Virtual Reality to Improve Social Perspective Taking in Youth with Disruptive Behavior Disorders

Tom Hummer, PhD
Department of Psychiatry, Indiana University School of Medicine

Health Information and Translational Sciences
Room 1001R
410 W. 10th Street
Indianapolis, IN 46202

William Kronenberger, PhD, IUSM Department of Psychiatry
Dawn Neumann, PhD, IUSM Department of Physical Medicine and Rehabilitation
Susan Perkins, PhD, IUSM Department of Biostatistics
Zeb Wood, MS, IUPUI School of Informatics and Computing

Support Provided by:
National Institute of Mental Health

Table of Contents:

1.0 Background & Rationale

Oppositional defiant disorder (ODD) and conduct disorder (CD), collectively known as disruptive behavior disorders (DBDs), involve persistent physical or verbal confrontations, antisocial behavior, and emotional outbursts. Despite a range of biological and environmental risk factors for DBD, social-cognitive impairments are a common link, and improving these deficits should be beneficial for all patients with DBD.

Children and adolescents with DBD have deficits in social perspective taking that contribute significantly to these behavior problems.[1, 2] Perspective taking is the ability to perceive the world from another person's point of view,[3-6] including making inferences about the capabilities, feelings, and expectations of others.[7, 8] It is often measured via self-report measures such as the Perspective Taking subscale of the Interpersonal Reactivity Index.[9]

Perspective taking requires substantial motivation and cognitive resources and can be difficult to achieve, particularly for children.[10, 11] A failure to understand or value another person's perspective inhibits helping behavior without clear direct benefits.[12, 13] Perspective taking skills are related to empathic concern, which encompasses feelings of sympathy and concern for unfortunate others,[14] and theory of mind, the ability to accurately infer others' mental states, such as intentions.[15, 16] Negative attribution biases are more likely in individuals with poor theory of mind.[15, 17] Thus, improving children's perspective-taking skills should allow them to better understand a counterpart's thinking and intentions, increasing empathic concern, and reducing hostile attribution biases–and therefore improving the likelihood that prosocial behavior occurs.

In the brain, perspective taking engages circuitry underlying empathic concern and theory of mind. In fMRI studies, imagining pain to the self or other, often in conjunction with images depicting painful scenarios, engages a network of regions including anterior insula, dorsal anterior cingulate cortex (dACC), somatosensory cortex, supramarginal gyrus, and amygdala.[18-22] A meta-analysis by Lamm et al.[21] detected that dACC and bilateral anterior insula, the regions most commonly activated in response to other's pain, also show strong responses to self-perspective pain. However, in youth with DBD, there is a decreased response to other-perspective pain in dACC and anterior insula, despite no change or a heightened response to self-perspective pain.[23-25]

Current treatments to address DBD include a range of pharmaceutical options, one-on-one therapies, and extended prevention programs. For instance, outpatient therapy options include parent management training, which focuses on parent-child interactions, and cognitive-behavioral therapies that specifically target emotion regulation and social problem-solving.[26, 27] Strategies to improve children's social perspective taking include social skills training, video modeling, acting classes, role-playing, mindfulness training, and parental conversational techniques.[2, 4, 28-38] However, these strategies often require continued engagement, motivation, and interest from children, and they can be difficult to implement in a self-directed or individualized manner.

To address these concerns, software interventions have shown some promise to improve perspective taking. In a recent adult study,[30] users could inhabit the first-person perspective (via a computer screen) of a negotiation counterpart by experiencing parts of their day. This

alternative perspective was found to improve perspective taking and result in more equitable conflict resolution relative to text instructions or other ways of learning about the counterpart. With virtual reality (VR), research in adults has found that inhabiting the virtual body of a member of a specified outgroup reduces stereotypes and increases positive feelings for the elderly,[39] different races,[40] and patients with schizophrenia[41] or colorblindness.[42] Enacting long-term cognitive or behavioral changes is difficult in children with DBD, and we do not expect small doses to have an extended long-term impact. However, our hope is that extended VR software packages can be developed to work over the long-term, likely in conjunction with more traditional therapy strategies.

VR has exciting therapeutic potential to address perspective-taking deficits because it provides naturalistic yet controlled environments in which users can experience interactions from multiple viewpoints. VR interventions typically provide better generalization to real-world behavioral changes compared to traditional methods.[43] VR has an advantage over traditional interventions because it provides an embodied experience that is a middle ground between therapy room settings and the real world (e.g., school, home) where problematic behaviors occur. Our own preliminary data with a VR school cafeteria environment indicates that children find VR to be enjoyable and easy to use, and it invokes real-world reactions—youth with greater conduct problems interpreted encounters with virtual counterparts as more hostile.

In this investigation, we will build upon our current VR design using an Oculus Quest virtual reality headset. After experiencing virtual interpersonal conflicts, subjects will re-experience scenarios in one of two manners: an enriched perspective from the virtual counterpart's point-of-view, with internal dialogue and background information; or a control perspective, which replays the original point-of-view. During this proof-of-concept phase, our primary target is social perspective taking. We will assess functional engagement of this target by quantifying (1) the ability to recognize and understand the virtual counterpart's perspective; and (2) the neural response (in pain circuitry) to pain experienced by the virtual counterpart, a common marker for perspective taking that is abnormal in DBD.[23, 24, 44]

Medical Device:

The Oculus Quest virtual reality headset will be categorized as a medical device for this investigation. Oculus Quest is commercially available for use by all ages and does not present any serious risks to the health, safety, or welfare of subjects. The headset is a standalone device with goggles and headphones that is used outside the laboratory for both educational and entertainment purposes (for video games, movies, sporting events, etc.). It is similar to other commercially available VR headsets. When using the Oculus Quest, visual stimuli are presented via the goggles along with corresponding sounds. With this investigation, we will program software to present virtual scenarios to participants for short periods at a time (<3 minutes). A minority of participants may experience VR sickness during their experience, which is similar to motion sickness (e.g., mild nausea or lightheadedness). These effects are temporary and dissipate soon after removing the headset, which can be easily done at any time. In addition, these effects are no different than could be experienced if the participant was using the headset outside the laboratory for entertainment purposes.

2.0 Objectives

To investigate the impact of virtually experiencing alternative perspectives on social perspective-taking mechanisms, we will target the following specific aims in youth aged 9-12 who have been diagnosed with a disruptive behavior disorder.

Aim 1: To determine if experiencing alternate perspectives within a VR scenario (with internal dialogue and background context) engages social perspective-taking processes in youth with disruptive behavior disorders.

Aim 2: To evaluate whether VR perspective-taking scenarios increase neural sensitivity to pain experienced by virtual counterparts.

3.0 Outcome Measures

Primary Outcome Measure: VR Perspective Taking Scale
This scale measures the degree to which participants understand the perspective of their virtual counterpart. It will be completed after each VR scenario, both pre- and post-intervention. Each participant's change score will be as Post-treatment (Endpoint; following all VR) vs. Pre-treatment (Baseline; after first scenario). The Cohen's d effect size will be calculated using the difference in mean change scores between treatment and control conditions (e.g., $[Mean_{Enriched\ Post\text{-}Pre} - Mean_{Control\ Post\text{-}Pre}] / SD_{pooled}$), resulting in an effect size measurements for both scales with each treatment condition.

Primary Outcome Measure: Acknowledgement of Other Perspective Scale
This scale allows participants to rate the relative importance of the virtual counterpart's perspective with a scenario-specific question. It will be completed after each VR scenario, both pre- and post-intervention. Each participant's change score will be as Post-treatment (Endpoint; following all VR) vs. Pre-treatment (Baseline; after first scenario). The Cohen's d effect size will be calculated using the difference in mean change scores between treatment and control conditions (e.g., $[Mean_{Enriched\ Post\text{-}Pre} - Mean_{Control\ Post\text{-}Pre}] / SD_{pooled}$), resulting in an effect size measurements for both scales with each treatment condition.

Primary Outcome Measure: Neural response to Self vs. Other Pain
This is an fMRI measure of brain function while imagining pain happening to oneself or the virtual counterpart. Following standard preprocessing of fMRI data, we will calculate the regression coefficient for each stimulus type (Self Pain; Self No Pain; Other Pain; Other No Pain). We will extract mean activity from a priori regions-of-interest (ROIs), established as 10-mm radius spheres around MNI coordinate peaks in dACC (-2,33,40) and anterior insula (left: -40,22,0; right: 39,23,-4), which were identified as key regions for pain response in a recent meta-analysis. Brain activity will be quantified by contrasting self-perspective pain (Self Pain vs. Self No Pain) with other-perspective pain (Other Pain vs. Other No Pain). Cohen's d effect size will be calculated separately for each treatment and each ROI. For more traditional statistical measures, a 2x3 (pain perspective condition by group) within-subjects ANOVA test will be performed on data from each ROI.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

Children:

- Aged 9-12 at time of enrollment
- English-speaking
- Meet DSM-5 criteria for oppositional defiant disorder (ODD), conduct disorder (CD), or Other Specified or Unspecified Disruptive, Impulse-Control, and Conduct Disorder
- Right-handed
- Estimated full-scale IQ greater than 70

Parents/Guardians:

- English-speaking
- Must live with child participant
- Reliable reporter of child's personality and behavior

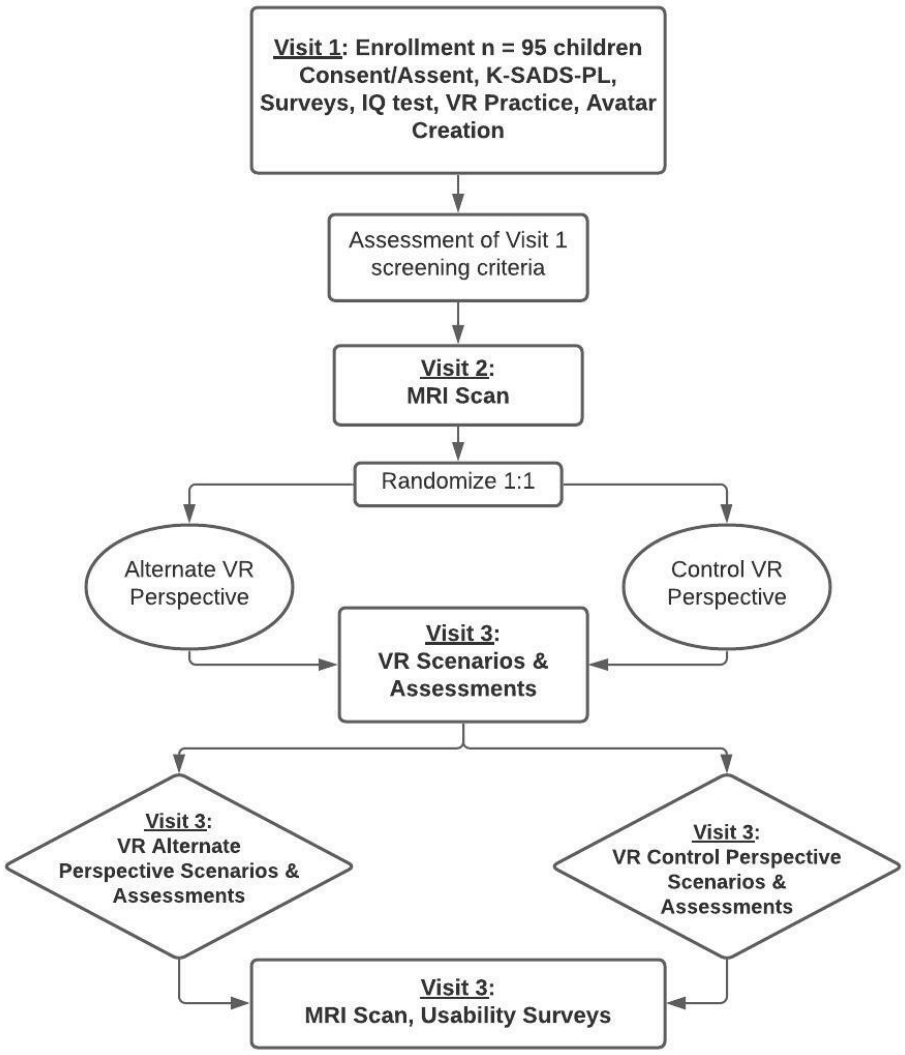
4.2 Exclusion Criteria

Children:

- Bipolar disorder, any disorder involving psychosis, pervasive developmental disorders, current or past substance use disorder, or current major depressive disorder
- History of neurological problems (e.g., epilepsy, traumatic brain injury)
- Contraindications for MRI
- Sibling who has participated in this study
- Experience negative side effects during use of virtual reality (e.g., VR sickness)
- In opinion of investigator, cannot complete study procedures or is inappropriate for study participation

5.0 Study Design

This project will examine how levels of a virtual reality treatment that provides users with the alternate perspective of an interpersonal interaction impacts psychological and neurobiological markers of perspective taking. Prior to Visit 3, participants will be randomly assigned to different VR perspective conditions, stratified by sex, presence/absence of ADHD diagnosis, and ODD/CD diagnosis, via an a priori randomization chart. An equal number of youth will be randomly assigned to either the alternate perspective condition or control condition. Assignment will be sealed for the experimenter until immediately prior to Visit 3 (for visit preparation, experimenter must be unblinded). Visits 1 and 2 will be identical for both groups. At Visit 3, the initial VR scenarios and assessments will be identical. The participant will then re-experience the VR scenarios depending on their assigned condition. Additional VR assessments and the MRI scan will be identical for both groups.



6.0 Recruitment & Enrollment/Randomization

Participants will be recruited in a variety of manners, including direct contact and flyers at the Riley Child and Adolescent Psychiatry Clinic (RCAPC) and Eskenazi Health, print and radio advertisements, community flyers, work with local organizations, and potential contact through recruitment services and health databases.

At the RCAPC, all clinical psychologists, psychiatrists, and social workers at the clinic will be informed of the study and provided informational flyers for patients, which will also be posted in the waiting room. The same will occur at Eskenazi Health. Providers may also post a brief description of the study along with our contact information, links to our lab Facebook page and REDCap landing page (described below), and a QR code linked to our REDCap Landing Page in their virtual waiting rooms seen by patients waiting for their remote visits to begin.

We will also recruit subjects from a medical records review with information provided to us by the IU Health Research Data Extraction process. The IU Health Information team will evaluate the medical records from the RCAPC and provide our study team the general information (name, MRN#, birthdate, date of diagnosis, etc.) and contact information of patients who meet our study's inclusion and exclusion criteria. Once provided with a list of children who may match our study's qualifications, we will reach out to parents via the contact information provided to describe our study and gauge their interest in participating, through a postcard mailed to their address and then follow-up with phone calls or emails, or via direct email contact.

Paper flyers will also be posted in public arenas around the Indianapolis area, including libraries, bus stops, coffee shops, and other community boards. Flyers may also be posted in IUPUI and IU Health facilities, or additional local child mental health facilities where permission has been provided. Flyers will also be provided to current subjects who indicate an interest in providing information to other interested subjects. We will also contact local organizations, including local schools and summer camps. Potential participants and parents will be asked to email or call our recruitment-designated email address and/or phone number.

We may partner with community organizations who may post information about our study on their social media sites (Facebook, Instagram, Twitter, etc.). These posts may include study details, pertinent inclusion/exclusion information, study contact information including our recruitment website, and will not emphasize payment for participation. Partner organizations may also provide contact information of potentially interested parties. The research team can then initiate contact with potential subjects to gauge their interest in participating in our study.

We will also recruit parents/guardians of potential participants via study information provided to the All IN for Health Research and Clinical Studies database (https://allin4health.info/) and the ResearchMatch database (https://www.researchmatch.org/). The All IN for Health Research and Clinical Studies database is powered by TrialX iConnect and provides a list of active studies being conducted in Indiana by faculty at Indiana University and other research institutions in the surrounding area. Anyone can browse studies by location, keywords, health topics, or conditions and directly contact the study team. ResearchMatch is a similar database, although national in scope. Another aspect of the All IN for Health database and ResearchMatch is their volunteer registry. Researchers can browse users who have agreed to input their medical history, and request to contact those who might match the qualifications for our study. Some study flyers will also include a QR code directing participants to our information on these sites.

Study information will be included in the iConnect All IN for Health e-updates newsletter, emailed bi-monthly to more than 32,000 subscribers which includes those in the All IN for Health volunteer database. The newsletter shares what's going on in the community to improve Indiana health. Study information will also be posted from the iConnect social media accounts (Facebook, Instagram, Twitter, etc).

A study posting with a brief description of the study will also be sent to IUHealth News, which is sent to all IUHealth employees.

We will post study information to online community boards, such as craiglist.org, nuvo.net, IU classified pages, and similar sites.

Information about the study and a link to our All IN For Health page and our REDCap landing page will also be posted on our lab website, on our lab Facebook page, and on the IU School of Medicine Facebook page. Members of the study team may also share or post information about the study on their personal social media sites. This information will note that the study is paid but will not include specific payment information (e.g., dollar amounts).

We will also recruit parents/guardians of potential participants via social media. We will run Facebook ads from our lab account and from the IUSM account that show information about the study to targeted Facebook users. Our target user will be adults in Indianapolis with children ages 9 – 12. If a user would like more information and clicks on the post, they will be directed to one of two places: either our study's All IN for Health Research and Clinical Studies website where there is an opportunity to contact the study team directly, or to our REDCap landing page where there's an opportunity to answer some brief eligibility questions then contact the study team. The REDCap page will ask broad, preliminary questions related to study criteria, but these responses will not be used to assess eligibility. We will reach out to individuals who provide contact information via the REDCap page, in order to provide additional study information.

IndyVRstudy.com is our study website that displays information about the study (what's involved, who is eligible, etc.) and information about the research team (contact info, link to our lab Facebook page). There are also multiple buttons that redirect visitors to our REDCap landing page for additional information. The site will be used with word-of-mouth recruitment, on social media posts, and with other recruitment materials as study contact information.

Parents and children will also be recruited via an online blog post by the Indy's Child magazine. This blog post will include information about the study and links to the lab Facebook page as well as the All IN For Health page. If interested, potential subjects will be able to enter their information via All IN For Health. This blog post will target our specific demographic of parents in the Indianapolis area.

We will also use on-air radio and tv commercials to recruit potential subjects. This ad will briefly describe the study, potentially mention compensation, and direct those interested to reach out by phone or email or to visit our recruitment website (IndyVRstudy.com).

Digital ads containing a brief description of the study with a hyperlink to our recruitment website will be displayed on the WFYI website, as well as sent out in e-newsletters to WFYI subscribers.

We will also run a people-based marketing campaign. Digital ads such as emails, social media, website banner ads etc. will be presented to parents and teachers in the Indianapolis area who voluntarily submitted their information to a media habit database managed by Cumulus Media. The research team does not have access to this database and will only learn identifying information of those included in the campaign audience if one chooses to express interest in the research via phone, email, All IN for Health or REDCap Landing Page.

If a parent expresses interest in the study via phone or email, we will contact them via phone to describe the study and ensure the child meets inclusion/exclusion criteria. We will ask them

screening questions derived from DSM-5 criteria for oppositional defiant disorder, as well as excluded disorders (e.g., neurodevelopmental disorders, current depression). If they potentially qualify via review by the PI and clinical co-Is, they will be scheduled for their screening session. We will send directions and informed consent and assent forms for them to review (these will be reviewed and signed in person). We will provide reminder contacts (email or phone, as preferred) at least one week prior to their session date.

Participants may also opt-in to text reminders about study visits. When scheduling the first visit, we will ask questions whether they want to be texted from our Google Voice account. We will note that messages will only be sent from lab-issued devices and we will delete all contacts and contact info from devices following completion of their participation. However, Google Voice may maintain a call history with the account.

All text messages will be sent from our Google Voice number via the lab tablets. These tablets are password-protected, and any contacts with study participants made via the Google Voice account, including texts and contact info, will be deleted upon completion of the subject's participation.

Participants will be instructed that if they need to contact the study team on the day of their study visit (e.g., if they are running late), to call or text us via our Google Voice number, which can be connected to our lab tablets.

For Visit 3, we will remind parents of the information they completed on the Medication Log (see Visit 2 Study Procedures), as it would be helpful for the same medications to be used at that visit. However, we will caution that they should use their best judgement and follow doctor's orders when providing medication, and that this is not a study requirement.

Randomization will occur only for those participants that meet all inclusion/exclusion criteria following the first study visit and are able to be scheduled. A randomization table will be created by our statistical team, stratified by sex, ADHD status, and ODD/CD diagnosis to create equal numbers of boys and girls in each condition. This assignment will be sealed to the research team until within 24 hours of the third study visit.

Previously active subjects whose visits were cancelled due to the COVID-19 outbreak will be permitted to restart all study procedures, including being reconsented using the most recent informed consent documents.

7.0 Study Procedures

Visit 1

Visit 1 procedures may take place over a single visit or may be broken up into multiple visits for ease of scheduling. In addition, some procedures may be carried out remotely to limit in-person interactions and reduce infection risks associated with COVID-19. For remote participation, the order of Visit 1 procedures (following informed consent) may be altered. All in-person study procedures will take place at Goodman Hall. For all visits, we will follow up-to-date IU and IU

Health safety guidelines, which may require children and parents to wear masks while in Goodman Hall.

The consent and assent procedures will be carried out prior to any study procedures. These may be carried out in person or remotely. Parents will provide written consent for their own and their child's participation. Children will provide written assent. For participants conducting the process in person, these forms will be presented in a private room to both parents and children together, and they will be given the opportunity to ask investigators any questions they may have. For participants and parents undergoing the process remotely, they will be sent a link to a REDCap survey. The person obtaining consent will conduct the consent and assent processes over the phone or video link (e.g., Zoom) while parents and children view documents electronically. All signatures will be obtained and recorded electronically and parents will be sent a copy of all signed documents via email or regular mail, as preferred.

Following the consent/assent process, we will collect personal information, including parent and child names, dates of birth, and the child's birthplace. This information will be maintained on a secure REDCap database, separate from personal health information and research databases. If the REDCap database is not available, we will take the information on a paper form, which will be shredded after entering the information into REDCap.

At the beginning of each remote study visit, the researcher will confirm the exact location of the subjects for safety purposes. If this is the same as the address provided on the form, that will be noted. If not, the subject's address will be written on paper or a white board and will be shredded after the visit.

Parents and child participants will undergo a semi-structured clinical interview, the **K-SADS-PL**, with a trained clinician, social worker, or clinical graduate student. This interview may be conducted in-person or remotely and may be scheduled on a separate day if necessary. This process is started by the completion of the **DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure** questionnaire, which asks about the presence of child mental health symptoms over the previous two weeks. The interview allows the clinician to complete a diagnostic checklist. Parent(s) will be informed about results of the K-SADS clinical interview after it has been completed. If follow-up treatment is desired, we will provide information about local mental health treatment options. If requested, a brief written summary will be provided.

After the interview, in-person subjects will be given a short break. Snacks and small trinkets (~$1) may be given to the child to help motivate them and maintain attention. These may also be given out at Visits 2 and 3.

Parents and children will also complete surveys. Survey questions will be presented and recorded via REDCap or the IU Qualtrics system, an online survey system. For remote participation, these surveys can be completed prior to the K-SADS-PL clinical interview. Prior to the clinical interview, the DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure will be administered electronically. For in-person visits, both parents and children will complete surveys via electronic tablets (paper copies of surveys will be used if tablets are not functioning properly). Paper forms will be provided only if the electronic system is not working.

Children will first complete a practice survey to become familiar with the mechanics of using the tablet to answer questions. This practice will consist of all question types found in the surveys below.

Children will then complete the following surveys, expected to last 30 minutes in duration:

1. A child version of the **Interpersonal Reactivity Index (IRI)**, which provides subscales for Perspective Taking, Fantasy, Empathetic Concern, and Personal Distress.
2. **NIH Toolbox Perceived Hostility, Perceived Rejection, and General Life Satisfaction Fixed Forms**
3. The **Inventory of Callous-Unemotional Traits**, a 24-item questionnaire to provide an assessment of the child's callous and unemotional traits among antisocial youth.
4. **Media Exposure Questionnaire**. This questionnaire is a modified version of the Media Exposure Measure, which quantifies the child's television, video game and VR exposure.
5. **Virtual Reality Experience Survey**, which quantifies how much previous experience the child has had using virtual reality and specifies how often the technology was used for certain activities.
6. **Video Game Motivations and Desires**. This 30-item survey measures children's reasons for playing video games, based on the GAMES survey of video game motives and preferences.
7. **UPPS-P Impulsive Behavior Scale**. This 20-item self-report measures personality traits that lead to impulsive-type behavior.

For in-person participation, children will complete the K-BIT-2 IQ test[45] upon completion of surveys. If surveys are completed remotely, this IQ test will be conducted during the in-person portion of Visit 1.

Parents will complete separate surveys. These surveys include the following:

1. **Demographics** – Parents will report background information on their child and the family, including age, sex, grade, handedness, and parental income and employment. This questionnaire also collects information on the child's medical history, primarily focusing on mental health treatment.
2. **Parent Pubertal Development Scale**, which measures the child's stage of development.
3. **NIH Toolbox Emotion Battery Ages 8-12 Parent Report**, which includes surveys assessing the child's Positive Affect, General Life Satisfaction, Emotional Support, Friendship, Loneliness, Perceived Rejection, Perceived Hostility, Self-Efficacy, Sadness, Perceived Stress, Fear, and Anger
4. The **Outburst Monitoring Scale (OMS),[46]** which measures the child's verbal, physical, property, and self-directed aggression.
5. **Media Exposure Questionnaire**. This questionnaire is a modified version of the Media Exposure Measure, which quantifies the child's television and video game exposure.
6. **Virtual Reality Experience Survey**, which quantifies how much previous experience the child has had using virtual reality and specifies how often the technology was used for certain activities.
7. **Family Environment Scale (FES): Short Version**,[47] a 9 item questionnaire designed to assess personal relationships and the overall social environment of a family through three categories: interpersonal relationships, growth, and organization/structure.

8. The **Sleep Disturbance Scale for Children**,[48] a 27 item questionnaire used to gauge overall sleep habits and disorders in children. This scale uses five subdomains: initiating and maintaining sleep, breathing, arousal, sleep wake transitions, excessive somnolence and hyperhidrosis.
9. The Indiana Institute of Biomedical Imaging Sciences (IIBIS) **MRI Safety Screening Form** to confirm that there are no MRI contraindications (paper only)

Remaining procedures require in-person participation. Participants will practice using the Oculus Quest VR headset, which includes goggles and headphones. As part of this practice, participants will develop their virtual avatar, which will be used during virtual scenarios at the next visit and may be provided to them prior to the second visit. To increase identification with their virtual self, participants will be directed to create a virtual avatar that best resembles them (sex, hair color/length, skin tone, choice of t-shirt). Following this use, child participants will complete the **Simulation Sickness Questionnaire**,[49] which quantifies physical symptoms such as general discomfort, nausea, and dizziness. If there is time, parents may also be provided the opportunity to wear the headset.

Lastly, participants will visit and lay in a mock scanner, to increase their comfort with the MRI scanner. The mock scanner provides a similar environment and can play similar noises as the real scanner.

If there are concerns about potential signal loss from orthodontics or implants that are MRI-safe, the participant may also receive a brief (roughly 10 minute) MRI scan to assess the extent of signal loss in the brain.

For all parent and child surveys, subjects may be asked to retake all or parts of these surveys where there may have been errors (e.g., technical difficulties or noncompliance), as determined by the research team.

If the VR practice or avatar creation could not be completed during Visit #1, it can be completed at the beginning of Visit #2.

Visit 2

Participants will undergo an MRI scan that will last about 1 hour. Prior to the scan, the parent and child will complete the Indiana Institute of Biomedical Imaging Sciences (IIBIS) **MRI Safety Screening Form** to confirm that there are no MRI contraindications. They will also complete the **Medication Log** form to indicate what medications or caffeine the subject had taken that day. This information will also be provided to parents during the reminder call or email for Visit 3, with a request that the same substances be utilized at Visit 3 if possible.

Participants will also see examples of stimuli that they will view during the scan and be instructed on what the MRI task will entail. They will practice button-press tasks as well.

MRI scans will take place on a research-dedicated 3T Siemens Magnetom Prisma MRI scanner at Goodman Hall. First, we will conduct a 3D magnetization prepared rapid gradient echo (MPRAGE) scan for individual anatomical reference, comprised of 160 sagittal slices with 1.0x1.0x1.2 mm voxel dimension. In the scanner, images will be presented via E-prime

software and back-projected to participants. Functional scans will be acquired using T2*-weighted gradient spin echo-planar imaging (EPI) sequence with TR/TE 1200/29 ms for 54 axial slices and voxel size of 2.5x2.5x2.5 mm.

The fMRI task employs a paradigm that has compared self vs. other perspective taking in the response to painful stimuli.[18-21] A mixed block fMRI design will be used, with two 8-minute runs of our task. There are four conditions: self pain, self no pain, other pain, and other no pain. Each block (40sec duration) will be either "Self" or "Other," as indicated by task instructions prior to the block ("Imagine these situations are happening to you/him/her) and an image of the virtual avatar (virtual self or virtual counterpart; image remains in corner throughout block). Within the block, participants will be shown Pain images (e.g., hand slammed in door) and No Pain images (e.g., hand on door handle) (3 each/block; 2sec duration; jittered interstimulus interval 2-5sec).[18-20] There will be 6 blocks of each type during both 8-minute runs (96 total trials/run), with block order pseudorandomized across participants.

An additional task will present subjects with child faces with different emotional faces and ask them to respond to specific questions that probe emotion recognition, empathy, or the sex of the face.

After the MRI, the subject will be presented with a series of images. They will then determine which of the images they saw while completing the tasks in the MRI. This task measures how well subjects were attending to stimuli during the brain scan.

Visit 3

Participants will take part in the VR task with the Oculus Quest VR headset. We will fit the headgear to the child and ensure that it is comfortable. Subjects will remain seated while interacting with the virtual world and use hand-held controls to move or control objects. Subjects can turn their head to look in any direction in the virtual world. Using state-of-the-art 'Oculus Touch' hand-held controllers that react to hand movements, the user will be able to move and interact with virtual objects and characters. Headphones play auditory stimuli.

Children will first explore the virtual cafeteria for three minutes to allow them to understand hand controls and become acquainted with the environment before starting the task scenarios. They may ask questions and talk with investigators during this time, who will ensure that subjects are able to use controls and move around in the environment properly.

The virtual environment is a school cafeteria setting. Following practice, participants will take part in three scenarios in the school cafeteria. Each scenario will last up to two minutes. In two scenarios, after the subject hears the school bell ring, the goal is to place trash on their cafeteria tray and take the tray to the trash. In a third scenario, the subject is directed to clean up the mess at their table. Once the task is complete, the scenario will be complete. In each scenario, virtual characters will populate the environment to make it more realistic, including some characters (students) who will also be returning their trays. However, the social environments will differ, and each scenario includes a virtual counterpart that interferes with the goal.

After each scenario, children will remove the headset and complete questions via electronic tablet. First, they will complete our **VR Perspective Taking Scale**, which assesses how well they understand the virtual counterpart's perspective. Next, they will complete a question for the **Acknowledgement of Other Perspective Scale**, which reflects the relative importance given to the perspective of the participant and the virtual counterpart.

They will also complete a **Post-scenario Survey** regarding how they interpreted the intentions of the virtual counterpart (Were any of the characters trying to be nice to you? Were any of the characters trying to be mean to you?) and real-life responses (Would you be mad if this happened in real life? Would you try to hit other characters if this happened in real life?). Responses will be provided on a continuous sliding scale from 0 to 100 with labeled endpoints. We will also quickly assess current mood state (happy, sad, stressed, frustrated, calm) on sliding scales and complete the **Simulation Sickness Questionnaire** and a **VR Usability Survey**.

Following completion of each scenario, subjects will then experience the scenario again. Each subject will be randomly assigned to the (a) Alternate Perspective or (b) Control Perspective. In the Alternate Perspective condition, participants will experience the scenarios again from the virtual counterpart's perspective within the VR system. The Control Perspective will repeat the initial interaction from the same perspective. After each scenario, participants will answer questions identical to those after initial scenarios: the **VR Perspective Taking Scale** and the **Acknowledgement of Other Perspective Scale**, as well as questions about character intent, real-life responses, mood, the **Simulation Sickness Questionnaire,** and **VR Usability**.

If errors with the VR technology are observed, subjects may restart the scenarios and subsequent surveys.

Parents will also once again complete the Indiana Institute of Biomedical Imaging Sciences (IIBIS) **MRI Safety Screening Form** and the **Medication Log**.

Participants will be instructed about the MRI task and will briefly practice again. Participants will then undergo an MRI scan for about 1 hour. This scan may not be performed if the previous scan (at Visit 2) was not completed successfully. This scanning session will be identical to Visit 2, including an anatomical scan and functional scans in which participants will see images of painful and non-painful actions, under conditions where they are told to imagine scenes happening to themselves or the virtual counterpart, as well as the emotional face task.

After the scan, participants will be presented with images and asked to identify which ones they remember from the MRI scan.

Following the MRI scan, children will complete an end-of-study **Usability** and **Environmental Presence** survey, that asks additional questions about overall usability, environmental presence (how "real" the environment feels), and opinions on its helpfulness. Investigators will then answer any questions that they may have about their involvement or the VR scenarios.

At the beginning of each in-person visit, parents are to complete the **Parent/Guardian Safety Contact Sheet**. This asks for the parent/guardian's name and phone number where they can be reached for the duration of the visit. This form gets shredded after each visit.

Prior to receiving compensation for the visit, the parent and child will be asked briefly about real-life situations that prompted recent arguments. The responses will be recorded by the researcher and used to develop content for the next phase of research.

At the end of each visit, parents and children will then be compensated and thanked for their time. A school note will be provided upon request confirming the child attended our study visit.

Compensation
Participants will be compensated at the completion of each study visit. For remote participation, compensation will be provided via electronic gift cards. Children will receive $75 for Visit 1 ($25 for surveys, $25 for K-SADS-PL, $25 for VR practice/MRI mock scanner), $100 for Visit 2 (including $75 for MRI), and $150 for Visit 3 (including $75 for VR procedures and $75 for MRI). Parents will receive $25 for Visit 1. In addition, a parking voucher will be provided for each study visit. If a participant withdraws prior to completion of all visit procedures (including Visit 1 procedures scheduled on a separate day), they will be compensated only for tasks that have been completed. Parking will be compensated in full for each visit regardless of which tasks have been completed.

8.0 Study Calendar

Phone Screen (Expected duration 10-15 minutes)

----------Variable time to Visit 1; Up to 6 months----------

Visit 1 (Expected duration 3-4 hours)
Procedures may be split into multiple visits

1. **Informed Consent/Assent***
2. **K-SADS-PL***
3. **Parent/Child surveys***
4. **IQ test**
5. **VR Practice & Avatar Creation**
6. **Mock Scanner**

***May be conducted remotely**

----------Up to 6 weeks from K-SADS-PL until Visit 2----------

Visit 2 (Expected duration 2 hours)
1. **MRI Scan**

----------Up to 2 weeks until Visit 3----------

Visit 3 (Expected duration 2-3 hours)

1. **VR Scenarios & Assessments**
2. **VR Scenarios (Assigned Perspective Condition) & Assessments**
3. **MRI Scan**

	Visit 1	Visit 2	Visit 3
Parent & Child: K-SADS Clinical Interview	X		
Parent: Demographics; Outburst Monitoring Scale; NIH Toolbox Emotion Battery; Media Exposure Questionnaire; VR Experience Survey; Family Environment Scale; Sleep Disturbances Scale for Children	X		
Child: Interpersonal Reactivity Index; NIH Toolbox measures; Inventory of Callous-Unemotional Traits; Media Exposure Questionnaire; VR Experience Survey; Video Game Motivations and Desires Scale; Impulsive Behavior Scale	X		
Parent & Child: MRI Screening Form	X	X	X
Child: VR Practice & Avatar Creation	X		
Child: Simulation Sickness Questionnaire	X		X
Child: Mock Scan	X		
Child: MRI Scan		X	X
Child: VR task & assessments (VR Perspective Taking Scale; Acknowledgement of Other Perspective Scale; Post-scenario Survey; Mood state; VR Usability & Environmental Presence)			X

9.0 Reportable Events

All serious adverse events (SAEs) and Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) will be immediately reported to the Indiana University Institutional Review Board (IRB) within 5 working days; other adverse events or protocol deviations will be reported to the IRB based on IRB guidelines (typically reported at the time of renewal). We will also

report to the NIMH program officer within 10 working days. An example of a rare but serious adverse event is injury from metal objects in the proximity of the MRI scanner. Mild, temporary VR sickness (e.g., nausea) will be considered an adverse event but not a serious adverse event.

Any adverse events (serious or not), as well as the progress of the study will be reviewed and discussed in detail at the meetings of our DSMB. Non-serious adverse events or protocol deviations will be reported to the IRB based on IRB guidelines (typically reported at the time of renewal).

For all AEs and SAEs deemed unexpected and/or unrelated to the study, a summary will be submitted to the NIMH PO with the annual progress report. Protocol violations will also be included in this annual progress report. Temporary suspension of the study will be reported to NIMH within three working days, along with a statement of the reason(s) for the action.

10.0 Data Safety Monitoring

PI Dr. Hummer, in consultation with co-Investigators Dr. Kronenberger and Dr. Neumann, is responsible for data and safety monitoring and ensuring that the protocol is being properly followed, with independent oversight also provided by a local Data and Safety Monitoring Board (DSMB). Data quality, subject recruitment, accrual, retention, outcome and adverse event (AE) data, procedures designed to protect the privacy of subjects, and subject satisfaction will be monitored. Any unanticipated problems encountered or observed by research staff will be promptly reported to Dr. Hummer. If Dr. Hummer will be unavailable for contact for an extended period while study procedures are ongoing, he will designate a co-investigator to be the primary contact for research staff should such problems arise.

Co-investigators Dr. Kronenberger and Dr. Neumann will help Dr. Hummer distinguish serious from non-serious adverse events, as well as relatedness to study participation. SAE's will be graded based on the Mild-Moderate-Severe grading scale. The scale is as follows: Mild - no limitation of usual activities, Moderate - some limitation of usual activities, or Severe - inability to carry out usual activities.

Any adverse events (serious or not), as well as the progress of the study will be reviewed and discussed in detail at the meetings of our ad hoc DSMB. These meetings will occur at least once every six months. Additional meetings will be scheduled "as needed." This board consists of experts in child psychology, information technology, clinical trials, and biostatistics. This DSMB is currently headed by Dr. Flora Hammond (Professor of Physical Medicine & Rehabilitation).

A report is generated on this study from each meeting, which will be shared with the NIMH program staff. The reports contain a summary of enrolled, discontinued, and recruited subjects, a list of any adverse events and details reviewed by the DSMB. Any findings, concerns or recommendations of the DSMB, along with an action plan for how to implement those recommendations, will be provided.

Dr. Hummer's lab team (research assistant, research coordinator, postdoctoral fellow, volunteer student researchers) will meet weekly discuss study progress and issues, and all study

personnel (PI, co-investigators, research staff) will meet semi-annually to review data, number of subjects, responses observed, and any concerns not otherwise addressed (i.e., other than adverse events or protocol deviations). At weekly lab meetings, a different co-investigator will be involved once a month, so each co-investigator will be present at least once every 3-4 months, in addition to semi-annual meetings.

Each meeting will have specific time dedicated to any issues in study data that pertain to safety of subjects. Any safety issue that requires temporary suspension of the study will be reported to the IRB and NIMH within three working days, along with a statement of the reason(s) for the action. In addition, Dr. Hummer and research staff will review study enrollment at weekly lab meetings and compare present status to enrollment targets. Data will be presented on enrollment numbers, screen fails, and withdrawn subjects, as well as race/ethnicity and sex of subjects. If necessary, we will modify recruitment efforts in order to maintain ability to reach target enrollment for race, ethnicity, and sex.

All study staff, including the PI, will complete (and as needed, renew) required training regarding the protection of human subjects, informed consent procedures, and confidentiality. This training includes completion of CITI (Social/Behavioral/Educational Researchers) and Good Clinical Practice training. The trial will not begin until researchers have completed the Good Clinical Practice training.

11.0 Study Withdrawal/Discontinuation

A child participant or their parent may withdraw from the study at any time by letting the research team know they wish to discontinue their participation. The participant(s) will be paid for their time completed in the study.

Participants will be precluded from continuing the intervention if they report adverse health consequences from using virtual reality equipment during practice or intervention. In addition, inability to complete the MRI scan, including claustrophobia or an unforeseen health consequence, will also halt a subject's participation.

If a worsening of DBD symptoms is identified via voluntary report or visit assessments, the family will be queried to determine the nature of symptoms, including relationship and proximity to study procedures. Dr. Hummer and clinical psychologists on the team will review these data, and if a worsening of symptoms is judged to be significant and likely related to study participation, the subject will be discontinued from participation. Additionally, depending on the severity of symptoms, the subject may be offered or referred for further evaluation of symptoms; the urgency of this evaluation will depend on the nature and severity of symptoms but may range from a standard outpatient visit to an urgent/emergent evaluation.

12.0 Statistical Considerations

We will enroll 95 children in order to target 40 completers (n = 20/group, allowing for 15-20% screen fail and 15-20% attrition). Attrition (apart from screen fails) will occur between the two scanning visits, which are only one week apart and are expected to be due to noncompliance or in-scanner subject motion that renders data unusable. Attrition rates are not expected to

change from year to year, as subjects will remain active only from the time of screening to Visit 3 (up to 8 weeks).

In similar research, pre/post correlations of 0.72 and 0.89 were found for measures of Theory of Mind (closely related to social perspective taking) in a VR intervention for social cognition training.[50] In research by co-I Dr. Neumann involving a multi-session skill-building intervention,[51] pre/post scores had a correlation of 0.69 on the Perspective Taking subscale of the Interpersonal Reactivity Index. Here, we use a more conservative estimate for a pre/post correlation of social perspective taking of 0.6. With 20 subjects per group and assuming an ANCOVA model (specified below) is used with a pre/post correlation for social perspective taking of 0.6 an effect size of 0.73 (observed for the meanness rating in the preliminary study) can be detected between two groups with 80% power using a two-sided two-sample t-test with alpha level of 0.05.

For each primary outcome measure, a separate linear mixed model will be employed to determine predictors of post-treatment scores, with pre-treatment scores, condition, time, group, and a time-by-condition interaction term as regressors. Time-by-condition is a regressor to account for potential improvements in perspective taking with treatment (since there are two conflict scenarios presented). From this model, using appropriate contrast statements we can both test for the primary endpoint (change at end of Scenario 3) and examine trends over time between the three groups. We will also conduct with fMRI data a 2x3 (pain perspective condition by group) within-subjects ANOVA on data from each ROI.

Across the entire sample, we will calculate the correlation of IRI Perspective Taking with our pre-treatment VR Perspective Taking and AOP scales, to further validate these measures. Similarly, we will assess the relationship between target engagement measures with VC Intentions and Real-life Responses. Exploratory regression analyses will also examine whether target engagement measures are associated with age, sex (to address sex as a biological variable), IQ, task completion, mood, callous-unemotional traits, past experience with video games or VR, or Environmental Presence (each variable examined separately due to the small sample sizes). Finally, we will conduct whole-brain fMRI analysis (2x3 pain perspective condition-by-group ANOVA), in order to identify neural changes in areas outside our primary ROIs (cluster-corrected $p<.05$).

13.0 Statistical Data Management

The PI and primary research assistant are responsible for overseeing data collection and accuracy of record keeping and the researchers will convey an attitude that the data management procedures be treated with unwavering gravity, therefore maintaining a high level of quality for this project. A rigorous and systematic approach to data management is critical for the quality of any study. The substantial effort and resources that will be devoted to collecting data in this project will be matched by an equally substantial commitment of effort and resources to edit, verify, correct, update, and assemble the resulting data files. By limiting the amount of data that must be entered by hand, we aim to minimize the chances for errors data entry. Our data management system incorporates quality control at every juncture from data collection through analysis. We have found that this bottom-up approach to data quality is essential, since there is no single procedure that will verify and correct erroneous data.

Data for the the K-SADS-PL will be collected by clinicians and recorded either electronically or on a paper checklist/questionnaire. The K-BIT-2 IQ test responses and results will likewise be initially recorded on paper. These responses will be entered into our REDCap database, with double-entry of data to confirm accuracy of entry. For remaining surveys, either remote electronic devices or in-person electronic tablets will be used to administer testing instruments via the IU Qualtrics system, which will directly record responses to our electronic database. These data will be stored electronically in REDCap, IU Box Health, or Microsoft Secure Storage. The storage location will be backed up automatically. In addition, MRI data will be stored on IU's Geode system, which is backed up automatically and can seamlessly be integrated with IU's high-performance computing systems. These data will be merged for analysis, with full datasets maintained on secure systems if containing identifiable information. Analysis of de-identified data will take place on local computers and the IU Research Desktop. Prior to the enrollment of the first participant, these databases will be thoroughly tested to ensure they are working properly, recording and storing data as intended. The study data manager will regularly query the data for completeness, consistency, and accuracy to allow for prompt data quality management, generate monthly data completeness reports for discussion at monthly meetings of the investigators and research assistant (with more frequent communication as needed), and implement study closeout.

14.0 Privacy/Confidentiality Issues

Subject procedures will take place in private rooms, with only research staff present. MRI scans will take place in a dedicated research MRI suite at the IU Center for Neuroimaging with trained clinical staff with appropriate privacy and confidentiality training.

Any information obtained about subjects from this research, including answers to questionnaires, medical history, and cognitive status will be kept confidential, with the exception of information that meets mandatory reporting requirements within the state of Indiana (e.g., indications of child abuse/neglect (including sexual abuse) and threats of immediate harm to self or others). Confidentiality is protected by omission of individual identifiers associated with study responses in research databases. Subjects' identities will not be revealed in any description or publication of this research. De-identified data will be shared with the NIMH Data Archive (NDA). For this purpose, the child's name, date of birth, and birthplace will be used to establish a global unique identifier (GUID) in the NDA. The tool to create the GUID is used on a local computer, so no identifiable information will be shared with NIMH.

Subjects are free not to participate in the study, and they may continue in the study even if they do not want de-identified data shared with the NIMH Data Archive. Additionally, other procedures to ensure confidentiality will follow the regulations and policies of the Indiana University School of Medicine.

For MRI scheduling purposes, we are required to share the child's name and birthdate with the Research MRI team. All members of this team are trained research technicians with up-to-date training in research compliance, including HIPAA. This information will be sent in accordance with IU HIPAA policies for electronic communications, including labeling this email as "Confidential." This personally identifiable information will not be included with MRI scan files.

All records with identifiable information will be maintained in a secure location, with access limited to study personnel. All electronic records will be encrypted or stored on an encrypted device. The electronic database used to house these data until analyses are needed will be created uniquely for this project. The database will be password protected and only certain research personnel will be given access to the database. This will protect the electronic data from any unauthorized persons entering the dataset and jeopardizing the integrity of the data or engaging in some sort of malicious piracy. Any electronic protected health information (PHI) will be stored in REDCap, IU Box Health, or Microsoft Secure Storage.

Any physical study records that link individual identifiers with study identification numbers will be maintained in a locked file cabinet in a locked office, and computer data will be kept on secure, password-protected servers. Electronic data linking identifiable information to study identification numbers will be stored on REDCap, IU Box health, or Microsoft Secure Storage. Only select research personnel will have access to these linkages. Linkages between individual identifiers and study identification numbers will be destroyed at the conclusion of the investigation.

To protect against digital threats to confidentiality, three types of security are employed:

- The data system is only accessible to investigators and study staff by a unique identifier and password, via an encrypted internet connection that is secured by a 256-bit SSL certificate. Each user's access to data, modules and files is limited to the items to which they are assigned.
- Next, the network is protected by a firewall to prevent access by unauthorized users, and data is stored in a secure Microsoft SQL Server database that is electronically and physically restricted to key study personnel. Regular backups of the database are compressed and encrypted before being securely stored at an off-site facility. Data system developers use their best good faith effort to implement policies necessary to minimize the possibility of unauthorized access pursuant to the "Security of Information Technology Resources" policy IT-12 of Indiana University (http://informationpolicy.iu.edu/policies/IT12) and follow the pre-established guidelines for handling electronic institutional and personal information as set forth by the Indiana University Information Policy Office (http://informationpolicy.iu.edu/resources/safedata/guidelines.shtml).

15.0 Follow-up and Record Retention

The active study duration is expected to last three years, although data analysis will continue beyond that period. Linkages between individual identifiers and study identification numbers will be removed at the conclusion of the investigation. De-identified information may be archived and accessed for an indefinite period of time. Study records with identifiable information (e.g., copies of Informed Consent documents) will be retained throughout data collection, analysis, and manuscript development, and will be destroyed as recommended by NIH guidelines.

16.0 References

1. Anastassiou-Hadjicharalambous X, Warden D. Cognitive and affective perspective-taking in conduct-disordered children high and low on callous-unemotional traits. Child Adolesc Psychiatry Ment Health. 2008;2(1):16. doi: 10.1186/1753-2000-2-16. PubMed PMID: 18601753; PMCID: PMC2500005.
2. Chandler MJ, Greenspan S, Barenboim C. Assessment and training of role-taking and referential communication skills in institutionalized emotionally disturbed children. Dev Psychol. 1974;10(4):546.
3. Gasser L, Keller M. Are the Competent the Morally Good? Perspective Taking and Moral Motivation of Children Involved in Bullying. Soc Dev. 2009;18(4):798-816. doi: 10.1111/j.1467-9507.2008.00516.x. PubMed PMID: WOS:000269809500004.
4. Sessa VI. Using perspective taking to manage conflict and affect in teams. The Journal of applied behavioral science. 1996;32(1):101-15.
5. Litvack-Miller W, McDougall D, Romney DM. The structure of empathy during middle childhood and its relationship to prosocial behavior. Genet Soc Gen Psychol Monogr. 1997;123(3):303-24. PubMed PMID: 9259121.
6. Dodge KA, Price JM, Bachorowski JA, Newman JP. Hostile Attributional Biases in Severely Aggressive Adolescents. J Abnorm Psychol. 1990;99(4):385-92. doi: Doi 10.1037/0021-843x.99.4.385. PubMed PMID: WOS:A1990EH05100009.
7. Light P. The development of social sensitivity: A study of social aspects of role-taking in young children: Cambridge University Press Cambridge; 1979.
8. Selman RL. Taking another's perspective: Role-taking development in early childhood. Child development. 1971:1721-34.
9. Davis MH. A multidimensional approach to individual differences in empathy1980.
10. Webster DM, Richter L, Kruglanski AW. On leaping to conclusions when feeling tired: Mental fatigue effects on impressional primacy. J Exp Soc Psychol. 1996;32(2):181-95. doi: DOI 10.1006/jesp.1996.0009. PubMed PMID: WOS:A1996UH24000004.
11. Gehlbach H. A new perspective on perspective taking: A multidimensional approach to conceptualizing an aptitude. Educ Psychol Rev. 2004;16(3):207-34. doi: Doi 10.1023/B:Edpr.0000034021.12899.11. PubMed PMID: WOS:000222473700002.
12. Batson CD. The altruism question: Toward a social-psychological answer: Psychology Press; 2014.
13. Oswald PA. The effects of cognitive and affective perspective taking on empathic concern and altruistic helping. J Soc Psychol. 1996;136(5):613-23. doi: 10.1080/00224545.1996.9714045. PubMed PMID: 8942318.
14. Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional approach. Journal of personality and social psychology. 1983;44(1):113.
15. Jeon IH, Kim KR, Kim HH, Park JY, Lee M, Jo HH, Koo SJ, Jeong YJ, Song YY, Kang JI, Lee SY, Lee E, An SK. Attributional Style in Healthy Persons: Its Association with 'Theory of Mind' Skills. Psychiat Invest. 2013;10(1):34-40. doi: 10.4306/pi.2013.10.1.34. PubMed PMID: WOS:000316039600005.
16. Harwood MD, Farrar MJ. Conflicting emotions: The connection between affective perspective taking and theory of mind. Brit J Dev Psychol. 2006;24:401-18. doi: 10.1348/026151005x50302. PubMed PMID: WOS:000237974700008.
17. Penn DL, Roberts DL, Combs D, Sterne A. Best practices: The development of the Social Cognition and Interaction Training program for schizophrenia spectrum disorders. Psychiatr Serv. 2007;58(4):449-51. doi: 10.1176/ps.2007.58.4.449. PubMed PMID: 17412842.

18. Jackson PL, Brunet E, Meltzoff AN, Decety J. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia. 2006;44(5):752-61. doi: 10.1016/j.neuropsychologia.2005.07.015. PubMed PMID: 16140345.
19. Jackson PL, Meltzoff AN, Decety J. How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage. 2005;24(3):771-9. doi: 10.1016/j.neuroimage.2004.09.006. PubMed PMID: 15652312.
20. Lamm C, Batson CD, Decety J. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci. 2007;19(1):42-58. doi: 10.1162/jocn.2007.19.1.42. PubMed PMID: 17214562.
21. Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage. 2011;54(3):2492-502. doi: 10.1016/j.neuroimage.2010.10.014. PubMed PMID: 20946964.
22. Decety J, Michalska KJ, Akitsuki Y. Who caused the pain? An fMRI investigation of empathy and intentionality in children. Neuropsychologia. 2008;46(11):2607-14. doi: 10.1016/j.neuropsychologia.2008.05.026. PubMed PMID: 18573266.
23. Decety J, Chen C, Harenski C, Kiehl KA. An fMRI study of affective perspective taking in individuals with psychopathy: imagining another in pain does not evoke empathy. Front Hum Neurosci. 2013;7:489. doi: 10.3389/fnhum.2013.00489. PubMed PMID: 24093010; PMCID: PMC3782696.
24. Decety J, Skelly LR, Kiehl KA. Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. JAMA Psychiatry. 2013;70(6):638-45. doi: 10.1001/jamapsychiatry.2013.27. PubMed PMID: 23615636; PMCID: PMC3914759.
25. Lockwood PL, Sebastian CL, McCrory EJ, Hyde ZH, Gu X, De Brito SA, Viding E. Association of Callous Traits with Reduced Neural Response to Others' Pain in Children with Conduct Problems. Current Biology. 2013;23(10):901-5. doi: 10.1016/j.cub.2013.04.018.
26. Farrington DP, Gaffney H, Losel F, Ttofi MM. Systematic reviews of the effectiveness of developmental prevention programs in reducing delinquency, aggression, and bullying. Aggress Violent Beh. 2017;33:91-106. doi: 10.1016/j.avb.2016.11.003. PubMed PMID: WOS:000400227400009.
27. Sukhodolsky DG, Smith SD, McCauley SA, Ibrahim K, Piasecka JB. Behavioral Interventions for Anger, Irritability, and Aggression in Children and Adolescents. J Child Adolesc Psychopharmacol. 2016;26(1):58-64. doi: 10.1089/cap.2015.0120. PubMed PMID: 26745682; PMCID: PMC4808268.
28. Chandler MJ. Egocentrism and antisocial behavior: The assessment and training of social perspective-taking skills. Dev Psychol. 1973;9(3):326.
29. Clore GL, Jeffery KM. Emotional role playing, attitude change, and attraction toward a disabled person. J Pers Soc Psychol. 1972;23(1):105-11. PubMed PMID: 4261340.
30. Gehlbach H, Marietta G, King AM, Karutz C, Bailenson JN, Dede C. Many ways to walk a mile in another's moccasins: Type of social perspective taking and its effect on negotiation outcomes. Computers in Human Behavior. 2015;52:523-32.
31. Goldstein TR, Winner E. Engagement in role play, pretense, and acting classes predict advanced theory of mind skill in middle childhood. Imagination, Cognition and Personality. 2011;30(3):249-58.
32. Goldstein TR, Winner E. Enhancing Empathy and Theory of Mind. J Cogn Dev. 2012;13(1):19-37. doi: 10.1080/15248372.2011.573514. PubMed PMID: WOS:000302059800002.

33. Hilliard LJ, Buckingham MH, Geldhof JG, Gansert P, Stack C, Gelgoot ES, Bers MU, Lerner RM. Perspective taking and decision-making in educational game play: A mixed-methods study. Applied Developmental Science. 2016:1-13. doi: 10.1080/10888691.2016.1204918.
34. Krevans J, Gibbs JC. Parents' use of inductive discipline: relations to children's empathy and prosocial behavior. Child Dev. 1996;67(6):3263-77. PubMed PMID: 9071781.
35. LeBlanc LA, Coates AM, Daneshvar S, Charlop-Christy MH, Morris C, Lancaster BM. Using video modeling and reinforcement to teach perspective-taking skills to children with autism. J Appl Behav Anal. 2003;36(2):253-7. doi: 10.1901/jaba.2003.36-253. PubMed PMID: 12858990; PMCID: PMC1284438.
36. Todd AR, Bodenhausen GV, Richeson JA, Galinsky AD. Perspective taking combats automatic expressions of racial bias. J Pers Soc Psychol. 2011;100(6):1027-42. doi: 10.1037/a0022308. PubMed PMID: 21381852.
37. Todd AR, Galinsky AD. Perspective-Taking as a Strategy for Improving Intergroup Relations: Evidence, Mechanisms, and Qualifications. Social and Personality Psychology Compass. 2014;8(7):374-87. doi: 10.1111/spc3.12116.
38. Winegardner J, Keohane C, Prince L, Neumann D. Perspective training to treat anger problems after brain injury: Two case studies. NeuroRehabilitation. 2016;39(1):153-62. doi: 10.3233/NRE-161347. PubMed PMID: 27341369.
39. Yee N, Bailenson JN. Walk a mile in digital shoes: The impact of embodied perspective-taking on the reduction of negative stereotyping in immersive virtual environments. Proceedings of PRESENCE. 2006;24:26.
40. Peck TC, Seinfeld S, Aglioti SM, Slater M. Putting yourself in the skin of a black avatar reduces implicit racial bias. Conscious Cogn. 2013;22(3):779-87. doi: 10.1016/j.concog.2013.04.016. PubMed PMID: 23727712.
41. Kalyanaraman S, Penn DL, Ivory JD, Judge A. The Virtual Doppelganger: Effects of a Virtual Reality Simulator on Perceptions of Schizophrenia. The Journal of Nervous and Mental Disease. 2010;198(6):437. doi: 10.1097/NMD.0b013e3181e07d66.
42. Ahn S, Le A, Bailenson J. The Effect of Embodied Experiences on Self-Other Merging, Attitude, and Helping Behavior. Media Psychology. 2013;16(1):7-38. doi: 10.1080/15213269.2012.755877.
43. Morina N, Ijntema H, Meyerbroker K, Emmelkamp PM. Can virtual reality exposure therapy gains be generalized to real-life? A meta-analysis of studies applying behavioral assessments. Behav Res Ther. 2015;74:18-24. doi: 10.1016/j.brat.2015.08.010. PubMed PMID: 26355646.
44. Decety J, Michalska KJ, Akitsuki Y, Lahey BB. Atypical empathic responses in adolescents with aggressive conduct disorder: a functional MRI investigation. Biol Psychol. 2009;80(2):203-11. doi: 10.1016/j.biopsycho.2008.09.004. PubMed PMID: 18940230; PMCID: PMC2819310.
45. Kaufman AS. Kaufman Brief Intelligence Test–Second Edition (KBIT-2). Circle Pines, MN: American Guidance Service. 2004.
46. Kronenberger WG, Giauque AL, Dunn DW. Development and validation of the outburst monitoring scale for children and adolescents. J Child Adolesc Psychopharmacol. 2007;17(4):511-26. doi: 10.1089/cap.2007.0094. PubMed PMID: 17822345.
47. Moos RH, Moos BS. Family environment scale manual: Consulting Psychologists Press; 1994.
48. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, Giannotti F. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res. 1996;5(4):251-61. Epub 1996/12/01. doi: 10.1111/j.1365-2869.1996.00251.x. PubMed PMID: 9065877.

49. Kennedy RS, Lane NE, Berbaum KS, Lilienthal MG. Simulator sickness questionnaire: An enhanced method for quantifying simulator sickness. The international journal of aviation psychology. 1993;3(3):203-20.
50. Kandalaft MR, Didehbani N, Krawczyk DC, Allen TT, Chapman SB. Virtual reality social cognition training for young adults with high-functioning autism. J Autism Dev Disord. 2013;43(1):34-44. doi: 10.1007/s10803-012-1544-6. PubMed PMID: 22570145; PMCID: PMC3536992.
51. Neumann D, Malec JF, Hammond FM. Reductions in Alexithymia and Emotion Dysregulation After Training Emotional Self-Awareness Following Traumatic Brain Injury: A Phase I Trial. J Head Trauma Rehabil. 2017;32(5):286-95. doi: 10.1097/HTR.0000000000000277. PubMed PMID: 28060205; PMCID: PMC5498277.