BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023682
Article Type:	Protocol
Date Submitted by the Author:	18-Apr-2018
Complete List of Authors:	Scherf, K. Suzanne; Pennsylvania State University, Psychology Griffin, Jason; Pennsylvania State University, Psychology Judy, Brian; Pennsylvania State University, Psychology Whyte, Elisabeth; Pennsylvania State University, Psychology Geier, Charles; Pennsylvania State University, Human Development and Family Studies Elbich, Daniel; Pennsylvania State University, Psychology Smyth, Joshua; Pennsylvania State University, Biobehavioral Health
Keywords:	MENTAL HEALTH, Developmental neurology & neurodisability < PAEDIATRICS, Child & adolescent psychiatry < PSYCHIATRY

Improving Sensitivity to Eye Gaze Cues in Autism Using Serious Game Technology: Study Protocol for a Phase I Randomized Controlled Trial

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Word Count : 4216

Keywords: Adolescent, Autism Spectrum Disorder, Face, Social Skills, Video Game

Protocol Version: 4_17_2018_v1

Protocol Amendments: 0

Abstract

Introduction: Autism spectrum disorder (ASD) is characterized by impairments in social communication. Core symptoms are deficits in social looking behaviors, including limited *visual attention to faces* and *sensitivity to eye gaze cues.* We designed an intervention game using serious game mechanics for adolescents with ASD. It is designed to train individuals with ASD to discover that the eyes, and shifts in gaze specifically, provide information about the external world. We predict that the game will increase understanding of gaze cues and attention to faces.

Methods and analysis:
The Social Games for Adolescents with Autism (SAGA) trial is a preliminary, randomized controlled trial comparing the intervention game with a waitlist control condition. 34 adolescents (10-18 years) with ASD with a Full-Scale IQ between 70-130 and a minimum 2nd grade reading level, and their parents, will be randomly assigned (equally to intervention or the control condition) following baseline assessments. Intervention participants will be instructed to play the computer game at home on a computer for ~30 minutes, 3 times a week. All families are tested in the lab at baseline and approximately 2 months following randomization in all measures. Primary outcomes are assessed with eye-tracking to measure sensitivity to eye gaze cues and social visual attention to faces; secondary outcomes are assessed with questionnaires to measure social skills and autism-like behaviors. The analyses will focus on evaluating the feasibility, safety, and preliminary effectiveness of the intervention.

Ethics and dissemination: SAGA is approved by the Institutional Review Board at Pennsylvania State University (00005097). Findings will be disseminated via scientific conferences and peer-reviewed journals and to participants via newsletter. The intervention game will be available to families in the control condition after the full data are collected and if analyses indicate that it is effective.

Trial registration number: NCT02968225; pre-results

Article Summary

- This is a randomized controlled trial that employs an immersive computer game with serious game mechanics to maximize opportunities for adolescents with ASD to discover the functional utility of eye gaze cues.
- This intervention targets the developmental period of adolescence when eye gaze cues are especially important to changing social demands and when there are declining developmental trajectories in ASD.
- Multiple eye-tracking/behavioral metrics will be measured to assess improvements in social looking behavior, a core symptom of ASD.
- Given the nature of this design, the inability to utilize a completely blinded procedure is a limitation.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communicative behaviors. Core symptoms of these impairments are deficits in social looking behaviors including limited *visual attention to faces* and *sensitivity to eye gaze cues*[1]. Reduced visual attention to faces is one of the earliest behavioral indicators of autism[2-4], persists across the lifespan[5-7], and may serve as a reliable predictor of general social impairments in ASD[8]. It is related to difficulties recognizing face identity[9] and emotional expressions [10] and interferes with learning in domains outside of face perception as well[11-13]. Similarly, reduced understanding of eye gaze cues is present in infants later diagnosed with autism[14] and persists through the first two decades of life[12,15,16]. It also has long-term consequences for understanding goal-directed behavior[6,17,18], learning language and social communication[19,20]. People with ASD have difficulty computing the trajectory of eye gaze, understanding the referential nature of gaze, and assigning social relevance to gazed-at objects[17,18]. This deficit impacts the ability to use eye gaze direction to predict the actions and intentions of others.

One hypothesis about the underlying mechanism for these deficits suggests that individuals with ASD avoid looking at faces because doing so leads to an increased negative emotional response, as indexed by increased activation in the amygdala[21]. However, a review of the literature suggests that there is little support for this hypothesis[22]. Also, recent neuroimaging findings suggest that the neural systems for face processing are not impaired in autism; they are just tuned differently (i.e., they exhibit typical levels of activation when looking at animal, but not human, faces)[23]. Together, these findings suggest the need to consider other mechanisms for atypical social looking behavior in ASD; we hypothesize an early disruption in the learning environment for individuals with autism that contributes to this altered tuning of the face processing system. Although the origin of this disruption is not clear, one

hypothesis is that it emerges from atypical coordination between early developing subcortical social orienting and later developing cortical social perception systems[24]. The long-term developmental consequence from this disrupted learning environment is that it could deprive individuals with autism the opportunity to learn about the functional significance of social signals, like eye gaze, from the face. Accordingly, this atypical developmental context and learning cycle could lead to a state in which the face and eyes are not meaningful[25] to people with autism. Using this conceptual framework, we hypothesize that it may be possible to, in part, re-tune the face processing system by employing an intervention that encourages individuals with ASD to focus visual attention on faces and discover the functional significance of eye gaze cues. We propose to train individuals with ASD to discover that the eyes, and shifts in gaze specifically, provide critical information about the world around them. Our prediction is that attention to faces, particularly in more social contexts, will also improve as a result of increased understanding how to interpret eye gaze cues. The hope is that such training may begin to ameliorate core symptoms of ASD and potentially facilitate aspects of social functioning (e.g., face processing and social communication).

Existing studies have employed computer-based interventions for children and adolescents with ASD with the goal of improving aspects of face processing behavior[26-29]. Most of these interventions, however, have not been very successful in producing long-term changes in behavior for several reasons. First, they often target multiple components of face processing behavior, including accuracy of gazed-at objects[29,30], but do not isolate the active ingredients of the intervention on the outcome measures. Second, they often use highly repetitive and specific learning trials, which can lead to inflexible learning and behavior in autism[31]. Third, none of the existing interventions used eye-tracking measures as outcome behaviors nor have they evaluated changes in visual social attention. Fourth, although some of these studies have demonstrated learning during the course of the intervention, they have had

only limited success in showing evidence of clinical change, particularly in real-world social skills[32]. We innovate beyond these previous computer-based interventions by embedding eye gaze direction cues within simulated social interactions with computer-animated characters and embed these interactions in an age-appropriate narrative storyline. This simulates the way social information cues are used in the real world and, we posit, is more likely to generalize to real-world behavior. We designed the intervention game for adolescents because our prior work suggests that it is an important window of opportunity for altering declining developmental trajectories in autism[33-40].

Current Serious Game Intervention

We propose an intervention strategy that employs evidence-based "serious game" principles (e.g., storylines, long-term goals, scaling difficulty) to design a learning environment that maximizes opportunities for adolescents with ASD to discover the functional utility of eye gaze cues. *Serious games* are unique intervention tools that are designed to promote learning of targeted skills that are difficult and not rewarding for participants with the goal of improving real life outcomes[32]. To do so, they integrate educational objectives with evidence-based game mechanics that support learning and generalization of learning. We designed a serious game in which participants discover that eye gaze cues are useful for guiding their own goal-directed behavior to solve problems in the game. Participants learn to interpret increasingly subtle nonverbal behaviors (e.g., pointing, head turning) of game characters for the purpose of solving narrative-related quests (i.e., mixing a potion in the chemistry lab to get gum off a locker in school). The game increases in scope and task difficulty in response to successful demonstration of skills. Initial levels of the game focus on learning to use eye gaze cues exclusively over time and with practice. This transitions to requiring participants to determine the direction of eye gaze cues with more precision, avoid highly salient objects that are not target gazed-at objects, and differentiate predictive (e.g., looking at an object of interest) from non-

predictive (e.g., avatar looking up as if to think before acting) eye-gaze cues. Finally, in the most advanced levels of the game, participants learn to process eye gaze cues in episodes of joint attention between two avatars with all the same levels of complexity as are presented with the single avatar.

Aims & Objectives

The aims of this study are to assess the feasibility and safety of this serious game intervention and examine the initial evidence for its effectiveness to alter sensitivity to eye-gaze and social visual attention to faces in adolescents with ASD. The preliminary RCT will be conducted to determine:

1. Is it possible to recruit and randomize participants into the serious game intervention versus a waitlist control condition;
2. Do adolescents engage with the game at the intended level (playing 90 min/week for 2 months);
3. Is the intervention tolerable and safe (i.e., does retention remain high across all data collection points with minimal to no adverse events);
4. Does sensitivity to eye-gaze improve disproportionately in the intervention compared to the waitlist control group;
5. Does social visual attention to faces improve disproportionately in the intervention compared to the waitlist control group?

The trial will also allow exploratory analyses of changes in social skills and autism behaviors between the intervention and waitlist control group as a secondary measure of effectiveness of the intervention.

METHODS

Study Design

This study will be a preliminary, experimental randomized controlled trial including an experimental group and a waitlist control group. The experimental group will consist of adolescents with ASD who will play an immersive computer game for 90 minutes a week over 2 months in their own home. For this early trial, we will compare outcomes to a waitlist control group comprised of adolescents with autism receiving treatment as usual in the community. The flow of participants through the study is shown in Figure 1. These methods are reported with SPIRIT reporting guidelines[41].

Setting

The study will be conducted in the United States in the Laboratory of Developmental Neuroscience at Penn State University, University Park, PA, and in the homes of intervention participants.

Participants

Inclusion Criteria

Inclusion criteria are: 1) parent/caregiver of an adolescent with a diagnosis of ASD, 2) parent/caregiver and adolescent with ASD both native English speakers, 3) adolescent with ASD aged between 10-18 years at enrollment, 4) adolescent has normal vision and hearing with correction, 5) adolescent is able to use a computer for the purposes of game play, 6) adolescent scores ≤ 80% correct (i.e., 0.5 SD less than M of TD adolescents) on online eye gaze screening task, 7) ASD diagnosis of adolescent confirmed in lab via the Autism Diagnostic Observation Schedule[42], 8) Full Scale IQ of adolescent determined to be between 70-130 on the Kaufman Brief Intelligence Test[43], 9) reading ability of adolescent determined to be at least a second grade level as assessed by the Oral and Written Language Scales[44], 10) adolescent is capable of cooperating with testing, 11) parent/caregiver and adolescent both consent/assent to participate in the research.

Exclusion Criteria

Exclusion criteria are: 1) adolescent has had seizures within the previous two years, 2) family lacks stable home internet, 3) parent or adolescent refuses to consent/assent to take part in the research, 4) adolescent is 18 and has a legal guardian, prohibiting him/her from legally consenting, or 5) adolescent is 18 and cannot understand the consent (i.e., fails consent quiz).

Sample Size

A meta-analysis indicates that computer-based interventions for individuals with ASD generally have a medium effect size (Cohen's $d = 0.47$)[45]. Power calculations indicate that with a sample size of 34 (17 per group), and an expected correlation between the pre/post-test measures of 0.58, we will have statistical power of .80 to detect a medium effect size for the expected Group (intervention, control) x Time (pre-, post-intervention) interaction with an $\alpha < .05$ in this repeated-measures design.

Recruitment

Our primary recruitment approach will be to recruit families who have registered with research databases like the Interactive Autism Network (IAN) Research Database at the Kennedy Krieger Institute, Baltimore and autismMatch at the Center for Autism Research, Philadelphia. Recruitment will proceed via a three-step process (see Figure 1). First, the initial inclusion/exclusion criteria will be determined via brief phone interview or by completing an online survey. Second, eligible adolescents will be invited to take an online test of sensitivity to eye gaze through a secure website (Testable.org). Participants view complex images of an actor in a naturalistic scene looking at one of many possible objects and have to identify the target gazed-at object from a list of 4 labels [46]. Participants who score ≤ 80% (TD adolescent M - 0.5 SD) on this task are invited to the lab to be evaluated for the remaining set of inclusion criteria. We will obtain written informed consent from the parent and 18-year old adolescents and written assent from the 10-17-year-old adolescents to participate in the study (see Appendices for consent/assent). Only after both consent and assent are obtained will we

administer the remaining eligibility assessments. Participants who meet the final eligibility criteria are invited to continue with the pre-test procedures.

Randomization Procedures

Following completion of the pre-intervention testing procedures, participants will be randomized in a 1:1 ratio into either the intervention game or waitlist control condition. The randomization list will be computer-generated prior to the enrollment of any participants and will be stratified by sex and Full Scale IQ (>100, <100). None of the researchers collecting data will have access to the randomization list.

Blinding Procedures

Given the design of the study, parents and adolescents will know the condition to which they have been assigned. However, researchers involved in data collection will be blinded from condition assignment during the pre-intervention data collection session as these data will be collected prior to randomization. Also, the research team is not involved in the randomization process. The research team members who are involved in ensuring the fidelity of the intervention are not involved in data collection procedures. Although we will attempt to limit unblinding, it is not possible for researchers involved in data collection to be completely blinded to the assignment of participant condition at the post-intervention visit as we cannot prohibit participants from talking to researchers about their experience in the study.

INTERVENTION CONDUCTED IN THE EXPERIMENTAL GROUP

The intervention video game is designed to engage and shape learning of sensitivity to eye gaze information and social attention to faces. Specifically, the game is structured around learning to use eye gaze as a cue for 1) directional reference (e.g., put the object there), first when gaze cues are highly predictive and subsequently when they are embedded in noisy cues that are not predictive of directional information; 2) reference to a specific object identity (e.g., I want that one), first when gaze cues are highly predictive and subsequently when they are embedded in noisy cues that are not predictive of object information; and 3) joint attention

episodes when two people engage in mutual gaze with each other and then engage in joint attention on the same specific object (e.g., hey Matt, look at that red one), first when gaze cues are highly predictive and subsequently when they are embedded in noisy cues that are not predictive of joint attention.

The game is an adventure game with embedded gamification techniques in which participants solve mysteries in a 3D environment that is programmed in Unity (https://unity3d.com/unity). The core training mechanisms are delivered via character interactions, with participants learning skills via simulated social interactions with avatars in the game as participants solve problems related to the game narrative. Each of these puzzles has variable elements so that they can be dynamically altered with different objects, locations, and levels of difficulty. Moreover, they are executed with a variety of characters and environmental contexts to support generalized learning opportunities.

The training paradigm is much like a perceptual staircase paradigm in which participants start at a level meant to be easily processed and accomplished by all participants. Individuals advance through levels, until they hit a threshold where their skills plateau. When participants fail a level, they go back to the preceding level where they succeeded and must complete it before progressing to the failed level again. This keeps participants challenged without becoming too frustrated and allows them to practice and learn new skills. When participants repeat a level, they do so in a new context with new avatars, to foster generalization of the learned skills. If players are unable to progress from the easiest levels, they are redirected to remedial training in which more explicit guidance is provided about how eye gaze cues provide information about objects and locations in the local environment (once completed, they are returned to the main game).

Difficulty increases in several ways and is all controlled by choices of the individual participant, within design constraints of the game. First, the number of locations or objects that the avatars reference gradually increases so that the precision of gaze sensitivity has to

improve. Second, in the early stages of the game, participants are provided with multiple kinds of non-verbal social cues in their interactions with the avatars. For example, the avatars simultaneously point, turn their head, and shift their eye gaze as cues to direct participants to solve quests in the game. As play progresses, learning is scaffolded by slowly removing the non-gaze social behaviors; ultimately avatars only direct participants via eye gaze cues. Third, once a participant has mastered the easiest levels of gaze shifts, the levels increase in difficulty by reducing the spacing between the objects (requiring more precise tracking of gaze trajectory) and by increasing the salience of the non-target objects (requiring increasing focus of attention on the target gazed-at object). Finally, at the most advanced levels of the game, it is necessary to learn to ignore non-predictive shifts of gaze (e.g., looking up pensively, looking across all object before landing on target object) and only focus on the predictive gaze shifts.

OUTCOME MEASURES

Feasibility outcomes

To measure intervention feasibility, in addition to participant attrition, we will report the mean number of sessions, total number of minutes played, total number of minutes engaged in eye gaze tasks, frequency of each level visited in the game, and accuracy of performance within each level of the game.

Safety outcomes

Potential adverse events and unintended effects occurring during the intervention period or during testing will be reported and explored.

Primary outcomes (intervention effectiveness)

Primary and secondary outcomes will be measured at both the pre- and post-intervention sessions. We hypothesize that the intervention will improve eye gaze and social visual attention behaviors; therefore, all the primary measures of the intervention effectiveness are assessed with eye tracking technology. The secondary measures evaluate changes in

autism-like behaviors, social competence, and problematic behaviors, which may be indirectly impacted by the intervention.

Visual Attention to Faces

This task is similar to that previously described[47]. Participants passively view 6 42-second clips from age-appropriate movies of social interactions with two or more characters that are matched by adult raters on emotional intensity and valence, number of visible faces, and amount of time faces are present. Four of the movies are unique at each time point (pre, post) and two movies repeat across time points to assess reliability of measurement. The dependent measures include the *average gaze time to faces* and the *proportion of total gaze time to faces*.

Eye Gaze Sensitivity

We will assess eye gaze sensitivity in two tasks. In the static version of the task, participants view still images ($N = 40$) of an actor in a naturalistic scene looking a one of many possible objects[17,46]. Each image is displayed on a computer screen for 4 seconds. Participants must then identify the specific object the person is looking at from a list of four labels presented on a subsequent screen. The dependent measures include both performance accuracy and the ratio of average gaze time to the target object versus average gaze time to non-target objects. Twenty-six images are unique at each time point and 14 images repeat across time points.

To measure sensitivity to real-time eye gaze cues, we will create a dynamic version of this static task that is modeled after dynamic stimuli used to test infant joint attention[15]. On each trial, participants watch a movie of a female actress looking into the camera, then directing her gaze to a target object, holding the gaze on the target object for several seconds, and returning her gaze back to the camera. At the end of each trial, participants identify the target gazed at object from a list of four labels presented on a subsequent screen. The dependent measures include performance accuracy, gaze shifts between the face and target- and non-target objects[15], and ratio of average gaze time to the target object versus average gaze time

to non-target objects. Twenty videos are unique at each time point and six videos repeat across time points.

Secondary outcomes (intervention effectiveness)

Autism, Social, & Problem Behavior Questionnaires

To assess if the intervention influences autism symptoms, social skills, and adaptive functioning, parents and adolescents will complete the Social Skills Improvement System (SSIS)[48] and parents will complete the Social Responsiveness Scale-2nd Edition (SRS-2)[49]. On the SSIS measures, total scores will be computed separately for social skills and problem behavior domains. Higher scores indicate the presence of more of these behaviors. We will compute the total score on the SRS-2; higher scores reflect more social impairment.

DATA COLLECTION

Intervention data

Strategies for maximizing the fidelity of the video game intervention include, 1) establishing minimum computer requirements for participants, 2) designing instructional videos for participants about the game, 3) designing a web page portal for participants to find frequently asked questions about the game and submit electronic help tickets for technical problems, 4) establishing a texting reminder system on scheduled game play days for participants, 5) establishing a protocol for contacting parents when participants miss scheduled sessions of game play, 6) providing explicit directions to parents that no one else in the home is to play the intervention game, and 7) paying participants $5 for every 30 min of game play up to $200. Throughout the intervention, log files are generated for each participant with feasibility data (see outcomes) for each day of game play. Log files will be uploaded every 8 minutes onto a secure, password protected server that only designated research personnel can access. Data from the log files will be summarized across days and sessions for each participant.

Eye tracking data.

Eye tracking data will be collected using a Tobii X2-60 eye tracker, which has a sampling rate of 60 Hz and approximate accuracy of 0.4° and precision of 0.34°. This eye-tracker allows for bright and dark pupil eye-tracking and small head movements, maximizing comfort during testing (i.e., no chin rest required). A 9-point automatic calibration procedure will be employed prior to each task to customize and accurately estimate gaze point calculations. To reduce fatigue and restlessness, we will incorporate breaks in the eye tracking protocol for participants. The entire data collection procedure for eye tracking will last approximately 70-90 minutes. The fidelity of the eye-tracking data will be assessed through quality of the calibration procedure. Eye gaze samples in which there is no recordable information from at least one eye on the stimulus will be quantified as missing data.

Questionnaire data

Parents complete questionnaires while adolescents are tested in the eye-tracking protocol. Adolescents complete the questionnaires following completion of the eye tracking protocol. The SSIS is clinically relevant and is sensitive to changes in social abilities from behavioral interventions in individuals with ASD[50]. The SRS-2 is a reliable and valid measure of social impairment and repetitive behavior as a single quantitative trait[50], and also includes multiple questions specifically related to eye gaze behaviors and face-processing abilities. Missing data will be handled in congruence with the standardized SSIS/SRS-2 procedures.

DATA MANAGEMENT & ANALYSIS PLAN

All analyses will be completed using standard statistical software (e.g., R[51]). Data will be scored and entered into the program for further preprocessing/data reduction and backed up in multiple locations (i.e., lab server, back-up hard drive). Data will be de-identified and stored on a lab server and in password-protected partitions of cloud and lab servers. Only research project investigators and staff approved to work on the project and listed in the IRB protocol will have access to the de-identified data.

Prior to statistical analyses, all the data will be investigated for deviations from normality and transformed if necessary, and we will examine and manage statistical outlier data points (> 2 SD of the group mean) where appropriate. Once the pre-intervention data collection is completed, we will analyze the groups (intervention vs. waitlist control) for potential differences in demographic characteristics. Any observed differences will be accounted for in subsequent analyses.

For the primary study outcomes, we will utilize linear mixed effects modeling to test the effectiveness of the intervention on outcome measures while accounting for repeated measures (i.e., time-point). Additionally, we plan to model random variability in both stimulus items and participants by including them as random factors in our statistical models. For each dependent variable, we will fit a model with Group (intervention, control) and Time-point (pre-intervention, post-intervention) as fixed factors and participant, age, IQ, ADOS total score, and stimulus as random factors. The amount of missing eye gaze data will also be submitted as a covariate in analyses of intervention effectiveness.

Study Monitoring

A Data Safety Monitoring Board (DSMB) will be established and will be composed of independent researchers who have expertise complementary to the aims of the project. We will meet with the DSMB prior to enrolling participants in the study and bi-annually during the duration of the intervention to review the safety and tolerance of the intervention for our participants. Procedures are in place to monitor suicidal ideation and self-injurious behavior among adolescents and to make recommendations about care based on the assessment outcome. Any adverse events will be reported to both the DSMB and the Penn State Internal Review Board.

Ethics and Dissemination

Approval to conduct this study has been granted from the Pennsylvania State University Internal Review Board (IRB# 00005097). Results will be disseminated to the scientific

community at scientific conferences and in the form of empirical articles in peer-reviewed scientific journals. Results will also be reported to the funding agency (National Institutes of Mental Health) annually. Finally, we will present summaries of the findings in the form of a newsletter to study participants and the intervention game will be made available to families in the waitlist control condition after the full data have been collected if analyses indicate that it is effective.

DISCUSSION

This intervention game may have great potential for translation and dissemination. By combining serious game design principles with intervention science, the resulting intervention game has the potential to be highly motivating, scalable to individual skill level, inexpensive, engaging, and accessible by adolescents in their own homes at their own convenience. We will continue to develop the intervention game with the goal of testing it against an active control game, evaluating if it is effective for improving a boarder range of face processing behaviors that are difficult for individuals with ASD (e.g., face identity recognition), and improving social skills in ASD. These data, including the generation of effect size estimates, will inform a future confirmatory clinical trial. More generally, these goals represent significant innovation in the design of RCTs for computer-based interventions for autism and may help advance theory and clinical practice.

Competing Interests Statement:

All authors have completed the ICMJE uniform disclosure form at *www.icmje.org/coi_disclosure.pdf* and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Elisabeth Whyte was at the Dept of Psychology at Pennsylvania State University when she contributed to this work. She is currently working for Daybreak Games in San Diego, CA.

Funding Statement:

This work is supported by National Institutes of Mental Health (R61-MH110624-01; PI KSS).

Data Sharing Statement:

Participants will be invited to share de-identified data acquired from this study with the National Institutes of Health Data Archive.

Author Contributions:

KSS, EMW, JS, and CFG secured funding to support this project. KSS, EMW, and JS conceived and designed the study. KSS, EMV, JS, and BJ designed the intervention game. JG will be responsible for testing participants. DE, JS, CFG, and KSS are responsible for designing the procedures to manage the fidelity of the intervention. JG and DE will be responsible for managing the data generated during the project. JG and KSS will conduct the statistical analyses of the data. KSS and JG drafted the manuscript and all authors reviewed the manuscript for intellectual content and approved the final version.

Figure Legends

Figure 1. CONSORT Diagram for SAGA Protocol

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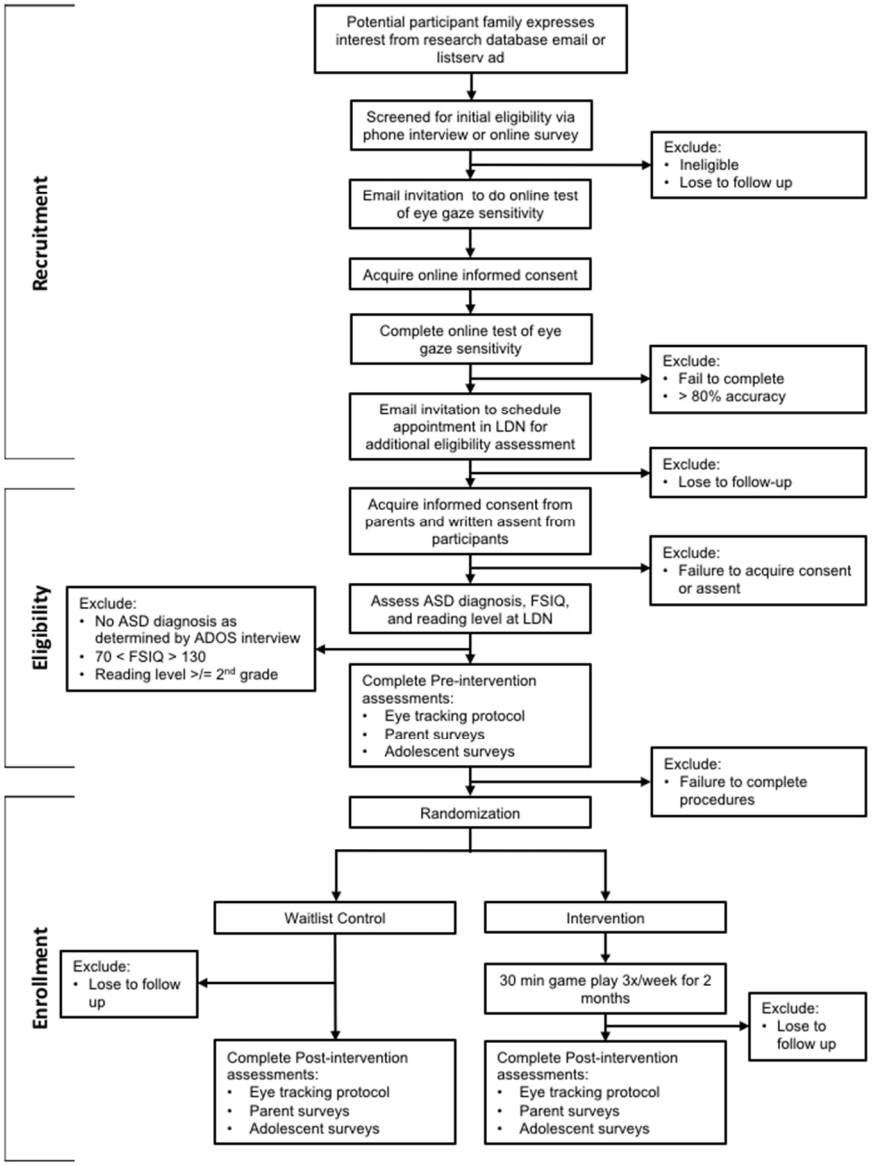

Figure 1. CONSORT Diagram for SAGA Protocol

190x254mm (96 x 96 DPI)

CONSENT FOR RESEARCH - Intervention
The Pennsylvania State University

Title of Project: *Using Serious Game Technology to Improve Sensitivity to Eye Gaze in Autism*

Principal Investigator: *K. Suzanne Scherf*
Address: 113 Moore Building
University Park, PA 16802
suzyscherf@psu.edu
Telephone Number: (814) 867-2921

Subject's Printed Name: _____

We are asking you to be in a research study. This form gives you information about the research.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.

Please ask questions about anything that is unclear to you and take your time to make your choice.

Some of the people who are eligible to take part in this research study may not be able to give consent because they are less than 18 years of age (a minor). Instead we will ask their parent(s)/guardian(s) to give permission for their participation in the study, and we may ask them to agree (give assent) to take part. Throughout the consent form, "you" always refers to the person who takes part in the research study.

1. **Why is this research study being done?** We are asking adolescents to be in this research because you may learn social skills from playing a computer game. This research is being done to find out find out how adolescents with autism learn social skills from a computer game. Adolescents may be asked to play the game or you may be asked to be part of a control group who does not play the game. We hope that the information we obtain from the way adolescents perform on these tests and respond to the computer-based training will lead to better understanding about the nature of face-to-face social skills in people with autism. Approximately 150 people will take part in this research study at Penn State.

2. **What will happen in this research study?** Dyads (adolescents ages 10 to 17 and their parents) have been invited to participate in two behavioral sessions over the course of three months. Adolescents will also be randomly assigned to either the intervention (playing a social skills video game) or control condition (not assigned to play a video game).

Parents will complete the following: The parent of each adolescent will complete several paper and pencil questionnaires asking about their child's behavior and health history at each of the two sessions. If your family is randomly assigned to participate in the intervention, you will help administer your child's computer-based intervention at home.

Adolescents (age 10 to 17) will complete the following:

Pre-test Session: The pre-test session completed by adolescents consists of two parts.

- *PART 1:* During the first portion of the pre-test session, adolescents will complete standardized testing as part of confirming the eligibility criteria. This consists of completing a reading test, an intelligence test, and a standardized observational measure of autistic symptoms (the ADOS). You will be video recorded while you complete the ADOS testing. *Based on your responses on these measures, you will*

be further assessed for eligibility in the behavioral intervention trial. A summary report of the ADOS and IQ results is available to parents upon request.

- *PART 2 for adolescents*: If you qualify for the study based on your standardized testing scores, adolescents will complete the second portion of the pre-test session, you will complete several computer-based eye-tracking tasks. You will be given a break before the second portion of the pre-test session. The eye tracker records your eyes and measures your eye movements while looking at pictures or videos. You will be asked to make decisions about what you see on the screen. The pictures and videos include scenes of people looking at objects. The videos will include scenes of people interacting, like from age-appropriate entertainment movies. Adolescents will also complete questionnaires about your behavior and social skills.

Group Assignment (Randomization): Because we want to understand whether the computer-based intervention has an impact on social behavior, we need to compare the intervention group to a control group who does not complete the intervention. To do this, we will assign adolescents taking part in this research into two groups. The two groups are selected by chance, as if by tossing a coin. This randomization happens at the end of the first session, so you won't know your group assignment until the end of your pre-test session. One group will be assigned to complete the computer game intervention. The other group will be the control group and will **not** be assigned to play our computer game. If you are assigned to the control group, you will be scheduled to return in 2 months for the post-test session and will not be assigned to any particular intervention procedures between sessions.

Intervention Group Procedures:

- If you are an adolescent assigned to the intervention group, you and your parents will be given the option to install the software directly on your home computer. Your family may also be provided a laptop if needed. A research assistant will teach families how to use the computer software programs for this testing at the end of the pre-test session. Families will be given a unique login account name and password at the lab, along with instructional materials. As the data will be submitted electronically to Penn State over the Internet, the game will require Internet connectivity to play.
- A parent will help adolescents complete the training sessions in a quiet room in your own home. The research assistant will also maintain daily contact with a parent, via text messaging, telephone, or e-mail, during the intervention to monitor your progress and address any questions or concerns. If you have technical difficulties with the program at home, adolescents can ask your parent to contact the researchers and our staff will assist in identifying and fixing the problem.
- This computer-based social skills intervention involves social interactions with animated characters in a adventure-themed game. Adolescents are be asked to recognize nonverbal social cues, such as pointing, head turns, or eye gaze cues. This training will take approximately 20 total hours over 2 months. Adolescents will play the game for 3 days per week (approximately 60 minutes per session), every week, for 2 months.

Post-test Session: The post-test session will be scheduled for approximately 2 months after your first session, for both groups. Adolescents will complete the same self-report questionnaires as done at pre-test. Adolescents will also complete the same eye tracking tasks that were completed at pre-test. Adolescents from the intervention group will also be asked to rate your enjoyment of the intervention game.

3. Who can be in this study? You are an adolescent diagnosed with autism who passed the initial pre-screening for the study, and:

- are between the ages of 10 and 17 at the time of enrollment

- are capable of cooperating with testing, and are able to use a computer keyboard and mouse
- have normal vision and hearing (with correction)
- have no history of seizures within the last 2 years

Adolescents will complete background testing today, to confirm your eligibility to participate in the intervention. Completion of the background measures will allows researchers to confirm that you:

- have a full scale and verbal intelligence (IQ) greater than 70 (as confirmed on the KBIT-2)
- are able to speak in full sentences and can read at or above a 2nd grade reading level (as confirmed on the OWLS-2 reading comprehension scale)
- have current symptoms reflecting a diagnosis of autism (as confirmed in the ADOS interview).

If you meet these criteria, you will complete the remaining study measures. If you do NOT meet these criteria, you will not be enrolled in the remainder of the study. In such an event, you will not suffer any penalty or loss of benefits or rights, which you or might otherwise be entitled.

4. What are the risks and possible discomforts from being in this research study?

The risks and discomfort associated with participation in this study are no greater than those ordinarily encountered in daily life. The risk to you is minimal for the eye tracking and computer-based tasks. At most, participants may find the testing too simple and become bored or too difficult and become frustrated. Previous experience with these sorts of tests suggests that participants can perform them reasonably well with minimal impact on them. Sometimes people worry about how well they do on tests or become tired. To reduce these problems, testing will not begin until you are comfortable with the laboratory, procedures and research personnel. There are no consequences for poor performance on any of the tests. You can take breaks at any time.

The eye-tracking device uses near-infrared light to create reflections off the eyes. This type of light can be commonly found in the environment. The infrared light is emitted from the eye tracker at very low amperage and causes no damage to the eye. This kind of infrared eye tracking has been used for many years at many universities and no negative consequences have been reported.

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Incidental findings: The investigators for this project are not trained to perform medical diagnosis, and the testing procedures are not optimized to diagnose disorders. However, on occasion, scores on the self-report measures by adolescents may indicate that they are at risk for suicide or other serious self-injury. If an adolescent displays suicidal behavior or ideation, a member of the research staff will inform the principle investigator and will ask a staff member in the clinical psychology department at Penn State to conduct a suicide risk assessment. Based on levels of risk, the clinical staff at Penn State may suggest various options for your family. In rare cases, this may involve suggesting the seeking of emergency services or providing information to help parents arrange for future follow-up monitoring and/or medical attention with your primary care providers. Costs for clinical follow-up are not covered in the cost of research.

Video Recording: Adolescents will be videotaped when you complete the ADOS. This video recording is required so that the researchers can review this video for scoring the observational assessment. During eye

tracking, a video may be recorded of your eye-movements, in order to determine where your eye movements fall on the screen, and will not be associated with your personal information. Any video collected during this research study is kept confidential and is not shared with other researchers.

5. What are the possible benefits from being in this research study?

5a. What are the possible benefits to you?

If you participate in the intervention, adolescents may experience improved social skills or face-processing abilities as a direct result of participating in the intervention training. In addition, you may experience a sense of satisfaction from contributing to research about autism.

5b. What are the possible benefits to others?

We hope that the information we obtain from the way participants perform on these tests and respond to the computer-based training will lead to better understanding about the nature of face-to-face social skills in people with autism. Findings from this study will be used to improve future computer-based interventions for people with autism.

6. What other options are available instead of being in this research study?

You may decide not to participate in this research at any time.

Because it is investigational, the therapy offered in this research is only available to you if you take part in the research study.

7. How long will you take part in this research study?

If you agree to take part, it will take about 2 months to complete this research study. During this time, we will ask adolescents and your parents to make 2 visits to the lab. Adolescents may also be invited complete an intervention at home lasting up to 20 hours (3 times per day for 2 months). For adolescents, the first visit will consist of background standardized tests (approximately 2.5 hours) and a testing session consisting of computer-based eye tracking tasks and paper-and-pencil surveys (approximately 2.5 hours). The post-test session involves computer-based eye tracking tasks and paper-and-pencil surveys (approximately 2 hours). During each lab visit, parents will complete questionnaires, lasting 60 minutes.

8. How will your privacy and confidentiality be protected if you decide to take part in this research study?

Your participation in this research is confidential. All possible steps have been taken to assure your privacy. You will be assigned a code number that will be used throughout the study. Only this code (and never your name) will be used when analyzing or reporting the data. Any identifying information will be kept in a locked location and password protected electronic files.

All personally identifiable records pertaining to your involvement in this research will be stored in a locked file cabinet and room in our office and your computerized data will be password protected. This information will only be accessible to the investigators listed on the cover page, and their research staff. All research records will be kept indefinitely with identifiers removed.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. The results of the research may be published and presented at lectures and professional meetings, but neither you or your parents will be identified in any such publication or presentation. Your data and consent form will be kept separate. Your consent form will be stored in a locked location on Penn State property and will not be disclosed to third parties.

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed.

We will do our best to keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may find out about your participation in this research study. For example, the following people/groups may check and copy records about this research.

- The Office for Human Research Protections in the U. S. Department of Health and Human Services
- The Institutional Review Board (a committee that reviews and approves research studies) and
- The Office for Research Protections.

To help us protect your privacy, we have obtained a Certificate of Confidentiality (CoS) from the study sponsor, the National Institutes of Health. We can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. We will use the Certificate to resist any demands for information that would identify you, except as in the following circumstances.

The Certificate cannot be used to resist a demand for information

- from personnel of the United States federal or state government agency sponsoring the project (NIH)
- that will be used for auditing or program evaluation of agency funded projects
- for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA)
- to prevent disclosure to state or local authorities such as child abuse and neglect, or harm to self or others

A CoS does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then we will not use the Certificate to withhold that information.

9. What are the costs of taking part in this research study?

9a. What will you have to pay for if you take part in this research study?

For costs of tests and procedures that are only being done for the research study:

- The Game Intervention will be provided by The Laboratory of Developmental Neuroscience and The NIH at no cost to you while you take part in this study.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- The research-related tests and procedures that will be provided at no cost to you include: ADOS-2 Evaluation.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

10. Will you be paid or receive credit to take part in this research study?

If you decide to participate in this research, you will receive $20/hour for each of the two sessions in the lab (approximately $80 for the first session and $50 for the second session). If you participate in the training intervention, you will also receive $5 per 30 min session, up to $200 for the training. If applicable, parents will also be reimbursed for transportation fees (e.g. mileage, flight, hotel, parking). Meal expenses will not be reimbursed.

Total payments within one calendar year that exceed $600 will require the University to report these payments to the IRS annually. This may require you to claim the compensation that you receive for participation in this study as taxable income.

11. Who is paying for this research study? This study is funded by the National Institutes of Health.

12. What are your rights if you take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

Refusal to take part in or withdrawing from this study will involve no penalty or loss of benefits you would otherwise receive. If you decide to leave the research, contact the investigator so that the investigator can cancel future lab visits and/or intervention sessions and can ask you questions about why you chose to leave the study.

The Principal Investigator may at his/her discretion remove you from the study after you have been enrolled for any number of reasons including demonstration of an inability to complete the behavioral testing. In such an event, you will not suffer any penalty or loss of benefits or rights, which you or might otherwise be entitled.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

13. If you have questions or concerns about this research study, whom should you call?

Please call the head of the research study (principal investigator), Dr. Suzy Scherf at (814) 867-2921, if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the Office for Research Protections at (814) 865-1775, ORProtections@psu.edu if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

INFORMED CONSENT TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

_____ _____ _____

Signature of person who explained this research Date Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent (PARENT)

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject - Parent

By signing this consent form, you indicate that *you voluntarily choose* to be in this research and agree to allow your information to be used and shared as described above.

_____ _____ _____

Signature of Subject Date Printed Name

Signature of Parent(s)/Guardian for Child

By signing this consent form, you indicate that you *permit your child* to be in this research and agree to allow his/her information to be used and shared as described above.

_____ _____ _____

Signature of Parent/Guardian Date Printed Name

Optional part(s) of the study
In addition to the main part of the research study, there is another part of the research. You can be in the main part of the research without agreeing to be in this optional part.

Data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share de-identified information with each other. A data repository is a large database where information from many studies is stored and managed. De-identified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send de-identified information about your health and behavior to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your de-identified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

PARENTS: Please let us know if you will allow us to share the data for you and your child with NDAR by checking one of the following choices:

_____ Provided that our identities stay private, my data and my child's data may be shared with NDAR.

_____ My data and my child's data MAY NOT be shared with NDAR.

Signature of Subject - Parent
By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part(s) of the research study for your data.

_____	_____	_____
Signature of Subject -Parent	Date	Printed Name

Signature of Parent(s)/Guardian for Child
By signing this consent form, you indicate that you have read the information written above and have indicated your choices for the optional part(s) of the research study for your child's data.

_____	_____	_____

Signature of Parent/Guardian Date Printed Name

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the optional part(s) to the research to the subject or subject representative and have answered any questions he/she has about the research.

_____ _____ _____
Signature of person who explained this research Date Printed Name

Permission to Contact for Future Studies

I would like to be contacted about future opportunities to participate in research conducted by Dr. Scherf.

_____ _____ _____
Parent Participant Signature Printed Name Date

_____ _____
Email Phone number

Child Assent (10 to 17 Years)

The Pennsylvania State University

Title of Project: *Using Serious Game Technology to Improve Sensitivity to Eye Gaze in Autism*

Principal Investigator: *K. Suzanne Scherf*
Address: 113 Moore Building
University Park, PA 16802
suzyscherf@psu.edu
Telephone Number: (814) 867-2921

We would like you to be in our research study. We want to understand how teenagers learn social skills.

If you decide you want to be in our study, you will come to the lab two times. You will answer some questions about your social skills. You will also complete tests that measure your communication skills. You will also look at pictures of real faces and watch movies on the computer. We may ask you questions about what you see and record where you are looking on the screen.

We might also ask you to play a game at home on the computer. You will play the game 3 days a week for three months (up to 20 total hours). In the game, you will play a detective. You will talk to people in the game to help you find the clues.

Other people will not know if you are in our study. We will combine information from a lot of people. No one can tell where the information came from. When we tell other people about our research, we will not use your name.

Your parents have to say it's OK for you to be in the study. After they decide, you get to choose if you want to participate. If you do not want to be in the study, no one will be mad at you. If you want to be in the study now and change your mind later, that's OK. You can stop at any time.

Do you have any questions?

We will give you a copy of this form in case you want to ask questions later.

AGREEMENT

The research study has been explained to you. You have had a chance to ask questions to help you understand what will happen in this research. You Do Not have to be in the research study. If you agree to participate and later change your mind, you can tell the researchers, and the research will be stopped.

You decide: **(Initial one)**

___ YES, I want to take part in the research.
___NO, I do NOT want to take part in the research.

_____	_____	_____
Signature of Subject	Date	Printed Name
_____	_____	_____
Signature of Researcher	Date	Printed Name

Optional part(s) of the study

You can be in the main part of the research without agreeing to be in this optional part.

If your parents agree, information from this study will be sent to the National Institutes of Health Data Archive (NDA). NDA allows researchers studying mental processes and illness to share information with each other. This helps them learn new things about conditions, like autism, more quickly than before. We will only share information from the study, not your name or other personal information. No one will be able to tell who you are and no one from NDA can contact you.

AGREEMENT

This part of the research study has been explained to you. You have had a chance to ask questions to help you understand what will happen. You Do Not have to agree to share your information with NDA. If you agree to share your information with NDA and later change your mind, you can tell the researchers, and they will notify NDA to stop sharing your information with other researchers.

You decide: **(Initial one)** ___ YES, my information can be shared with NDA.
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Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,18
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	10

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	16

		imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of	#28	Financial and other competing interests for principal	18

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16-17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Improving Sensitivity to Eye Gaze Cues in Autism Using Serious Game Technology: Study Protocol for a Phase I Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023682.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Jul-2018
Complete List of Authors:	Scherf, K. Suzanne; Pennsylvania State University, Psychology Griffin, Jason; Pennsylvania State University, Psychology Judy, Brian; Pennsylvania State University, Psychology Whyte, Elisabeth; Pennsylvania State University, Psychology Geier, Charles; Pennsylvania State University, Human Development and Family Studies Elbich, Daniel; Pennsylvania State University, Psychology Smyth, Joshua; Pennsylvania State University, Biobehavioral Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Paediatrics
Keywords:	MENTAL HEALTH, Developmental neurology & neurodisability < PAEDIATRICS, Child & adolescent psychiatry < PSYCHIATRY

Improving Sensitivity to Eye Gaze Cues in Autism Using Serious Game Technology: Study Protocol for a Phase I Randomized Controlled Trial

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Word Count : 5289

Keywords: Adolescent, Autism Spectrum Disorder, Face, Social Skills, Video Game

Protocol Version: 4_17_2018_v2

Protocol Amendments: 0

Abstract

Introduction: Autism spectrum disorder (ASD) is characterized by impairments in social communication. Core symptoms are deficits in social looking behaviors, including limited *visual attention to faces* and *sensitivity to eye gaze cues.* We designed an intervention game using serious game mechanics for adolescents with ASD. It is designed to train individuals with ASD to discover that the eyes, and shifts in gaze specifically, provide information about the external world. We predict that the game will increase understanding of gaze cues and attention to faces.

Methods and analysis: The Social Games for Adolescents with Autism (SAGA) trial is a preliminary, randomized controlled trial comparing the intervention game with a waitlist control condition. 34 adolescents (10-18 years) with ASD with a Full-Scale IQ between 70-130 and a minimum 2nd grade reading level, and their parents, will be randomly assigned (equally to intervention or the control condition) following baseline assessments. Intervention participants will be instructed to play the computer game at home on a computer for ~30 minutes, 3 times a week. All families are tested in the lab at baseline and approximately 2 months following randomization in all measures. Primary outcomes are assessed with eye-tracking to measure sensitivity to eye gaze cues and social visual attention to faces; secondary outcomes are assessed with questionnaires to measure social skills and autism-like behaviors. The analyses will focus on evaluating the feasibility, safety, and preliminary effectiveness of the intervention.

Ethics and dissemination: SAGA is approved by the Institutional Review Board at Pennsylvania State University (00005097). Findings will be disseminated via scientific conferences and peer-reviewed journals and to participants via newsletter. The intervention game will be available to families in the control condition after the full data are collected and if analyses indicate that it is effective.

Trial registration number: NCT02968225; pre-results

Article Summary

- This is a randomized controlled trial that employs an immersive computer game with serious game mechanics to maximize opportunities for adolescents with ASD to discover the functional utility of eye gaze cues.
- This intervention targets the developmental period of adolescence when eye gaze cues are especially important to changing social demands and when there are declining developmental trajectories in ASD.
- Multiple eye-tracking/behavioral metrics will be measured to assess improvements in social looking behavior, a core symptom of ASD.
- Given the nature of this design, the inability to utilize a completely blinded procedure is a limitation.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communicative behaviors. Core symptoms of these impairments are deficits in social looking behaviors including limited *visual attention to faces* and *sensitivity to eye gaze cues*[1]. Reduced visual attention to faces is one of the earliest behavioral indicators of autism[2-4], persists across the lifespan[5-7], and may serve as a reliable predictor of general social impairments in ASD[8]. It is related to difficulties recognizing face identity[9] and emotional expressions [10] and interferes with learning in domains outside of face perception as well[11-13]. Similarly, reduced understanding of eye gaze cues is present in infants later diagnosed with autism[14] and persists through the first two decades of life[12,15,16]. It also has long-term consequences for understanding goal-directed behavior[6,17,18], learning language and social communication[19,20]. People with ASD have difficulty computing the trajectory of eye gaze, understanding the referential nature of gaze, and assigning social relevance to gazed-at objects[17,18]. This deficit impacts the ability to use eye gaze direction to predict the actions and intentions of others.

One hypothesis about the underlying mechanism for these deficits suggests that individuals with ASD avoid looking at faces because doing so leads to an increased negative emotional response, as indexed by increased activation in the amygdala[21]. However, a review of the literature suggests that there is little support for this hypothesis[22]. Also, recent neuroimaging findings suggest that the neural systems for face processing are not impaired in autism; they are just tuned differently (i.e., they exhibit typical levels of activation when looking at animal, but not human, faces)[23]. Together, these findings suggest the need to consider other mechanisms for atypical social looking behavior in ASD; we hypothesize an early disruption in the learning environment for individuals with autism that contributes to this altered tuning of the face processing system. Although the origin of this disruption is not clear, one

hypothesis is that it emerges from atypical coordination between early developing subcortical social orienting and later developing cortical social perception systems[24]. The long-term developmental consequence from this disrupted learning environment is that it could deprive individuals with autism the opportunity to learn about the functional significance of social signals, like eye gaze, from the face. Accordingly, this atypical developmental context and learning cycle could lead to a state in which the face and eyes are not meaningful[25] to people with autism. Using this conceptual framework, we hypothesize that it may be possible to, in part, re-tune the face processing system by employing an intervention that encourages individuals with ASD to focus visual attention on faces and discover the functional significance of eye gaze cues. We propose to train individuals with ASD to discover that the eyes, and shifts in gaze specifically, provide critical information about the world around them. Our prediction is that attention to faces, particularly in more social contexts, will also improve as a result of increased understanding how to interpret eye gaze cues. The hope is that such training may begin to ameliorate core symptoms of ASD and potentially facilitate aspects of social functioning (e.g., face processing and social communication).

Existing studies have employed computer-based interventions for children and adolescents with ASD with the goal of improving aspects of face processing behavior[26-29]. Most of these interventions, however, have not been very successful in producing long-term changes in behavior for several reasons. First, they often target multiple components of face processing behavior, including accuracy of gazed-at objects[29,30], but do not isolate the active ingredients of the intervention on the outcome measures. Second, they often use highly repetitive and specific learning trials, which can lead to inflexible learning and behavior in autism[31]. Third, none of the existing interventions evaluated changes in social visual attention, which is a diagnostic feature of ASD, using eye-tracking measures as outcome behaviors. Fourth, although some of these studies have demonstrated learning during the course of the

intervention, they have had only limited success in showing evidence of clinical change, particularly in real-world social skills[32]. We innovate beyond these previous computer-based interventions by embedding eye gaze direction cues within simulated social interactions with computer-animated characters and embed these interactions in an age-appropriate narrative storyline. This simulates the way social information cues are used in the real world and, we posit, is more likely to generalize to real-world behavior. We designed the intervention game for adolescents because our prior work suggests that it is an important window of opportunity for altering declining developmental trajectories in autism[33-40].

Current Serious Game Intervention

We propose an intervention strategy that employs evidence-based "serious game" mechanics (e.g., storylines, long-term goals, scaling difficulty) to design a learning environment that maximizes opportunities for adolescents with ASD to discover the functional utility of eye gaze cues. *Serious games* are unique intervention tools that are designed to promote learning of targeted skills that are difficult and not rewarding for participants with the goal of improving real life outcomes[32]. The game mechanics that are especially relevant for enhancing motivation in serious games include immersive storylines, goals directed around targeted skills, rewards and feedback about goal progress, increasing levels of difficulty, individualized training, and the provision of choice [32]. We designed a serious game in which participants discover that eye gaze cues are useful for guiding their own goal-directed behavior to solve problems in the game. Participants learn to interpret nonverbal behaviors (e.g., pointing, shoulder turns, head turning, eye gaze cues) of game characters for the purpose of solving narrative-related quests (i.e., mixing a potion in the chemistry lab to get gum off a locker in school). The game increases in task difficulty in response to successful demonstration of skills. Initial levels of the game allow participants to use multiple non-verbal behavioral cues to solve problems and increasingly focus on learning how to use eye gaze cues exclusively over time and with

practice. This transitions to requiring participants to determine the direction of eye gaze cues with more precision, avoid highly salient objects that are not target gazed-at objects, and differentiate predictive (e.g., looking at an object of interest) from non-predictive (e.g., avatar looking up as if to think before acting) eye-gaze cues. Finally, in the most advanced levels of the game, participants learn to process eye gaze cues in episodes of joint attention between two avatars with all the same levels of complexity as are presented with the single avatar.

Aims & Objectives

The aims of this study are to assess the feasibility and safety of this serious game intervention and examine the initial evidence for its effectiveness to alter sensitivity to eye-gaze and social visual attention to faces in adolescents with ASD. The preliminary randomized controlled trial (RCT) will be conducted to determine:

1. Is it possible to recruit and randomize participants into the serious game intervention versus a waitlist control condition;
2. Do adolescents engage with the game at the intended level (playing 90 min/week for 2 months);
3. Is the intervention tolerable and safe (i.e., does retention remain high across all data collection points with minimal to no adverse events);
4. Does sensitivity to eye-gaze improve disproportionately in the intervention compared to the waitlist control group;
5. Does social visual attention to faces improve disproportionately in the intervention compared to the waitlist control group?

The trial will also allow exploratory analyses of changes in social skills and autism behaviors between the intervention and waitlist control group as a secondary measure of effectiveness of the intervention.

METHODS

Study Design

This study will be a preliminary, experimental RCT including an experimental group and a waitlist control group. The experimental group will consist of adolescents with ASD who will play an immersive computer game for 90 minutes a week over 2 months in their own home. This "dose" of treatment was estimated based on the tolerance and relative amount of training required to evince learning in prior face-processing intervention studies of children and adolescents[28, Scherf, Whyte, Minshew & Behrmann, "Adolescents with autism learn to individuate novel objects holistically: Replicated Longitudinal Intervention Studies"] and adults[41] with ASD. The goal is for participants to obtain a minimum of 10 hours of training specifically on eye gaze tasks across the 2-month training period, which may require a total of 15-20 hours of total game play. For this early trial, we will compare outcomes to a waitlist control group comprised of adolescents with autism receiving treatment as usual in the community. The flow of participants through the study is shown in Figure 1. These methods are reported following the SPIRIT guidelines[42].

Setting

The study assessments will be conducted in the United States in the Laboratory of Developmental Neuroscience at Penn State University, University Park, PA, and the intervention, itself, will be executed in the homes of intervention participants.

Participants

Inclusion Criteria

Inclusion criteria are: 1) parent/caregiver of an adolescent with a diagnosis of ASD, 2) parent/caregiver and adolescent with ASD both native English speakers, 3) adolescent with ASD aged between 10-18 years at enrollment, 4) adolescent has normal vision and hearing with correction as indicated by parent report, 5) adolescent is able to use a computer for the purposes of game play, 6) adolescent scores ≤ 80% correct (i.e., 0.5 SD less than M of TD adolescents) on online eye gaze screening task, 7) ASD diagnosis of adolescent confirmed in

lab via the Autism Diagnostic Observation Schedule[43], 8) Full Scale IQ of adolescent determined to be between 70-130 on the Kaufman Brief Intelligence Test[44], 9) reading ability of adolescent determined to be at least a second grade level as assessed by the Oral and Written Language Scales[45], 10) adolescent is capable of cooperating with testing, 11) parent/caregiver and adolescent both consent/assent to participate in the research.

Exclusion Criteria

Exclusion criteria are: 1) adolescent has had seizures within the previous two years, 2) family lacks stable home internet, 3) parent or adolescent refuses to consent/assent to take part in the research, 4) adolescent is 18 and has a legal guardian, prohibiting him/her from legally consenting, or 5) adolescent is 18 and cannot understand the consent (i.e., fails consent quiz).

Sample Size

A meta-analysis indicates that computer-based interventions for individuals with ASD generally have a medium effect size (Cohen's d = 0.47)[46]. Power calculations indicate that with a sample size of 34 (17 per group), and an expected correlation between the pre/post-test measures of 0.58, we will have statistical power of .80 to detect a medium effect size for the expected Group (intervention, control) x Time (pre-, post-intervention) interaction with an $\alpha < .05$ in this repeated-measures design.

Recruitment

Our primary recruitment approach will be to recruit families who have registered with research databases like the Interactive Autism Network (IAN) Research Database at the Kennedy Krieger Institute, Baltimore and autismMatch at the Center for Autism Research, Philadelphia. Recruitment will proceed via a three-step process (see Figure 1). First, the initial inclusion/exclusion criteria will be determined via brief phone interview or by completing an online survey. Second, eligible adolescents will be invited to take an online test of sensitivity to eye gaze through a secure website (Testable.org). Participants view complex images of an actor in a naturalistic scene looking at one of many possible objects and have to identify the

target gazed-at object from a list of 4 labels. We have used this task previously to investigate the influence of autistic-like traits on sensitivity to detect eye gaze cues in typically developing (TD) adults[47]. To evaluate the developmental appropriateness of the task, we tested a sample of 50 TD adolescents (ages 11-17 years). The TD adolescents performed above chance (*M* = 85%, *SD* = 9%) and below ceiling levels, which indicates sensitivity of the task to measure eye gaze cues in adolescents. Therefore, ASD participants who score minimally ½ *SD* below that of the TD adolescent mean (≤ 80%) on this online screening task will be invited to be evaluated for the remaining set of inclusion criteria. We will obtain written informed consent from the parent and 18-year old adolescents and written assent from the 10-17-year-old adolescents to participate in the study (see Appendices for consent/assent). Only after both consent and assent are obtained will we administer the remaining eligibility assessments. Participants who meet the final eligibility criteria are invited to continue with the pre-test procedures.

Randomization Procedures

Following completion of the pre-intervention testing procedures, the Principal Investigator, who will not be involved in testing participants, will randomize participants in a 1:1 ratio into either the intervention game or waitlist control condition. The randomization list will be computer-generated prior to the enrollment of any participants and will be stratified by sex and Full Scale IQ (>100, <100). None of the researchers collecting data will have access to the randomization list.

Blinding Procedures

Given the design of the study, parents and adolescents will know the condition to which they have been assigned. However, researchers involved in data collection will be blinded from condition assignment during the pre-intervention data collection session as these data will be collected prior to randomization. Also, the research team is not involved in the randomization process. The research team members who are involved in ensuring the fidelity of the intervention are not involved in data collection procedures. Although we will attempt to limit

unblinding, it is not possible for researchers involved in data collection to be completely blinded to the assignment of participant condition at the post-intervention visit as we cannot prohibit participants from talking to researchers about their experience in the study. Importantly, the primary outcome measures are believed to be robust to investigator bias.

INTERVENTION CONDUCTED IN THE EXPERIMENTAL GROUP

The intervention video game is designed to engage and shape learning of sensitivity to eye gaze information and social attention to faces. Specifically, the game is structured around learning to use eye gaze as a cue for 1) directional reference (e.g., put the object there; see Fig 2a for a screenshot from the game), first when gaze cues are highly predictive and subsequently when they are embedded in noisy cues that are not predictive of directional information; 2) reference to a specific object identity (e.g., Grab that one; see Fig 2b), first when gaze cues are highly predictive and subsequently when they are embedded in noisy cues that are not predictive of object information; and 3) joint attention episodes when two people (i.e., avatars) engage in mutual gaze with each other and then engage in joint attention on the same specific object (e.g., hey Matt, look at that one; see Fig 2c), first when gaze cues are highly predictive and subsequently when they are embedded in noisy cues that are not predictive of joint attention. The game is organized around three phases (see Fig. 3a), which are composed of multiple levels (See Fig 3b), which are themselves composed off multiple stages (see Fig 3c). Figure 3 provides a schematic illustration of the structure of the game.

The game is an adventure game with embedded gamification techniques in which participants solve mysteries in a 3D environment that is programmed in Unity (https://unity3d.com/unity). The core training mechanisms are delivered via character interactions, with participants learning skills via simulated social interactions with avatars in the game as participants solve problems related to the game narrative. Each of these puzzles has variable elements so that they can be dynamically altered with different objects, locations, and

levels of difficulty. Moreover, they are executed with a variety of characters and environmental contexts to support generalized learning opportunities.

The training paradigm is much like a perceptual staircase paradigm in which participants start at a phase (Fig. 3a), level (Fig. 3b), and stage (Fig. 3c) meant to be easily processed and accomplished by all participants. Individuals advance through stages within levels and then between levels and phases, until they hit a threshold where their skills plateau (see Fig 3c). When participants fail a stage, they go back to the preceding stage (and potentially phase or level) where they succeeded and must complete it before progressing to the failed stage/level/phase again. This keeps participants challenged without becoming too frustrated and allows them to practice and learn new skills. When participants repeat a stage or level, they do so in a new context with new avatars, to foster generalization of the learned skills. If players are unable to progress from the easiest levels, they are redirected to remedial training in which more explicit guidance is afforded about how eye gaze cues provide information about objects and locations in the local environment (once completed, they are returned to the main game). See Supplementary Figures 1-3 for the full UML diagrams illustrating progression through the game.

Difficulty increases in several ways and is all controlled by choices of the individual participant, within design constraints of the game. First, the number of locations or objects that the avatars reference gradually increases across stages so that the precision of gaze sensitivity has to improve (see Fig 3c). Second, in the early levels of each phase of the game, participants are provided with multiple kinds of non-verbal social cues in their interactions with the avatars (See Fig 3b). For example, in the earliest levels of Phase 1 of the game, the avatars simultaneously point, orient their shoulders, turn their head, and shift their eye gaze as cues to direct participants to solve quests in the game. As play progresses, learning is scaffolded by slowly removing the non-gaze social behaviors; ultimately avatars only direct participants via eye gaze cues (see Fig 3b). Third, once a participant has mastered the easiest levels of gaze

shifts, the levels increase in difficulty by reducing the spacing between the objects (requiring more precise tracking of gaze trajectory) and by increasing the salience of the non-target objects (requiring increasing focus of attention on the target gazed-at object) as participants move into the more advanced Phases of the game. Finally, at the most advanced Phase and levels of the game, it is necessary to learn to ignore non-predictive shifts of gaze (e.g., looking up pensively, looking across all object before landing on target object) and only focus on the predictive gaze shifts (See Fig 3a).

OUTCOME MEASURES

Feasibility outcomes

To measure intervention feasibility, in addition to participant attrition, we will report the mean number of sessions, total number of minutes played, total number of minutes engaged in eye gaze tasks, frequency of each level visited in the game, and accuracy of performance within each level of the game. The feasibility of the testing procedures will also be assessed. We will report adherence rates, means, and standard deviations for each outcome measure separately for each group in the pre- and post-intervention testing sessions. This will allow us to assess potential floor or ceiling effects in any of our measures, collect information relevant for determining effect sizes, and estimate sample sizes for a full trial.

Safety outcomes

The intervention is expected to have minimal risk because it is designed from an empirically informed approach, administered remotely, designed to flexibly accommodate participants' schedule, and is semi-supervised. However, potential adverse events and unintended effects occurring during testing or the intervention period will be reported and explored. A Data Safety Monitoring Board will be instituted (see Study Monitoring). Additionally, self-report and behavioral measures will be used to monitor unanticipated risks. This includes a Usability questionnaire about the intervention game experience in which participants rate multiple aspects of game play on a Likert scale (e.g., Experience was fun; I felt discouraged) at

the post-intervention testing session. Procedures are in place to monitor suicidal ideation and self-injurious behavior among adolescents and to make recommendations about care based on the assessment outcome.

Primary outcomes (intervention effectiveness)

Primary and secondary outcomes will be measured at both the pre- and post-intervention sessions. We hypothesize that the intervention will improve eye gaze and social visual attention behaviors; therefore, all the primary measures of the intervention effectiveness are assessed with eye tracking technology. The analyses will focus on time spent looking at faces, which include the eyes, and gazed-at objects in the stimuli. Limiting the analyses to time spent looking at eyes may underestimate the effectiveness of the intervention, if adolescents only learn social communication cues related to turns of head, which are correlated with gaze cues, for example. Also, defining eye-specific areas of interest in dynamic stimuli can be imprecise and unreliable. The secondary measures evaluate changes in autism-like behaviors, social competence, and problematic behaviors, which may be indirectly impacted by the intervention.

Visual Attention to Faces

This task is similar to that previously described[48]. Participants passively view 6 42-second clips from age-appropriate movies of social interactions with two or more characters that are matched by adult raters on emotional intensity and valence, number of visible faces, and amount of time faces are present. Four of the movies are unique at each time point (pre, post) and two movies repeat across time points to assess reliability of measurement. The dependent measures include the *average gaze time to faces* and the *proportion of total gaze time to faces*.

Eye Gaze Sensitivity

We will assess eye gaze sensitivity in two tasks. In the static version of the task, participants view still images (N = 40) of an actor in a naturalistic scene looking a one of many possible objects, like in the online eye gaze screening task [17,47]. Each image is displayed on

a computer screen for 4 seconds. Participants must then identify the specific object the person is looking at from a list of four labels presented on a subsequent screen. The dependent measures include both performance accuracy and the ratio of average gaze time to the target object versus average gaze time to non-target objects. Twenty-six images are unique at each time point and 14 images repeat across time points. None of the stimuli used in the online screening task will be used in the pre- or post-intervention testing sessions.

To measure sensitivity to real-time eye gaze cues, we will create a dynamic version of this static task that is modeled after dynamic stimuli used to test infant joint attention[15]. On each trial, participants watch a movie of a female actress looking into the camera, then directing her gaze to a target object, holding the gaze on the target object for several seconds, and returning her gaze back to the camera. At the end of each trial, participants identify the target gazed at object from a list of four labels presented on a subsequent screen. The dependent measures include performance accuracy, gaze shifts between the face and target- and non-target objects[15], and ratio of average gaze time to the target object versus average gaze time to non-target objects. Twenty videos are unique at each time point and six videos repeat across time points.

Secondary outcomes (intervention effectiveness)

Autism, Social, & Problem Behavior Questionnaires

To assess if the intervention influences autism symptoms, social skills, and adaptive functioning, parents and adolescents will complete the Social Skills Improvement System (SSIS)[49] and parents will complete the Social Responsiveness Scale-2nd Edition (SRS-2)[50]. On the SSIS measures, total scores will be computed separately for social skills and problem behavior domains. Higher scores indicate the presence of more of these behaviors. We will compute the total score on the SRS-2; higher scores reflect more social impairment.

Patient and Public Involvement

Dr. Scherf has been working with adolescents with ASD and their families in research settings for 15 years. The decision to design an intervention that targets sensitivity to eye gaze cues has been informed by her personal interactions with families and their desire to improve adaptive social skills in their children. The decision to employ serious game mechanics was informed by positive feedback from adolescents with ASD tested in previous home-based computerized interventions [Scherf, Whyte, Minshew & Behrmann, "Adolescents with autism learn to individuate novel objects holistically: Replicated Longitudinal Intervention Studies"]. The staff training and testing procedures used in this protocol, including accommodations in the testing rooms (i.e., lighting, seating) and strategies for working with participants, are all informed by experiences and conversations with previous study participants with autism. Several adolescents with autism provided feedback to us about the intervention game during its development in pilot testing. Autism family networks will be used to facilitate recruitment into the study as described in the Recruitment section. We will inform participating families about findings from the study in the form of a newsletter (see Ethics and Dissemination). We will assess the burden of the intervention with a Usability questionnaire (see Safety Outcomes). We thank all the families who have helped inform the development of this study.

DATA COLLECTION

Intervention data

Strategies for maximizing the fidelity of the video game intervention include, 1) establishing minimum computer requirements for participants, 2) designing instructional videos for participants about the game, 3) designing a web page portal for participants to find frequently asked questions about the game and submit electronic help tickets for technical problems, 4) establishing a texting reminder system on scheduled game play days for participants, 5) establishing a protocol for contacting parents when participants miss scheduled sessions of game play, 6) providing explicit directions to parents that no one else in the home is to play the intervention game, and 7) paying participants $5 for every 30 min of game play up to $200.

Throughout the intervention, log files are generated for each participant with feasibility data (see outcomes) for each day of game play. Log files will be uploaded every 8 minutes onto a secure, password protected server that only designated research personnel can access. Data from the log files will be summarized across days and sessions for each participant.

Eye tracking data.

Eye tracking data will be collected using a Tobii X2-60 eye tracker, which has a sampling rate of 60 Hz and approximate accuracy of 0.4° and precision of 0.34°. This eye-tracker allows for bright and dark pupil eye-tracking and small head movements, maximizing comfort during testing (i.e., no chin rest required). A 9-point automatic calibration procedure will be employed prior to each task to customize and accurately estimate gaze point calculations. To reduce fatigue and restlessness, we will incorporate multiple breaks in the eye tracking protocol for participants. To acclimate participants to the testing room and eye tracking equipment, we will include a 10-minute warm up procedure and provide participants with an overview of the schedule of testing events. Based on pilot data collection with typically developing children, we estimate that the entire procedure for eye tracking will last approximately 70-90 minutes. The fidelity of the eye-tracking data will be assessed through quality of the calibration procedure. Eye gaze samples in which there is no recordable information from at least one eye on the stimulus will be quantified as missing data. Measurement error of the eye tracking data will be minimized by having the same small number of highly trained researchers collect the data at both the pre- and post-intervention sessions.

Questionnaire data

Parents complete questionnaires while adolescents are tested in the eye-tracking protocol. Adolescents complete the questionnaires following completion of the eye tracking protocol. The SSIS is clinically relevant and is sensitive to changes in social abilities from behavioral interventions in individuals with ASD[51]. The SRS-2 is a reliable and valid measure of social impairment and repetitive behavior as a single quantitative trait[52], and also includes

multiple questions specifically related to eye gaze behaviors and face-processing abilities. Missing data will be handled in congruence with the standardized SSIS/SRS-2 procedures.

DATA MANAGEMENT & ANALYSIS PLAN

All analyses will be completed using standard statistical software (e.g., R[52]). Data will be scored and entered into the program for further preprocessing/data reduction and backed up in multiple locations (i.e., lab server, back-up hard drive). Data will be de-identified and stored on a lab server and in password-protected partitions of cloud and lab servers. Only research project investigators and staff approved to work on the project and listed in the IRB protocol will have access to the de-identified data.

Prior to statistical analyses, all the data will be investigated for deviations from normality and transformed if necessary, and we will examine and manage statistical outlier data points (> 2 SD of the group mean) where appropriate. Following randomization, and after the pre-intervention data are collected, we will determine whether the intervention and waitlist control groups differ on any demographic characteristics (e.g., age, FSIQ, ADOS total score, online eye gaze screening scores). Variables with reliable differences will be submitted to the subsequent analyses of group differences as covariates.

For the primary study outcomes, we will utilize linear mixed effects modeling to test the effectiveness of the intervention on outcome measures while accounting for repeated measures (i.e., time-point). Additionally, we plan to model random variability in both stimulus items and participants by including them as random factors in our statistical models. For each dependent variable, we will fit a model with Group (intervention, control) and Time-point (pre-intervention, post-intervention) as fixed factors and participant, age, IQ, ADOS total score, and stimulus as random factors. The amount of missing eye gaze data will also be submitted as a covariate in analyses of intervention effectiveness.

Study Monitoring

A Data Safety Monitoring Board (DSMB) will be established and will be composed of independent researchers who have expertise complementary to the aims of the project. We will meet with the DSMB prior to enrolling participants in the study and bi-annually during the duration of the intervention to review the safety and tolerance of the intervention for our participants. Any adverse events will be reported to both the DSMB and the Penn State Internal Review Board.

Ethics and Dissemination

Approval to conduct this study has been granted from the Pennsylvania State University Internal Review Board (IRB# 00005097). Results will be disseminated to the scientific community at scientific conferences and in the form of empirical articles in peer-reviewed scientific journals. Results will also be reported to the funding agency (National Institutes of Mental Health) annually and to ClinicalTrials.gov. Finally, we will present summaries of the findings in the form of a newsletter to study participants and the intervention game will be made available to families in the waitlist control condition after the full data have been collected if analyses indicate that it is effective.

DISCUSSION

This intervention game may have great potential for translation and dissemination. By combining serious game design principles with intervention science, the resulting intervention game has the potential to be highly motivating, scalable to individual skill level, inexpensive, engaging, and accessible by adolescents in their own homes at their own convenience. Although we are enthusiastic about this approach, we do note several limitations of this study. First, we are not able to fully blind the researchers during the post-intervention testing session; however, we think the outcome measures are likely to be fairly robust to experimenter bias. Second, our ability to estimate the feasibility of the intervention is potentially influenced by the fact that our participants are compensated for their time. Importantly, given that the intervention game was designed to foster intrinsic motivation, we expect that participants will want to play

the game because it is interesting and motivating. Also, in order to be compensated for the full amount that is offered to participants, they have to play 25% more sessions (100) than the maximum we are asking them to play (72) and 75% than the minimum (24) we are asking them to play. Therefore, given the nature of the intervention game and compensation schedule, we think that the influence of financial compensation in this study will be less of a concern than it might be in other studies.

In the future, we will continue to develop the intervention game with the goal of testing it against an active control game, evaluating if it is effective for improving a boarder range of face processing behaviors that are difficult for individuals with ASD (e.g., face identity recognition), and improving social skills in ASD. These data, including the generation of effect size estimates, will inform a future confirmatory clinical trial. More generally, these goals represent significant innovation in the design of RCTs for computer-based interventions for autism and may help advance theory and clinical practice.

Competing Interests Statement:

All authors have completed the ICMJE uniform disclosure form at *www.icmje.org/coi_disclosure.pdf* and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Elisabeth Whyte was at the Dept of Psychology at Pennsylvania State University when she contributed to this work. She is currently working for Daybreak Games in San Diego, CA.

Funding Statement:

This work is supported by National Institutes of Mental Health (R61-MH110624-01; PI KSS).

Data Sharing Statement:

Participants will be invited to share de-identified data acquired from this study with the National Institutes of Health Data Archive.

Author Contributions:

KSS, EMW, JS, and CFG secured funding to support this project. KSS, EMW, and JS conceived and designed the study. KSS, EMW, JS, and BJ designed the intervention game. JG will be responsible for testing participants. DE, JS, CFG, and KSS are responsible for designing the procedures to manage the fidelity of the intervention. JG and DE will be responsible for managing the data generated during the project. JG and KSS will conduct the statistical analyses of the data. KSS and JG drafted the manuscript and all authors reviewed the manuscript for intellectual content and approved the final version.

Figure Legends

Figure 1. CONSORT Diagram for SAGA Protocol

Figure 2. Screenshots from multiple training conditions in the intervention game. A.) The avatar is instructing the participant select 1 of 5 possible drawer locations using pointing, shoulder, head direction and gaze cues in a colorful room scene. B.) The avatar is directing the participant to select 1 of 6 possible tools to put on the peg board using pointing, shoulder, head direction and gaze cues in a tool shed scene. C.) The two avatars are engaged in an episode of joint attention together and are inviting the participant to select 1 of 5 possible objects using pointing, shoulder, head direction and gaze cues in a library scene.

Figure 3. Schematic illustration of the intervention game structure. The game is designed to train learning about three functional uses of eye gaze cues including, the use of gaze to reference locations and objects in the world via a single informant and in episodes of joint attention between multiple informants (a). The game is organized around 3 sequential phases. The tasks in Phase 1 are structured to help participants learn that eye gaze is an important cue to solving problems in the game. The tasks in Phase 2 help participants learn to estimate precise gaze trajectories by making target gazed-at objects closer together and to ignore salient objects that are not the target-gazed at object. Episodes of joint attention are also introduced in Phase 2 in which participants have to determine the target object that two avatars are looking at together. This is difficult because the timing of the non-verbal cues to identify the object is not perfectly synchronous between the two avatars. In Phase 3, the tasks are structured around helping participants learn the difference between a goal-directed gaze cue (e.g., looking at a target object to solve a puzzle) and a non-goal-directed gaze cue (e.g., looking around at all the objects before deciding which one to select). To complete a phase of the game, participants must finish all *levels* within a phase. Each phase has multiple levels (b). Levels are defined by

the number of non-verbal cues avatars use to guide participants to solve puzzles in the game. Easy levels have multiple cues. Level progression increasingly focuses learning to use eye gaze cues exclusively by stripping away other cues. Within each level, there are 6 stages (c). Each stage represents the number of potential objects or locations that the participant has to discriminate between based on the cue from the avatar. In the easiest stage, the participant choses between two objects or locations that the avatar is pointing, directing shoulders, head and gaze to (as in Level 1), whereas in Stage 6, the participants chooses between 6 possible objects or locations that the avatar could be referring to with the non-verbal cue(s). Within each stage, participants have 5 trials. They must perform with 80% accuracy to advance to the next stage and they must finish all stages within a level before then can progress to the next level within a phase. When they do not reach 80% accuracy within a stage, they are returned to the previous stage to reify the learning where they were recently successful. Sometimes that means they are returned to later stages of previous levels.

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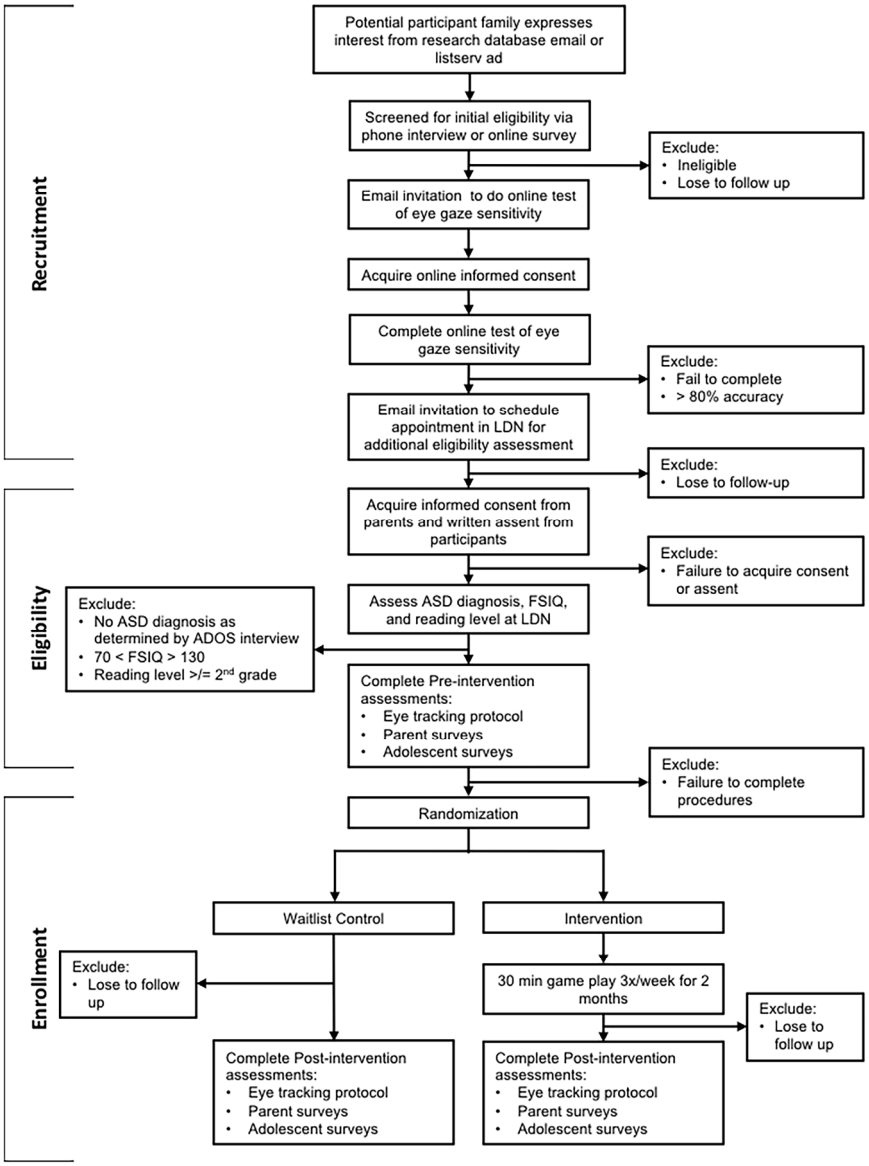

Figure 1. CONSORT Diagram for SAGA Protocol

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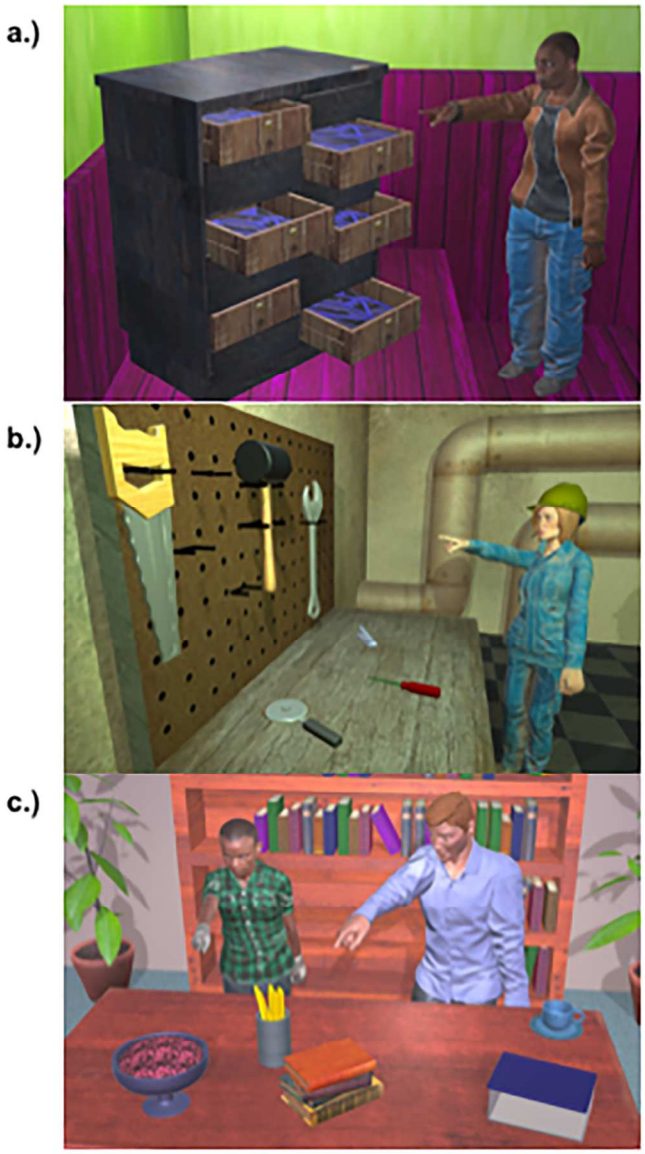

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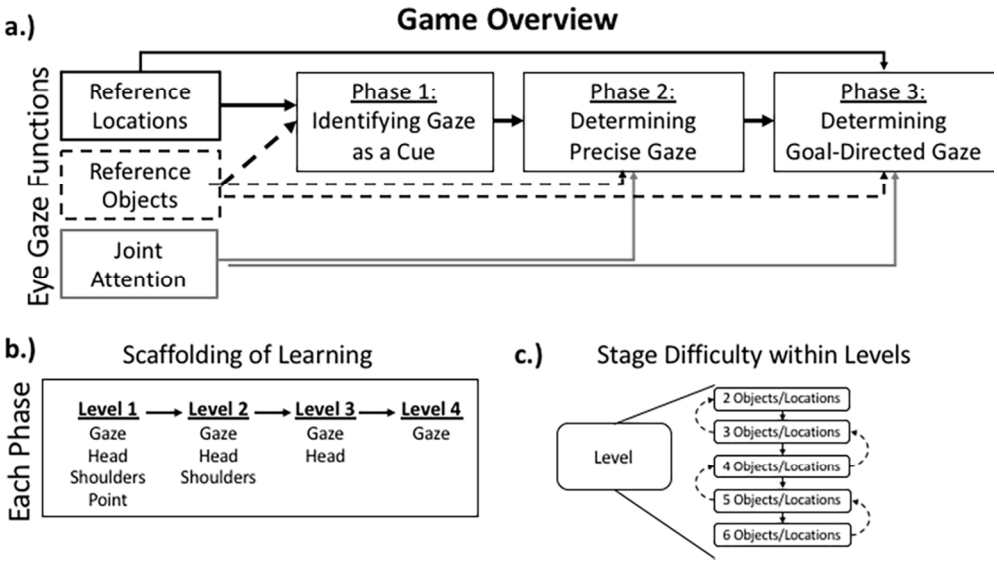
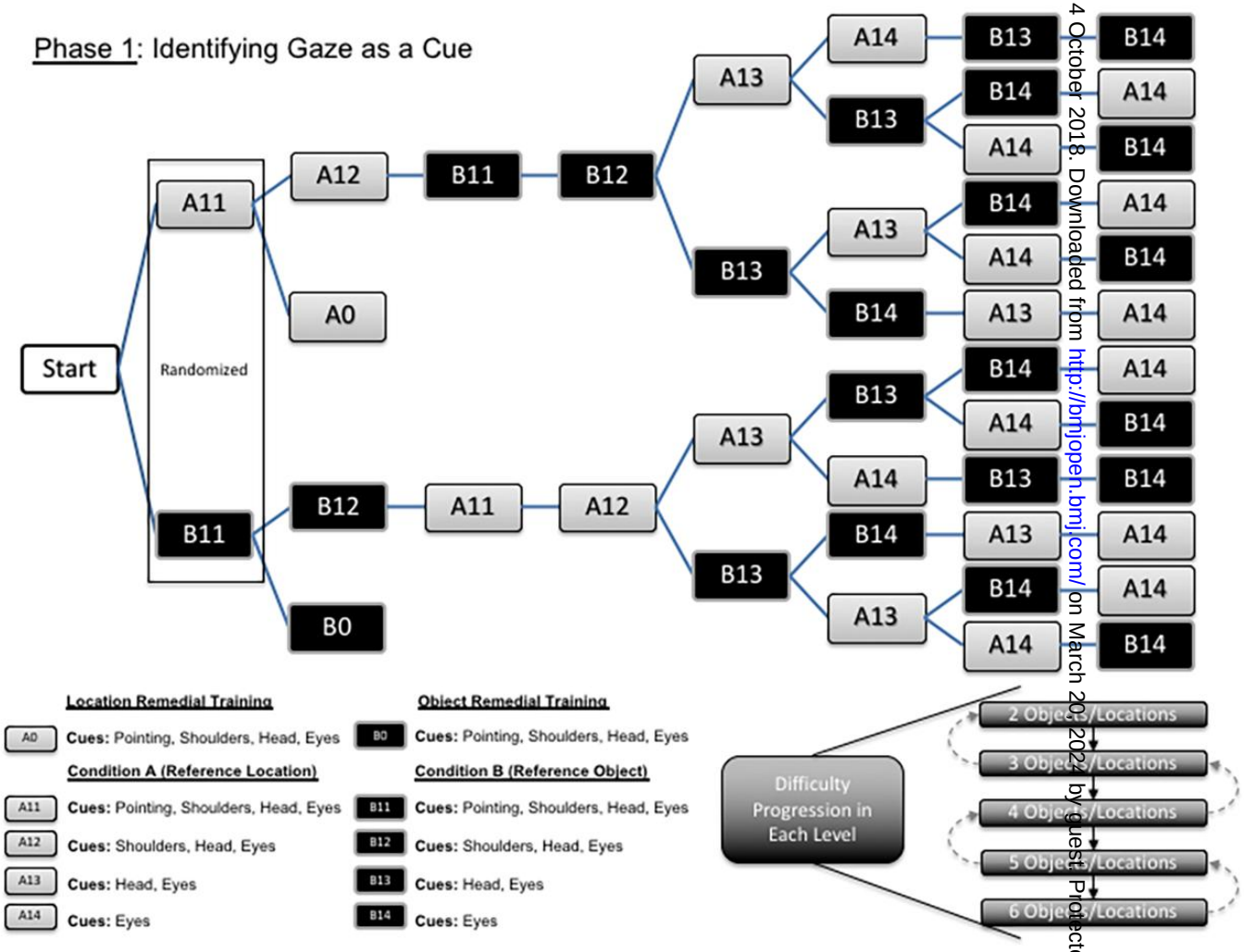


Figure 3. Schematic illustration of the intervention game structure. The game is designed to train learning about three functional uses of eye gaze cues including, the use of gaze to reference locations and objects in the world via a single informant and in episodes of joint attention between multiple informants (a). The game is organized around 3 sequential phases. The tasks in Phase 1 are structured to help participants learn that eye gaze is an important cue to solving problems in the game. The tasks in Phase 2 help participants learn to estimate precise gaze trajectories by making target gazed-at objects closer together and to ignore salient objects that are not the target-gazed at object. Episodes of joint attention are also introduced in Phase 2 in which participants have to determine the target object that two avatars are looking at together. This is difficult because the timing of the non-verbal cues to identify the object is not perfectly synchronous between the two avatars. In Phase 3, the tasks are structured around helping participants learn the difference between a goal-directed gaze cue (e.g., looking at a target object to solve a puzzle) and a non-goal-directed gaze cue (e.g., looking around at all the objects before deciding which one to select). To complete a phase of the game, participants must finish all levels within a phase. Each phase has multiple levels (b). Levels are defined by the number of non-verbal cues avatars use to guide participants to solve puzzles in the game. Easy levels have multiple cues. Level progression increasingly focuses learning to use eye gaze cues exclusively by stripping away other cues. Within each level, there are 6 stages (c). Each stage represents the number of potential objects or locations that the participant has to discriminate between based on the cue from the avatar. In the easiest stage, the participant choses between two objects or locations that the avatar is pointing, directing shoulders, head and gaze to (as in Level 1), whereas in Stage 6, the participants chooses between 6 possible objects or locations that the avatar could be referring to with the non-verbal cue(s). Within each stage, participants have 5 trials. They must perform with 80% accuracy to advance to the next stage and they must finish all stages within a level before then can progress to the next level within a phase. When they do not reach 80% accuracy within a stage, they are returned to the previous stage to reify the learning where they were recently successful. Sometimes that means they are returned to later stages of previous levels.

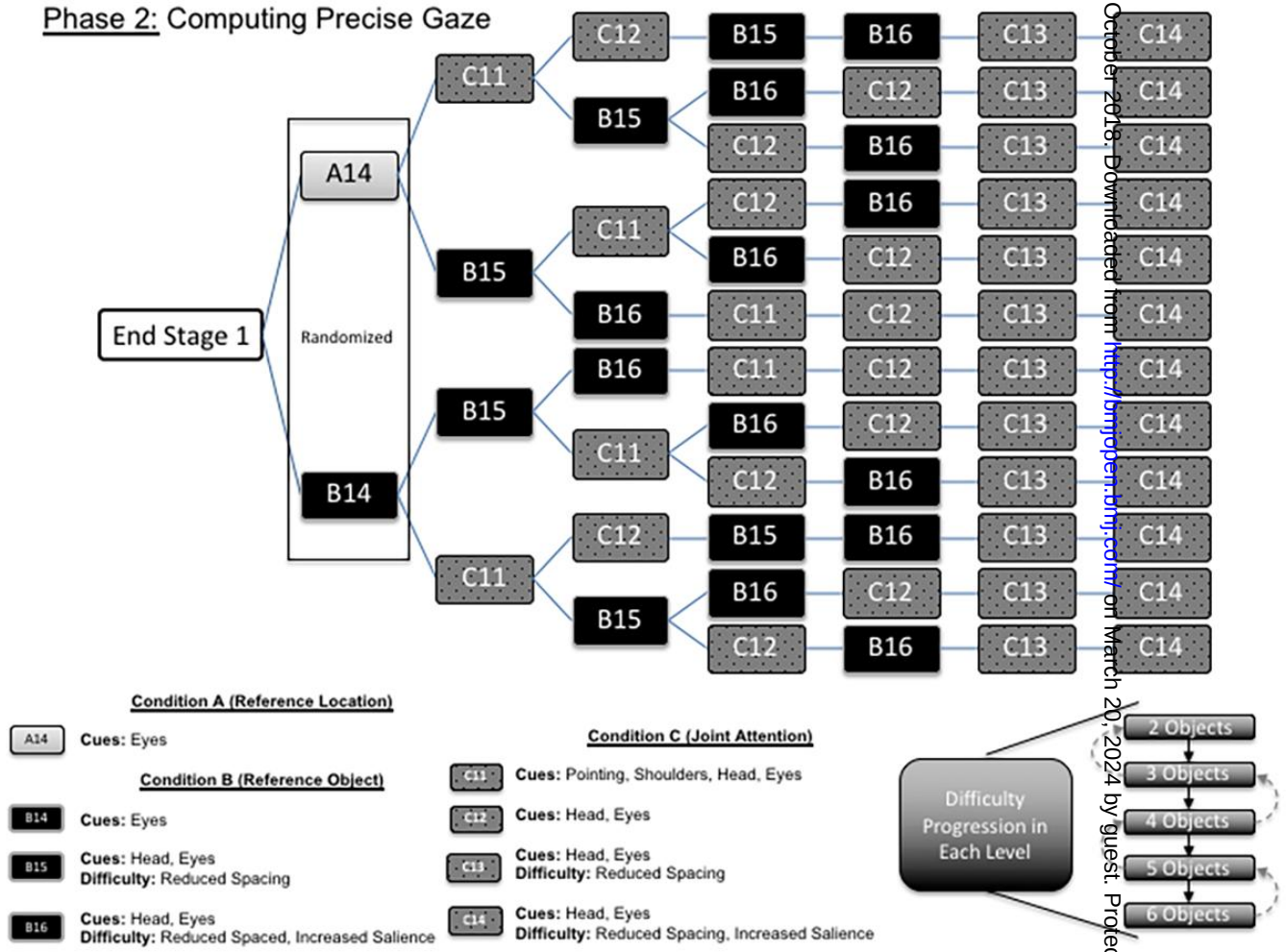
104x59mm (300 x 300 DPI)

Supplementary Figures



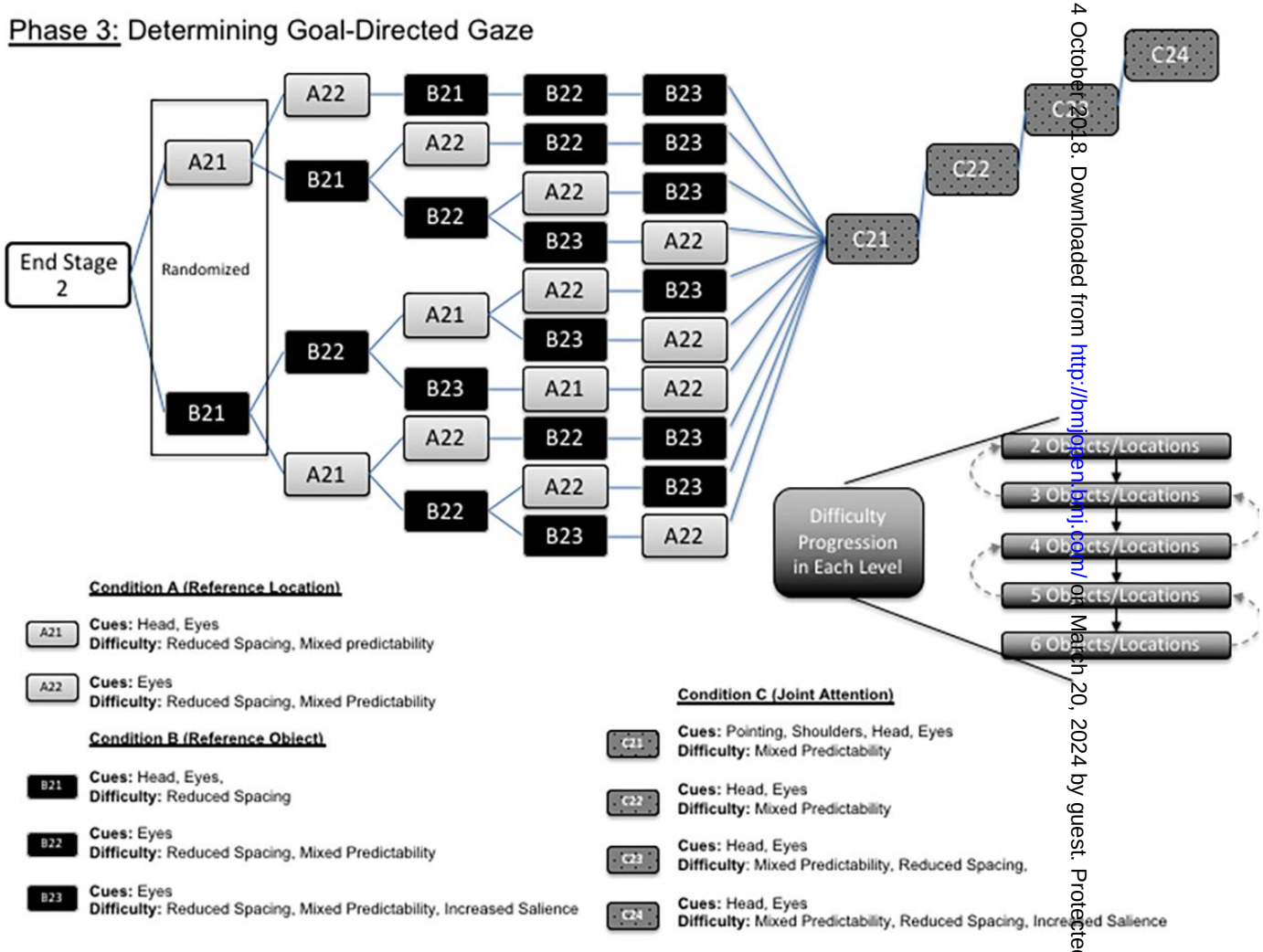
Supplementary Figure 1. UML Diagram of Phase 1 of Intervention Game. The tasks in Phase 1 of the game are organized to help participants identify eye gaze as useful information for solving problems in the game and to generalize that knowledge across

contexts and avatars. Participants are randomly assigned to begin training in one of two conditions that train 1 of 2 functional uses of eye gaze cues. In Condition A they learn to use eye gaze cues to reference locations in the world. In Condition B they learn to use gaze cues to references specific objects in the world. Once in a condition, participants start with the easiest level (e.g., A11), which is defined by the number of non-verbal cues used to signal to the participant about how to solve a puzzle. Within each level, they work through stages of difficulty as the number of objects or locations increases. They have to perform with 80% accuracy within a stage to progress to next stage. When they fail a stage, the regress to the previous stage where they were successful and practice using the cues to solve problems in the game. If participants do not succeed solving the easiest levels (A11, B11), they are temporarily send to remedial training (A0, B0) in which the cues are more exaggerated and slowed down to help participants understand how to interact with the avatars. When the succeed in the remedial training, they come back into the elementary level of the condition they were working on. The lines show the progression of the possible choices through the levels as the game progresses through Phase 1. Note that participants must master comparable levels in both conditions before they can progress to more advanced levels in either condition.



Supplementary Figure 2. UML Diagram of Phase 2 of Intervention Game. The tasks in Phase 2 of the game are organized to help participants use eye gaze in a more fine-grained way. Specifically, as levels increase, the spacing between objects is reduced,

which requires participants to compute more precise trajectories of gaze to identify the correct gazed-at object to solve puzzles. Also, as levels increase, the non-target objects become increasingly more salient to draw attention away from the target gazed-at object. Participants have to learn to ignore the more salient objects and continue to focus on the gaze cues and the gazed-at object to solve the puzzles. Participants also start learning about joint attention on specific objects in this phase of the game (Condition C). As with the other conditions, the earliest levels of joint attention episodes include multiple non-verbal cues to facilitate understanding of the object of the joint attention. As the levels of difficulty increase, the cues are focused on the head and eye gaze direction. Also, as in Phase 1, each level has multiple stages that participants have to progress through with 80% accuracy to complete the level. The lines show the progression of the possible choices through the levels as the game progresses through Phase 1. Note that participants must master comparable levels in both conditions before they can progress to more advanced levels in either condition.



Supplementary Figure 3. UML Diagram of Phase 3 of Intervention Game. The tasks in Phase 3 of the game are organized to help participants determine the difference between a goal-directed and non-goal-directed gaze cue. Participants learn to do so in

conditions in which they use cues to reference locations (A21, A22), reference objects (B21-B23), and in episodes of joint attention (C21-C24). To learn about goal-directed gaze cues, the easiest levels of this phase of the game reintroduce head direction cues and newly introduce directional gaze information that is not goal-directed. For example, the avatars look up to the ceiling (as if thinking about something), or they scan all the objects with their eyes. These non-goal-directed cues are embedded within the goal-directed cues of looking at a location or an object for specific referential purpose. Participants have to learn to sort out which of the gaze cues are goal-directed and which are not to solve the puzzles in the game. In the most advanced levels of this phase, participants have to contend with all the difficulty, mixed predictability of the goal-directedness of the gaze, reduced spacing of the objects, and increased salience of the non-target objects. Also, as in the earlier phases, each level has multiple stages that participants have to progress through with 80% accuracy to complete the level. The lines show the progression of the possible choices through the levels as the game progresses through Phase 1. Note that participants must master comparable levels in in the object and location conditions before they can progress to practicing these skills in the joint attention condition.

CONSENT FOR RESEARCH - Intervention
The Pennsylvania State University

Title of Project: *Using Serious Game Technology to Improve Sensitivity to Eye Gaze in Autism*

Principal Investigator: *K. Suzanne Scherf*
Address: 113 Moore Building
University Park, PA 16802
suzyscherf@psu.edu
Telephone Number: (814) 867-2921

Subject's Printed Name: _____

We are asking you to be in a research study. This form gives you information about the research.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.

Please ask questions about anything that is unclear to you and take your time to make your choice.

Some of the people who are eligible to take part in this research study may not be able to give consent because they are less than 18 years of age (a minor). Instead we will ask their parent(s)/guardian(s) to give permission for their participation in the study, and we may ask them to agree (give assent) to take part. Throughout the consent form, "you" always refers to the person who takes part in the research study.

1. **Why is this research study being done?** We are asking adolescents to be in this research because you may learn social skills from playing a computer game. This research is being done to find out find out how adolescents with autism learn social skills from a computer game. Adolescents may be asked to play the game or you may be asked to be part of a control group who does not play the game. We hope that the information we obtain from the way adolescents perform on these tests and respond to the computer-based training will lead to better understanding about the nature of face-to-face social skills in people with autism. Approximately 150 people will take part in this research study at Penn State.

2. **What will happen in this research study?** Dyads (adolescents ages 10 to 17 and their parents) have been invited to participate in two behavioral sessions over the course of three months. Adolescents will also be randomly assigned to either the intervention (playing a social skills video game) or control condition (not assigned to play a video game).

Parents will complete the following: The parent of each adolescent will complete several paper and pencil questionnaires asking about their child's behavior and health history at each of the two sessions. If your family is randomly assigned to participate in the intervention, you will help administer your child's computer-based intervention at home.

Adolescents (age 10 to 17) will complete the following:

Pre-test Session: The pre-test session completed by adolescents consists of two parts.

- *PART 1:* During the first portion of the pre-test session, adolescents will complete standardized testing as part of confirming the eligibility criteria. This consists of completing a reading test, an intelligence test, and a standardized observational measure of autistic symptoms (the ADOS). You will be video recorded while you complete the ADOS testing. *Based on your responses on these measures, you will*

be further assessed for eligibility in the behavioral intervention trial. A summary report of the ADOS and IQ results is available to parents upon request.

- *PART 2 for adolescents*: If you qualify for the study based on your standardized testing scores, adolescents will complete the second portion of the pre-test session, you will complete several computer-based eye-tracking tasks. You will be given a break before the second portion of the pre-test session. The eye tracker records your eyes and measures your eye movements while looking at pictures or videos. You will be asked to make decisions about what you see on the screen. The pictures and videos include scenes of people looking at objects. The videos will include scenes of people interacting, like from age-appropriate entertainment movies. Adolescents will also complete questionnaires about your behavior and social skills.

Group Assignment (Randomization): Because we want to understand whether the computer-based intervention has an impact on social behavior, we need to compare the intervention group to a control group who does not complete the intervention. To do this, we will assign adolescents taking part in this research into two groups. The two groups are selected by chance, as if by tossing a coin. This randomization happens at the end of the first session, so you won't know your group assignment until the end of your pre-test session. One group will be assigned to complete the computer game intervention. The other group will be the control group and will **not** be assigned to play our computer game. If you are assigned to the control group, you will be scheduled to return in 2 months for the post-test session and will not be assigned to any particular intervention procedures between sessions.

Intervention Group Procedures:

- If you are an adolescent assigned to the intervention group, you and your parents will be given the option to install the software directly on your home computer. Your family may also be provided a laptop if needed. A research assistant will teach families how to use the computer software programs for this testing at the end of the pre-test session. Families will be given a unique login account name and password at the lab, along with instructional materials. As the data will be submitted electronically to Penn State over the Internet, the game will require Internet connectivity to play.
- A parent will help adolescents complete the training sessions in a quiet room in your own home. The research assistant will also maintain daily contact with a parent, via text messaging, telephone, or e-mail, during the intervention to monitor your progress and address any questions or concerns. If you have technical difficulties with the program at home, adolescents can ask your parent to contact the researchers and our staff will assist in identifying and fixing the problem.
- This computer-based social skills intervention involves social interactions with animated characters in a adventure-themed game. Adolescents are be asked to recognize nonverbal social cues, such as pointing, head turns, or eye gaze cues. This training will take approximately 20 total hours over 2 months. Adolescents will play the game for 3 days per week (approximately 60 minutes per session), every week, for 2 months.

Post-test Session: The post-test session will be scheduled for approximately 2 months after your first session, for both groups. Adolescents will complete the same self-report questionnaires as done at pre-test. Adolescents will also complete the same eye tracking tasks that were completed at pre-test. Adolescents from the intervention group will also be asked to rate your enjoyment of the intervention game.

3. Who can be in this study? You are an adolescent diagnosed with autism who passed the initial pre-screening for the study, and:

- are between the ages of 10 and 17 at the time of enrollment

- are capable of cooperating with testing, and are able to use a computer keyboard and mouse
- have normal vision and hearing (with correction)
- have no history of seizures within the last 2 years

Adolescents will complete background testing today, to confirm your eligibility to participate in the intervention. Completion of the background measures will allows researchers to confirm that you:

- have a full scale and verbal intelligence (IQ) greater than 70 (as confirmed on the KBIT-2)
- are able to speak in full sentences and can read at or above a 2nd grade reading level (as confirmed on the OWLS-2 reading comprehension scale)
- have current symptoms reflecting a diagnosis of autism (as confirmed in the ADOS interview).

If you meet these criteria, you will complete the remaining study measures. If you do NOT meet these criteria, you will not be enrolled in the remainder of the study. In such an event, you will not suffer any penalty or loss of benefits or rights, which you or might otherwise be entitled.

4. What are the risks and possible discomforts from being in this research study?

The risks and discomfort associated with participation in this study are no greater than those ordinarily encountered in daily life. The risk to you is minimal for the eye tracking and computer-based tasks. At most, participants may find the testing too simple and become bored or too difficult and become frustrated. Previous experience with these sorts of tests suggests that participants can perform them reasonably well with minimal impact on them. Sometimes people worry about how well they do on tests or become tired. To reduce these problems, testing will not begin until you are comfortable with the laboratory, procedures and research personnel. There are no consequences for poor performance on any of the tests. You can take breaks at any time.

The eye-tracking device uses near-infrared light to create reflections off the eyes. This type of light can be commonly found in the environment. The infrared light is emitted from the eye tracker at very low amperage and causes no damage to the eye. This kind of infrared eye tracking has been used for many years at many universities and no negative consequences have been reported.

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Incidental findings: The investigators for this project are not trained to perform medical diagnosis, and the testing procedures are not optimized to diagnose disorders. However, on occasion, scores on the self-report measures by adolescents may indicate that they are at risk for suicide or other serious self-injury. If an adolescent displays suicidal behavior or ideation, a member of the research staff will inform the principle investigator and will ask a staff member in the clinical psychology department at Penn State to conduct a suicide risk assessment. Based on levels of risk, the clinical staff at Penn State may suggest various options for your family. In rare cases, this may involve suggesting the seeking of emergency services or providing information to help parents arrange for future follow-up monitoring and/or medical attention with your primary care providers. Costs for clinical follow-up are not covered in the cost of research.

Video Recording: Adolescents will be videotaped when you complete the ADOS. This video recording is required so that the researchers can review this video for scoring the observational assessment. During eye

tracking, a video may be recorded of your eye-movements, in order to determine where your eye movements fall on the screen, and will not be associated with your personal information. Any video collected during this research study is kept confidential and is not shared with other researchers.

5. What are the possible benefits from being in this research study?

5a. What are the possible benefits to you?

If you participate in the intervention, adolescents may experience improved social skills or face-processing abilities as a direct result of participating in the intervention training. In addition, you may experience a sense of satisfaction from contributing to research about autism.

5b. What are the possible benefits to others?

We hope that the information we obtain from the way participants perform on these tests and respond to the computer-based training will lead to better understanding about the nature of face-to-face social skills in people with autism. Findings from this study will be used to improve future computer-based interventions for people with autism.

6. What other options are available instead of being in this research study?

You may decide not to participate in this research at any time.

Because it is investigational, the therapy offered in this research is only available to you if you take part in the research study.

7. How long will you take part in this research study?

If you agree to take part, it will take about 2 months to complete this research study. During this time, we will ask adolescents and your parents to make 2 visits to the lab. Adolescents may also be invited complete an intervention at home lasting up to 20 hours (3 times per day for 2 months). For adolescents, the first visit will consist of background standardized tests (approximately 2.5 hours) and a testing session consisting of computer-based eye tracking tasks and paper-and-pencil surveys (approximately 2.5 hours). The post-test session involves computer-based eye tracking tasks and paper-and-pencil surveys (approximately 2 hours). During each lab visit, parents will complete questionnaires, lasting 60 minutes.

8. How will your privacy and confidentiality be protected if you decide to take part in this research study?

Your participation in this research is confidential. All possible steps have been taken to assure your privacy. You will be assigned a code number that will be used throughout the study. Only this code (and never your name) will be used when analyzing or reporting the data. Any identifying information will be kept in a locked location and password protected electronic files.

All personally identifiable records pertaining to your involvement in this research will be stored in a locked file cabinet and room in our office and your computerized data will be password protected. This information will only be accessible to the investigators listed on the cover page, and their research staff. All research records will be kept indefinitely with identifiers removed.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. The results of the research may be published and presented at lectures and professional meetings, but neither you or your parents will be identified in any such publication or presentation. Your data and consent form will be kept separate. Your consent form will be stored in a locked location on Penn State property and will not be disclosed to third parties.

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed.

We will do our best to keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may find out about your participation in this research study. For example, the following people/groups may check and copy records about this research.

- The Office for Human Research Protections in the U. S. Department of Health and Human Services
- The Institutional Review Board (a committee that reviews and approves research studies) and
- The Office for Research Protections.

To help us protect your privacy, we have obtained a Certificate of Confidentiality (CoS) from the study sponsor, the National Institutes of Health. We can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. We will use the Certificate to resist any demands for information that would identify you, except as in the following circumstances.

The Certificate cannot be used to resist a demand for information

- from personnel of the United States federal or state government agency sponsoring the project (NIH)
- that will be used for auditing or program evaluation of agency funded projects
- for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA)
- to prevent disclosure to state or local authorities such as child abuse and neglect, or harm to self or others

A CoS does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then we will not use the Certificate to withhold that information.

9. What are the costs of taking part in this research study?

9a. What will you have to pay for if you take part in this research study?

For costs of tests and procedures that are only being done for the research study:

- The Game Intervention will be provided by The Laboratory of Developmental Neuroscience and The NIH at no cost to you while you take part in this study.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- The research-related tests and procedures that will be provided at no cost to you include: ADOS-2 Evaluation.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

10. Will you be paid or receive credit to take part in this research study?

If you decide to participate in this research, you will receive $20/hour for each of the two sessions in the lab (approximately $80 for the first session and $50 for the second session). If you participate in the training intervention, you will also receive $5 per 30 min session, up to $200 for the training. If applicable, parents will also be reimbursed for transportation fees (e.g. mileage, flight, hotel, parking). Meal expenses will not be reimbursed.

Total payments within one calendar year that exceed $600 will require the University to report these payments to the IRS annually. This may require you to claim the compensation that you receive for participation in this study as taxable income.

11. Who is paying for this research study? This study is funded by the National Institutes of Health.

12. What are your rights if you take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

Refusal to take part in or withdrawing from this study will involve no penalty or loss of benefits you would otherwise receive. If you decide to leave the research, contact the investigator so that the investigator can cancel future lab visits and/or intervention sessions and can ask you questions about why you chose to leave the study.

The Principal Investigator may at his/her discretion remove you from the study after you have been enrolled for any number of reasons including demonstration of an inability to complete the behavioral testing. In such an event, you will not suffer any penalty or loss of benefits or rights, which you or might otherwise be entitled.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

13. If you have questions or concerns about this research study, whom should you call?

Please call the head of the research study (principal investigator), Dr. Suzy Scherf at (814) 867-2921, if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the Office for Research Protections at (814) 865-1775, ORProtections@psu.edu if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

INFORMED CONSENT TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

_____ _____ _____

Signature of person who explained this research Date Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent (PARENT)

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject - Parent

By signing this consent form, you indicate that *you voluntarily choose* to be in this research and agree to allow your information to be used and shared as described above.

_____ _____ _____

Signature of Subject Date Printed Name

Signature of Parent(s)/Guardian for Child

By signing this consent form, you indicate that you *permit your child* to be in this research and agree to allow his/her information to be used and shared as described above.

_____ _____ _____

Signature of Parent/Guardian Date Printed Name

Optional part(s) of the study
In addition to the main part of the research study, there is another part of the research. You can be in the main part of the research without agreeing to be in this optional part.

Data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share de-identified information with each other. A data repository is a large database where information from many studies is stored and managed. De-identified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send de-identified information about your health and behavior to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your de-identified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

PARENTS: Please let us know if you will allow us to share the data for you and your child with NDAR by checking one of the following choices:

_____ Provided that our identities stay private, my data and my child's data may be shared with NDAR.

_____ My data and my child's data MAY NOT be shared with NDAR.

Signature of Subject - Parent
By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part(s) of the research study for your data.

_____	_____	_____
Signature of Subject -Parent	Date	Printed Name

Signature of Parent(s)/Guardian for Child
By signing this consent form, you indicate that you have read the information written above and have indicated your choices for the optional part(s) of the research study for your child's data.

_____	_____	_____

Signature of Parent/Guardian Date Printed Name

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the optional part(s) to the research to the subject or subject representative and have answered any questions he/she has about the research.

_____ _____ _____
Signature of person who explained this research Date Printed Name

Permission to Contact for Future Studies

I would like to be contacted about future opportunities to participate in research conducted by Dr. Scherf.

_____ _____ _____
Parent Participant Signature Printed Name Date

_____ _____
Email Phone number

Child Assent (10 to 17 Years)

The Pennsylvania State University

Title of Project: *Using Serious Game Technology to Improve Sensitivity to Eye Gaze in Autism*

Principal Investigator: *K. Suzanne Scherf*
Address: 113 Moore Building
University Park, PA 16802
suzyscherf@psu.edu
Telephone Number: (814) 867-2921

We would like you to be in our research study. We want to understand how teenagers learn social skills.

If you decide you want to be in our study, you will come to the lab two times. You will answer some questions about your social skills. You will also complete tests that measure your communication skills. You will also look at pictures of real faces and watch movies on the computer. We may ask you questions about what you see and record where you are looking on the screen.

We might also ask you to play a game at home on the computer. You will play the game 3 days a week for three months (up to 20 total hours). In the game, you will play a detective. You will talk to people in the game to help you find the clues.

Other people will not know if you are in our study. We will combine information from a lot of people. No one can tell where the information came from. When we tell other people about our research, we will not use your name.

Your parents have to say it's OK for you to be in the study. After they decide, you get to choose if you want to participate. If you do not want to be in the study, no one will be mad at you. If you want to be in the study now and change your mind later, that's OK. You can stop at any time.

Do you have any questions?

We will give you a copy of this form in case you want to ask questions later.

AGREEMENT

The research study has been explained to you. You have had a chance to ask questions to help you understand what will happen in this research. You Do Not have to be in the research study. If you agree to participate and later change your mind, you can tell the researchers, and the research will be stopped.

You decide: **(Initial one)**

___ YES, I want to take part in the research.
___NO, I do NOT want to take part in the research.

_____	_____	_____
Signature of Subject	Date	Printed Name
_____	_____	_____
Signature of Researcher	Date	Printed Name

Optional part(s) of the study

You can be in the main part of the research without agreeing to be in this optional part.

If your parents agree, information from this study will be sent to the National Institutes of Health Data Archive (NDA). NDA allows researchers studying mental processes and illness to share information with each other. This helps them learn new things about conditions, like autism, more quickly than before. We will only share information from the study, not your name or other personal information. No one will be able to tell who you are and no one from NDA can contact you.

AGREEMENT

This part of the research study has been explained to you. You have had a chance to ask questions to help you understand what will happen. You Do Not have to agree to share your information with NDA. If you agree to share your information with NDA and later change your mind, you can tell the researchers, and they will notify NDA to stop sharing your information with other researchers.

You decide: **(Initial one)** ___ YES, my information can be shared with NDA.
___NO, do not share my information with NDA.

_____	_____	_____
Signature of Subject	Date	Printed Name
_____	_____	_____
Signature of Researcher	Date	Printed Name

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,21
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	16
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	10

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17-18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple	17-18

		imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of	#28	Financial and other competing interests for principal	21

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a