Improving Driving in Adults with Autism Spectrum Disorders
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I. BACKGROUND AND SIGNIFICANCE

Autism Spectrum Disorder (ASD) is a common, childhood-onset, lifelong neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction as well as restricted interests and activities (American Psychiatric Association, DSM 5)[1]. Individuals with ASD frequently struggle with cognitive inflexibility and non-verbal learning disability (NVLD), which can compound the clinical picture. It is estimated that up to 1% of children are affected with ASD and more than half of them have adequate cognitive and language abilities (hence "high functioning" [HF]) Such HF-ASD individuals can more successfully participate in educational programs and achieve adequate educational skills that could facilitate them joining the workforce and attain independence [2]. Although a key factor towards attaining independence is the ability to drive [3], recent estimates indicate that only one-third of individuals with HF-ASD drive [4], a much lower rate that non-affected youth. This finding suggests that driving may pose unique challenges to individuals with HF-ASD.

Although the reasons for driving challenges in individuals with HF-ASD remain unclear, findings from a recent pilot driving simulation study [5] in HF-ASD drivers suggested that anxiety could be an important contributor. In that study, during the driving simulation, drivers with HF-ASD manifested significantly abnormalities in gaze directionality relative to controls as well as elevated heart rates and abnormal skin conductance relative to controls. Because these physiological correlates are well-known proxies for hyperarousal and anxiety, these findings raise the possibility that driving induces hyperarousal and anxiety in this population that could lead to the abnormalities in atypical eye tracking behaviors observed. These findings raise the possibility that if driving induced anxiety could be mitigated, it could improve driving performance of HF–ASD individuals.

One such intervention is the atypical anxiolytic medicine busporine. Unlike other anxiolytics, the pharmacology of buspirone is not related to that of benzodiazepines, barbituates or carbamates (it is not a GABA receptor agonist) and so buspirone does not carry abuse potential risk for which other anxiolytics are known. As such, buspirone is not considered to be a drug-of-abuse and is unscheduled. Buspirone is rapidly acting and non-sedating. It is also a very safe medicine with a benign adverse effect profile, no meaningful drug-drug interactions, and lacks withdrawal reactions. Because of its short duration of action, it can be used on as needed basis making it an ideal and safe compound to target driving-induced anxiety in HF-ASD individuals. The main aim of the current study is to test the hypothesis that pharmacological pre-treatment (2 days before and during the simulation) of adult drivers with HF-ASD with low doses of buspirone (5.0 mg BID) will be associated with reduction in hyperarousal as measured by elevated heart rates and abnormal skin conductance, and improvement in driving performance in a simulator as measured by eye tracking deviations. To this end, we propose to conduct a randomized cross-over trial of treatment with buspirone for 2 days before and during the simulation in 24 HF-ASD subjects using an AB-BA design.

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II. SPECIFIC AIMS

Main Aim: To examine the effects of treatment with the anti-anxiety medicine buspirone on driving performance (eye tracking) in individuals with HF-ASD.

Hypothesis: We hypothesize that, compared to the untreated performance, treatment with buspirone will improve 1) physiologically measured hyperarousal (through heart rate and skin conductance) and 2) driving performance (eye tracking deviations) while performing a simulated driving task in a driving simulator.

III. SUBJECT ENROLLMENT

We propose to enroll 24 adult drivers with HF-ASD. Subjects will be males and females, ages 18-45, with a diagnosis of DSM-V Autism Spectrum Disorder. Potential subjects will be recruited from advertising in the local media (newspapers, radio, etc.), MBTA advertisements, flyers posted in the local community and on college campuses, and through the MGH recruitment website, Rally. Potential subjects may also be recruited from local associations that provide programming for individuals with HF-Autism Spectrum Disorder (e.g. AANE, Aspire) or through outpatient clinics at MGH that service individuals with HF-ASD. If a potential subject expresses interest to participate in the study via email, the coordinator will reply and instruct the subject to review the Partner's required language surrounding encrypted and unencrypted emails and will verify their preference prior to proceeding with email communication.

A brief phone screen will be completed with subjects who are interested in participating in the study by a member of study staff. The phone screen asks some questions regarding medical and psychiatric history. If the subject is eligible after the screen, a member of study staff will schedule a time for them to come into the office.

Informed consent will be obtained by a licensed physician investigator prior to the performance of any study procedures. The informed consent will be used to explain, in simple terms, the risks and benefits of study participation to the subject. The subjects may take as much time as they feel necessary to consider their participation in the study, as well as consult with their family members or a physician.

Inclusion Criteria:

- Males and females, ages 18-45, with a diagnosis of DSM-V Autism Spectrum Disorder
- Has a valid Driver's License or a current state-issued driving permit who are actively driving, as deemed appropriate by the investigator

Exclusion Criteria:

- Major sensorimotor handicaps (e.g. deafness, blindness)
- Individuals who have never held a valid driver's license or a current state-issued driving permit
- Intellectual Deficiency (Verbal Comprehension Index < 80)
- Inadequate command of the English language

- Subjects with any clinically meaningful medical or psychiatric condition as determined by the investigator
- Individuals who are currently taking a monoamine oxidase inhibitor (MAOI) for any reason
- Pregnant

IV. STUDY PROCEDURES

Completion of this study will be dependent on the availability of the participant and includes a clinical assessment visit at Massachusetts General Hospital and two driving simulation visits (approximately 1.5 hours each) at Massachusetts Institute of Technology.

Assessment Visit

Before any study procedures are initiated, subjects will provide informed consent. The informed consent documents will be used to explain in simple terms the risks and benefits of study participation. The nature of the study will be fully explained to the subject by a board-certified physician who is either the primary investigator or a co-investigator. The subject will be encouraged to ask questions pertaining to their participation in the study, and the subject may take as much time as they feel necessary to consider their participation in the study. Participation in this study is voluntary, and the subject may withdraw at any time for any reason. The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent.

After providing informed consent, if a subject has been previously diagnosed with a DSM Autism Spectrum Disorder by a licensed psychiatrist and documentation of that diagnosis is available then the K-SADS direct and indirect interviews will be bypassed. Otherwise, all subjects will be interviewed by a licensed physician or psychologist to confirm the DSM-V diagnosis of Autism Spectrum Disorder. The interview will use the questions and probes from the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) model on ASD. Because the K-SADS-PL was designed for use in clinical and epidemiological research to obtain past and current history of psychiatric disorders in children and adolescents aged 6 to 17, it will be adapted to be used as a direct interview with adults with suspected ASD. Whenever the direct assessment for the diagnosis of ASD with the subject is unclear, if possible and feasible, an additional indirect interview will be conducted with a parent as informant. The subject must grant permission for the research team to contact a parent for the indirect interview. If they agree, the parent will be contacted via telephone. Interviews can be done in person, via telephone, or via telemedicine through the MGH secure site based on subject preference. The subject's responses will be recorded on paper and entered in RedCap by the clinician or a member of study staff. If both a direct and indirect interview are completed for a participant the we will combine data by considering a diagnostic criterion positive if it was endorsed in either interview.

Subjects will also be asked to complete the Adult Self Report (ASR), a 126-item self-report questionnaire that assesses aspects of adaptive functioning and problems, and asks individuals to rate items on a 3-point scale (0-Not True, 1-Somewhat or Sometimes True, 2-Very True or Often

True). Subjects will have a choice to complete this instruments remotely through a RedCap secured link or in person. RedCap is a platform for electronic data capture that streamlines data collection and management, and ensures data integrity, resulting in improved data quality. If RedCap is unavailable for use, the subject will complete the ASR on paper and it will later be entered into RedCap by a member of study staff.

In addition, we may ask a parent, guardian, or third-party informant to complete the Adult Behavior Checklist (ABCL). The ABCL is an informant version of the ASR that assesses similar aspects of adaptive functioning and problems, and asks informants to rate items on a 3-point scale (0- Not True, 1- Somewhat or Sometimes True, 2- Very True or Often True). If this is the case, the subject must grant permission for the research team to contact a parent, guardian, or third-party informant for the completion of this questionnaire. If the participant agrees, this instrument will be provided to the informant through a Redcap secured link or in person. If RedCap is unavailable for use, the informant will complete the ABCL on paper and the data will be entered into RedCap by a member of the study staff. This questionnaire will either be used instead of the ASR or to supplement the provided answers on the ASR.

Each subject will be compensated $90.00 in the form of a check for completing the MGH Assessment Visit.

Driving Simulation Visits

Previous work between MGH and MIT utilized the simulator that will be used in this study [6,7]. After completion of the Assessment Visit, the subject will schedule the two driving simulation visits at Massachusetts Institute of Technology during this time they will be given or emailed an information sheet regarding what the MIT driving simulation visit will entail. Each driving simulation visit will be approximately 1.5 hours long. At the first driving simulation visit, subjects will be asked to review and sign the MIT consent form before proceeding.

Half of eligible and consenting subjects (A-B group) will be tested on the driving first on medication while the other half (B-A group) will be tested first unmedicated based on a randomization list. The subjects will be instructed to take 5.0 mg of buspirone with breakfast and 5.0mg of buspirone with dinner for 2 days before their driving simulation. On the day of the simulation, they will be instructed to take the dose 1 hour before the simulation. A member of study staff will remind the subjects via phone call and/or email to take their medication on the two days preceding their driving simulation, and remind them of the specific times at which they should take the medication.

If a subject is assigned to the A-B group per the randomization list, they will receive the buspirone at the completion of their assessment visit at MGH. A member of study staff will remind the subject that they should not take the medication until 2 days before the driving simulation. Written instructions will also be provided explaining the dates and times when the medication should be taken. If the individual is currently taking buspirone they will be instructed to take the busiprone, as prescribed, prior to their first simulation visit. However, prior to their second simulation visit with MIT they will be asked to withhold their medication starting 24 hours prior to their second visit.

The other half of the eligible and consenting subjects (B-A group), per the randomization list, will take the buspirone the two days preceding their second driving simulation, and on the day of their second driving simulation at MIT. On the day of their first scheduled driving simulation visit at MIT, a member of study staff from MGH will meet the subject at MIT. After the first driving simulation is complete, the member of study staff will provide the subject with the buspirone, and instruct the subject that he/she should take the medication for two days preceding their second scheduled driving visit, and the day of their second scheduled driving visit. The member of study staff will also provide the subject with written instructions of the dates and times when the medication should be taken, and send a reminder to the subject via phone call or email. If the individual is currently taking buspirone, they will be instructed to withhold their medication starting 24 hours prior to their first visit and then take the buspirone, as prescribed, prior to their second visit. If the member of study staff from MGH is unable to attend the subject's first driving simulation visit at MIT, the prescription of buspirone will be picked up from the Clinical Trials Pharmacy, and the research coordinator will package the medication. The medication will be shipped to the subject using UPS. The subject will be notified on which day they should expect to receive the medication, and that they will need to sign for the delivery. The package will include dosing instructions for the medication and will indicate which dates the medication should be taken based on when their driving simulation visit at MIT is scheduled.

MIT AgeLab driving simulation experiments are conducted in a high fidelity driving simulator designed and fabricated by RTI (Realtime Technologies Inc., Ann Arbor, MI), running the SimCreator and SimVista software packages. The simulator consists of the full cab of a 2001Volkswagen New Beetle. Three exterior screens provide a 180-degree simulated forward and partial side field of view of a virtual roadway and associated environment. A rear projector screen behind the car displays the rear roadway, which is viewable using the vehicle's standard rearview mirror. Two LCD displays placed in the cab's side mirrors present images of the rear roadway in a perspective corresponding to what actual side mirrors provide. Images of the roadway are displayed at 60 frames per second. The steering wheel, accelerator, and brake pedals all provide force feedback to the subjects. Internal and external speakers produce simulated vehicle and environmental sound during the experiment. The cab is instrumented with three cameras and one microphone to record the environment in the cab. One camera is focused on the driver's face to capture head and eye movements, one is positioned to recorded hand movements and interactions with steering wheel and center stack, and the final camera is positioned to record the forward screen to validate video and simulator data synchronization. The simulator is also instrumented with the capacity to record from a wide variety of physiological sensors using medical grade instrumentation (FDA 510(k) reviewed class II) (NeuroDyne Medical Corp., model MEDAC System/3) to monitor changes in a subject's internal state (sensors to be used are detailed below) associated with the environmental stimulation of the virtual roadway and the driving task.

Upon reporting to the driving simulation lab, subjects will be asked to complete questionnaires. Sensors for monitoring heart rate (via ECG) and skin conductance will then be attached. For the ECG sensors, the skin will be cleaned with isopropyl alcohol and disposable electrodes (Vermed A10005) applied in a modified lead II configuration with the negative lead immediately under the right clavicle, the common immediately under the left clavicle, and the positive lead over the

lowest left rib. This placement has been found minimize movement artifact induced by fundamental vehicle control (i.e. steering) while also involving minimal intrusiveness during placement. Skin conductance is measured using a constant current configuration and non-polarizing, low-impedance gold-plated electrodes. The skin conductance electrodes will be placed on the underside of outer segments of the ring and middle finger of the left hand. Data sampling is carried out at a rate of 250 Hz to provide sufficient resolution for detecting the ECG R-wave to calculate heart rate. Where appropriate, statistical computations for physiological data will be completed based upon transforms designed to control for individual variability. Eye glance behavior will be coded from the in-cab video recordings and reduced to numeric values prior to further analysis. Source data will be labeled with subject identification numbers and maintained on password access controlled computers.

At each of the driving simulation visits, subjects will complete some questionnaires. The pre - experiment questionnaire includes the Beck Anxiety Inventory (BAI), which is a 21-item self-report inventory that is used for measuring the severity of anxiety in children and adults. Each question on the BAI is scored on a scale value of 0 (not at all) to 3 (severely), and higher total scores indicate more severe anxiety symptoms. Also included in the pre-experiment questionnaire is a standard MIT short questionnaire that includes basic demographics, driving history information, a state anxiety checklist, and a sleep-awake scale.

For the actual driving simulation, subjects will be seated in the driving simulator and introduced to interacting with the simulation environment through a brief adaptation drive of approximately 10 minutes. This training drive will begin under low speed and with no oncoming traffic. The speed limit will be gradually increased along with increased visual complexity of the roadway and density of on-coming traffic. This gradual increase in visual complexity follows guidelines designed to reduce the likelihood of simulator sickness. This period is also intended to allow subjects the opportunity to become accustomed to the mechanisms of the simulator and to reduce the novelty of driving the simulator[8].

Following the adaptation period, subjects will be asked to “stop” the vehicle. A staff member will check with the subject to see if they are comfortable to proceed with the study. Upon accent to continue, the general characteristics of the primary drive will be explained and any questions that the subject has will be answered. The driving protocol will include periods of both high and low task stimulation. If the subject follows typical travel behavior based upon posted speed limits and surrounding traffic flow, the duration of the primary drive should run for approximately 45 minutes. As described previously, the primary dependent measures collected during the simulated drive will focus on driving performance related eye glance / scanning behavior and physiological measures indicative of relative arousal levels (heart rate and skin conductance). Other driving performance metrics related to variables such as speed control and lane discipline maintenance will be collected as secondary measures.

After the simulation, subjects will complete the post-experiment questionnaire, which includes the short state anxiety scale and questions about the subject’s experience in the simulator. Subjects will also complete the Kennedy Simulator Sickness Questionnaire[9], which is a 16-item questionnaire to assess the extent to which simulator sickness may have been experienced. Each experience is rated on a scale of 1 (None) to 4 (Severe).

Subjects will be compensated by MIT $60 at the completion of each of the two driving simulation visits ($120 total) for the MIT portion of the study.

During study participation, if an individual expresses spontaneous suicidality or endorses suicidality through any study questionnaires or procedures, the principal investigator of the study will be contacted immediately via phone or page to assess the risk of the current situation and recommend a suggested plan of action to assist the current participant. The participant may be referred to the emergency department for immediate evaluation upon recommendation of the principal investigator.

The Institutional Review Board at Massachusetts Institute of Technology will review the driving simulation protocol. No study procedures will be performed until IRB approval is granted from both institutions, and the MIT IRB approval letter is submitted the PHRC for approval.

V. BIOSTATISTICAL ANALYSIS

Our tests of hypotheses will rely heavily on random regression models (RRM) [also known as the hierarchical linear model and random (or mixed) effects model]. This approach has several advantages over traditional methods such as repeated measures ANOVA or MANOVA. We will estimate our RRMs using the generalized estimating equation (GEE) framework. Canonical links will be used to correctly model the distribution of dependent variables. For binary outcomes, logistic regression models will be fit with the binomial family and the logit link. For count data, Poisson regression models will be fit with the Poisson family and the log link, and for normally distributed data, linear regression models will be fit with the Gaussian distribution and identity link. Working covariance structures will be specified with Huber-White robust estimators of variance to account for repeated measures of each subject.

VI. RISKS AND DISCOMFORTS

Participants will be told that they can stop study participation at any time for any reason. Study information and all other personal and identifying information will be kept on a password-protected computer within the secure Partners firewall. All research-related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Data obtained from this study will not identify the subjects individually. Subjects will be assigned ID numbers, and data obtained may be published, but published data will not identify individual participants.

Risks of taking buspirone
Buspirone can cause one or more of the side effects listed below:
Common side effects (experienced by 2 to 12 out of every 100 subjects in previous studies):

- nausea and vomiting
- headache

- dizziness
- drowsiness
- fatigue
- weakness
- numbness
- difficulty sleeping
- depression
- excitement

Less common side effects (experienced by 1 out of 100 subjects):

- Skin rash
- itching
- fast or irregular heartbeat
- blurred vision
- unusual movements of the head or neck muscles

Pregnancy
The effects of buspirone to an embryo or fetus are unknown and may be harmful. Therefore, individuals who are pregnant cannot take part in the study. The research coordinator will complete the pregnancy screening form with women of childbearing age. During the assessment visit, if the subject is a menstruating female, the pregnancy screening form will be completed by a member of study staff. She will be asked if she is pregnant or if there is any possibility that she may be pregnant, if she is experiencing a late menstrual period, the date of her last menstrual period, and about any contraceptive use. If she confirms that she is not pregnant and there is no possibility that she may be pregnant during screening, we will proceed. If there is a possibility that she is pregnant, a urine pregnancy test will be performed. If the test is negative, we will proceed.

Some subjects may feel uncomfortable when asked to answer detailed questions. Subjects may refuse to answer any of these questions. During the driving simulation, there is a chance that subjects may experience simulator sickness that is similar to motion sickness. Subjects may choose to stop their participation at any time.

The Principal Investigator will be available 24 hours per day via pager to respond to all reports of adverse events, including those that emerge outside of regularly scheduled visits. Adverse events and unanticipated problems will be reported to the PHRC according to current guidelines. We will follow and adhere to all guidelines as defined and outlined on the Partners Human Research Committee website: http://healthcare.partners.org/phsirb/adverse_events.htm.

VII. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Potential benefits to the participants include education about ASD, a trial of medication that could be continued after the study, and the opportunity to contribute to medical science and thus help others with ASD.

VIII. MONITORING AND QUALITY ASSURANCE

The principal investigator will be responsible for monitoring and ensuring the integrity of the data and adherence to the IRB-approved protocol. He will review any questions or concerns regarding data collected. Each staff member will undergo focused training on each task for which they are responsible and will perform quality control for others similarly engaged.

The study clinicians, research coordinator, and Principal Investigator will monitor study progress including enrollment, adherence to inclusion/exclusion criteria and study protocol, as well as any adverse events. The Principal Investigator will be responsible for ensuring that adverse events are reported to the Partners Human Research Committee in compliance with requirements. Any changes to the protocol will be made in accordance with local IRB policies.

Any paper material, including the names of subjects or other identifying information (e.g., consent forms and check requests) will be locked up and will be accessible only by study staff. Digital material including the names of subjects or other identifying information (e.g., subject tracking logs) will be kept in password-protected files on protected servers accessible only to departmental staff. All study materials, such as rating scales and neuroimaging data, will be labeled with ID numbers only and will not include identifying information.

Data for all scales collected at the MGH will be entered in RedCap, a platform for electronic data capture that streamlines data collection and management, and ensures data integrity, resulting in improved data quality.

IX. REFERENCES

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