Neurally Targeted Interventions to Reduce Early Childhood Anxiety

NCT04960813

May 17th, 2024

Office of IRB Social/Behavioral/Educational Research (SBER) Protocol

1. STUDY TITLE

Neurally Targeted Interventions to Reduce Early Childhood Anxiety

2. PRINCIPAL INVESTIGATOR

Kate Fitzgerald, MD. Department of Psychiatry, Columbia University
Jason Moser, Ph.D. Department of Psychology, Michigan State University

3. STUDY RATIONALE

Deficits of effortful control (EC) have been posited to underlie early emerging anxiety such that improving EC may help to reduce anxiety symptoms. This study will test a play-based EC training intervention (Kidpower-Structured Games) against an active comparator (Child-led Play) in clinically anxious preschoolers to test the hypothesis that EC training will improve EC and thereby reduce anxiety.

4. SPECIFIC AIMS/HYPOTHESES

Aim 1: Confirm that Kidpower-Structured Games engages neural and behavioral markers of EC. We hypothesize that Kidpower-Structured Games will produce greater increases in neurophysiological and behavioral markers of EC than Kidpower-Child-Led Play (CLP, active comparator).

Aim2: Assess the relationship between pre- to post-Kidpower-Structured Games change in neurobehavioral markers of EC and change in clinically significant anxiety. We hypothesize that increases in neurophysiological and behavioral measures of EC will relate to reductions in clinically significant anxiety from pre-to-post Kidpower- Structured Games. Exploratory analyses will examine the moderating effects of baseline threat reactivity on the relation between pre- to post-treatment increase in EC and reduction in anxiety severity.

Aim 3: Explore dosing effects of Kidpower-Structured Games on behavioral EC targets and anxiety symptoms. We hypothesize that greater at-home practice of Kidpower-Structured Games exercises will relate to greater engagement of neural and behavioral markers of EC targets and greater reduction in anxiety symptoms. Dosage will be assessed by weekly parent report on child practice of EC exercises at home (frequency, duration).

5. BACKGROUND AND SIGNIFICANCE

Preschool anxiety is prevalent, with 20% of children affected (Buffered et al, 2012). Among these, a majority will continue to experience symptoms throughout adolescence and adulthood (Bittner et al, 2007). Early childhood anxiety also predisposes to a host of negative, long-term outcomes, including major depression and substance abuse (Bittner et al, 2007; Zimmerman et al, 2003), underscoring the importance of early intervention.

We will test a neuroscientifically-derived intervention targeting effortful control (EC) skills, low levels of which have been linked to greater emotional reactivity and clinical anxiety. Defined as the ability to effectively regulate behavior and emotion, EC reflects the activity of frontal brain systems and can be indexed by an event-related brain potential, the error-related negativity (ERN) and time frequency interchannel phase synchrony (ICPS) (Moran et al, 2015). The ERN is a neurophysiological response, localized to the dorsal anterior cingulate cortex, signaling the need for adaptive behavioral adjustments following errors (Gehring et al, 2018). The ICPS reflects the transmission of this error signal to the dorsolateral prefrontal cortex in order to implement the specified control (Cavanagh et al, 2009).

Findings from our labs and the work of others have shown that reduced ERN and ICPS relate to behavioral deficits in EC and enhanced threat reactivity (Lo et al, 2015) similar to that documented in clinically anxious children (Meyer, 2017). In response, our team developed a child-friendly group EC training, Camp Kidpower-Structured Games, designed to increase ERN, ICPS and related EC behaviors in the service of decreasing anxiety symptoms in preschoolers. Results of our pilot study indicate that this brief EC training approach engaged the intended EC neural and behavioral targets and reduced anxiety symptoms (Schroder et al, 2022). Building on this pilot work, the current project aims to replicate and extend these findings in a larger sample using a randomized controlled design.

The Kidpower-Structured Games condition will be tested against an active comparator "Child-led Play" condition (Kidpower-CLP). Kidpower-Structured Games will involve executive function training games, shown to improve executive function skills in preschoolers (Diamond and Ling, 2016) and tested previously for the treatment of children with ADHD (Halperin et al, 2013). Kidpower-CLP will permit identification of specific effects of the EC training by controlling for confounds including: a) participation in a fun playgroup; b) interaction with new children during activities; c) separation from parents; and d) time spent with new adults. As detailed next, Kidpower-CLP is derived from evidence based treatment for early childhood psychopathology; in this study, it will include structured play activities (art activities, dramatic play, and story time), but not EC games. Both Kidpower-Structured Games and -CLP conditions will be delivered to small groups of clinically anxious preschoolers by study team members at the same staff to child ratio.

Child-led play has been shown to foster the development of cognitive, physical, social, and emotional well- being of children (Ginsburg et al, 2007). Moreover, play is important to healthy brain development (Shonkoff and Phillips, 2000; Frost, 1998; Tamis-Lemonda et al, 2004). When play is allowed to be child driven, children practice decision-making skills, move at their own pace, discover their own areas of interest. Additionally, child-led play promotes healthy parent-child attachment. The most widely employed early childhood psychotherapy, Parent Child Interaction Therapy (PCIT), focuses on Child-led Play for the first half of treatment. During this portion of PCIT, children experience child-directed play with their parents to encourage warm, secure caregiver–child relationships (Lieneman et al, 2017). The child-led play condition in Camp Kidpower gives children the opportunity to direct their own play at camp, while training parents to deliver child-led play at-home. As such, it fosters development across cognitive, social, neural and relational domains.

6. RESEARCH DESIGN AND METHODS (1 page maximum)

Participants are randomized to a camp-style intervention ("Camp Kidpower"), which includes either EC training (Kidpower-Structured Games) or child-led playgroup (active comparator; Kidpower-CLP). Before and after the 4-week intervention, a multi-level assessment will be completed, including clinical interview with parent about their child's anxiety symptoms, parent-report surveys on child and self, lab-observed behavioral tasks and electroencephalogram (EEG) with child. Primary analyses will test for group mean differences in neurophysiological and behavioral indices of EC from time 1 (pre-intervention) to time 2 (post-intervention) among children assigned to Kidpower- Structured Games training compared to those in assigned to Kidpower-CLP. Secondary analyses will test relationship of changes in neurophysiological targets with change in EC behaviors and change in anxiety severity.

The Kidpower-Structured Games were adapted from a group-based intervention originally designed to treat EC deficits in children with attention deficit hyperactivity disorder (Halperin et al, 2013) and a recently published review of executive function and effortful control interventions (Diamond and Ling, 2016). Kidpower-CLP was developed by the study team to include all of the same elements as Kidpower-Structured Games except for EC training games.

Both Kidpower-Structured Games and Kidpower-CLP will occur over 4-5 sessions, for approximately 3 hours each session. Sessions may be delivered back-to-back or over the course of four weeks. Times will be chosen to maximize child focus and energy and to provide the most convenience for families. Regardless of condition, children will begin with a group welcome activity, then will complete 1-2 of the intervention exercises for that day with their camp counselor. After a brief break and snack, children will complete the remaining 1-2 intervention exercises with their camp counselor, then come back together for a final group activity. The last 30 minutes of camp will include parents, who will be assigned daily homework involving the same play as at camp to complete with their child in between camp sessions. Two parent meetings (led by the lead camp counselor) will take place; the first will occur prior to the beginning of camp to orient parents, and the second will be held mid-way through camp to answer questions that may have arisen.

Error-eliciting Zoo Task: The “Zoo task”, a “Go/No-Go” paradigm assessing effortful control, has been found to reliably elicit ERN in preschoolers (Grammer et al, 2014). Before performing the task, children are instructed to help the game’s zookeeper find all the escaped animals. Children then view a series of animals on a computer screen and are asked to press a button when a new animal appears (Go trials), unless the animal is an orangutan (i.e., inhibit button response,

No-Go trials). The task includes 8 blocks, each containing 30 unique animals (Go trials) and 10 orangutans (No-Go trials) in random order.

Error Related Negativity (ERN): As children play the Zoo task, EEG data will be recorded from 32 scalp sensors embedded in an elastic cap using the BioSemi Active 2 system (Amsterdam, The Netherlands). ERPs from fronto-central recording sites time-locked (within 100 ms) to error and correct response will be examined. Differentiation between these trial types is the primary ERN measure, but we will also consider ERN on error trials, as well as ERPs on correct trials separately. Previous research indicates that the ERN demonstrates good psychometric properties across children, adolescents and adults. The number of NoGo errors and response times (RTs) to Go trials will also be considered in NP analyses, as performance can affect ERN amplitude.

Time Frequency Interchannel Phase Synchrony (ICPS): Using the same approach previously employed by our group, complex time-varying energy time-frequency distributions (TFDs) of all the EEG signals at each channel extracted from the Zoo task (described above) will be obtained using the reduced interference distribution (RID) Rihaczek distribution. RID based TFDs offer improved time-frequency support relative to wavelets. Functional connectivity will be assessed using interchannel phase synchrony (ICPS), based on the phase locking value (PLV), derived from the RID TFDs. Current source density (CSD) transform will be applied to EEG data before phase synchrony analysis to reduce volume conduction, using published methods. We will focus on ICPS within the theta band in the ERN time window. Consistent with previous work, the current study will report ICPS between FCz and lateral frontal sites, indexing mediolateral functional connectivity, indexing control processing.

Behavioral Measures: Pre/post behavioral tasks are drawn from widely employed temperament protocols - e.g., Lab-TAB, Kochanska battery (Kochanska et al, 1996), and the age-normed NIH Toolbox (Zelazo et al, 2013). In addition to these tasks, free play time will be given to children and parent during the session. Behavioral tasks will be videotaped (if consent is given) for analysis. Behavioral tasks total approximately 2 hours per visit.

While completing select behavioral tasks (potential threat task, speech task, and bubbles task) (McGinnis et al, 2016), children may be asked to wear a lab-owned smartphone attached to a belt that will be worn around the child's waist. The smartphone uses a custom program, designed specifically for this research application/data collection and is not publicly available. It will guide administrators through the tasks by prompting them to press a ‘start’ and ‘stop’ button for data collection. It stores raw motion and audio data from the smartphone's accelerometer and microphone, labeled only with a de-identified numeric ID. The smartphone will not be connected to either cellular or wireless networks during data collection. This de-identified data will be transferred to the secure servers via physical wire and immediately deleted from the device after each lab visit. Motion and audio data on tasks are especially helpful for generating behavioral indices of fear. In the potential threat task, children walk besides experimenter towards a covered terrarium, and motion data indexes reluctance to approach-- a behavioral correlate of Fear. In the speech task, audio data can be submitted to machine learning algorithms to discern speech patterns associated with anxiety severity. Motion and audio data during the Bubbles task will be used to generate a behavioral index of Reward.

Clinical Measures: May include a combination of clinician-assessed and clinical self-report measures for child anxiety and depression, temperament, development, intelligence, and parent psychopathology and experiences. These may be administered during screening, at either of the lab visits, and/or during the follow-up phone call. Questionnaires may be administered via paper forms or via online via a secure application such as Qualtrics. A summary of measures and timing for administration is included in the Uploads section.

Data collected in the current study will be collapsed together with data collected using the same study protocol at Michigan State (N = 71), New York State Psychiatric Institute (N =43) to test study aims.

In the current study, up to 20 participants will be enrolled at the Columbia University Site. The Michigan State University site has completed enrollment and will assist in data analysis.

7. RESEARCH PARTICIPANTS (2-3 paragraph maximum)

Children with clinical anxiety symptoms aged 4-5.99 years old

This study will examine the mechanistic plausibility of EC training for childhood anxiety, promoting developmental trajectories towards positive mental health.

Inclusion criteria

1. Participants must be 4.0-5.99 years old at time of consent.
2. Has primary clinical diagnosis of separation anxiety disorder, social anxiety disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and/or specific phobia if symptoms present more days than not.
3. Written informed consent by a parent/legal guardian.
4. Fluent in English (note: participant may be bilingual, but must be able to speak and understand fluent English to participate in study.)

Exclusion criteria

1. History of head injury
2. History of serious neurological illness or current medical illness
3. History of major depressive disorder (MDD)
4. History of post-traumatic stress disorder (PTSD)
5. History of neurodevelopmental delay, autism spectrum disorder (ASD), or intellectual disability
6. Currently taking medications that affect the central nervous system (e.g., stimulants for ADHD, SSRIs for anxiety/depression, alpha agonists for ADHD or tics).
7. Currently receiving psychotherapy or other behavioral interventions
8. Primary clinical diagnosis is selective mutism.
9. History of recent physically aggressive behaviors that have caused harm to other children
10. Sibling of a child who has participated or is currently participating in this protocol

Parents of children with clinical anxiety symptoms

Inclusion criteria

1. Fluent in English (note: Participant may be bilingual, but must be able to speak and understand fluent English to participate in Questionnaire study)
2. Parent lives with child at least 50% of time
3. Has access to internet and webcam
4. Written informed consent for self and for their child

Exclusion criteria

1. Under 18 years of age
2. Not able to meet scheduling demands of the study

8. RECRUITMENT

The majority of participants are expected to contact the study team after seeing study advertisements on social media or flyers posted in the community. Copies of IRB-approved study recruitment materials (e.g., flyers) may also be provided to clinic or school staff for them to share with potentially eligible participants; if interested, potential participants may then contact the study team to learn more. Once in touch with a study team member, potential participants will be provided with study information and their parent/caregiver will be assessed with an IRB-approved phone screen (see Telephone Screening Questionnaire). A waiver of written documentation of consent is requested for phone screening and retention of a password-protected "Subject Screen Log" that will contain child name, child age, parent name, parent email address and/or phone number, date of phone screen, and brief reason for likely eligibility or ineligibility. Retention of this information will be used by the study team to prevent from repeat screening of potential participants previously deemed ineligible or not interested, and to facilitate recontact for those who are eligible/interested but would like to participate at a later date. After the phone screen, potential subjects will proceed to signing a written consent ("enrolled"), followed by a detailed clinical assessment to confirm eligibility. If ineligible based on this assessment, the subject will be considered "withdrawn"; consent forms will be retained for those

withdrawn, but all other collected data will be destroyed except for reason for ineligibility and other information already contained in the Subject Screen Log.

Recruitment Settings at Columbia University:
The study team may provide approved recruitment materials to the following programs to share with potentially eligible participants:

CAPES Evaluation Service and the Youth Treatment and Evaluation of Anxiety and Mood (Y-TEAM) Program
The CAPES Evaluation Service and the Youth Treatment and Evaluation of Anxiety and Mood (Y-TEAM) Program is part of the Children's Day Unit at the New York State Psychiatric Institute. The CAPES/Y-TEAM provides free expert consultation, evaluation, and treatment referrals for children suffering from mood and anxiety disorders.

Morgan Stanley Children's Hospital of New York (CHONY)
Clinics at the Morgan Stanley Children's Hospital of New York (e.g., primary care Pediatrics, the Integrated Mental Health Program, School-Based Mental Health Program, and Pediatric Psychiatry Clinic).

Columbia University Center for Anxiety and Related Disorders (CUCARD) and Faculty Practice Organization (FPO)
CUCARD and the FPO sees 300 new children and adolescents per year referred for anxiety disorders. Clinic staff are experienced in providing families with information about potential research opportunities at Columbia University.

Private Practice
Mental health professionals who see children with anxiety disorders in private practice.

Primary Care Doctor's Offices and Clinics
Primary care clinics at CUIMC or identified through publicly available sources (i.e., websites, Google search). Initial outreach to provide study information to clinics is shared by email from research assistants to clinic leadership, copying Dr. Fitzgerald, the study Principal Investigator, noting that she is available to address any questions/concerns (see email template, "Coordinator_to_Clinic_Email_Template_2.18.23").

Schools & Daycares
As with primary care clinics, preschool/kindergarten programs will be identified through publicly available sources (e.g., websites, Google search). Initial outreach to provide study information will be sent by research assistants to leadership at schools & daycares, copying Dr. Fitzgerald, the study Principal Investigator, noting that she is available to address any questions/concerns (see email template, "Coordinator_to_Preschool_Email_Template_2.18.23").

Advocacy and Support Groups
Patient advocacy (e.g., International Obsessive Compulsive Disorder Foundation) and support groups (e.g, parent support groups).

Craigslist and Nextdoor
Craigslist website and on Nextdoor in local communities.

Social Media (e.g. Facebook, Twitter, and study-related websites)
An IRB-approved description of our study will be advertised on social media and relevant websites (e.g. departmental, Psychology Today). Facebook advertising may include groups of treatment providers, support group leaders, and parents or paid Facebook ads.

New York Family
New York Family runs a website (www.NewYorkFamily.com) and publishes regional print magazines that describe resources and activities for families in the NYC area. They also provide opt-in email targeting, where they send emails on the behalf of organizations and other companies to parents in NYC who have subscribed to their emails and who

have allowed third party partner promotions. InsideSchools is a project of the Center for New York City Affairs at The New School and runs a website (www.InsideSchools.org) that provides information about the NYC school system. New York Family sends newsletters to InsideSchoolssubscribers.

LinkedIn
LinkedIn to communicate with colleagues about our research efforts.

Google Ads
Google advertisements to advertise Dr. Fitzgerald's recruitment webpage as one of the top search results for parents who make searches regarding pediatric anxiety in the NYC area.

RecruitMe:Columbia
Columbia University's RecruitMe, an online tool to connect potential research participants with researchers conducting relevant studies.

Flyers
Posted on bulletin boards in Columbia University Medical Center buildings as well as in local laundromats, grocery stores, public libraries, and community centers. Please see the attached flyers.

Recruitment Settings at Michigan State University:
None. The MSU site has completed recruitment and will not be enrolling any future participants.

9. INFORMED CONSENT

Prior to conducting the eligibility portion of the telephone screen, research staff will document verbal consent to proceed with the conversation in the Subject Screening Log. Additionally, a waiver of documentation of consent is requested for the phone screen.

Prior to initiating baseline clinical assessment procedures, research staff will obtain written consent from the participant's parent/legal guardian for themselves to participate in the study (parent informed consent) and for their child to participate in the study (parental permission). Research staff will describe the purpose and nature of the research study and answer any questions. Parents/legal guardians will receive signed copies of both the parent informed consent and the parental permission.

Informed consent is a process that is initiated prior to the potential child subject's parent agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this intervention will be provided to the parent/legal guardian, including risks related to travel for in-person visits during COVID-19. The parent will be made aware that the study team requests they not initiate other treatment for their child's anxiety during their participation in this study. It will be made clear that this study is voluntary, so they are free to seek other treatment for their child at an any point if they feel it is needed. If they are considering said additional treatment, the researcher obtaining consent will request that they discuss this with the study team first, and may need to be withdrawn from the study as a result.

Consent for remote clinical or research procedures will be documented, and the consent discussion process will include discussion of the technology HIPAA-compliant platforms to be used and any concerns the patient may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or internet.

Consent forms (written in non-technical language, understandable by the parent of the participant to be enrolled in the study) describing in detail the study interventions, procedures, and risks will be given to the parent. Upon reviewing the documents, one of the investigators (or their designee) will explain the research study to the subject/parent and answer any questions that may arise.

Informed consent will be obtained via e-signature in REDCap. At the beginning of the first study visit, research staff will review the consent with the parent/guardian and collect e-signatures for each of the following:

Parent Informed Consent

1. Consent for parent study participation
2. Consent to use parent audio and video recording for sharing/training purposes:
    - For training purposes within the research team at CU/MSU.
    - For training purposes outside CU/MSU.
    - For community outreach and to raise general awareness of this work.

Parental Permission

1. Consent for child's study participation
2. Consent to use child audio and video recording for sharing/training purposes:
    - For training purposes within the research team at CU/MSU.
    - For training purposes outside CU/MSU.
    - For community outreach and to raise general awareness of this work.

A waiver of documentation of consent is used for the phone screen.

Persons designated to discuss and document consent:

- Fitzgerald, Kate, MD
- Chen, Yu-Hsuan (Sherry), BA
- Hay, Briana, BS
- Risdon, Caroline, BS

10. PRIVATE, IDENITIFABLE INFORMATION ABOUT RESEARCH PARTICIPANTS

We collect the following identifiable information: Parent name, child name, parent date of birth, child date of birth, parent email address, parent cell phone number, parent city of birth, child city of birth.

To ensure adequate protection of human subjects, the investigators and research staff will complete human subjects training as required by their respective institutions (e.g., CITI Training at CU). Every possible effort will be made to limit identifiable information on potential subjects during recruitment. The minimum amount of necessary information will be recorded, and staff are aware of the dangers of emailing, printing, and faxing sensitive information. Conversations in which a patient or participant's name must be mentioned (e.g., determining study eligibility) will occur in private settings. Phone calls with potential research subjects will occur behind closed doors. Remote visits will be conducted via HIPAA-compliant video teleconferencing to protect confidentiality, all in accordance with the CU Remote Communications Guidance.

During camp, children will only be addressed by first name (or first initial if desired by family and the child is responsive to this option) to help protect participant privacy.

Privacy of each parent and child's clinical research information will be protected and only reviewed by the PI and study staff. Mandatory reporting of child abuse and neglect (e.g., detected in surveys, reported in interviews) is required in accordance with clinical standard practice. If a study team member learns that a subject has the potential to harm him or herself, or another individual, we will break confidentiality and take steps to prevent harm. Similarly, any evidence of potential child abuse will be reported to Child Protective Services. Mandatory reporting is explained to subjects in the informed consent document as a limit to confidentiality.

In all records from this study, the names of participants and their family members will be available only to the team of researchers working on the study. Neither their names nor any identifying information will be used in any scientific reports from this study or from secondary data analyses conducted with de-identified data from this study. Participants will be assigned a unique coded subject identification number and their names will not be on any study materials. We will use the study data only for scientific, education, or instructional purposes. To ensure confidentiality, the master list of identifying information needed for participant contact, such a names, addresses, and telephone numbers, will be kept in a password-protected and encrypted database. All virtual information is saved on password-protected computers, and all email communication is secure and encrypted. The computing systems are protected from outside access by firewall systems. Paper records are kept in file drawers in a locked room and paper records with identifying information (e.g., payment records) are kept in locked file cabinets physically separate from the research records. Only authorized research personnel will have access to the locked rooms in which these records are contained.

All questionnaire and task responses, including data from the data from clinical interviews will be kept confidential, and will only be marked with subject ID numbers. An electronic database will be used to store the coded data, and the key linking to identifiable subject information will be kept separate from the database with research data. This coded data will be stored using MSU Qualtrics which is a secure, HIPAA- compliant application. Access to Qualtrics requires authorization and the study's database is encrypted and password-protected (see Data Management Plan for details).

Mandatory reporting of child abuse and neglect (e.g., detected in surveys, reported in interviews) is required in accordance with clinical standard practice. If a study team member learns that a subject has the potential to harm him or herself, or another individual, we will break confidentiality and take steps to prevent harm. Similarly, any evidence of potential child abuse will be reported to Child Protective Services. Mandatory reporting is explained to subjects in the informed consent document as a limit to confidentiality.

11. RISK MINIMIZATION

Participation in clinical, EEG and behavioral assessments involve everyday procedures that are similar to those a participant could encounter during doctor's visits or at school (i.e., no more than minimal risk).

Risks Associated with All Study Assessments

1. Loss of confidentiality around sensitive information.

To minimize risk: All research subjects are assigned research numbers, and only this number links all data collected to the subject. A single tracking file contains links to the research records and subject codes. Paper records are kept in locked file drawers in a locked room to which only authorized research personnel have access. Paper records with identifying information are kept in locked file cabinets physically separate from the research records. Computer records with identifying information are kept on secure, password protected servers. All research staff will be well trained to protect the confidentiality of sensitive information.

2. Some psychological (emotional) discomfort for parents answering questions included in the standard surveys.

To minimize risk: When collecting measures, the study team will pay particular attention to questions regarding self-harm. We will require participants to complete the two measures that include these questions (the PHQ-9 and CBCL) prior to leaving the lab visit. If suicidality is suspected based on parent surveys/answers or revealed by the parent or child during the assessment, the PI Kate Fitzgerald (child psychiatrist) will be contacted and readily available to conduct a comprehensive suicidal assessment and establish a safety plan or referral to Psychiatric Emergency Services in accordance with standard psychiatric care.

3. Discomfort or anxiety in child participants at separation from parents, during the camp intervention and/or pre- and post-visits.

To minimize risk: Upon arrival for assessment, children will be given ample time to interact and play with research staff under supervision of their parent or guardian (typically while the adult is completing the informed consent). This will allow children to meet the research staff in a safe context with parent nearby. Children may be shown parent's location in a nearby room during the assessment, and parents will be able to view their children at any point during the assessment through a secure, closed-circuit camera if needed. If a child's distress at separation becomes extreme, then the child will be reunited with parent based on evaluator discretion.

Risks Associated with Neurophysiological Assessment

1. Most likely risk to participants is minor physical discomfort (e.g., needing to sit still while performing the experiment, coolness of electrode gel applied to scalp) or anxiety associated with placement of the electrophysiological equipment.

To minimize risk: We will rely on procedures that have been widely employed in the developmental psychophysiology literature and which have been used when conducting similar tasks in pilot work in our lab. For EEGs, we will take special measures to reduce children's anxiety about the novel equipment. This will involve play time in our EEG collection room as well as sharing a short video/story with the parent and child about the experiment.

2. Participants may experience some discomfort upon removal of the electrophysiological equipment – specifically, facial electrode sensors.

To minimize risk: Participants will be informed that facial electrode sensors are similar to Band- Aids and will help guide their preference for removal.

Risks Associated with Neurophysiological Assessment

1. Most likely risk to participants is minor physical discomfort (e.g., needing to sit still while performing the experiment, coolness of electrode gel applied to scalp) or anxiety associated with placement of the electrophysiological equipment.

To minimize risk: We will rely on procedures that have been widely employed in the developmental psychophysiology literature and which have been used when conducting similar tasks in pilot work in our lab. For the youngest child participants, we will take special measures to reduce children's anxiety about the novel equipment. This will involve play time in our EEG collection room as well as sharing a short video/story with the parent and child about the experiment.

2. Participants may experience some discomfort upon removal of the electrophysiological equipment – specifically, facial electrode sensors.

To minimize risk: Participants will be informed that facial electrode sensors are similar to Band- Aids, to help guide their preference for removal.

Risks Associated with Behavioral Battery

1. Some children may experience some emotional discomfort or apprehension when engaging in the behavioral "potential threat task." During this task, children enter a room and are asked to approach a covered terrarium. When they get close, the cover is lifted by the experimenter to reveal a benign object (e.g., a tissue box). This task elicits uncertainty during approach.

To minimize risk: Particular care will be taken during debriefing of the potential threat task. Child participants will be reassured that the covered object is not threatening immediately after its presentation. If a child becomes overly distressed, the protocol may be interrupted and parent can interact with child to provide comfort. The task may be

ended early if the child becomes tearful or otherwise highly distressed. All participants will be given a 5-minute free play with the parent immediately after the fear task to regulate and debrief.

Risks Associated with Intervention Training

1. Risks of participating in the camp are minimal, and include boredom or frustration with training tasks, similar to experiences children may encounter in a day-to-day school environment.

To minimize risk: Participants will be allowed breaks throughout daily training. Study team members conducting the camp will have experience with young children and be closely supervised by Dr. Fitzgerald.

2. As with any group activity with children, there is always the possibility of unpredictable behavior, which could cause children discomfort or distress.

To minimize risk: Every precaution will be taken to ensure the safety of all children participating in the camp. This includes reserving the right to ask children to discontinue participation if there is reasonable concern for unsafe behavior.

Risks Associated with COVID-19

1. Travel to CU for the onsite sessions may increase risk of exposure to COVID-19.

To minimize risk: The safety regulations put forth by CU will be strictly adhered to while onsite, and the study team will work with participants to find convenient and safe ways to commute (also providing transportation reimbursement if requested). During consenting procedures, participants will be reminded to exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. If they do not feel safe traveling at a certain time, they can call to reschedule visits. Finally, all personnel administering in-person behavioral tasks, EEG, and camp interventions will maintain social distancing when able, wear masks at all times, and sanitize hands and surfaces frequently to reduce risk of infection.

___ Check here if the **only risk** of the research is a breach in confidentiality. If so, no additional information is required in this section.

12. POTENTIAL BENEFITS

Regarding the prospect of direct benefit to participants, both arms of this study involve an active intervention: Effortful Control and Child-Led Play (the control group). As cited in the protocol, the Effortful Control activities are based on prior studies demonstrating the benefit of these game-like tasks for a variety of children's skills, such as executive functioning, attention, and motor skills. Additionally, decades of research support the benefits of Child-Led Play. Play is a crucial context in which children learn important social emotional skills and build relationships with peers and adults. Both of the study arms involve positive, structured experiences with supportive adults and with children, which is beneficial for youth development, particularly among clinically anxious children. Lastly, parents may obtain important information and insight from the course of participation, including via the comprehensive assessment conducted to determine eligibility.

13. REFERENCES

Bittner, A., Egger, H. L., Erkanli, A., Jane Costello, E., Foley, D. L., & Angold, A. (2007). What do childhood anxiety disorders predict? Journal of Child Psychology and Psychiatry, and Allied Disciplines, 48(12), 1174–1183.

Bufferd, S. J., Dougherty, L. R., Carlson, G. A., Rose, S., & Klein, D. N. (2012). Psychiatric disorders in preschoolers: continuity from ages 3 to 6. The American Journal of Psychiatry, 169(11), 1157–1164. https://doi.org/10.1176/appi.ajp.2012.12020268

Cavanagh, J. F., Cohen, M. X., & Allen, J. J. B. (2009). Prelude to and Resolution of an Error: EEG Phase Synchrony Reveals Cognitive Control Dynamics during Action Monitoring. Journal of Neuroscience, 29(1), 98–105. https://doi.org/10.1523/JNEUROSCI.4137-08.2009

Diamond, A., & Ling, D. S. (2016). Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. DevelopmentalCognitiveNeuroscience,18,34–48. https://doi.org/10.1016/j.dcn.2015.11.005

Frost JL. (1988). Neuroscience, play and brain development. *Paper presented at: IPA/USA Triennial NationalConference*

Ginsburg, K. R., Committee on Communications, & Committee on Psychosocial Aspects of Child and Family Health. (2007). The importance of play in promoting healthy child development and maintaining strong parent-child bonds. *Pediatrics*, 119(1), 182-191.

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (2018). The Error-Related Negativity. Perspectives on Psychological Science: A Journal of the Association for Psychological Science, 13(2),200–204.

Halperin, J. M., Marks, D. J., Bedard, A.-C. V., Chacko, A., Curchack, J. T., Yoon, C. A., & Healey, D. M. (2013). Training executive, attention, and motor skills: a proof-of-concept study in preschool children With ADHD. Journal of Attention Disorders, 17(8), 711–721.

Lieneman et al, 2017. Parent Child Interaction Therapy: Current Perspectives Psychol Res Behav Manag 10:239-256

Lo, S. L., Schroder, H. S., Moran, T. P., Durbin, C. E., & Moser, J. S. (2015). Neurophysiological evidence of an association between cognitive control and defensive reactivity processes in young children. Developmental Cognitive Neuroscience, 15, 35–47.

Meyer, A. (2017). A biomarker of anxiety in children and adolescents: A review focusing on the error-related negativity (ERN) and anxiety across development. Developmental Cognitive Neuroscience, 27, 58-68.

Moran, T. P., Bernat, E. M., Aviyente, S., Schroder, H. S., & Moser, J. S. (2015). Sending mixed signals: worry is associated with enhanced initial error processing but reduced call for subsequent cognitive control. Social Cognitive and Affective Neuroscience, 10(11), 1548–1556. https://doi.org/10.1093/scan/nsv046

Schroder HS*, Ip KI*, Hruschak JL, Horbatch F, Hall M, Liu Y, Manella K, Muzik M, Rosenblum KL, Moser JS, **Fitzgerald KD**. Targeting cognitive control to reduce anxiety in very young children: A proof-of-concept study (2022). *Depression and Anxiety:* **39(8-9)**:646-656. *Co-first authors. PMID: 35708131.

Shonkoff, J. P., & Phillips, D. A. (2000). From Neurons to Neighborhoods: The Science of Early Childhood Development. eric. ed. gov. *National Academy of Sciences Press: Washington DC. Accessed on May, 8, 2015*

Tamis-LeMonda C.S., Shannon J.D., Cabrera N.J., & Lamb M.E. (2004). Fathers and mothers at play with their 2- and 3-year-olds: contributions to language and cognitive development. *Child Dev*., 75:1806–1820

Zimmermann, P., Wittchen, H. U., Höfler, M., Pfister, H., Kessler, R. C., & Lieb, R. (2003). Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. Psychological Medicine, 33(7), 1211–1222.

14. BIBLIOGRAPHY

List up to five relevant articles that the IRB can use to provide necessary background for the protocol. Do not append an extensive grant-style bibliography.

Grammer, J. K., Carrasco, M., Gehring, W. J., & Morrison, F. J. (2014). Age-related changes in error processing in young children: a school-based investigation. Developmental Cognitive Neuroscience, 9, 93–105.

Kochanska, G., Murray, K., Jacques, T. Y., Koenig, A. L., & Vandegeest, K. A. (1996). Inhibitory control in young children and its role in emerging internalization. Child Development, 67(2), 490–507.

McGinnis, E., McGinnis, R., Muzik, M., Hruschak, J., Lopez-Duran, N., Perkins, N., … Rosenblum, K. (2016). Movements indicate threat response phases in children at-risk for anxiety. IEEE Journal of Biomedicaland Health Informatics 21(5):1460-1465.