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Protocol

1. Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and restricted, repetitive behaviors, which affects approximately 1 in 68 children in the United States. Pharmacotherapies are often a significant component of treatment of ASD, but most are directed at psychiatric symptoms, such as agitation, anxiety, repetitive and obsessive behaviors, and depression. Evidence for pharmacological treatments aimed at improving cognitive aspects of ASD, including language and socialization, is not yet established. This is an important area of new investigation. Most published studies specifically directed at the cognitive aspects of ASD are small case series reports, single dose studies, or small pilot trials. Both social and language benefits have been reported in a small, uncontrolled case series of autism patients with the beta-adrenergic antagonist, propranolol. Work from our lab has demonstrated benefits in verbal problem-solving and social interaction with propranolol in adults and adolescents with ASD in double-blinded placebo-controlled single dose challenge studies. Due to the potential benefits from cognitive pharmacotherapy, and evidence suggesting social and language benefits from propranolol in ASD, we now wish to determine whether the benefits we observed with single doses also occur with repeated doses in a double-blinded placebo-controlled pilot trial. Our aim is to examine the effects of serial doses of propranolol on social interaction, as well as on language tasks, anxiety, adaptive behaviors, global function in high-functioning children and youth with ASD. We will also examine whether response to treatment can be predicted based upon markers of anxiety and autonomic nervous system activity. This trial will entail one 15-week drug period, during which participants will be randomized to take propranolol or placebo daily in a double-blinded manner. Participants will also have the option of completing a 12-week open label extension during which they will be prescribed propranolol by their primary care physician. Successful completion of this work could result in the development of a new evidence-based treatment option for core features of ASD, which does not currently exist. It may also result in markers to predict who is most likely to respond.

2. Objectives

Our specific aim is to examine the effects of serial doses of propranolol on social interaction, and secondarily on language tasks, anxiety, adaptive behaviors, and global function in high functioning adults and adolescents with autism in a double-blinded, placebo-controlled trial. We will also examine whether response to treatment can be predicted based upon markers of autonomic functioning, such as skin conductance, heart rate variability (HRV), and the pupillary light reflex (PLR), and whether anxiety can predict treatment response. Our hypothesis is that social functioning and language abilities will benefit from serial doses of propranolol, as we have demonstrated in previous single-dose studies. We also predict that

those with the greatest degree of autonomic dysregulation, or the lowest functional connectivity, will demonstrate the greatest benefit from the drug.

3. **Background**

Previous studies support the existence of altered noradrenergic activity in ASD, including early studies suggesting increased plasma (1) and urine (2) adrenergic metabolites in autism. Additionally, multiple studies indicate that ASD may be characterized by hyper-restrictive associative networks (3, 4) which may be related to increased noradrenergic signaling (5). These findings suggest the potential benefit of a pharmacological agent aimed at the noradrenergic system for this population. Propranolol, a centrally and peripherally active nonselective beta-adrenergic antagonist, reduces noradrenergic system activity. This anxiolytic has been used off-label for test anxiety (6) and performance anxiety (7) for several decades. Propranolol was first explored within the context of ASD in an uncontrolled case series, which reported improvements in language and sociability (8). Our laboratory has since investigated this agent's effects on a wide range of behaviors known to be affected in ASD, including verbal abilities (9, 10), working memory (11), and facial scanning (12) in single-dose psychopharmacological challenge studies in adults and adolescents with ASD. Most recently, we demonstrated a benefit of a single dose of propranolol on social functioning, assessed via conversational reciprocity, in a sample of 20 high-functioning adults and adolescents with ASD (13) and a potential association between resting autonomic activity, assessed via heart rate variability, and response to propranolol on the social task (14). These findings suggest a potential benefit of propranolol on core features of ASD and that treatment response may be predicted by certain markers. Accordingly, further study is necessary to examine if these potential benefits are maintained in serial doses in the form of a trial in children and youth with autism.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

The proposed study is a between-subject, placebo-controlled trial. For the purposes of this study, we will recruit two groups of participants—the first being children age 7-14 with ASD, the second being youth age 15-24 with high functioning ASD. High-functioning autism is defined in this study by Autism Diagnostic Interview-Revised (ADI-R) criteria *and* Autism Diagnostic Observational Scale (ADOS) criteria for autism, and a WASI-II IQ full scale of at least 85. Participants will be screened for this information as well as inclusion/exclusion criteria to determine their eligibility to participate in this study through their medical record and over the phone prior to obtaining written consent. A waiver of documentation consent is requested only for these screening purposes and to distribute the Rome IV Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders - Child (R4PDQ-Child), (for adults, the Rome IV Diagnostic Questionnaire for Adults (R4DQA) will be used), and the Gastrointestinal Symptoms Inventory (GSI). Written consent will be obtained prior to any other study-related procedures.

If a prospective participant does not have IQ scores available through the Thompson Center database or EMR, such as Powerchart, or if the participant's scores are not reflective of his/her current level of functioning, the WASI-II may be given at the beginning of the initial study visit or at a separate visit. The ADI-R may be administered to the parent/caregiver of a prospective participant at the beginning of the initial study visit or at a separate visit, if the prospective participant does not have ADI-R scores from a previous assessment. Prior to participation in the study, informed

consent will be obtained from each subject. In addition, the subjects will be informed that they can terminate the procedure and exit the study at any time.

Procedure outline for ages 15-24:

General study visit outline:

Upon study enrollment, participants will be randomized to receive either placebo or propranolol via oral capsule, crushed tablet, or liquid daily. The drug dosage will be titrated slowly to ensure the drug is tolerated well (detailed titration schedule below). The following are brief descriptions of the drugs to be administered:

> *Propranolol [pro-pran'-o-lol]* blocks the brain's and body's use of norepinephrine both centrally and peripherally and also is commonly used to decrease high blood pressure.
> *Placebo [pla-see'-bo]*, also commonly referred to as a "sugar pill," is an inactive substance that looks like other drugs.

Subjects in the youth age group will undergo magnetic resonance imaging (MRI) before initiating drug. (See details below.)

During the study, participants will undergo psychophysiological and behavioral assessments (discussed below) at three separate study visits at the following time points: (1) prior to drug administration, for establishment of a baseline; (2) halfway through drug period (approximately week 6); (3) the end of drug period (approximately week 12).

Prescription for the drug will be given after the completion of the imaging and baseline sessions.

At each study visit, psychophysiological measurements will be performed to assess autonomic activity (details below). A small sample of cheek cells will be taken using a buccal swab for genetic processing. Behavioral tasks and questionnaires will also be performed at each study session, except for the Vineland, which will only be performed at baseline and week 12. Different forms of each behavioral task will be used at each of the six visits. Questionnaires will remain the same for each visit. (See detailed description below.)

Imaging visit specifics:

The imaging personnel will go over the MRI screening form in detail with the subject and give specific instructions on how to safely complete the session. Subjects will also be given the option to practice in a mock scanner before the actual scanning session to acclimatize them better. The MRI session will consist of a T1 weighted anatomical scan, functional MRI (task-based activation), resting state functional connectivity MRI and diffusion tensor imaging (DTI). Prior to each scanning session, the subjects will be given practice fluency tasks to familiarize with the task. For the semantic word fluency task imaging, a block design with two sets of three task blocks (30 seconds) and 4 rest blocks (30 seconds) for a total of 3 min 30 sec for each set. During the task block, participants will be asked to generate as many words as they can that are related to a particular category. The categories used in the scanner will be distinct from the ones used on subsequent cognitive testing. Verbal responses will be recorded offline with an MRI compatible microphone. The stimuli, presented visually, will be the category

(semantic fluency) from which the subject will generate words, which will remain on screen for the full 30 seconds. During the rest block, the participants will be asked to fixate their eyes on a crosshair in the center of the screen. All stimuli for subject instruction will be displayed using an LCD projector (Avotec, Inc.). A laptop computer using E-Prime (Version 2.0, Psychological Software Tools, Inc.) will generate the stimuli. The second task based activation will have 2 sets of subjects looking at emotional faces versus neutral faces versus shapes in a randomized block design where each block would last 30 seconds for a total of 3 minutes per set. Images will be collected with the 3T Siemens Trio MRI scanner at The University of Missouri Brain Imaging Center. High-resolution structural three-dimensional T1-weighted images will be acquired for anatomic localization and co-registration of the functional data, using a high-resolution sagittal MP-RAGE sequence (TR = 1920 ms; TE = 3.75 ms; 8 degree flip angle; in-plane resolution = 1x1 mm; slice thickness = 1mm; number of slices = 160). The BOLD contrast functional data will be collected using a T2*-weighted EPI pulse sequence (TR = 2000 ms; TE = 30 ms; 90 degree flip angle; 3.8 x 3.8 mm in-plane resolution, slice thickness = 3.8 mm, number of slices = 28), which will be acquired parallel to the anterior-posterior commissure plane. The acquisition parameters for the resting state functional connectivity MRI (fcMRI) and the ROIs will be identical to those with the above described task-based imaging, and the z-transformed correlations will be compared similarly for its relationship to response to propranolol. Diffusion tensor imaging (DTI) will be acquired using standard sequences, and fractional anisotropy, and mean diffusivity will be calculated to establish white matter integrity and how this relates to response to propranolol. A custom VacFix cushion (S&S Par Scientific, Inc.) can be used to provide head and upper body restraint. The imaging session will last no longer than 1 hour.

Study visit task specifics:

Measurements will include skin conductance, measured by finger transducers, and heart rate variability, measured by electrocardiogram. Two adjustable transducers will be placed on the fingers to collect skin conductance data, and three electrodes will be placed on the chest in the typical manner, and signal from the transducers and electrodes will be amplified by GSR 100C and ECG 100C amplifiers connected to a BIOPAC MP150 Data Acquisition System. Alternatively, for skin conductance, two transducers may be placed on the palmar surface of the hand if sufficient data are not obtained from the finger transducers. Measurements will be recorded for a period of 8 minutes, allowing for 3 minutes of acclimation to the equipment. Heart rate and blood pressure will also be measured via wrist cuff at each study visit. Respiration will be monitored with a BIOPAC TSD201 respiration transducer placed around the abdominal area. The transducer is affixed to an adjustable strap and in non-invasive. The TSD201 is connected to a RSP100C amplifier that is attached to the MP150 system.

Pupillary light reflex (PLR) will be collected at baseline and again at week 12. PLR is a simple functional neurological test that measures the pupil size changes in response to a short light flash. A novel remote PLR system will be used to measure PLR in participants. During the test, the participant will sit comfortably in a chair about 1 m from the PLR system. A movie will be shown on a projector screen behind the PLR system to attract the attention of the participant so that the PLR responses can be measured. The movie is red-filtered to avoid affecting pupil size. The operator will observe the participant's head and pupil images on the control PC and initialize the PLR test at appropriate times. The projector screen will be illuminated using LEDs (530nm) to provide stimuli. PLR measurements will be first made with a stimulation

intensity of 9.5 cd/m^2 in the light-adaptation condition; then the room light will be turned off while the participant continues to watch the video for 15 mins; and PLR will be then tested again with 0.75 cd/m^2 stimulation in dark-adaptation. A total of 10 trials will be performed under each stimulation condition, and the multiple measurement results will be averaged. Each PLR trial takes 2.5 sec and there is a 25-30 sec interval between two trials. The whole PLR test will be completed in about 30 min (including 15 min dark-adaptation). Breaks will be allowed at the participant's request.
The pupil size will be automatically computed using custom software from saved image stacks to construct the pupillogram. Initial pupil diameter, the measure most closely related to sympathetic and parasympathetic balance, and PLR latency, the measure most specific to autism, will be the primary measures of interest.

Buccal Swab: To collect a sample, researchers will ask the participant how long since their last food or drink to ensure nothing had been consumed for 30 prior to collection. Researcher will then scrape the swab firmly against the inside of each cheek 6 times. The swab must air-dry for at least two hours after collection. The swab will be stored in a -80 degree freezer until processing. These samples will be analyzed to examine whether or not different genes are related to symptoms of autism and/or affect how people with autism respond to the drug propranolol.

The following assessments will be completed by the participant with ASD:

1. General Social Outcomes Measure (GSOM): To address our primary outcome measure: determining whether our previously reported social effects with single doses of propranolol are also observed with serial doses, the General Social Outcomes Measure will be administered, as with our previous work with single doses. This is designed to allow repeated assessments, consisting of a semi-structured assessment of social functioning assessing ability staying on topic, sharing information, reciprocity, transitions/interruptions, nonverbal communication, and eye contact, during a semi-structured conversation with the researcher for Conversational Reciprocity score, as developed by Dr. Stichter. In our initial study, we assessed only the Conversational Reciprocity portion of the GSOM. We will also secondarily assess the other portions, and thus will also obtain scores on Facial Expressions, Social Problem Solving, Affect Demonstration, and Emotional Perspective Taking as well, that have been developed in the newest version of the GSOM. As our previous study demonstrated effects of single doses on the Conversational Reciprocity portion of the GSOM, as well as prediction of response based on HRV, this sub-test will be the primary outcome measure for the effect of serial doses of propranolol in this study. The utilization of a novel assessment is necessary due to the lack of existing measures allowing repeated measure of social interaction in the testing environment in response to a treatment. Dr. Stichter designed this for serial assessment of response to interventions for this purpose.
2. Social Responsiveness Scale, second edition (SRS-2): This 65-item, parent-report measure asks questions about a participants' social awareness, social information processing, capacity for reciprocal social responses, social anxiety or avoidance, and characteristic autistic preoccupations or traits. Depending on the child's age, the preschool or school-age version of the SRS-2 will be administered.
3. Anagrams (Youth age group only): Subjects will be given a set of 20 anagram tasks (word unscrambling tasks, where letters are rearranged to form a word: IRCKB → BRICK) similar to those used in our previous research.8 As with our previous work, a maximum of 120 seconds will be allowed for each anagram. Number solved and solution latency (with failed anagrams recorded as 120 seconds) will be recorded. Six distinct test versions of equivalent difficulty are available for this task, and additionally

they will be presented counterbalanced across the conditions and visits in order to further minimize any potential confounding effect of variation in difficulty between test versions, as with our previous work. This task has been extensively utilized with normative data in our previous work.

4. Semantic fluency (Youth age group only): Subjects will also be given the word fluency task, a widely utilized, validated language task in a variety of populations. Subjects will be asked to generate as many words as possible within one minute each from 3 different categories (e.g. set1: animals, things to wear, vegetables; set2: drinks, things in the kitchen, hobbies). These categories will be distinct from those used in the initial fcMRI. Six distinct test versions of equivalent difficulty are also available for this task, in addition to the version used during imaging, and they also will be presented counterbalanced across the conditions and visits in order to further minimize any potential effect of variation in difficulty between test versions, as with our previous work. Total number of distinct words (not including proper nouns) will be recorded for each session.

5. Clinical Global Impression of Severity (CGIS), Clinical Global Impression of Change (CGIC), Clinical Global Impression of Severity & Change – Anxiety (CGIA), and Clinical Global Impression of Severity & Change – Gastrointestinal (CGIG) (purpose-overall clinical change, and change in anxiety and gastrointestinal symptoms): These tools are semi-structured interviews that are now leading reliable and validated primary outcome measures in clinical trials for other cognitive disorders and are currently in use in autism clinical trials. The CGIC consists of a 7-point subjective scale assessing change from baseline. On this scale, scores of 1, 2, and 3 represent marked, moderate, and mild improvement, respectively. A score of 4 represents no change. Scores of 5, 6, and 7 represent mild, moderate, and marked worsening, respectively. CGIC scores from both the parent/caregiver and the blinded clinician (Dr. Beversdorf) will be utilized. Since this reflects change, this will only be done at week 6 and 12 sessions, not at the beginning. The CGIS is a similar 7-point subjective scale for severity, which will be assessed at each time point including at the beginning to provide a baseline upon which to base the CGIC. The CGIS, CGIC, as well as the subsequent assessments, will provide pilot data to determine the necessary sample size for obtaining a significant result utilizing this measure more commonly utilized in larger trials. The CGIA and CGIG severity and change versions will be administered in a similar manner to assess changes in anxiety and gastrointestinal symptoms, respectively. The purpose of the CGIC, as well as the subsequent assessments, is to obtain critical information for optimizing design for future trials utilizing measures more commonly used in larger trials.

6. Autism Impact Measure (AIM) (purpose: autism severity impact): This is a tool developed by Drs. Kanne and Mazurek that has been developed to assess the impact of the autism-associated behaviors. Subjects are asked a series of 41 questions regarding the frequency and the impact, or interference resulting from, a series of autism-associated behaviors, in order to determine the impact of these autism associated behaviors. Overall impact scores and frequency scores will be obtained from this measure. This assessment will be utilized in an exploratory manner as it may represent a more sensitive measure for the overall impact of autism than other measures focusing on specific aspects, such as behavior.

7. Clinical Evaluation of Language Fundamentals-5th Edition (CELF-5): The CELF-5 is a comprehensive language assessment that is validated across the full range of our subjects' ages and yields a Core Language score in addition to Index scores for Receptive Language, Expressive Language, Language Content, and Language Memory, and also includes a Pragmatics subtest.

8. Vineland Adaptive Behavior Scales-Second Edition (VABS-2) (purpose- communication, living skills, socialization): The VABS-2 is a well validated assessment used for the full range of our subjects' ages and yields standard scores in Communication, Daily Living Skills, Socialization, and Motor Skills. VABS-2 scores for Communication, Daily Living Skills, and Socialization will be monitored in this study.

9. Aberrant Behavior Checklist (ABC) (purpose- overall behavioral disturbances): The ABC is a well validated, reliable, and widely used assessment tool for interventions for a range of cognitive disorders. It is a 58-item questionnaire of the parent/caregiver, rated on a four-point scale (0=not at all a problem, 3=the problem is severe). Items are scored on five subscales: I-Irritability, Agitation, Crying, II-Lethargy, Social Withdrawal, III-Stereotypic Behavior, IV-Hyperactivity, Noncompliance, V-Inappropriate Speech. Each subscale will be utilized in our assessment. It has been validated and utilized in a wide range of ages and cognitive conditions including autism. It is sensitive to early effects of drugs (within a few weeks) in autism, including non-antipsychotic agents.

10. Gastrointestinal Symptomatology: The Rome IV Diagnostic Questionnaire on Pediatric Functional Gastrointestinal Disorders (R4PDQ-child) assesses the frequency, severity, and duration of functional GI symptoms in children and adolescents, and contains parent/caregiver and self- report versions. For participants age 18 and older, the adult version of the Rome IV Diagnostic Questionnaire (R4DQA) may be used. The R4PDQ and/or the R4DQA will be administered at baseline, 6-week, and 12-week sessions. Paper and/or on-line versions of the questionnaire may be utilized. Furthermore, the GI Severity Index (GSI) will be administered to the participant or their parent/caregiver in-person or over the phone during the baseline, week 1, week 2, week 6, and week 12 periods.

11. Pet Demographics Questionnaire (PDQ): The PDQ assesses demographics regarding the presence of a pet or pets in the home, and the level of attachment to the animals by the participant. The PDQ will be administered at baseline.

12. The Companion Animal Bonding Scale (CABS): The CABS is an 8-item scale assessing an individuals' interactions with their companion animal in the home. The CABS will be administered at baseline, 6-weeks, and 12-weeks.

13. Sympathetic Tone and Anxiety: As above, to determine effects on sympathetic tone or anxiety, the HRV, heart rate (via standard electrocardiogram procedure using adhesive pads on the chest), skin conductance, blood pressure, PLR and SCAS will be repeated at 12 weeks to determine how the effect of treatment on these markers relate to response to treatment for the outcomes above.

14. Salivary Cortisol: To determine the effects on the stress response, salivary cortisol samples will be collected immediately when the participant enters the testing room and again after administration of the GSOM during the baseline, 6-week, and 12-week sessions to determine how the effect of treatment on cortisol relates to response to treatment for the outcomes above. Samples will be collected using the Salimetrics SalivaBio Children's Swab (SCS) method and analyzed using enzyme-linked immunosorbent assay (ELISA).

15. Sensory Over-Responsivity: To examine the effects of propranolol on sensory over-responsivity, the SenSOR will be administered at baseline, 6-weeks, and 12-weeks. The SenSOR is a 76-item yes/no questionnaire examining sensory over-responsivity in multiple domains.

Our team has experience with all of these assessments from our previous research in our single-dose studies with propranolol, as well as with other research.

Drug Titration schedule:

This study involves a titration schedule in which participants will begin with small doses (single capsules) of the drug and increase to a larger dosage (divided over 3 capsules) over the course of three weeks. To maintain blinding, participants will be given bottles labeled "A" and "B," containing different doses of propranolol. Participants will be given a drug diary to keep track of their doses throughout the study. Participants will be asked turn in their drug diary and empty capsule bottles after each drug period ends. In addition, participants will be given a personalized calendar, marked with labels denoting which pills to take when on each day of the drug period.

The drug titration schedule will be as follows for the drug period and its subsequent tapering-off period:

Week 1: 40 mg propranolol (1 capsule, nightly)
Week 2: 80 mg propranolol (2 40mg capsules, morning & night)
Weeks 3 - 12: 100 mg propranolol (3 capsules, 40 mg/morning, 20mg/afternoon, & 40mg/night)
Week 13: 60 mg propranolol (2 capsules, 40 mg/morning & 20mg/night)
Week 14: 20 mg propranolol (1 capsule, nightly)
Week 15: no capsules
[Participants may choose to continue on with open label extension described below]

During the titration schedule, heart rate and blood pressure measurements will be taken via automated wrist cuff by the participant or parent/caregiver within 48 hours after each change in drug dosage. At the initial study visit, participants and/or their parent/caregiver will be trained on the use of the wrist cuff or pediatric arm cuff, depending on needs of participant, given a sheet of instructions for its use, and given a wrist/arm cuff to take home for the duration of the study. A member of the study staff will call the family to obtain the heart rate and blood pressure results. If on any measurement the heart rate is below 55 for youth or 60 for children or systolic blood pressure is below 90 for youth or 80 for children, the PI will be immediately notified, and he will call and/or examine the participant to assess his or her condition. At this point, the PI may make the decision to have the participant drop back to the previous dosage level or to withdraw the participant from the study for safety reasons. A member of the study staff will also call the participant to confirm no further problems before each increase in dosage. During this call, parts A and B of the Safety Monitoring Uniform Research Form (SMURF) will be performed. The SMURF is a rating scale for measuring the presence and intensity of medication side effects. Abnormal ratings on the SMURF will result in notification of the PI who may then call or examine the participant to further assess his/her condition.

Study procedure for ages 7-14:

General study procedures:

Procedures for the child age group will be the same as for the youth age group *except:*

1) Child age group will not participate in the imaging portion of the study.

2) Child age group will not complete the anagrams or semantic fluency tasks.
3) Titration schedule for the child age group is based on weight.
4) Minimum heart rate allowed for children will be 60 and the minimum systolic blood pressure allowed will be 80.

Drug titration schedule for the child age group will be based on weight as follows:

For patients >50kg:
Same titration as youth age group
For patients 40-50kg: 75% youth dosage
Week 1: 30 mg propranolol (nightly)
Week 2: 60 mg propranolol (30mg morning & night)
Weeks 3 - 12: 75 mg propranolol (30 mg/morning, 15mg/afternoon, & 30mg/night)
Week 13: 45 mg propranolol (30 mg/morning & 15mg/night)
Week 14: 15 mg propranolol (nightly)
Week 15: no medication
For patients 30-40kg: 50%
Week 1: 20 mg propranolol (nightly)
Week 2: 40 mg propranolol (20mg morning & night)
Weeks 3 - 12: 50 mg propranolol (20 mg/morning, 10mg/afternoon, & 20mg/night)
Week 13: 30 mg propranolol (20 mg/morning & 10mg/night)
Week 14: 10 mg propranolol (nightly)
Week 15: no medication
For patients 20-30kg: 25%
Week 1: 10 mg propranolol (nightly)
Week 2: 20 mg propranolol (10mg morning & night)
Weeks 3 - 12: 25 mg propranolol (10 mg/morning, 5mg/afternoon, & 10mg/night)
Week 13: 15 mg propranolol (10 mg/morning & 5mg/night)
Week 14: 5 mg propranolol (nightly)
Week 15: no medication
[Participants may choose to continue with open label extension described below]

Optional Open Label Extension
Participants will also have the option to participate in an open label extension period after week 15 of the study. After at least two weeks taking no initial study medication, participants will be prescribed propranolol by their primary care physician, a researcher will retake baseline GSOM, SRS, ABC, R4PDQ/R4DQA, and GSI measures, and participants will be titrated on the schedule dictated by their age and/or weight. After 12 weeks on propranolol, a researcher will take final GSOM, SRS, ABC, R4PDQ/R4DQA, and GSI measures.

b. Study duration and number of study visits required of research participants.

Participation in this study will last 15 weeks, with the option to extend another 12 weeks depending on participation in the open label extension. The youth group will have 1 visit to the Brain Imaging Center (lasting approximately 1.5hr), 3 visits to the Thompson Center, and an optional 2 visits to the Thompson Center (lasting

approximately 2hrs). The child group will not have the visit to the Brain Imaging Center.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

This study will be double-blinded for the purposes of removing any bias that could be introduced if either the researchers or the study participants are aware of which drug they are taking at a given time. Blinding of the drugs will be conducted by the University Hospital's Investigational Pharmacy. In the case of emergency, the PI and research staff running study sessions will have access to unblinding information in the form of a sealed envelope.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Routine care for this population will not be affected by this study. Participants will be able to continue routine care, including behavioral therapy or other medications. Potential participants taking medications that are exclusionary for this study will not be enrolled.

e. Justification for inclusion of a placebo or non-treatment group.

A placebo arm of this study will allow for statistical comparisons between behavioral performance while participants are taking placebo and propranolol

f. Definition of treatment failure or participant removal criteria.

As this is an initial trial exploring the effects of propranolol on social and language abilities, there are no behavioral endpoints that we would consider treatment failure. However, for the safety of the participants, if at any measurement taken, a participant's heart rate or blood pressure are very low or if the participant is experiencing an adverse reaction to the drug the PI will be notified and will examine or speak with the participant. At that point, if the PI determines it is necessary, the participant will be instructed to discontinue taking the drug and will be removed from the study.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

When the study ends or if a participant's participation ends prematurely, the participants will no longer take propranolol or placebo capsules. Participants will continue with their routine care as they would have done throughout the study.

5. Inclusion/Exclusion Criteria

Participants

Youth: *Inclusion:*
Autism
IQ >= 85
Age 15-24yrs
Native English speaker
General Exclusion:

Alpha 2 agonists
Non-autism LD (ADHD, dyslexia, etc)
Other major psych diagnosis
Other neuro diagnosis
Major head trauma
Reaction to adhesives
Drug Exclusions:
Diabetes
Reactive airway disease
Thyroid disease
Bradyarrhythmias
Unexplained syncope
Pregnancy
Possible interacting drugs
Underweight
Imaging Exclusions:
Metallic implants
Metal foreign body exposure
Pacemakers
Claustrophobia
Any other MRI exposure risk
Pregnancy

Children:
Inclusion:
Autism
Age 7-14yrs
Native English speaker
General Exclusion:
Alpha 2 agonists
Other major psych diagnosis
Other neuro diagnosis
Major head trauma
Reaction to adhesives
Drug Exclusions:
Diabetes
Reactive airway disease
Thyroid disease
Bradyarrhythmias
Unexplained syncope
Possible interacting drugs
Underweight (<20kg)

Parent/caregiver

Inclusion: >=18yo, native English speaker
Exclusion: None

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Propranolol is a beta-adrenergic antagonist that dampens the stress response system. We predict that propranolol's effects on stress and anxiety will positively impact social

and language abilities in individuals with ASD. The dose (starting with 40 mg and titrating up to 100 mg) has been previously used in neuropsychiatric populations (15) and is within the dosage recommended by the FDA for hypertension.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Previous studies from our laboratory indicate a potential effect of propranolol on social and language abilities in adults and adolescents with ASD. Thus, this trial investigation will explore the effects of serial doses of propranolol in the same population. Participants taking propranolol in this study may be at risk for the side effects described below. Measures to maintain the safety of study participants will be further discussed below. Subjects will be encouraged to discuss these with the PI (David Q. Beversdorf, MD) and/or their own doctor. Subjects will also be told that there may be other side effects that we cannot predict.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

NA

7. Study Statistics

a. Primary outcome variable.

We are primarily exploring the effects of propranolol on social abilities, as assessed via the GOSM.

b. Secondary outcome variables.

Our secondary outcome variables include, effects on anxiety (assessed via the SCAS, and salivary cortisol), language abilities (assessed via anagrams and semantic fluency tasks), adaptive/global functioning (assessed via the Vineland), and change in clinical impression/impact of ASD symptoms (assessed via CGIC, CGIS, SRS, ABC, and AIM). Effects of propranolol on gastrointestinal functioning, as measured by the R4PDQ-child/R4DQA and the GSI will be assessed to obtain pilot data. Furthermore, effects of propranolol on bonding with a pet in the home will be assessed.

c. Statistical plan including sample size justification and interim data analysis.

The analysis for the primary outcome (GSOM) will be a two-factor ANOVA with repeated measures on one factor (Time) and so this is the model we base our sample size estimates on. Sample size estimation for a repeated measures model is complex and requires considerable prior information to be well informed. Not only is the expected configuration of means needed but also information on an appropriate covariance structure for the ANOVA residuals. For purposes of sample size calculations, we assumed a first-order autoregressive (AR) model for the residuals with $\rho = 0.20$. Perhaps because the time between pre- and post-propranolol measurements was very short in the pilot study the correlation was 0.74, and so the assumption of an AR process with $\rho = 0.20$ seems to be a reasonably pessimistic assumption for sample size purposes. We further assume that in the control group

mean GSOM will be stable over the 12 weeks of the study and in the propranolol group the mean improvement in GSOM score at 6 and 12 weeks will be one-half and one-standard deviation above baseline. In our pilot work we saw about 0.375 of a standard deviation improvement on the GSOM with only a single dose so we feel these are both meaningful and plausible expectations for change. Thus when testing at the 0.05 level of significance, a sample size of 40 subjects per group (pooled across Aim 1a and b to maximize the power for the main effect of propranolol on GSOM in this parallel design study) will provide better than 80% power to detect a statistically significant Time by Group interaction and similar power for the follow-up within- and between-group pairwise comparisons. Prior experience with ASD subjects leads us to expect a high level of motivation and compliance, but to protect against potential drop out will recruit 48 subjects per group, i.e. approximately 20% loss to follow-up. The sampling plan will be stratified to provide balanced sample to within each age group, with half of the sample representing adults and adolescents and half younger ASD subjects.

The imaging data acquired will be analyzed using Statistical Parametric Mapping (SPM) and FMRIB Software Libraries (FSL) (FMRIB, UK), adjusted for acquisition delay, corrected for motion artifacts, co-registered to the mean image and registered to the Montreal Neurological Institute (MNI) template and smoothed with a Gaussian spatial smoothing function (with a FWHM of 5 mm). Specially designed processing pipelines will be used to account for subject motion-related error during the assessment of resting state functional connectivity. Group analyses will be performed for both the task based activation studies and functional connectivity data and the activation maps will be superimposed on the standard template.

Functional connectivity will be determined using average time-courses of all activated voxels in the regions-of-interest (ROI) and the linear associations of the temporal activation patterns in each ROI pair. The four a priori regions of interest for the word fluency task are the right and left inferior frontal, left parietal and left middle temporal areas. Subsequently, Fisher's z transformations will be applied to assess statistical significance in the comparison of the observed correlations. Mean connectivity across all ROI pairs activated with the language tasks will be the measure utilized to determine relationship to response with propranolol. Fractional anisotropy, and radial and axial mean diffusivity will be calculated from the DTI session to establish white matter integrity and how it relates to response to propranolol.

For PLR, the pupil size will be automatically computed using custom software from saved image stacks to construct the pupillogram. The following basic PLR parameters will be recorded for each measurement: initial pupil diameter (D_0), maximal constriction diameter (D_m), relative constriction (A), PLR latency (t_L), constriction time (t_C), recovery time (t_R), constriction velocity and recovery velocity. The mean value of each PLR parameter will be calculated at all stimulus conditions, and entered into the regression analysis. Participants with uncorrectable visual acuity issues will be excluded from this aspect of the study. Initial pupil diameter, the measure most closely related to sympathetic and parasympathetic balance, and PLR latency, the measure most specific to autism, will be the primary measures of interest.

For skin conductance, heart-rate variability, heart rate, and blood pressure, regression will be used to determine the relationship between performance on the GSOM and autonomic nervous system functioning.

d. Early stopping rules.

As this is an initial trial exploring the effects of propranolol on social and language abilities, there are no behavioral endpoints that we could consider treatment success or failure prior to the completion of the study, thus we would not stop the study based on early evidence of treatment efficacy or futility. If safety becomes a concern due to side effects associated with propranolol, the PI (in consultation with the HS IRB) may decide to stop the study early. However, this is not expected to occur given the well-established minimal side effects known to be associated with this drug.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The medical risks participants may encounter are those associated with taking the drugs used in this study and an MRI scan.

Below are the descriptions and side effects associated with each drug:

Propranolol [pro-pran'-o-lol] is commonly used to decrease high blood pressure. This drug can cause problems for persons with depression, diabetes, thyroid disease, very slow heart rates, very low blood pressure, fluid in the lungs from heart failure, and asthma. The side effects related to this drug are given below. These symptoms are most present within 5 hours of the drug administration. None of these symptoms will be present once the single dose is washed out of the system, which can take up to 24 hours.

Side Effect	**Frequency**	**Severity**
Bradycardia (abnormally slow heart action)	Common	Mild
Fatigue (extreme tiredness)	Common	Mild
Dizziness	Common	Mild
Hypotension (abnormally low blood pressure)	Common	Moderate
Light headedness	Occasional	Mild
Constipation	Uncommon	Mild
Paresthesia (abnormal sensation, typically tingling or pricking) of hands	Rare	Mild
Vivid dreams	Rare	Mild
Dry eyes	Rare	Mild
Urticaria (hives)	Rare	Mild
Diarrhea	Rare	Mild
Abdominal cramping	Rare	Mild
Nausea	Rare	Mild
Epigastric distress (Upper abdominal pain)	Rare	Mild
Impotence (inability to achieve or maintain an erection)	Rare	Mild
Nightmares	Rare	Mild
Depression	Rare	Moderate
Lassitude (lack of energy)	Rare	Moderate
Weakness	Rare	Moderate
Visual disturbances	Rare	Moderate
Hallucinations (experience of something that is not actually present)	Rare	Moderate

Disorientation (mental confusion about time, place or identity)	Rare	Moderate
Emotional lability (excessive emotional reactivity and frequent mood changes)	Rare	Moderate
Slightly clouded sensorium (inability to think clearly or concentrate)	Rare	Moderate
Decreased performance on neuropsychometrics (tests to assess psychological functioning)	Rare	Moderate
Peyronie's disease (scar tissue inside the penis causing curved, painful erections)	Rare	Moderate
Allergy	Rare	Serious
Catatonia (inability to move normally)	Rare	Serious
Intensification of AV block (Worsening of a type of heart block)	Rare	Serious
Arterial insufficiency (slowing or stopping of blood flow through arteries (blood vessels))	Rare	Serious
Alopecia (sudden hair loss with one or more circular patches)	Very rare	Mild
Exfoliative dermatitis (reddening and scaling of skin)	Very rare	Moderate
Psoriasisform rashes (plaque-like rashes)	Very rare	Moderate
Vomiting	Very rare	Moderate
Amnesia (partial or total loss of memory)	Very rare	Serious
Erythema multiforme (bulls-eye-shaped lesions on skin)	Very rare	Serious
SLE-like reaction (a disorder where the body mistakenly attacks healthy tissues in the body)	Very rare	Serious
Congestive heart failure (inefficient pumping of the heart)	Very Rare	Severe
Stevens Johnson Syndrome (disorder of skin and mucous membranes)	Extremely Rare	Serious
Agranulocytosis (deficiency of granulocytes in blood; increased vulnerability to infection)	Extremely rare	Serious
Nonthrombocytopenic purpura (spontaneous bruising without decrease in levels of blood cells that prevent bleeding)	Extremely rare	Serious
Thrombocytopenic purpura (low levels of blood cells that prevent bleeding)	Extremely rare	Serious
Toxic Epidermal Necrolysis (skin condition)	Extremely Rare	Life threatening
Mesenteric arterial thrombosis (injury of the small intestine due to lack of blood supply)	Extremely rare	Life threatening
Ischemic colitis (injury of the large intestine due to lack of blood supply)	Extremely rare	Life threatening

Placebo [pla-see'-bo] : Also known as a "sugar pill." The placebo capsules contain lactose, necessitating the exclusion of any potential participants who have extreme lactose allergies.

Below are the risks associated with MRI scan:

Unlike x-rays or CT-scans, MRI does not involve any ionizing radiation. However, the tasks may cause some fatigue similar to reading a book or doing homework. Participants may also experience discomfort from lying still.

The safety of MRI has been evaluated over the past 20 years and no short-term effects have been observed. However, the long-term effects of MRI on the body are not fully known. Some individuals with claustrophobia (fear of closed or confining spaces) may find the MRI equipment too confining

The MRI scanner makes sounds variously described as "thumping", "pounding", "banging", "chirping" and "buzzing"; these sounds can be loud. Participants will be required to wear protective earplugs and headphones during scanning to reduce the noise.

The MR imaging in this study is being performed at a research dedicated scanner and the personnel performing the imaging are not Licensed or Trained Diagnosticians or Clinicians. The testing performed in this project is not intended to find abnormalities, and the images or data collected do not comprise a diagnostic or clinical study. The Investigators and the University of Missouri are not responsible for failing to find abnormalities. However, on occasion the Investigators may perceive possible abnormalities. When this occurs, the Brain Imaging Center will consult with a Specialist. If the Specialist determines that additional inquiry is warranted, a staff person from the Brain Imaging Center will contact the participant. In such case, participants are advised to consult with a Licensed Physician to determine whether further examination or treatment would be prudent. The Investigators, Specialist, Brain Imaging Center and the University of Missouri are not responsible for any decision made with regard to examination or treatment. Because the images collected for this research project do not comprise a diagnostic or clinical study, the images will not be made available for diagnostic or clinical purposes.

No short-term effects to a fetus from this procedure have been observed. However, the long-term effects of MRI on the fetus are not fully known. Therefore, participants will be screened for pregnancy before imaging.

Participants cannot have an MRI if they have any metal in or near the brain such as an aneurysm clip or a cochlear implant, or other contra-indicated implants such as a pacemaker for the heart or metal-containing prostheses (like a 'stent' or a heart valve, hearing aids, etc.). For example, welders and metal workers may be at risk for a MRI because they may have gotten small metal fragments in their eyes. This would be dangerous inside the magnet. There are also possible risks for participants if metal objects are drawn to the magnet while a participant is within or near the bore. Accordingly, participants will be asked to leave all jewelry and metal objects outside of the testing area. No loose metal objects will be allowed near the magnet. Many items of clothing contain metal hooks, wires, etc. and some of these cannot be worn in the MRI device. Clean garments will be provided in this case.

There may be some unanticipated risks or side effects involved with participation in this research study. Since 1981, there is no evidence that high magnetic fields endanger health on a short or long term basis. Therefore, the potential health risk is thought to be minimal, if any.

Other potential risks:

Participants may also encounter minor risks associated with the adhesives used to collect psychophysiological data via electrocardiogram. Participants may develop a small rash where the sensors attach to their chest. If this occurs, the rash normally subsides shortly after the study visit. Participants will be asked to notify a member of the study staff or the PI if the rash persists.

There are also psychological risks of boredom and probing for personal and/or sensitive information in the tasks and questionnaires the participants will complete as part of this study.

There is the potential risk of a loss of privacy, in which information related to participants' autism diagnosis and their answers to the tasks and questionnaires being administered will be obtained.

b. Steps taken to minimize the risks.

Strict adherence to the exclusionary criteria of this study will minimize the chance of enrolling participants who might be put at risk by taking propranolol. Before enrollment in the study, the PI (a licensed physician) will meet in person with prospective participants to evaluate their ability to safely take part in this study. Upon enrollment in the study, participants will be given a business card containing contact information for lead study staff and the PI in case of questions and/or emergency.

Given the chance of unforeseen side effects associated with the drug in participants who met criteria for participating in the study, regular monitoring of heart rate and blood pressure will occur throughout the study. During titration of the drug from the initial to the full dose, heart rate and blood pressure measurements will be taken via wrist cuff or pediatric arm cuff by the participant or parent/caregiver within 48 hours after each change in drug dosage. A member of the study staff will call the family to obtain these results. If on any measurement the heart rate is below 55 (60 for children) or systolic blood pressure is below 90 (80 for children), the PI will be immediately notified, and he will call and/or examine the participant to assess his or her condition. At this point, the PI may make the decision to have the participant drop back to the previous dosage level or to withdraw the participant from the study for safety reasons. A member of the study staff will also call the participant to confirm no further problems before each increase in dosage. During this call, the SMURF will be performed, and blood pressure and heartrate will be taken. Abnormal ratings on the SMURF or too low blood pressure or heartrate will result in notification of the PI who may then call or examine the participant to further assess his/her condition.

At each study visit taking place at the Thompson Center for Autism & Neurodevelopmental Disorders, a member of the study staff will first confirm that there are no changes in the participant's physical condition since he/she met with the PI in person. A medical and pharmaceutical history will also be obtained to ensure the participant's condition has not changed in a way that would increase the risk of taking propranolol. Any new symptoms or diagnoses will be reported to the PI, who will follow-up with the participant if necessary. Blood pressure and heart rate will also be measured at each of these study visits.

To minimize risk associated with MRI, all participants will be screened to ensure they do not meet any exclusionary conditions, and scrubs and a metal detecting wand will be available to prevent metal from being introduced into the scanning room.

Participants with previously documented history of rash from adhesives will be excluded from the study. This will minimize the risks associated with the psychophysiological measurements taken during the study sessions.

To minimize the risk of boredom, participants will be given the opportunity to take breaks and ask any questions they have.

To minimize the risk of probing for personal and/or sensitive information, testing will take place in a private room at the Thompson Center. If participants have difficulty with disclosure of information on some surveys, they will be reminded that their answers will be kept secure and are confidential.

To minimize the risk of loss of privacy, the data will be coded, password-protected, and stored separately from the consent and screening forms in a locked filing cabinet. However, in the unfortunate event that a loss of privacy occurs, it is possible that information related to a participant's autism diagnosis and performance on the tests being administered will be obtained.

c. **Risks specific to genetic testing**

When disease, including autism, is tied to genetic abnormalities, this can create problems for families with regards to obtaining insurance coverage. To keep this from happening, the results of the genetic analysis through buccal swab will not be given to anyone outside of the research team. Also, a Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate based on genetic information.

However, this Federal law does not protect participants or their families against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Also, GINA does not prohibit discrimination of individuals with a genetic disorder that has been diagnosed. However, in order to do everything possible to prevent genetic discrimination, the results of the DNA test will NOT be given to anyone outside the study staff. This means that it will not be made available to participants or their family members, their private physician, employer, insurance company or any other party as allowed by law.

d. Plan for reporting unanticipated problems or study deviations.

Any unanticipated problems or study deviations will be immediately reported to the PI and HS IRB via an Event Report for further investigation.

The Research Monitor, John Hall, MD, is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can

assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

e. Legal risks such as the risks that would be associated with breach of confidentiality.

The risk of loss of privacy is minimized as the data will be coded, password-protected, and stored separately from the consent and screening forms in a locked filing cabinet. However, in the unfortunate event that a loss of privacy occurs, it is possible that information related to a participant's autism diagnosis and performance on the tests being administered will be obtained.

f. Financial risks to the participants.

There are no expected financial risks associated with this study. However, in the event of an injury associated with the study, participants may be responsible for paying for medical expenses associated with that injury. This determination would be made in consultation with the University of Missouri Risk Management Officer.

9. Benefits

a. Description of the probable benefits for the participant and for society.

All participants will be receiving medical surveillance beyond the standard of care with frequent call checks for symptoms and blood pressure checks throughout participation. Participants will also be receiving behavioral and psychological assessments beyond general standard of care.

Also, there is evidence that serial doses of propranolol will be beneficial for people with autism in the realm of social interaction and anxiety (13, 14, 16). Therefore, participants taking propranolol (including those one the placebo arm who choose to take part in the open label extension) have the potential for direct benefit. Beyond that, if propranolol is shown to improve ASD-related symptoms, with the greatest benefits being for those with the greatest dysregulation in autonomic activity, propranolol may be used to treat others with similar conditions.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be compensated $25.00 for each completed study visit they complete, for a maximum total of $125.00 if they complete all five study visits. The final payment of $25.00 will be authorized once the participant returns the heart rate and blood pressure cuff to a member of the study staff. Participants in youth age group can also receive $50.00 for completing the fMRI session. If a participant lives more than 50 miles from the Thompson Center in for Autism & Neurodevelopmental Disorders in Columbia, MO, the family will be eligible for a flat rate of $75 per visit to offset of costs of travel to the Thompson Center. Payments will be made in cash at the end of each study visit.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All test procedures, materials, and medications are paid for by the study. The only expected direct cost to the participants will be transportation to and from the Thompson Center for Autism & Neurodevelopmental Disorders. Participants may also be responsible for costs incurred in the research for ancillary resources, such as medical treatment, psychological counseling, emergency services or concomitant medications.

12. References

a. List of references supporting research question.

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