$35).

Exclusion Criteria

1. Serious, current suicidality or in need of more intensive services (e.g., partial or inpatient programs)
2. Current substance or alcohol use disorders
3. A lifetime history of schizophrenia, psychosis, mania, or conduct disorder

4.0 ENROLLMENT/RANDOMIZATION Eligible participants will be randomized to either CBT+SCT or CBT only; randomization will be stratified by teens' age (12-14, 15-17), sex, race/ethnicity, and current medication use.

5.0 Study Procedures

Phone Screen. Study team members will conduct an initial phone screen with parents/guardians to determine initial study eligibility of the child for the study. Participants who appear eligible following the phone screen will be invited to complete a diagnostic interview to verify study eligibility.

Eligible teens will be randomly assigned to one of the two individual treatments with a Masters-level or PhD therapist for up to 12 sessions and they will complete assessments before and after treatment

Treatment appointments will be scheduled at a time that is mutually agreed upon among participants and providers – most likely afternoons or early evenings. Participants taking medications will be able to continue. All appointments may be conducted remotely (i.e., Zoom).

Assessments

-- The first assessment is an interview with the parent and teen separately to determine eligibility for the study.
-- Interviews take about 2 hours and are recorded via Zoom.
-- The second interview will occur at the end of treatment about 12 weeks after the start of treatment.
-- Participants will complete online surveys at pre- and post-treatment evaluations (about 60 minutes).
-- Teens also will complete measures on the computer administered by a research assistant (60 minutes).

Treatment

-- Eligible teens will be assigned randomly to one of the treatments. Both therapies teach skills for coping with stress, problem solving, assertive communication, engaging in positive activities, and realistic thinking. In addition, CBT+SCT teaches additional skills for taking others' perspectives.
-- Teens will meet remotely with a therapist for individual sessions (about 50 minutes). Therapy sessions will be recorded via Zoom for quality control (i.e., to ensure that the therapist covers the material correctly).
-- Teens will receive up to 12 individual therapy sessions as part of the study. Additional sessions beyond 12 are not considered part of the research protocol, but teens may continue therapy with their original therapist, or we can provide referral information to another therapist if desired.

Compensation for participation

Parents and children will be paid for completing the assessments. Gift cards (e.g., Amazon) will be given after completion of each assessment as follows:

- A parent and teen participant will be paid for completing all parts of the study as follows:
  $50 for the first assessment (pre-treatment: to determine eligibility)
- If eligible and child participates in the study, then $50 for the post-treatment assessment
- Payments will be made through gift cards (e.g., Amazon), given after completion of each assessment.

6.0 **Reporting of Adverse Events or Unanticipated Problems involving Risk**

Data and safety monitoring plan general description: The PIs will monitor the accuracy (reliability and validity) of all data collected. All measures were selected based in part on their established levels of reliability and validity. All data will be checked for errors prior to any analysis. Assessment data will be obtained through online electronic forms and on standard paper-and-pencil forms as needed; all interviews will be audio-recorded, and responses will be recorded on standard forms. Data will be reviewed by the research coordinator for missing data or outlying values and these questions will be referred to the relevant interviewer. All data will be stored in a secure, shared Box folder with locked sharing permissions using the SAFER add-on. Participants will be identified by alphanumeric codes only; names and other possible identifiers will **not** be included in the electronic database. Identification numbers do not reveal the identity of participants (e.g., no birth dates, initials, social security numbers). An archival record of all data collected that has passed through the above-noted checks will be maintained on a secured server.

Data Safety Monitoring Board: A Data and Safety Monitoring Board (DSMB) monitors the clinical trial and serves as a reporting body to the NIH as well as to the respective IRBs. The primary role of the DSMB is to monitor the safety of participants in both intervention conditions, receive reports of all adverse events in a timely and consistent fashion, and check the validity and integrity of the data. The DSMB is composed of three members, none directly involved in the project or employed by the participating institutions. The DSMB consists of experts knowledgeable in several areas relevant to this study including social cognitive development and emotion regulation in children and adolescents (Janice Zeman, Ph.D.), prevention and treatment of depression in youth (Jane Gillham, Ph.D.) and biostatistics (Scott Maxwell, Ph.D.).

Data monitoring and participant safety: The DSMB first will review and approve the protocol and subsequently conduct annual reviews to determine whether participant safety has been adequately safeguarded and enrollment goals have been met. The DSMB will be informed of any protocol-related serious adverse events when they occur. The PI will take whatever immediate action is necessary to safeguard the welfare of participants; the DSMB also will be called upon to render judgments if any serious clinical problems (e.g., serious suicidal intent) occur. The DSMB will serve as the final arbiters of whether individual participants should be removed from the study. The DSMB also will be called upon to render judgments when any serious clinical problems (e.g., serious suicidal intent) occur. Psychiatric or other life crises that are high risk and imminent will be acted upon immediately with staff linking participants to appropriate crisis services. These are reviewed immediately with the clinically responsible PI. Lower risk and less imminent crises are reviewed within 48 hours by the clinically responsible PI. Interim analyses will be conducted at each annual review for safety only, not effectiveness. Assuming there are no safety issues, we will prepare the data for analysis.

Critical Incident Protocol & Reporting of Adverse Events: We will collect interview and questionnaire data that could indicate potential harm to participants (e.g., participants expressing intent to harm self or others, or data indicating child, spousal, elder or other forms of abuse or neglect). The *Critical Incident Protocol* will be triggered if a participant reveals information indicating possible or actual harm to themselves or others. Information collected by questionnaires will be monitored by research staff within a day of data collection. All adverse events or unanticipated problems involving risk to participants or others will be reported to the appropriate agency as required including the IRB, specific state agency and stakeholders (TN), the Data Safety and Monitoring Board, and the National Institute of Mental Health. The clinically responsible PIs will monitor and report any adverse events. The PIs also will supervise all study staff, interviewers, and therapists to ensure that all required protocol procedures are followed.

Adverse events and clinical worsening of symptoms. Because the intervention sessions address sensitive issues for participants and are designed to help youth modify their cognitions, there may be a temporary increase in anxiety or other negative emotions. Therapists will monitor youth for such adverse reactions. If significant problems are identified, then the therapist will discuss the case with Drs. Garber or Hollon to determine if further intervention is needed. We will follow the guidelines defining adverse events, serious adverse events, and unanticipated problems set forth by the IRB at Vanderbilt University. All serious adverse events will be reported to the IRB according to the procedures outlined in their regulations. We will monitor participants' depressive symptoms at the pre- and post-intervention. We also have participants complete the PHQ each week to check for individuals whose symptoms may have worsened requiring further evaluation and clinical service. If a participant reveals currently active suicidal ideation, attempts, or non-suicidal self-injury during therapy or the clinical evaluation, therapists and evaluators will follow the "critical incident" plan that specifies what should be done if such an event occurs. Therapists and evaluators will have information about how to contact clinical supervisors (PIs) if they have any questions about what to do at any point. All such serious incidents are reported within 48 hours to the Vanderbilt IRB and DSMB.

7.0 Study Withdrawal/Discontinuation

The PI may recommend that a participant be taken out of the research study to ensure his/her safety and well-being. Some reasons include:

- If the PI or therapist determines that a participant is not receiving the appropriate treatment
- The participant’s condition worsens, reports serious suicidality, or is deemed to be a risk to

him/herself or others. A participant may require more intensive treatment. In either case, the research team will discuss this with participants and will provide them with other appropriate clinical resources, as needed.

If a participant wants to withdraw from study participation, they should tell the therapist, interviewer, or Project Coordinator. Deciding not to be part of the study will not affect their medical care in any way.

8.0 Statistical Analysis Plan

We will use the general linear model (i.e., MANCOVA) to test hypotheses. The between subjects factor will be *Condition* with two levels (CBT+SCT vs. CBT only) and the within-subjects factor will be Time with two levels (baseline, post-test). We will adopt a multivariate approach to repeated measures (as assumptions of compound symmetry are untenable). Dependent variables (DVs) will vary across analyses; child age and sex, will be covariates in all analyses.

Specific Aims. To test whether youth in CBT+SCT have better SC skills at post-treatment than youth in CBT only at post-treatment.

Hypothesis: We will test the effect of CBT+SCT on SC skills (target) using the *Faux Pau* task as the DV. We will first test the 2x2 Condition x Time interaction. We expect that a 2x2 partition of this interaction will be significant, reflecting the Condition effect from baseline to post-test.

Exploratory Hypothesis: To test the effect of CBT+SCT on depressive symptoms, the DV will be the clinician-rated depression measure (CDRS). Analyses will be the same as described for the main hypothesis except that we will test the depression measure as the dependent variable.

Power. To estimate power, we assumed that autocorrelations among the repeated measures were .4 - .6. With N=42 (21 per cell), alpha = .05, and a medium effect size (e.g., a .40 SD Condition effect at T2), we will have approximately .82 power to detect the initial 2x2 Condition x Time interaction (f_V = .32). Assuming correlations of .3-.6 among the same measure over time, alpha = .05, and medium effect sizes we will have .85 power for the 2x2 Condition by Time interaction.

9.0 Privacy/Confidentiality Issues: *Methods for protecting privacy and confidentiality.*

All research data will be coded with a study ID number rather than names. No identifying information will be stored with research data. A database linking participant contact information to study ID numbers will be password-protected and stored on a secure server. Only key study personnel involved in contacting participants will have access to this information. Questionnaire data will be collected and stored online.

We will generate codes to protect participant identities; these codes will be comprised of a 4-digit number. Following the completion of the study, de-identified research data will be maintained indefinitely to verify the integrity and validity of results of the study. Documents with identifying information and the database linking contact information to study codes will be destroyed seven years after completion of analyses of study data and publication of the results.

Confidentiality: Participants and parents will be informed during the consent process that confidentiality is limited in cases of child abuse/neglect or imminent risk of harm to self or others. In cases of suspected child abuse or neglect, the PI will be notified, and we will follow the requirements to file a report based on the law. If a teen expresses current severe suicidality, the interviewer or therapist will inform the parent/caregiver and then follow the procedures described in the critical incident protocol.

All efforts, within reason, will be made to keep participants' personal information in the research record confidential, but total confidentiality cannot be guaranteed. The research files at Vanderbilt include the following identifiers that are kept separately from the research data: participant's name, address, phone number, e-mail address, date of birth, and a unique study ID number.

- Research records will be labeled only with the study ID number and kept separate from any documents containing identifying information.
- The signed consent form will be stored separate from data.

The study has some support from the National Institutes of Health (NIH), and therefore participants' study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out participant information even if requested using legal means. It does not protect information that we have to report by law, such as child abuse or some infectious diseases.

The Certificate does not prevent us from disclosing information if we learn of possible harm to a participant or others, or if a participant needs medical help. Disclosures that participants consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that participants make themselves are also not protected.

- Participants' de-identified, coded research information may be put in one or more databases and used for future research. Information stored in these databases will not include any identifying information such as participants' name, address, telephone number, or date of birth. Participants' research data will only be available to researchers who have received approval from data access committees and/or Institutional Review Boards. Some of these databases are maintained by Vanderbilt, some are maintained by the federal government, and some are maintained by other institutions.
- If any publication or presentation results from the research, no personally identifiable information will be shared. Participants' de-identified research data will be maintained indefinitely to verify the integrity of the data and validity of results.

Privacy: All efforts, within reason, will be made to keep participants' information private. Using or sharing ("disclosure") such data must follow *federal privacy rules*. By signing the consent for this research study, participants are agreeing ("authorization") to these uses and sharing of data.
Vanderbilt University may share the results of the study to the following groups: the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, or the study sponsor (National Institute of Health). Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep participants' research data private. Participants' data will be shared with the appropriate authority as required by law if someone is in danger of being harmed, or a participant has experienced physical or sexual abuse or neglect.

The study results will be kept in participants' research record for at least seven years after analyses of the study data are finished. Unless told otherwise, participants' consent to use or share de-identified data does not expire. If participants change their mind, they should contact Dr. Garber in writing and let her know that they withdraw their consent. Her mailing address is Department of Psychology & Human Development, Peabody College #552, 230 Appleton Place, Nashville, TN 37203-5721. At that time, we will stop getting any more data from the participants, but the data we stored before withdrawal of consent may still be used for reporting and research quality.