SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **06/30/2022**
Revised Date:

Application Number: **1 R21 MH131959-01**

Principal Investigators (Listed Alphabetically):

HADAD, BAT SHEVA
YASHAR, AMIT (Contact)

Applicant Organization: UNIVERSITY OF HAIFA

Review Group: **CPDD**
Child Psychopathology and Developmental Disabilities Study Section

Meeting Date: **06/13/2022**
Council: **OCT 2022**
Requested Start: **12/01/2022**

RFA/PA: **PA21-200**
PCC: **B2-MBA**
Dual IC(s): **HD**

Project Title: **Perceptual decision criterion in individuals diagnosed with autism spectrum disorder**

SRG Action: **Impact Score:46 Percentile:48 +**

Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**

Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**

Animal Subjects: **10-No live vertebrate animals involved for competing appl.**

Gender: **1A-Both genders, scientifically acceptable**

Minority: **5U-Only foreign subjects, scientifically unacceptable**

Age: **3A-No children included, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	123,282	165,516
2	143,174	192,223
TOTAL	266,456	357,739

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R21MH131959-01 Yashar, Amit

INCLUSION OF MINORITIES PLAN UNACCEPTABLE

RESUME AND SUMMARY OF DISCUSSION: The objective of this new application is to systematically examine how prior knowledge, sensory uncertainty, and reward impact visual perception in adults with autism spectrum disorders (ASD) compared to typically developing adults. While some reviewers felt the application was highly significant as results would support clear interpretation of other perceptual decision-making studies by providing a foundation basis for components underlying Bayesian decision-making, others felt the narrow focus on visual perception and lack of direct impact on clinical practice reduced the overall impact. Strengths of the application included high innovation by examining both perceptual decision-making and metacognition in ASD adults, a strong empirical design with rigorous control procedures that reduce confounds, adequate power to detect effects, well defined hypotheses and compelling pilot data supporting Aim 1. However, despite these strengths several score driving weaknesses were noted. Specifically, Drs. Yashar and Denison lack publication or funding history in ASD research, and while a history of collaboration is present between the investigative team, this collaboration has not resulted in a strong publication history to date. Regarding the research plan, the sample lacked generalizability as it consists of ASD adults with normal IQ and SES and ethnic/racial diversity was not described. Further, it was unclear whether participants with ADHD or other comorbidities would be included and if so, how this issue would be handled in the analytic plan. There was also a lack of clarity about what the tasks look like to the participants and some concern that some participants will complete multiple conditions while others are expected to have missing data for return visits (20 non-overlapping participants across experiments) indicating that some data will be within subject and some between subjects. Concerns about the inclusion of minority participants were also present given the enrollment table included only White participants without a scientific rationale. During the discussion, the panel focused on the significance and whether this project would truly drive the research forward in the field. Following the discussion, reviewers and members of the panel held a difference of opinion about the strengths and weaknesses in the application, and a majority of the panel weighed the relative weaknesses noted in the application more strongly. As such, the concerns offset the strengths and reduced to a moderate level the overall impact of this application on the fields of cognitive neuroscience and ASD research.

DESCRIPTION (provided by applicant): Autism Spectrum Disorder (ASD) is a class of neurodevelopmental disorders that affect social interaction, communication, sensory processing, and other aspects of cognition and behavior. ASD is common; recent studies estimate that 1 in 54 children have ASD. Although ASD research has traditionally focused on social cognition, alterations to sensory processing are increasingly recognized as a core phenotype. However, little is known about processes that mediate between perception and complex cognition. Perceptual decision making lies at this interface, and influential theories propose a Bayesian decision-theoretic framework for understanding processing alterations in ASD. Yet perceptual decision making in ASD – and whether and how it is Bayesian – has received scant direct investigation. To address this gap in knowledge, we will study perceptual decision making in ASD. When we make a decision about something we see, we convert the raw sensory information into a discrete choice that guides behavior and complex cognition. For an ideal Bayesian observer, decisions should take into account three different sources of information: sensory input, prior knowledge, and expected reward for a correct decision versus the cost of an incorrect decision. Here we ask two questions about decision making in ASD. First, to what extent does perceptual decision making in ASD incorporate prior knowledge, sensory uncertainty, and reward? Second, to what extent does higher-level metacognitive decision making in ASD incorporate these three components? To answer these questions in the proposed study, we will determine which types of information individuals with ASD are sensitive or insensitive to when making perceptual and

metacognitive decisions. The findings will either identify or rule against the contribution of specific decision processes to ASD behavior. Any discovery of selective impairments to decision processes in ASD would introduce the new therapeutic targets for the disorder. The proposed study will test whether and how ASD decisions account for the three Bayesian components: prior knowledge (Aim 1), sensory uncertainty, or likelihood (Aim 2), and reward, or cost function (Aim 3). To assess both perceptual and metacognitive decisions, participants will be asked to categorize the orientation of shapes and to report their confidence about their choices. To test the three Bayesian components, we will manipulate the probability of stimulus categories (Aim 1), the contrast of stimuli (Aim 2), and the rewards for correct categorization (Aim 3). We will model the behavioral data to determine the influence of each Bayesian component on ASD decision behavior. This suite of experiments will provide a robust test of whether and in what way perceptual decision making in ASD follows Bayesian principles. The results will provide insight into whether alterations to Bayesian computations may be a general theory of processing changes in ASD.

PUBLIC HEALTH RELEVANCE: Autism Spectrum Disorder (ASD) is a class of neurodevelopmental disorders that affect social interaction, communication, sensory processing, and other aspects of cognition and behavior. Recent theories propose alterations to basic cognitive computations in ASD, which can be assessed by studying perceptual decision making. To evaluate such theories, here we will determine which types of information individuals with ASD are sensitive or insensitive to when making perceptual decisions.

CRITIQUE 1

Significance: 2
Investigator(s): 2
Innovation: 2
Approach: 3
Environment: 2

Overall Impact: The proposal tests the theory of whether perceptual decision making in adults with ASD is Bayesian, by experimentally manipulating prior knowledge, sensory uncertainty, and reward cost. Knowledge gained by this proposal will inform current literature and future studies regarding sensory processing in individuals with ASD. The proposal is highly significant as findings will support the clear interpretation of other perceptual decision-making studies by providing a foundational basis for components underlying Bayesian decision-making. The investigative team is strong, combining expertise in Bayesian modeling, visual perception, and ASD, contributing to the success of executing the proposed study. The study is highly innovative, combining perceptual decision-making with metacognitive (confidence) components in adults with ASD. By manipulating prior learning explicitly, the proposal decreases confounds to advance theoretical understanding of perceptual decision-making. The approach is also strong, providing appropriate controls to decrease confounds, being adequately powered and matched, and providing pilot data to support Aims. The environment provides the required access to adults with ASD, cognitive assessment laboratory, and statistical analyses, providing adequate academically rich environment to support the success of the proposal. In conclusion, the proposed application has the potential for a strong impact on understanding the theory behind perceptual decision-making in adults with ASD, with strengths in all score reviewed criteria, and only very minor negligible weaknesses.

1. Significance:

Strengths

- Proposal has the potential for high impact on understanding the theoretical basis underlying perceptual decision-making, which will advance science by supporting the interpretation of findings from other studies.
- Clear experimental design will provide clear evidence to support understanding of Bayesian framework in perceptual decision-making, which will clearly inform understanding of theoretical underpinnings of research findings.
- Manipulating prior learning explicitly improves science and decreases confounds by directly testing the components of Bayesian decision-making.

Weaknesses

- The direct impact on clinical practice is less evident yet this is only a very minor negligible weakness given the highly theoretical nature of this proposal.

2. Investigator(s):

Strengths

- Yashar is an early-stage investigator with productivity in publications and federal funding (in Israel), and demonstrated success in leading research studies.
- Hadad brings expertise in ASD and visual perception. Denison bring expertise in Bayesian modeling. Together with Yashar, the team provides a balance of expertise contributing to the potential for success in the project.

Weaknesses

- The team is newer to research in ASD, which is a very minor weakness.

3. Innovation:

Strengths

- Highly innovative to test the underlying theory of perceptual decision-making.
- Combining perceptual decision making and metacognitive (confidence) is novel to research in ASD.

Weaknesses

- Although signal detection theory isn’t novel itself, its application here to research in ASD is novel.

4. Approach:

Strengths

- Rigorous control within stimulus and procedures reduces the potential for confounds.
- Study is adequately powered to evaluate differences and provides alternative interpretations. These strengths increase the likelihood of study findings having an impact on future research and understanding of theoretical underpinnings of perceptual decision making in ASD.
- Pilot data supports Aim 1 and matching ensures appropriate control for confounds, enhancing the likely success of the proposal.

Weaknesses

- Recruitment is centered out of pediatric locations, a minor weakness given the target population of adults with ASD.
- Representation of the sample, as neurological and psychiatric disorders are excluded, is a minor weakness of the generalizability of the proposal.

5. Environment:

Strengths

- University of Haifa provides the necessary cognitive laboratory resources and access to individuals with ASD necessary to complete the proposal.
- Boston University provides the necessary computing software to ensure data analyses.
- Environment provides necessary supports for virtual meetings across two institutions.

Weaknesses

- None noted.

Study Timeline:

Strengths

- None noted by reviewer**.**

Weaknesses

- Limited detail on study timeline to evaluate its appropriateness.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections
Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution not justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- Race/ethnicity is reported to not be an exclusion criterion, yet the enrollment table is all White participants. Racial diversity of Israel not provided to justify zero race/ethnic diversity.

Applications from Foreign Organizations:

Justified

- Investigators and environment strong for justifying the foreign component. Collaboration with domestic investigator. Access to experimental stimuli necessary from foreign investigators.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 2
Investigator(s): 5
Innovation: 3
Approach: 4
Environment: 2

Overall Impact: This application aims to test perceptual decision making in ASD to determine how individuals with ASD account for prior knowledge, sensory uncertainty (likelihood), and reward (cost function) among 40 adults with ASD and forty typically developed adults. The application is significant in that it will investigate the impact of sensory issues on decision making thus providing a deeper understanding of this phenomena. The lead PI has expertise in the type of experiments proposed, however has limited experience with ASD research (as evidenced by grants and publications). Co-PI Hadad has some experience with ASD research. The approach is clearly described and aims to test the three components of the Bayesian framework separately which will provide new information not yet investigated. One weakness is the lack of generalizability of the sample given that participants were all normal IQ, a clinical sample, and possibly homogeneous in terms of demographic characteristics (these were not described). Facilities for the project appear to be acceptable. If successful, the application would lead to a larger study and eventually to new knowledge that could lead to the development of new interventions or confirm the rationale for existing one and would have a moderate to high impact on the field of the Bayesian framework related to sensory perception and decision making among adults with ASD.

1. Significance:

Strengths

- Given the high prevalence of sensory differences in autism, this study will allow a deeper examination of how sensory differences may impact decision making.
- This application seeks to better understand first order and higher order perceptual decisions adults with ASD make and whether they are different from TD adults. If successful, the findings could lead to the development of new treatments or confirm rationale for existing ones.

Weaknesses

- None noted by reviewer.

2. Investigator(s):

Strengths

- MPI Hadad has funding awards and listed two publications related to autism research.
- MPI Yashar has experience with studying and testing cognitive processes including the ones proposed in this application.

- Drs. Hadad and Yashar are in the same department and advise the same graduate students on similar topics, and co-authored a review paper.
- Drs. Denison and Hadad have collaborated and co-authored a paper together.

Weaknesses

- Yashar and Denison do not have a publication or funding history in autism research.
- Collaborations between the three investigators have not resulted in a strong publication history.

3. Innovation:

Strengths

- The study will investigate all 3 components of the Bayesian framework in an ASD population which has not been done in previous research.
- Investigators will apply methods used in testing this framework in TD populations to ASD.

Weaknesses

- It is not clear how this study would lead to new interventions; they may confirm rationale for existing ones.

4. Approach:

Strengths

- Investigators plan to manipulate each component of the Bayesian framework allowing them to tease out which component has which effects.
- The experimental procedures for each component are well described.
- Additional measures to confirm and measure severity of autism symptoms are acceptable.

Weaknesses

- The sample is a clinical sample of normal IQ autistic adults associated with Dr. Ashar's lab which limits generalizability. The SES and ethnic diversity are not described which further limits generalizability of findings.
- It is not clear whether participants with ADHD will be included. Investigators are excluding learning and other disorders with the exception of epilepsy given its high co-occurrence with ASD which is also the case for ADHD.

5. Environment:

Strengths

- Dr. Yashar's lab space has the resources to carry out the experiments.
- Dr. Denison's resources appear to be adequate to conduct statistical analysis.

Weaknesses

- None noted by reviewer.

Study Timeline:

Strengths

- Acceptable timeline

Weaknesses

- None noted by reviewer.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- minimal risks, mainly potential loss of confidentiality

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- minimal risk, computer tasks, board not necessary

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution not justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- The enrollment report chart is very US centric understandably, however the investigators did not contextualize the ethnic diversity within Israel and how the study will attempt to include ethnic minorities from that country.

Applications from Foreign Organizations:

Justified

- This is an application from investigators in Israel.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

Significance: 4
Investigator(s): 3
Innovation: 3
Approach: 4
Environment: 1

Overall Impact: This study aims to systematically examine how prior knowledge, sensory uncertainty, and reward impact visual perception in adults with autism compared to typically developing adults. The

premise of the study is that careful attention to whether individual factors will inform the underlying mechanisms of sensory disruption in autism, which may in turn inform intervention. The significance of the proposed study is moderate, given the narrow focus on visual perception rather than multimodal perception (more ecologically valid), although the systematic approach to examining the components that contribute to sensory processing is an appropriate way to approach the research question. The prior literature that addresses Bayesian theory in the context of sensory perception shows few differences between autistic and typical individuals, leading to a concern of limited significance for the current study. PI Yashar has expertise in visual perception. PI Haddad has expertise in visual cognition. Although MPIs do not have a lot of prior collaboration, they have one publication and are co-located. The systematic approach to manipulating aspects that contribute to perception independently is innovative. Strengths of the approach include the straightforward study design, clear inclusion and exclusion criteria, and detailed predictions of outcomes. A weakness of the approach is lack of clarity on what the tasks actually look like for participants, and the expectation that some participants will complete multiple conditions (20 in each group) and others are expected to have missing data for return visits (20 non-overlapping participants across experiments), indicating that some data will be within- and some will be between-subject. Environment is strong to support the proposed study.

Study Timeline:

Strengths

- Data collection is feasible in the 2-year study

Weaknesses

- Timeline is not well articulated

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Retention plan would benefit from additional strategies, given that the analyses will be more straightforward if all participants complete all conditions.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- Privacy protections are adequate. Study is low risk.

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution not justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- Unclear whether race/ethnicity is comparable from a non-US country, but there is no diversity in the proposed sample.

Applications from Foreign Organizations:

Justified

- MPIs bring expertise together with a US co-I to address a novel research question.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: UNACCEPTABLE The application does not provide adequate scientific justification for the inclusion of only White participants.

INCLUSION ACROSS THE LIFESPAN: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R21 MH131959-01; PI Name: Yashar, Amit

+ Derived from the range of percentile values calculated for the study section that reviewed this application.

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Child Psychopathology and Developmental Disabilities Study Section
Biobehavioral and Behavioral Processes Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
CPDD
06/13/2022 - 06/14/2022

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-22-044 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-044.html, including removal of the application from immediate review.

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.