**ANCILLARY REVIEWS**

**DO NOT DELETE. Submit the completed checklist below with your protocol.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Which ancillary reviews do I need and when do I need them?**  Refer to [HRP-309](https://drive.google.com/file/d/0B7644h9N2vLcMTl0ZE9yQkhLd3c/view) for more information about these ancillary reviews. | | | |
| **Select yes or no** | **Does your study…** | *If yes…* | ***Impact on IRB Review*** |
| **Yes**  **No** | Include Gillette resources, staff or locations | *Gillette Scientific review and Gillette Research Administration approval is required. Contact:*  [*research@gillettechildrens.com*](mailto:research@gillettechildrens.com) | **Required prior to IRB submission** |
| **Yes**  **No** | Involve Epic, or Fairview patients, staff, locations, or resources? | *The Fairview ancillary review will be assigned to your study by IRB staff*  *Contact:* [*ancillaryreview@Fairview.org*](mailto:ancillaryreview@Fairview.org) | **Approval must be received prior to IRB committee/ designated review.**  **Consider seeking approval prior to IRB submission.** |
| **Yes**  **No** | Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection? | *STOP – Complete* [*the Medical Template Protocol (HRP-590)*](https://drive.google.com/open?id=0Bw3yHuGQzD8CaExVUkZEWjBVSU0)  *The regulatory ancillary review will be assigned to your study by IRB staff*  *Contact:* [*medreg@umn.edu*](mailto:medreg@umn.edu)  *See* [*https://policy.umn.edu/research/indide*](https://policy.umn.edu/research/indide) |
|  | Require Scientific Review? Not sure? See guidance in the [Investigator Manual (HRP-103)](https://drive.google.com/uc?export=download&id=0B7644h9N2vLcOWtzU2FmSU5oS0U). | *ONLY REQUIRED BIOMEDICAL RESEARCH REVIEWED BY FULL COMMITTEE* |
| **Yes**  **No** | Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco? | *Complete the* [*CPRC application process*](https://www.cancer.umn.edu/for-researchers/investigator-resources/cancer-protocol-review-committee)*.*  *Contact:* [*ccprc@umn.edu*](mailto:ccprc@umn.edu) |
| **Yes**  **No** | Include the use of radiation?  (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy) | *Complete the* [*AURPC Human Use Application*](https://radsafety.umn.edu/human-use-application-and-resources) *and follow instructions on the form for submission to the AURPC committee.*  *Contact:* [*barmstro@umn.edu*](mailto:barmstro@umn.edu) | **Approval from these committees must be received prior to IRB approval;**  **These groups each have their own application process.** |
| **Yes**  **No** | Use the Center for Magnetic Resonance Research (CMRR) or MR at Masonic Institute for the Developing Brain (MIDB) as a study location? | *Complete the* [*CMRR pre-IRB ancillary review*](https://www.cmrr.umn.edu/preirb/user/user.php)  *Contact:* [*ande2445@umn.edu*](mailto:ande2445@umn.edu) |
| **Yes**  **No** | Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents? | *STOP – Complete* [*the Medical Template Protocol (HRP-590)*](https://drive.google.com/open?id=0Bw3yHuGQzD8CaExVUkZEWjBVSU0) |
| **Yes**  **No** | Include the use of human fetal tissue, human embryos, or embryonic stem cells? | *STOP – Complete* [*the Medical Template Protocol (HRP-590)*](https://drive.google.com/open?id=0Bw3yHuGQzD8CaExVUkZEWjBVSU0) |
| **Yes**  **No** | Include use of PHI (protected health information)?  OR  Include international collaborators that involves the collection, transmission, and storage of health data? | *If yes, HIPCO will conduct a review of this protocol.*  *Contact:* [*privacy@umn.edu*](mailto:privacy@umn.edu) |
| **Yes**  **No** | Include the use of a controlled substance? | *If yes, University Health and Safety Compliance for controlled substances will review the protocol.*  *Contact:* [*cshelp@umn.edu*](mailto:ancillaryreview@Fairview.org) | **Approval must be received prior to IRB approval.**  **These groups do not have a separate application process but additional information from the study team may be required.** |
| **Yes**  **No** | Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB? | *The CTSI monitoring ancillary review will be assigned to your study by IRB staff.*  *Please note eligibility criteria* [*here*](https://ctsi.umn.edu/services/regulatory/clinical-trial-monitoring)*.*  *Contact:* [*fencl003@umn.edu*](mailto:fencl003@umn.edu) |
| **Yes**  **No** | Use data from CTSI Best Practices Integrated Informatics Core (BPIC)  Formerly the AHC Information Exchange (AHC-IE)? | *The Information Exchange ancillary review will be assigned to your study by IRB staff*  *Contact:* [*bpic@umn.edu*](mailto:ics@umn.edu) |
| **Yes**  **No** | Use the Biorepository and Laboratory Services to collect tissue for research? | *STOP – Complete* [*the Medical Template Protocol (HRP-590)*](https://drive.google.com/open?id=0Bw3yHuGQzD8CaExVUkZEWjBVSU0)  *The BLS ancillary review will be assigned to your study by IRB staff.*  *Contact:* [*bionet@umn.edu*](mailto:bionet@umn.edu) |
| **Yes**  **No** | Have a PI or study team member with a conflict of interest? | *The CoI ancillary review will be assigned to your study by IRB staff*  *Contact:* [*becca002@umn.edu*](mailto:becca002@umn.edu) |
| **Yes**  **No** | Need to be registered on clinicaltrials.gov? | *If you select “No” in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff*  *Contact:* [*fencl003@umn.edu*](mailto:fencl003@umn.edu) |
| **Yes**  **No** | Require registration in OnCore? | *If you select “No” or “I Don’t Know” in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff*  *Contact:* [*oncore@umn.edu*](mailto:oncore@umn.edu) | **Does not affect IRB approval.** |
| **Yes**  **No** | Does your research include collaborations with Tribal partners, Tribal communities, Tribal-serving institutions, or include focused recruitment of Indigenous Peoples? | *See* [*University of Minnesota Guidelines for Indigenous Research*](https://libguides.umn.edu/ResearchWithIndigenousPartners)*.* | **May not impact IRB review/approval.** |
| **Yes**  **No** | Do you propose to use eConsent via REDCap? | *REDCap Ancillary Review will be assigned to confirm IRB approval status prior to moving your eConsent to production in* [*REDCap*](https://ctsi.umn.edu/tools/redcap)*.* | **Does not affect IRB approval.** |
| **Yes**  **No** | Propose to use [Community- University Health Care Center](https://www.google.com/url?client=internal-element-cse&cx=002834015805923805805:c-0k--9bdkk&q=https://cuhcc.umn.edu/&sa=U&ved=2ahUKEwistMi00onuAhWVGFkFHUbnAncQFjABegQIAhAB&usg=AOvVaw2R6-oZwyd0n55FZTLJdCRi) (CUHCC) resources or include access to patients or their data? | *Contact* [*hlogren@uumn.edu*](mailto:hlogren@uumn.edu) |

**PROTOCOL COVER PAGE**

|  |  |
| --- | --- |
| **Protocol Title** | Causal inference and impact of prior beliefs on perception |
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| Department: Neuroscience |
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| **Scientific Assessment** | Nationally-based, federal funding organizations |
| **Version Number/Date:** | Version 4.0. October 15th 2024 |

**REVISION HISTORY**

|  |  |  |  |
| --- | --- | --- | --- |
| **Revision #** | **Version Date** | **Summary of Changes** | **Consent Change?** |
| V2 | 08/17/2024 | Revisions from pre-review | No. |
| V3 | 08/31/2024 | Clarifications from IBR review | Yes. (funding). |
| V4 | 10/15/2024 | Add investigators, increase compensation (20/hour to 30/hour), update flyer and recruitment avenues, additional study location (CATSS Lab), increase age range from a maximum age of 28 to 36. | Yes. (compensation) |
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**ABBREVIATIONS/DEFINITIONS**

1. ASD: Autism Spectrum Disorder
2. EEG: Electroencephalography

# **Objectives**

## **Purpose:**

The purpose of this research is to investigate how neurotypical individuals and those on the Autism Spectrum Disorder (ASD) perform causal inference; attribute hidden causes to observed sensory signals. A key step in performing causal inference is the updating of expectations, or Bayesian priors. Thus, we will also examine how priors are updated as a function of statistical regularities embedded within the experimental stimuli (simple tones and flashes of gratings).

# **Background:**

## **Significance of Research Question/Purpose:**

The fact that individuals within the autism spectrum show anomalies in multisensory behavior is so well-established that it is now part of the diagnostic criteria for the conditions. However, the root cause for this anomaly is not known. Dr. Noel (PI of protocol) recently showed that differences in multisensory behavior in ASD is not due to a deficit in multisensory integration - as it had been long assumed but never rigorously tested under a computational framework - but because of an anomaly in causal inference; deducing whether (e.g., audio and visual) cues likely have a common cause and thus should be integrated, or deducing that they have separate causes and thus should remain segregated (Noel et al., 2022, *eLife*). Causal inference is a canonical computation impact a wide range of behaviors, and thus this behavioral anomaly in causal inference may explain the heterogenous and trans-domain phenotypes observed in ASD. In this work I propose to (1) examine the electroencephalography (EEG) correlates of causal inference and prior updating in ASD and neurotypical participants, and (2) use this data to develop a circuit-based model of causal inference.

## **Preliminary Data:**

## That in Noel et al., 2022, eLife. No preliminary data from the Noel Lab on this exact protocol.

## **Existing Literature:**

Causal inference is a canonical computation (Kording et al., 2007; Noppeney et al., 2021) underpinning a host of behaviors, including but not limited to audio-visual localization, speech intelligibility, weight perception, spatial navigation, bodily self-consciousness, and heading estimation, among other. Work from cognitive neuroscience performing functional neuroimaging or EEG has demonstrated that causal inference involves a cascade of processing through the neuraxis. Namely, early sensory areas respond to their preferred sensory modality (e.g., V1 to visual stimuli, and A1 to auditory stimuli) regardless of the causal structure of the world (e.g., whether they index a common source or not). Higher-order parietal “associative” areas always integrate cues, while fronto-parietal networks encoding prior-beliefs flexibly adapt their responses according to the inferred causal structure.   
  
I have recently demonstrated that individuals within the Autism Spectrum show an anomaly in casual inference, but no neuroimaging or EEG was conducted, and thus we do not know where in this hierarchical process the anomaly may reside. Here I propose to do the EEG work. More precise hypothesis as to function have been published in Noel & Angelaki (2022, Annual Rev. in Psychol.) and Noel & Angelaki (2023, Trends in Cognitive Science).

# **Study Endpoints/Events/Outcomes**

## **Primary Endpoint/Event/Outcome:**

The primary objective of this project is to detail the EEG correlates of performing causal inference in neurotypical participants and those on the Autism Spectrum. Behaviorally, based on prior work we hypothesize that individuals with ASD will update their priors more slowly, and have an inflexible causal inference, vis-à-vis neurotypical subjects. In terms of EEG there is no clear hypothesis, as this work has not been conducted previously. This part of the study can be considered hypothesis-generating. Participants will see a brief stream (1 second) of audio clicks (single tone) and visual flashes (gratings). On some trials, the cross-correlation between these streams will be high near zero ms, indicating a likely common cause. On other trials, the cross-correlation between these streams will be high far from zero ms, indicating that these streams come from different causes. Participants will perform a two-alternative forced-choice task, indicating “common” or “different” cause. In separate sessions, instead of being asked about common cause of streams of auditory and visual events, they will be asked about their temporal order (i.e., did auditory or visual come first?) or spatial location (to the left or right of fixation). Lastly, in a last session, they will observe the same visual stimuli now via virtual reality googles and they will also be asked to localize where this stimulus is in space.

## **Secondary Endpoint(s)/Event(s)/Outcome(s):**

The secondary objective of this project is to understand the updating of expectations in neurotypical participants and those on the Autism Spectrum. Thus, the streams of audio-visual stimuli will have a statistical regularity across trials, wherein blocks of stimuli will be presented with high-likelihood of common cause, and then switch to blocks of stimuli with low likelihood of common cause. The switching between clocks will be unsignaled to participants, who will have to learn about this statistical regularities.

# **Study Intervention(s)/Interaction(s):**

## **Description:**

Participants will be comfortably seated facing a computer monitor or a cloth onto which visual stimuli will be projected via a ceiling-mounted projector. Lastly, in one of the sessions, we may present visual stimuli in virtual reality googles. Behind the monitor or acoustically-transparent cloth will be a single speaker or a series of speakers. Participants will be outfitted with an EEG cap. They will be presented with streams of audio tones and visual flashed within 1 second. Each stream will be composed of 5 tones/flashes. At the end of each trial the participant will report via button-press whether the stream of stimuli pertained to a “common” or “different” cause. The association between button press and response will be varied across participants. Participants will be asked to fixate a cross to keep their eyes from moving. Participants will be given breaks every 10-12 minutes and will perform the experiment for a maximum of 90 minutes. Including the time for EEG setup and cleaning, each session will last a maximum of 2 hours. The experimental detail will follow that from Parise & Ernst (2016, *Nature Communications*) and Pesnot-Lerousseau et al. (2022, *Nature Communications*). Participants may partake in a total of 4 sessions (on different days).

# **Procedures Involved**

## **Study Design:**

The location of this study will be: (1) Nils Hasselmo Hall, room 2-128 (laboratory space of the PI, Dr. Jean-Paul Noel) and/or (2) dedicated EEG space at the Masonic Institute for the Developing Brain (MIDB; 2025 E River Pkwy, Minneapolis, MN 55414), and/or (3) dedicated EEG and experimental space within the CATSS Lab (Center for Applied & Translational Sensory Science; S39 Elliott Hall, 75 East River Parkway, Minneapolis, MN 55455).   
  
The experimental design follows Parise & Ernst (2016, *Nature Communications*) and Pesnot-Lerousseau et al. (2022, *Nature Communications*). Namely, during the experiment, participants will sit (or stand, according to their preference) before a visual display monitor, a cloth onto which visual stimuli are projected via a projector, and/or virtual reality googles. Behind the monitor/cloth will be a speaker or a series of speakers. Unless instructed otherwise, participants will maintain fixation on a small dot or cross at the center of the display. On each trial, 1 second in duration, participants will be presented with a sequence of 5 auditory and visual impulses (that is, a sequence of clicks and flashes) with random temporal structures. Participants will report whether the auditory and visual streams had a common cause or not, via button-press. Or a separate session they will be asked if the visual or auditory stimuli appeared first, and on yet another session they will be asked to localize these stimuli (to the left or right of a fixation point). The inter-trial interval will be 1 second, and I estimate collecting ~ 1500-2000 responses per participant in 90 minutes (i.e., a response every 3 seconds). Participants will be given breaks every 10-12 minutes, and/or as requested by the participant.

Visual stimuli will consist of a white disk (rad=6.5°) or grayscale gratings or same size. The duration of each visual flash will be 10ms. In some blocks, the contrast of the visual stimuli may be reduced (e.g., 10% contrast) in order to further incentivize participants to use a-prior beliefs. Auditory stimuli will be presented by means of a loudspeaker hidden behind the computer screen. Each click will last 10 ms and be a pure tone (e.g., 1000Hz). The baseline intensity of auditory clicks will be 60dB.   
  
To examine how prior-beliefs (i.e., expectations) influence the judgment of common cause, the statistics of the experiment will be manipulated as to have blocks with high- and low-likelihood of common cause. Block lengths will be chosen at random, with a minimum trial length of 10 trials, and a maximum of 60 trials (exponential distributed between the minimum and maximum, maintaining a continuous hazard rate). The change of blocks will be unsignaled to participants. Further, within each of these blocks, the contrast of visual and/or intensity of auditory stimuli may be reduced.

In order to localize EEG electrodes of interests, we may start or finish the session by passively presenting auditory, visual, or audio-visual stimuli without requiring the participant to make a judgment of any kind. This will allow isolating the impact of the stimuli, when no movement or judgment is made. We may also record 10 minutes of resting state EEG, where participants are asked to maintain their eyes either open (5 minutes) or closed (5 minutes), but no stimuli is presented.  
  
The experiment will be controlled by custom-built software based on the Psychtoolbox (MATLAB, MathWorks) or Unity, and timing of all experimental stimuli and synchronization with EEG will be controlled via external micro-controllers (Arduino).

## **Study Procedures:**

Upon arrival, participants will be informed of the task: maintain fixation and press a computer button depending on whether auditory and visual streams come from a common or different causes/ auditory or visual stimuli appeared first / auditory or visual stimuli were to the left or right of a fixation cross. They will be informed of the process of outfitting them with an EEG cap. Upon informed consent, the experiment will begin.

Safety Screening

As there are no safety concerns with this project, no safety screening will be conducted.

Post-Study Procedures

Participants will be asked for verbal consent to contact them regarding opportunities to participate in future studies. They will also indicate their willingness (and potentially their contact information) in a questionnaire.

## **Study Duration:**

We will recruit up to 270 local participants. This number of participants is in line with my prior work (hundreds in e.g., Noel et al., 2022, eLife), and assures robust statistical power of any conclusions we may draw. Further, it allow for putatively splitting the experimental groups by sex (in case there is a difference there worth exploring and reporting). The sex ratio of males to females in the US is 3:1. Approximately half of these participants will be individuals previously diagnosed as within the Autism spectrum by a research reliable clinician. We expect recruiting this number of participants in a maximum of 3 years.

## **Follow-Up:**

Participants who have given verbal consent may be contacted after the initial session to future experiments and/or may be asked for consent to access prior data that may have been collected at UMN as part of prior studies they have consented to. Participants will be recruited for a maximum of 4 sessions (each 2 hours long) and will be compensated with a modest bonus ($60) for participating across all 4 sessions.

# **Storing Data for Future Use**

## **Storage and Access:**

All data will be stored on secure servers at the Noel Lab (requiring password access). Data will be accessible only to lab members.

## **Data:**

Data will include behavioral responses (e.g., a collection of numbers indicating whether the participant reported streams of auditory and/or visual cues as belonging to a common or different causes, or the location/timing of this stimuli), a basic questionnaire recording the participants age, gender, and preferred writing hand, history of diseases, EEG data, and/or eye-tracking data to assure that participants are fixating on the cross as indicated. Any data acquired on paper will immediately be digitized and sent to the secure server at the Noel Lab. Hard copies, if any, will be shredded or stored securely in a locked filling cabinet in a locked office.

## **Release/Sharing:**

Acquired data will not be released to comply with SFARI Base requirements. If other investigators request the data, we will guide them to apply and comply with SFARI Base requirements, where they will be able to access the data. For the de-identification of the data, all information regarding name, location, contact information, and specific dates would be removed. To keep track of participants, a random ID may be used that shall contain no information about the participant. The de-identified data may also be shared with external collaborators outside of the University.

There will be no agreement solicited from participants regarding data release. The information sheet given to them prior to experiment will explain that their de-identified data is likely to be published and may be released via SFARI base (i.e., released to properly vetted researchers).

# **Sharing of Results with Participants**

## **Sharing Results:**

Results will not be shared with participants, other than through published articles. If a participant is curious about the results, we will informally discuss the general objectives of the research with them after the experiment.

# **Study Population**

## **Inclusion Criteria:**

Individuals within the ages of 12-36 years old. We will recruit both individuals within the autism spectrum, as well as age-, sex-, and IQ-matched neurotypical subjects. Given the complexity of the task, we will recruit high-functioning ASD individuals. Pregnant woman are allowed to participate too, without them being the focus of the study. Please see section 9.1. for further information on inclusion of vulnerable populations. Adults (i.e., 18+) will be asked for informed consent, while minors (12-17) will be asked for assent and parental permission.

## **Exclusion Criteria:**

We will exclude participants if they have ever had a seizure or if there is a family history of epilepsy (self-reported by participant or their parent). There is some evidence that seizures could be induced by visual stimuli (Brinciotti et al., 2021), although the nature and frequency of these visual presentations is much different than the one presented here. More importantly, given that we are recording EEG activity and want to make scientific conclusions applicable to the general population, epileptic-like activity would hinder the scientific premise of this project.

## **Screening:**

If a participant provides indication that they do not understand the consent or assent form, have been coerced or compelled to participate, are unable to follow spoken (or written, for adults) instructions in English, are unable to complete the experiment, or do not wish to complete it, the experiment will cease.

# **Vulnerable Populations**

## **Vulnerable Populations:**

|  |  |
| --- | --- |
| Population / Group | Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study. |
| Children | included but not the focus |
| Pregnant women/fetuses/neonates | included but not the focus |
| Prisoners | Excluded. |
| Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders | included but not the focus |
| Non-English speakers | Excluded |
| Those unable to read (illiterate) | included but not the focus |
| Employees of the researcher | included but not the focus |
| Students of the researcher | included but not the focus |
| Undervalued or disenfranchised social group | included but not the focus. |
| Active members of the military (service members), DoD personnel (including civilian employees) | included but not the focus. |
| Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc. | Excluded |
| Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare. | included but not the focus |
| Individual or group with a serious health condition for which there are no satisfactory standard treatments. | included but not the focus |
| Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior). | Excluded |
| Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research. | Excluded. |

## **Additional Safeguards, if any, to ensure inclusion is appropriate:**

Including the PI and future employees of the PI (to be included in the IRB when named) as individuals eligible for participation is important as it enables high-quality, well-trained, and motivated participants. This also limits the number of potential participants that may be recruited without an optimized experiment. It important not to specifically exclude other vulnerable populations indicated in the table above, as it is important to maximize diversity within the participant pool, and is possible, as we will not screen specifically for pregnancy, disenfranchisement, military status, or disadvantage. To ensure that participation is completely voluntary, the voluntary nature of participation will be emphasized throughout the recruitment and study process for all participants. We will make concerted efforts to protect against any potential coercion with respect to internal lab members. Internal recruitment for lab studies will be made via a general announcement during lab meeting. It will be emphasized in this announcement that participation is entirely voluntary and the willingness to participate will not affect any future employment decisions nor any other aspects of research productivity. Potential volunteers will be instructed to approach the experimenter in private to sign up for the study. There is no risk to the fetus or pregnant women. For additional safeguards to pregnant women no inducements, monetary or otherwise, shall be offered to terminate the pregnancy. For individuals within the Autism spectrum, we will equally emphasize that participation is voluntary, and of no clinical or diagnostic value.

Children will be included in this study because Autism is a neurodevelopmental condition and we have previously demonstrated a specific impairment in causal inference in this population. The main interest in this study is in detailing the EEG-correlate of impairments in causal inference, and thus including children within the Autism spectrum is an imperative. In order to safeguard this population, we will:

1. Solicit the permission of one parent or guardian (see Parental Permission Document)
2. Allow for assent monitoring by part of parent or legal guardian,
3. Assent all children with age-appropriate information regarding the participation in the study, and document assent in the consent logs
4. Emphasize the voluntary nature of participation, both to the parent(s) and/or guardian(s),
5. Continuously monitor children during the experiment for wellbeing,
6. Provide information regarding psychological support or counseling if needed during or after the study,
7. Provide an additional educational debriefing following the study to explain what we hope to learn from the current study and how the findings may benefit others,
8. Allow parents and children to reassess their decision to participate at multiple points during the study.

## **If research includes potential for direct benefit to participants, provide rational for any exclusions indicated in the table above:**

Not applicable.

# **Local Number of Participants**

## **Local Number of Participants to be Consented:**

We will recruit up to 270 local participants. In prior work, I have recruited 90 participants for experiments on causal inference. This number of here tripled in case we find sex differences that need to be explored, and because ASD is 3 times more common in male than female. Thus, we may need to recruit up to 270 participants, to assure 90 females (which is the minimum needed based on a power calculation to assure 80% statistical power given the effect sizes we anticipate). Participants are free to stop participation at any time, and we expect that a small fraction of participants may terminate their participation due to boredom.

# **Local Recruitment Methods**

## **Recruitment Process:**

The research team will recruit participants (both neurotypical and individuals with ASD) via flyers and word-of-mouth in the Psychology Department, the Masonic Institute for the Developing Brain, the Pediatrics Department, the Neuroscience Department, and the Institute of Child Development. Participants may also be recruited with aid of other local PIs who may have consented participants to be recruited for further studies. Recruitment flyers will be appropriately placed in the “other research opportunities” of bulletin boards. The recruitment flyers will be viewed by potential prospective participants at their own time, while walking through the University of Minnesota campus. Word-of-mouth recruitment will take place upon the completion of another experimenters study, and thus these participants will have already demonstrated a willingness to participate in research studies, and we will not disrupt clinic visit. Potential participants with ASD will also be recruited through referrals from other researchers at the University of Minnesota and Minneapolis VA Medical Center, as allowed by their IRBs and consent forms; research recruitment registry at the Psychiatry Clinic in the Department of Psychiatry & Behavioral Health, University of Minnesota; reviews of patient rosters by staff of community and mental health agencies; a study-specific webpage (BuildClinical), a website on the University of Minnesota Psychiatry department’s Discovery Partner website; and postings, in person, and telephone announcements made to and through support of local advocacy groups. Lastly, prospective participants may be recruited via SFARI Base and their SPARK directory, if and after approval by this organization.

To solicit control participants, advertisements and postings announcing the study may be placed in local newspapers, related websites (e.g. lab website, research recruitment website), organizational newsletters, and public places (e.g., hospital clinics, foyers and hallways of public and private institutions). Advertisements will announce the study and encourage people to call or email the laboratory to express their interest and leave contact information. Additionally, we will utilize the Psychiatry Research Registry in the Department of Psychiatry and Behavioral Sciences. This registry provides patients the opportunity to indicate interest in being contacted to hear about research studies. Non-Fairview or University of Minnesota patients may also sign a consent to be contacted through the registry. Access to this contact information is co-managed by the Department of Psychiatry Clinical Research Recruitment Specialist and securely stored and accessed by the Data Shelter Manager at BPIC and managed through CTSI. After receiving contact information study staff will telephone the potential control participant , explain the study, and complete the screening interview described above..

Participants may also be recruited from within the laboratory. Participants recruited from within the laboratory will be referred to as “internal volunteers” and may include: graduate students, post-doctoral trainees, undergraduate students (paid RAs or directed research students). It is common practice in the field of visual and auditory perception for researchers to volunteer for their own experiments, particularly for the initial visits, to be sure that all experimental details are correct from the participant’s perspective. Therefore this protocol includes practices for recruiting volunteers from among study personnel. Any internal volunteer who is named as personnel on the protocol will fill out a consent form only once. The voluntary nature of research participation will be emphasized at this time, and these forms will be archived to maintain a complete record of participation for all volunteers.

## **Source of Participants:**

See above.

## **Identification of Potential Participants:**

No private/protected records will be used in recruitment. Participants will self-identify in response to advertisement, flyers, and recruitment from PIs/co-investigators with whom they have participated in studies in the past.

## **Recruitment Materials:**

IRB-approved flyers (see attached) will be used for recruitment. In addition, prospective participants will be directed to lab websites (https://noel-lab.org/participate-in-research/). The website simply replicates the materials on the flyer. Lastly, we may hand-out business cards with lab personnel contact information in case potential participants may be interested in participating.

In addition, here is a sample e-mail that will be used for recruitment: “Volunteers are needed for a study of audio-visual perception. Dr. Jean-Paul Noel is recruiting research participants for an experiment that will involve looking at a computer screen while being presented with auditory and visual stimuli, wearing an water-based EEG cap, and making judgments about what you were shown. The study consists of up to 4 sessions, each session lasting up to 2 hours (including setup and clean-up), and will pay $30 per hour, with an additional $60 bonus if all 4 sessions are completed. Participants must be between the ages of 12 and 35. E-mail liu02936 @umn.edu for more information.”

In addition, here is an example of what would be verbally delivered at internal lab meetings for the purposes of recruitment: "The lab wishes to conduct a new behavioral experiment and is looking for volunteers. The experiment involves hearing auditory tones and looking at visual stimuli and making judgments about those stimuli. Please keep in mind that participation is completely voluntary, and has no bearing on professional standing, future employment decisions, or any other aspects of research productivity. Therefore, we stress that there is no expectation of participation. Volunteers will be provided financial compensation for their participation at the standard rate. If you are interested in participating, please contact me privately to sign up for the study."

## **Payment:**

All participants will be compensated $30/hr for their participation. Participants may come for 4 separate visits of up to 2 hours (4 sessions x 2 hours x $30 = $240) resulting in $240. If participants come for all 4 sessions, they will be given a small bonus of $60 (the equivalent of an additional 2-hour session). In total this will result in $300 maximum compensation. Subject payments will be issued and sent either by laboratory staff within several weeks of participation or via a reloadable debit card provided for the participant, known as a ClinCard.

# **Withdrawal of Participants**

## **Withdrawal Circumstances:**

Participants might be withdrawn from the study if they are unable to comply with the instructions of the experiment, or show evidence of distress.

## **Withdrawal Procedures:**

If either the participant wishes to terminate participation or if the research staff deems that the participant does not comply with the experiment instructions, data collection will cease and compensation will be provided for the time accrued thus far.

## **Termination Procedures:**

If the study procedures are complete or if the participant wishes to terminate participation, the participant will be thanked for their time. Data may not be used for analysis, depending on the discretion of the PI.

# **Risks to Participants**

## **Foreseeable Risks:**

The experiment involved looking at a computer screen and hearing tones. Neither of this stimulus has a meaningful content that could be either offensive or triggering. Participants make simple, 2 choice judgments. As such, there is no risk involved with the stimulus or responses beyond a small risk for boredom. Additionally, participants will wear a water-based EEG cap. The only risk here is minimal water exposure and hair becoming slightly wet.

## **Reproduction Risks:**

Not applicable.

## **Risks to Others:**

Not applicable.

# **Incomplete Disclosure or Deception**

## **Incomplete Disclosure or Deception:**

Not applicable.

# **Potential Benefits to Participants**

## **Potential Benefits:**

No direct benefit to participants.

# **Statistical Considerations**

## **Data Analysis Plan:**

Our approach to analysis of behavior data revolves around the development of computational models that explicitly characterize the relationship between sensory and cognitive information and observed behavioral measurements. Our methods are primarily implemented in MATLAB and/or Python with well-established software packages like Pandas, Numpy, Theano, and PyTorch. For EEG analyses, we will conduct classic evoked-response analyses (ERP), as well as time-frequency decomposition and linear decoding. These methods will be implemented either via custom-code in MATLAB and/or Python, or via well-established toolboxes such as EEGLAB or ERPLAB.

## **Power Analysis:**

Every effort is made to ensure that sufficient sample sizes are used for valid scientific inference. The work I propose here is most closely related to Noel et al., 2022, eLife, in which we had 90 participants. Given the effect size from this key experiments in this report, in assures at power >80%. However, this prior work (1) did not include EEG data/analyses, which can be noisy. Further, (2) it did not also query the impact of expectations (as in Noel et al., 2024). Lastly (3), the prior work did not allow a potential examination of sex differences. Given the above, and the fact that the ratio of ASD in males to females is 3:1, we believe a prudent sample size (optimizing for statistical power but also not recruiting more participants than needed) is 270 participants.

## **Statistical Analysis:**

Simple statistical analyses like determining means and standard deviations shall be done to determine outliers in the data. Complex data might involve cross-validation and regularization methods for decoding and encoding models. Statistics will involve both frequentists methods (due to their ease of interpretation for the majority of the field) as well as Bayesian methods (particularly when aiming to lend evidence for the null hypothesis).

## **Data Integrity:**

All data will be subject to quality control procedures that include identification of missing or corrupted data, and will be attached to any relevant documentation of extenuating circumstances that may inform proper interpretation of the data, e.g., computer malfunction, subject distress, confusion or boredom.

# **Health Information and Privacy Compliance**

## **Health Care Component:**

Are any research personnel working on this study part of the Health Care Component (HCC)?

Yes

## No

## **Select which of the following is applicable to your research:**

My research does not require access to individual health information and therefore assert HIPAA does not apply.

I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

**Appropriate Use for Research (Explain)**:

An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

## **Preparatory to Research. Please attest to one of the following statements:**

I will only be accessing participant medical information/records for the purpose of Preparatory to Research Activities

I will be accessing participant medical information/records beyond the purposes of Preparatory to Research Activities

I am unsure and require HIPCO guidance to determine if the activities I am proposing are considered Preparatory to Research Activities

## Not applicable to this study

## **Identify the source of Private Health Information you will be using for your research (check all that apply):**

I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me.

I will collect information directly from research participants.

I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

I will pull records directly from EPIC (Explain what, how, authority, exclusion):

I will retrieve record directly from axiUm / MiPACS

I will receive data from the Center for Medicare/Medicaid Services

I will receive a limited data set from another institution.

I will receive a de-identified data set from another institution.

Other. Describe:

## **Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed:**

Not applicable.

## **Approximate number of records required for review:**

Not applicable.

## **Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes:**

This research involves record review only. There will be no communication with research participants.

Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

Communication may require the use of interpreter service(s) or translation service(s).

## **Explain how the research team has legitimate access to patients/potential participants:**

The research team will be put in touch with potential participants within the Autism spectrum by researchers at the Masonic Institute for the Developing Brain and/or the Department of Pediatrics at the University of Minnesota, who routinely perform diagnoses and consent participants to take part in studies. Potential participants will only be recruited if they have previously agreed to be contacted by other researchers.

# **Health Science Technology (HST) HIPAA Compliant Devices and Data Storage**

## **HST Device Number:**

**Other non-HST managed devices:**

UMP Computer(s)

Store  Analyze  Share

Fairview Computer(s)

Store  Analyze  Share

Other non-HST managed device(s):

## **Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply):**

In the data shelter of the [Information Exchange (IE)](https://www.ctsi.umn.edu/consultations-and-services/data-access-and-informatics-consulting/bpic)

Store  Analyze  Share

In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

Store  Analyze  Share

In REDCap (recap.ahc.umn.edu)

Store  Analyze  Share

In Qualtrics (qualtrics.umn.edu)

Store  Analyze  Share

In OnCore (oncore.umn.edu)

Store  Analyze  Share

In the University’s Box Secure Storage (box.umn.edu)

Store  Analyze  Share

Sponsor Electronic Data Capture Tool (i.e. Advarra or other)

Store  Analyze  Share

In UMP devices/servers

Store  Analyze  Share

In Fairview devices/servers

Store  Analyze  Share

In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

Store  Analyze  Share

Other. I will use a server not previously listed. Describe:   
  
Data will be stored and analyzed on Noel Lab servers that are secured by password protection.

## **Consultants. Vendors. Third Parties:**

Not applicable.

## **Data Ownership (Check All that Apply):**

## UMN

UMP

Fairview

Sponsor:

Third-party university:

Other (specify):

## **Links to identifiable data:**

Participants will be assigned a digital ID number. IDs will be indicated in an experimental log. These documents will not be digitized, and will be stored in a locked file cabinet in the PI’s locked office.

## **Sharing of Data with Research Team Members:**

Data shall be shared within research team members based on the discretion of the PI.

## **Storage of Documents:**

Hard copies of any data collected from participants via writing on paper will be filed under lock-and-key in the PIs office.

## **Disposal of Documents:**

Disposal of any digital document shall be done via permanent deletion from servers. Any physical document shall be shredded.

# **Confidentiality**

## **Data Security:**

Paperwork is filed under lock-and-key in the PI’s office. An entry for the experiment is made into a document that is hosted on an internal lab server that is password protected and only accessible to PI and researchers in the lab. A Certificate of Confidentiality shall be issued to further protect any disclosure of identifiable information by researchers.

## **Data Sharing:**

Full de-identification of data from participants would be done if data is ever deemed to be necessary for public release or is distributed to collaborators. Data will be de-identified in accordance with standards in the field. Specifically, in the de-identified data, there will be no names, nor locations, nor specific dates, nor contact information, nor other information that could be used to identify participants. To keep track of participants in the released data, only a randomly generated digit-based ID will be associated with each participant.

For individuals who are or have participated in the SPARK study (and only those participants), the data we collect during this study here at The University of Minnesota may be shared with SPARK in order to add to the information that was collected during your participation in SPARK. Please note that because you are a participant in both studies, SPARK and this study will be able to share and link your identifying information, as well as any future data you may contribute to either project. This information will be shared using your linked research ID number and using a secure transfer system. SPARK provides coded data access (data with your identifying information removed) to qualified researchers. Researchers can file an application with the Simons Foundation to obtain access to your study data for research purposes. Experts at the Simons Foundation who protect health and science information will look at every request carefully to minimize risks to your privacy.

# **Provisions to Monitor the Data to Ensure the Safety of Participants**

## **Safety Plan:**

The study is a minimal-risk behavioral study. The experimenter will walk the participants through the instructions and shall be the present as a point of contact for any issues with PI being involved as the supervisor who shall help the experimenter with framing and reviewing guidelines and authorizing solutions to any uncertainty that may arise during the experiment. The PI shall be keeping up with the data-collection quality and safety procedures every week through personal meetings with the experimenter. As the PI themself shall be a part of the experiment, they can get a proper sense of how the data is being collected and whether all safety protocols are being made. The participant is free to stop the experiment at any time and the experimenter shall be available to help the participant discontinue or terminate the experiment in case of any discomfort including simple boredom.

## **Data Integrity Monitoring:**

Statistical monitoring of the data using a wide range of well-established, mathematically rigorous, statistical paradigms shall be used in monitoring the quality of the data. Computational analysis shall be done using established data handling and statistical packages like Pandas, Numpy and Scikit in Python.

## **Data Safety Monitoring:**

The Noel Lab server is password protected and each time a member access this server, a log is created to know which team member is logged-in, and what changes to documents have been made. Further, the server is backed-up at all times with version-controlled, thus assuring data safety and monitoring.

# **Provisions to Protect the Privacy Interests of Participants**

## **Protecting Privacy:**

No health or any other sensitive of private information will be acquired beyond the fact that some participants will have previously been diagnosed as within the Autism spectrum. Participants will be identified via a random 4-digit identifier information collected is deidentified and any information of the participants is kept private under lock-and-key.

## **Access to Participants:**

Only the experimenter conducting the session will have access to the participants. Further, at the end of the session they will be asked for consent to be contacted again for future experiments. Participants will only be contacted in the future if they consent to this.

# **Compensation for Research-Related Injury**

## **Compensation for Research-Related Injury:** Not applicable.

## **Contract Language:** Not applicable.

# **Consent Process**

## **Consent Process (when consent will be obtained):**

The PI has up-to-date CITI training and the study personnel will have up-to-date CITI training prior to being included in this protocol. For consent, a member of the research team consents potential participants when they meet to conduct the experiment. The research team member explains the aim of the study and the procedures, allows the participant to read the consent form, and ensures through verbal communication that the participant understands the study and consents to participate in it. Consenting is performed in a private setting.

## **Waiver or Alteration of Consent Process (when consent will not be obtained):**

Not applicable. Minors will give assent and parents will give permission.

## **Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):**

Not applicable.

## **Non-English Speaking Participants:**

Not applicable.

## **Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):**

For participants who are not yet adults, the consenting process will involve obtaining consent and permission from a parent or legal guardian, as well as assent from the child, if they are capable of providing it. The steps will be:

1. Parental/Guardian Consent:
   * Information: The experimenter will provide detailed information about the study, its purpose, procedures, risks, benefits, and the rights of the participants.
   * Understanding: The experimenter will ensure that the parents or guardians fully understand the information provided. This may involve discussions and addressing any questions or concerns they may have.
   * Voluntariness: Emphasize that participation is voluntary and that they can withdraw their child from the study at any time without any penalty or loss of benefits.
2. Child Assent:
   * Age-Appropriate Explanation: The experimenter will explain the study to the child in an age-appropriate manner. The complexity of the explanation will match the child’s level of understanding.
   * Voluntariness: The experimenter will make it clear that their participation is voluntary and they can refuse or withdraw from the study at any time.
   * Assent Form: If the child is capable, the experimenter will have the child sign an assent form indicating their willingness to participate. This form will be simple and understandable to the child.
3. Documentation:
   * Consent Form: Parents or guardians will sign a consent form that includes all necessary details about the study.
   * Assent Form: For children who are capable, an assent form will be signed by the child.

The consent, assent, and documentation will (1) be as approved by the IRB, and (2) a matter of training between the PI of this protocol (Dr. Noel) and the experimenter conducting the study.

## **Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:**

Not applicable. Given the need to repeated judgments on simple stimuli and the need for prolonged focused, only high-functioning individuals within the Autism spectrum will be recruited. These individuals will be within a neurotypical IQ range and able to consent/assent/dissent.

## **Adults Unable to Consent:**

### **Permission:**

Not applicable. Given the need to repeated judgments on simple stimuli and the need for prolonged focused, only high-functioning individuals within the Autism spectrum will be recruited. These individuals will be within a neurotypical IQ range and able to consent/assent/dissent.

### **Assent:**

Not applicable. Given the need to repeated judgments on simple stimuli and the need for prolonged focused, only high-functioning individuals within the Autism spectrum will be recruited. These individuals will be within a neurotypical IQ range and able to consent/assent/dissent.

### **Dissent:**

Not applicable. Given the need to repeated judgments on simple stimuli and the need for prolonged focused, only high-functioning individuals within the Autism spectrum will be recruited. These individuals will be within a neurotypical IQ range and able to consent/assent/dissent.

# **Setting**

## **Research Sites:**

Recruitment will be performed throughout the University of Minnesota Twin Cities campus. Participation in experiments will be at (1) Nils Hasselmo Hall, room 2-128 (laboratory space of the PI, Dr. Jean-Paul Noel) and/or (2) dedicated EEG space at the Masonic Institute for the Developing Brain (MIDB; 2025 E River Pkwy, Minneapolis, MN 55414) and/or (3) dedicated EEG and experimental space within the CATSS Lab (Center for Applied & Translational Sensory Science; S39 Elliott Hall, 75 East River Parkway, Minneapolis, MN 55455).

## **International Research:** Not applicable.

General Data Protection Regulation (GDPR) applies to this study. Explain:

This research will take place in one or more international locations. Explain:

This research will involve collaborators from outside the United States. Explain:

This research will involve data collection, sharing, access, or transmission between U.S. and international collaborators/institutions. Explain:

## **Community Participatory Research:** Not applicable.

# **Multi-Site Research**

## **Study-Wide Number of Participants:**

Not applicable.

## **Study-Wide Recruitment Methods:**

Not applicable.

## **Study-Wide Recruitment Materials:** Not applicable.

## **Communication Among Sites:** Not applicable.

## **Communication to Sites:** Not applicable.

# **Coordinating Center Research**

## **Role:** Not applicable.

## **Responsibilities:** Not applicable.

## **Oversight:** Not applicable.

## **Collection and Management of Data:** Not applicable.

# **Resources Available**

## **Resources Available:**

The PI has access to all resources needed to conduct these experiments, as part of his startup funds from the Department of Neuroscience at UMN. This includes space, as well as funds for participant compensation and materials needed for the experiment. The PI shall be involved in every step towards guiding trainee investigators and shall be available for help always. The PI trains all research staff to ensure that they understand the experimental protocol and associated privacy, safety, and ethical concerns. The PI has access to computational servers which shall be used for running our computer algorithms.

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