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Training Attention and Eye Movement in ASD

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Study Protocol and Statistical Plan

Current therapies for Autism Spectrum Disorder (ASD) target social and language behaviors, but due to the high-level nature of these skills any improvement rarely extends beyond the targeted behavior. This project uses new technology to implement a novel concept for behavioral intervention to improve basic attention and eye movement skills in ASD. Children will play gaze-driven video games at home during the intervention, receive pre- and post-training assessment of attention, and eye movement function. Because these basic skills form the foundation for good social communication, training these abilities has the potential to improve a broad spectrum of clinical symptoms, and in young children may affect the course of development.

This is a pilot project with a small clinical trial. The aims are:

1: Conduct video game training system with 2 groups of 20 ASD children/teens/young adults (aged 9-26).

2: Evaluate efficacy of training using 3 levels of outcome measures for pre- and post- testing and follow-up. Level 1 will be a direct test of attention and eye movement. Level 2 will test attention and eye movement function in a digital environment. Level 3 will test the effect of training on social skills measured by questionnaires and in a live social interaction.

Research Design and Methods

We will recruit 40 male and female children with ASD (ages 9-26) to participate in the clinical trial. Participants will meet the criteria for Inclusion and Exclusion described below (we have an existing pool of potential participants that meet inclusion criteria, but expect to screen 50 children to find 40 that meet study criteria).

Collaborator Dr. Christina Corsello (Rady Children's Hospital) will be responsible for diagnosis of participants who do not already have required diagnostic assessment. Dr. Corsello is the Clinical Director Rady Children's Hospital Autism Discovery Institute (ADI). Dr. Corsello is ADI-R and ADOS reliable and is a certified trainer for both instruments. ASD participants will be recruited by Dr. Corsello through ADI. We also have a large pool of children and teens with ASD from previous studies who meet diagnostic standards, the majority of whom will be willing to participate in the proposed project.

General inclusion/Exclusion criteria:

1. All participants must be cooperative and able to follow instructions.
2. All participants must have normal hearing acuity and corrected-to-normal vision.

Inclusion criteria: All ASD participants will meet diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), the Autism Diagnostic Interview-R (ADI-R), and the Autism Diagnostic Observation Schedule (ADOS). Nonverbal IQ must be 85 or greater, verbal IQ must be 70 or greater.

Exclusion criteria: ASD participants will be excluded if they have major medical or neurological problems including seizures, diagnosed epileptiform EEG abnormalities, migraine, tuberous sclerosis, fragile *X*, static encephalopathies resulting from prior CNS insults, significant premature birth, and history of exposure to teratogens, metabolic abnormalities, and history of head trauma, cerebral palsy, stroke, meningitis, brain tumor or additional psychiatric diagnoses. Children who are currently participating in vision therapy will be excluded. We will not exclude participation based on use of psychotropic medication.

All participants and parents/caregivers for children will give informed consent. ASD participants who do not have existing ADOS and ADI-R will receive the diagnostic assessment listed above. Diagnostic testing will take place at the Research on Autism and Developing Laboratory, and will be conducted by Dr. Christina Corsello or by a clinician under her direct supervision. The ADOS will be administered to potential ASD participants in a private testing office, and will take approximately 1 hour; concurrently, the potential participant's parent will fill out the ADI-R in a quiet waiting area. All participants will be paid for their participation in the study.

If individuals are unwilling or unable to complete in-lab testing, we will recruit new participants to complete those experiments. Based on our previous experience with similar clinical groups, we would expect no more than 10-15% of the clinical participants will fail to complete all in-lab testing. If more than two of the participants in the 8-

week study fail to complete more than four weeks of training, we will attempt to improve the user experience based on participant feedback and then recruit new participants to complete that study.

Gender and Minority Inclusion: Any participant who meets study criteria and agrees to participate will be included. We will not exclude participants based on ethnicity, but because we do not have standardized translations of the standardized testing instruments, we will restrict inclusion to children for whom English is the primary language. The ratio of males to females with ASD in California is 4.6:1, and we expect that our sample will reflect this ratio.

Participation of Children: Interventions to target attention and eye movement problems in ASD (our long-range goal from this feasibility study) are likely to be more effective in children than adults. The goal of this study is to test whether our portable eye-tracking system is easy and durable for children's use at home, and whether the video games are interesting enough to motivate children's compliance for almost daily use over an extended period. This research falls under section 404 of 45CFR 46 Subpart D ("Research not involving greater than minimal risk").

There are 3 phases of study participation: an initial assessment/orientation, an 8-week intervention training phase, and a final evaluation phase.

Assessment/Orientation Phase: Each participant will come to our lab for two sessions that will take place on separate days. Session 1 will include consent and overall instructions, IQ testing (WASI) [9], SRS [10], and baseline measures of attention and eye movement (Spatial Attention Task, Gap-Overlap and Anti-Saccade Eye Movement Tasks). Session 2 will establish baseline measures on the Simulation Task and Social Interaction Task, and will cover the introduction and trial use of the Training System and instructions for home use. Following this initial assessment, scores on the Spatial Attention and Eye Movement tasks will be used to assign children to one of two intervention groups so that the mean and range of those scores are equivalent between groups. During the intervention phase, Group 1 will receive the gaze-contingent training principles game. Group 2 will play the same game as Group 1 in daily training, except that instead of using gaze, the game play will be joystick-driven.

Intervention Phase: During this 8-week period, study participants will be asked to play a video game at home for a minimum of 30 minutes per day, 5 times per week. Parents/caregivers will oversee the daily in-home training and will be briefed along with the subjects at Session 2. Participants (and parents) will be phoned during the first 3 days of in-home testing to assure that there are no problems with equipment or use of equipment. Participants will return to our lab at 4 weeks, for an abbreviated round of tests (Level 1, to assess attention and eye movement, described below). Game play will be monitored as in our pilot testing using a secure 'dropbox' through which we will receive daily summaries of the amount of time each child has played the games, amount of time spent in calibration, and notes from the child regarding any problems or comments they might have about the games. If we find that a child is not playing the required amount of time, or has excessive calibration time, we will contact the family and follow-up with a home visit to assess the problem if necessary. This system worked very well for us in the pilot testing. Children who withdraw (or whose participation is terminated for failure to play the games) from the study will be replaced. An investigator from the project will always be available to troubleshoot any hardware/software problems, and discuss the child's progress by phone, e-mail, or in-home visits as required.

Final Evaluation Phase At the 8 week lab visit (the end of the intervention period), we will collect post-intervention assessment at three outcome levels (direct testing of attention and eye movement and social questionnaires; simulation task testing; real social interaction-- all described below). We will ask trainees and their parents to complete a questionnaire evaluating their experience with particular focus on the ease of use of the equipment and game and the enjoyability of the training game.

Attention/Eye Movement Tests: The following tasks are a direct test of improvement of spatial attention disengagement and orienting and eye movement accuracy and initiation speed.

Spatial Attention Task (E-Task): This task is patterned after Posner's classic cued spatial attention tasks, but uses target discrimination rather than detection. The task display is a central fixation cross on a computer monitor flanked by boxes on the left and right. Trials begin with either an attention directing cue (one of the boxes brightened) or a null cue (no change or both boxes brightened). Following a short (100 ms) or long (800 ms) delay, a target (letter "E" pointing up, down, left or right) is presented in either the cued (valid) or the opposite uncued (invalid) location. The subject moves a joystick lever to indicate target orientation (up, down, left, right). Results from a number of studies using this task demonstrate slowed disengagement and shifting of attention in ASD children and adults. A study that used this task to examine spatial attention development in typically functioning children and adults will provide estimates of typical behavior on this task.

Analysis: Measures to be used from this task are: attention disengagement index (difference between accuracy to cued and uncued targets); attention orienting index (difference between cued targets with short vs. long attention orienting delays)[3]. Analyses for pilot testing to assess improvement in attentional skills will test the disengagement and orienting indices to: 1) compare individual participants against control performance (using means and variability from age-matched typical controls at pre- and post-testing [8]. Simple analyses will use a t-test or repeated measures ANOVA to examine attention differences in pre- and post- measures and group differences and interactions.

Gap-Overlap Saccade Task: The Gap-Overlap saccade task is a classic oculomotor paradigm during which a participant's inclination to "get stuck" on an available fixation target is assessed. Each trial starts with a fixation cross at the center of the screen and a single target drawn randomly from 16 possible peripheral locations appears either synchronously with the offset of fixation (baseline condition), 400 ms after the offset of fixation (gap condition), or does not disappear at all (overlap condition). The participant is instructed to look directly at the target when it appears as quickly as possible. The difference between saccade latency in the gap and overlap conditions provide an index of gaze and attention disengagement. Studies from our lab in ASD adolescents and teens found large and significant differences with a longer (400 ms) gap duration[7]. In addition, the spatial accuracy measured to the peripheral targets in this task was significantly lower for ASD versus typically-developed adolescents and teens.

Analysis: Measures to be used from this task are: saccade latency (time to initiate a saccade to a target), saccade accuracy (degrees error of saccade to the target), time to disengage attention/gaze (difference between saccade latency in overlap compared to gap condition). Analyses for pilot testing to assess improvement in eye movement skills use these measures and are the same as those described above for spatial attention task. Simple analyses will use a t-test or repeated measures ANOVA to examine eye movement differences in pre- and post- measures and group differences and interactions.

Anti- Saccade Task: Measures of fixation variability from this anti-saccade task provide an assessment of response to distraction and so serve as a secondary measure of efficacy of the training intervention's targeted skill. The ability to maintain steady fixation is related to resistance to distraction and engages the frontal circuits involved in distraction suppression. Children and adults with ADHD symptoms who have difficulty suppressing distraction typically show difficulty maintaining steady fixation during an extended (1500ms) interval. This finding is consistent with disrupted fronto-striatal circuitry in ADHD and with animal work showing the role of fronto-striatal circuits in saccade suppression. Our results from previous work showing a decrease in fixation instability after training, suggest that our games improve resistance to distraction.

Analysis: Measures to be used from this task are: saccade latency (time to initiate a saccade to a target), saccade accuracy (direction of first saccade and degrees error of saccade to the target). Simple analyses will use a t-test or repeated measures ANOVA to examine eye movement differences in pre- and post- measures and group differences and interactions.

Video Games: All participants will play the same video games. For group 1, games are gaze-driven and for group 2, games are controlled by a joystick. Games are simple and colorful (e.g. Space Race in which the setting is a plain starfield with futuristic-looking gates spanning the width of the screen. One of the gates will be green and the others red, and the player must steer a starship through the proper (green) gate by looking directly at the gate (or by guiding with a joystick). We currently have 3 games programmed, and will add 3 new. Games will progress through levels of difficulty so that target behaviors (speed of attention/eye movement shifts; breadth of attentional field; size of attentional/saccade target; amount of irrelevant distraction) are increasingly shaped.

The gaming system is a small footprint PC with a standard LCD monitor and either a joystick (group 2) or a portable eye tracker mounted under the monitor (group 1). For group 1, game play begins with a simple calibration procedure. We will install the system in the participant's home and verify that it is working correctly.

Simulation Task: This task is a realistic appearing computer simulation of driving under various urban and rural conditions. Embedded in the task are measures of spatial attention and response to peripheral objects to test how well the trainee can negotiate a simulated environment with a variety of obstacles (i.e., test improvement in attentional and visual monitoring and speed and accuracy of response). We will test whether subjects able to effectively take advantage of cues to indicate that a new course of action is recommended (a street light changing, for example)? All position and timing data can be measured precisely, permitting detailed within-subject comparisons before and after training.

Analysis: Simple analyses will use a t-test or repeated measures ANOVA to examine attention differences in pre- and post- measures and group differences and interactions.

Social Interaction Task: The third level of outcome assessment will test change in social behavior measured by questionnaires (SRS) and a live social situation between the research participant and a tester. Trainees will be engaged in an interactive conversation in which the tester uses a scripted conversation or games and set of cues to direct attention and eye movement. The script will involve several explicit and implicit redirections of attention and eye movement during the conversation between participants, using props in some cases to guide attention and gaze. Eye movements during the interaction will be measured with a lightweight eye-tracker worn by both participant and tester (based on a tracker from Pupil Labs with our modified hardware and software). The entire interaction will also be videotaped for off-line coding and scoring of language and validation of automatic measures of eye contact.

Analysis: Standard analyses will compare number and timing of instances of orienting to or disengaging from a directed social stimulus (repeated measures ANOVA comparing pre- and post-training measures and groups and interactions). More advanced analysis will use methods developed by Dr. Janet Wiles. Linguistic and Nonverbal communicative behaviors will be annotated into the Eudico Linguistic Annotator (ELAN) (Brugman, H., & Russel, A., 2004; Crasborn, O., & Sloetjes, H., 2008). ELAN, a video interface integrates behavioral data at millisecond resolution across multiple channels such as speech, eye gaze, head movement and facial expression. Behavioral states and discreet behaviors can be coded yielding frequency counts, total duration and mean duration as well as the coordination across channels, e.g., integrating an eye gaze shift in response to a question. These analyses include following behavioral categories: (i) Gaze: Location (target), Duration, Frequency; (ii) Head: position and movement; (iii) Speech (transcribed using CHILDES): utterances (content and length) and pauses.

From these analyses, it is possible to determine the degree to which participants respond appropriately, both linguistically and behaviorally to social interactive cues. We will examine both speech and non-verbal indications of engagement, such as gaze and gestures. This high level outcome measure allows us to examine the subtleties of social engagement during a conversation. We expect that post-intervention improved attention and eye movement will promote more effective social interaction.

Statistical Plan

All outcome testing will be done before training then repeated after training completion.

Level 1 (and Screening for entry criteria): The first level will use tests we have developed and published to directly test whether the speed, accuracy, and spatial breadth of eye movements and attention have improved. These tasks will be used to screen participants for presence of attention and eye movement deficits and will be used as a direct test of improvement of spatial attention disengagement and shifting and eye movement accuracy and initiation speed.

Measures to be analyzed (indices of attention orienting and disengagement, saccade accuracy, latency and gaze/attention) disengagement are described above as are analyses to evaluate effects at the single case level. Analyses will evaluate treatment outcome and differences in outcome between the two groups. A multivariate analysis (MANOVA) will provide a global (linear vector) comparison of all outcome measures at pre- and post-testing points for the two groups (i.e., differences in all measures between pre- and post-testing and between groups). Repeated measures ANOVAs for each of the five outcome measures will test improvement over time (slope > 0) and trends (linear, non-linear), and differences between groups in these effects.

Level 2: The second level will use a driving simulation to test how well the trainee can negotiate a simulated environment with a variety of obstacles (i.e., test improvement in attentional and visual monitoring and speed and accuracy of response).

Simple analyses will compare (repeated measures ANOVA to examine differences in pre- and post-measures and group differences and interactions).

Level 3: The third level will test change in social behavior measured by questionnaires and a live social situation between the research participant and two testers. Trainees will be engaged in a three-way interactive conversation in which the testers use a scripted conversation and set of cues to direct attention and eye movement, videotaped for off-line coding and scoring. The script will involve several explicit and implicit redirections of attention and eye movement during the conversation between participants, using props in some cases to guide attention and gaze. We will work with our colleague and consultant on this project, Dr. Judy Reilly, an expert in designing and analyzing this sort of interaction. Dr. Reilly will ensure that the script and design are appropriate, the cameras are placed optimally for capturing the participants and that our plan for transcribing the interaction is sound and will reveal subtleties of social attention redirection. Dr. Reilly will develop the coding system and will train students to score the videotapes.

Standard analyses will compare number and timing of instances of orienting to or disengaging from a directed social stimulus (repeated measures ANOVA comparing pre- and post-training measures and groups and interactions). More advance analysis will use methods developed by Dr. Janet Wiles. Linguistic and Nonverbal communicative behaviors will be annotated into the Eudico Linguistic Annotator (ELAN) (Brugman, H., & Russel, A., 2004; Crasborn, O., & Sloetjes, H., 2008). ELAN, a video interface integrates behavioral data at millisecond resolution across multiple channels such as speech, eye gaze, head movement and facial expression. Behavioral states and discreet behaviors can be coded yielding frequency counts, total duration and mean duration as well as the coordination across channels, e.g., integrating an eye gaze shift in response to a question. Drs. Reilly and Wiles have developed methods for coding social behaviors in typical and atypical children and adults. These analyses include following behavioral categories: (i) Gaze: Location (target), Duration, Frequency; (ii) Head: position and movement; (iii) Speech (transcribed using CHILDES): utterances (content and length) and pauses. From these analyses, it is possible to determine the degree to which participants respond appropriately, both linguistically and behaviorally to social interactive cues. Novel analyses developed by Dr. Janet Wiles (a consultant on this project) use a recurrence technique in which the level of engagement of the participants is revealed in the pattern of their exchange (Figure 4). We will examine both speech and non-verbal indications of engagement, such as gaze and gestures. We will also obtain SRS scores to compare aspects of social engagement with a standardized assessment. This high level outcome measure allows us to examine the subtleties of visual and spoken engagement during a conversation. We expect that our intervention would promote more effective social interaction.