Applicant: William Mitchell

Application Number: 1F99NS134208-01A1

Project Title: Intersubject Synchrony in Neural and Behavioral Representations of Social Uncertainty Among Adults and Adolescents

September 11, 2023

Dear Dr. Jones-London,

Below, we address the concerns noted by reviewers (Reviewers = R1, R2, R3, & R4). Though many of these points were previously highlighted in our July 21st critique response, much of this discussion is also new since the limited space available to me did not allow me to previously respond to all of the original critiques:

1. **K00 Phase Training Plan.** The K00 Phase Training Plan lacked specificity, as was astutely noted by R2, R3, and R4. This was partially intentional to prioritize responses to initial feedback, but also a misunderstanding I had gleaned from conversations with staff and previous awardees of the appropriate level of specificity for the panel. The lack of specificity does not reflect the degree of thought or attention given to the gravity of this decision and this has been a regular topic of discussion during my meetings with Dr. Helion since starting the program. Beyond qualities outlined in Section B.2.6 of the Research Strategy, an ideal institution readily has access to research-specific MRI facilities, ideally onsite, much as I currently have at Temple University. Because of compliance and comfort concerns, this facility would need to have access to a mock scanner for training and would ideally regularly host child participants, thus having infrastructure to make both parents and children comfortable during their visit. Because this proposal, if funded, does not directly fund my research, an ideal lab and advisor would have access to substantive financial resources to conduct research or could meaningfully assist in securing financial resources to fund this research. They must necessarily have access to high performance computing (necessary for the analyses I am interested in) either through a cloud-based cluster service or private access to a local machine. My ideal advisor would be coming from a rich, mixed theoretical background integrating constructivist, appraisal, and basic theories of emotion through a developmental lens and, again, would have interests in social and self-regulatory neural mechanisms. These advisors would necessarily have to have interest, if not expertise, in the use of feature-rich stimuli within the context of fMRI, which could include video, sound, VR, or other multimodal experiences. Dr. Susan B Perlman, Dr. Kevin Ochsner, Dr. B.J. Casey, Dr. Erik Nook, Dr. Luke Chang, and Dr. Ajay Satpute are all researchers who meet most if not all of these criteria, are individuals with whom I have already established professional relationships, and, in some cases, are individuals with whom I have already begun discussing the possibility of pursuing a post-doctoral position. However, my search has not been limited strictly to researchers whom I have established working relationships with already; I will systematically explore all options available to me to identify the ideal post-doctoral environment to conduct my research.

R2 requested more specific target skills and growth while R4 noted minor concerns that the K00 transition was incremental. Both concerns may be addressed by outlining some of the specific challenges inherent to transitioning to social affective developmental neuroimaging which require skills training and guidance that I have not yet acquired. For example, the vulnerability of children requires additional training and attention paid to consent and assent procedures, safety concerns, such as identifying abuse and suicidality, and mitigating heightened anxieties of MRI scanning. While my proposed task can be adapted for non-adults, identifying age-appropriate instructional language and stimuli which also motivate engagement are crucial to maximize compliance and require guidance from individuals with far more developmental experience than I have acquired in my clinical experiences. Imaging adolescent populations come with a host of methodological issues, including normalization and registration to age-appropriate atlases and greater head motion issues and inappropriate approaches to either can complicate cross-age comparisons. Computational MVPA approaches have not seen widespread application in the developmental literature yet and the approaches I had outlined in the first training goal of my K00 Phase (specifically Hidden Markov Modeling [HMM], Intersubject Representational Similarity Analysis [IS-RSA]) would be among some of the first examples to explore social affective developmental phenomena. This training is absolutely crucial as it specifically fits well with my specific talents and interests in using programming solutions to apply quantitative methodology in modeling social affective phenomena, but is also necessary to answer questions about neural representations and responses of nuanced and complex social affective phenomena, which exist in activation patterns and cannot be readily detected with more traditional approaches. My first first-author publication emphasized the neurodevelopmental variance that exists in affective representations and more sophisticated approaches such as IS-RSA or HMM have the potential to propel the field towards a more complete theory of developmental differences in affective representations of social and non-social ambiguity as well as the chain of cognitions associated with processing ambiguous situations over time, respective. The prominence of social and affective development during adolescence makes answering these questions essential, but the application of these methods across age groups may be challenging. This is why support from my mentorship team, my K00 advisor, and collaborations that I establish at conferences like Flux and CCN will be crucial in bridging this divide. Although they lack the background in developmental neuroscience, relationships I have developed through experiences like my 2023 MIND Summer School fellowship with more computationally experienced researchers such as Dr. Luke Chang will also be essential to meeting these goals and providing sufficient training to justify my time spent in the postdoctoral role.

1. **F99 Phase Training Plan.** R2 expressed concerns that our responsible conduct of research (RCR) plan was not formalized. However, the “Ethics and Ethical Conflicts in Psychological Science” course cited in our RCR section should meet the criteria for formalized RCR training, as it is a graduate-level 3-credit semester-length class which features coursework ethics in data management, collection, consent, authorship, and other relevant topics in psychology and neuroscience and is faculty-led. I apologize if these details were unclear.

Additionally, R3 expressed concerns regarding how broad or generic my training plan appeared. I take this to suggest that I had not provided enough explicit detail to explain why the specific tasks and goals I had outlined are especially pertinent to my proposed research. I noted that I would learn how to conduct Generalized estimating equations (GEEs). These are a statistical approach which do not carry inherent assumptions about the correlational structure among predictors for specific subjects or groups. When capturing any phenomena in a timeseries, as we capturing in the neuroimaging data and behavioral data in this study, a significant covariate is autoregression, or the degree to which activity at Timepoint X influences or can predict activity at later timepoints. The assumption of data independence, inherent to most traditional general linear modeling approaches, would be violated with our experimental design, but GEEs provide a statistically-sound alternative option. However, GEEs can be computationally demanding and complex, thus some training is needed. Nonetheless, such a statistical approach would be applied to explore the degree to which behavioral synchrony could be predicted by neural synchrony. GEEs would not be of use in generating the synchrony values themselves, though, which are effectively transformed correlative values. nltools is currently the premier approach to conduct intersubject correlation analyses (ISC) and was built by faculty members at Dartmouth University. nltools does provide options to account for autoregression within one’s analytic pipeline to minimize effects upon later ISC values. Attending the MIND computational bootcamp is beneficial because it is hosted by the creators of nltools and much of the skills learned and reviewed during that fellowship revolve around nltools applications. Many of the individuals at the cutting edge of tool development in this space attend conferences such as Computational Cognitive Neuroscience, which would give me additional training and exposure to novel approaches relevant to this space. However, this is still very much an emerging field, especially as it relates to developmental neuroscience. My project would constitute an experimental paradigm (i.e., continuous collection of behavioral and neuroimaging data during video fMRI) that has not yet, to the best of our knowledge, been used before. It is pivotal to the continued growth of computational approaches to social affective neuroscience that new tools are built and existing tools are refined. The functions that I have generated would be of interest to anyone else studying behavioral and neural phenomena simultaneously and, thus, many of my Year 2 training goals focus specifically on sharing these tools for the improvement of the field, but also to deepen my understanding of the tools I use and phenomena I study. All of the activities associated with my second goal serve to prepare me for the transition to work with developmental populations by engaging with established theory (i.e., guided literature review) as well as cutting edge developmental neuroscience literature (i.e., participation in Flux and meetings).

R4 noted that that training plan could benefit from a more dedicated focus upon neuroscience accounts of uncertainty and decision-making and I completely agree. I note under F99 Phase of Goal 2 in the Training Goals and Objectives section that my literature review will focus specifically on adolescent neuroscience related to uncertainty, but I did not explicitly state decision-making and may have had too narrow of a focus limiting the literature to adolescent neuroscience. In conjunction with my sponsorship team, I will ensure that the literature that we select captures decision-making and uncertainty topics across the full range of human development.

1. **F99 Phase Primary Task.**  R1 expressed concerns regarding how the “…data from main task with and without the provision of subjective statements will be differentiated…”. I include that as a direct quote primarily because I am not sure that I understand the concern, but I will do my best to address it. During the primary task in which participants watch the crime mystery stimulus, they are randomly assigned to continuously quantitatively rate their certainty as to the target character’s guilt during one half of the video and to passively watch during the other half of the video. The primary analysis described within this grant is almost exclusively concerned with the rated half of each participant’s data. However, capturing an unrated portion of ensures that we can conduct neuroimaging analyses that rely on participants having nearly identical visual experiences and allows us to identify whether the neural circuitry implicated in social uncertainty judgment is differentially recruited when individuals are explicitly tracking their internal states (i.e., making ratings versus not making ratings).

R4 noted that concerns that our analytic approach (using intersubject correlations) may be too narrow and recommended applying a more traditional approach, perhaps for comparison. One example could conducting a contrast of activation across our parcellations relative to the baseline checkered pattern and then perhaps using the average activation during a defined period of time to predict average behavioral ratings during that timeframe as well. The application of more traditional analytic approaches is a great suggestion and something we had already intended to conduct to further explore our data. Such details were again excluded to prioritize details more central to the primary proposed analysis. However, I did want to clarify one detail regarding the parcellations because I fear there may have been confusion. I had noted the possibility of increasing or decreasing parcellation granularity not because it represented a fundamentally different approach from our primary ISC analysis, but rather as a supposition that because our representations of our phenomena of interest likely exist at the level of small voxel patterns that oversized parcellations may be missing meaningful heterogeneity within a given region. Exploring parcellation granularity, possibly in a multiverse analytic approach, would simply allow us to reduce the likelihood that an absence of effects could be caused by overly generalized regions of interest.

1. **F99 Phase Control Task.** R1 and R2 cited concerns regarding the analysis and use of our non-social control task and noted the value that a social but not-ambiguous control might add, which we agree could add a substantive contribution to the project and would explore as a possible addition in future iterations of the project. We do also take note of the critique that the control task lacks the motivational strength of the social task but also argue that some degree of motivational strength is inherently confounded with social stimuli. The short length of the non-social stimulus was a practical solution to an unfortunately difficult dilemma which prioritized data quality for our primary task (i.e., minimizing scanner time to avoid head motion issues and maximize financial resource efficiency). Even at its current length, the control task still provides 150 trials which should be sufficient for modeling our phenomena of interest. Although the control task is shorter in length, one of the advantages of our study design is that nearly all else is held constant; we can still apply the same analytic methods and expect to look for synchrony in the same way outlined in the proposal. Furthermore, the correlative values contained in the activation maps that these approaches generate can be contrasted across condition much as one might contrast beta values with a more traditional univariate approach. However, it’s important to note that this approach would not yield for us the same interpretation as a univariate approach: rather than identifying which regions, on average, show unique activation across participants during a specific task, this approach would identify which regions generate the same pattern of activity (which can be interpreted as a proxy for engaging similar cognitive processes) consistently across time and across participants, thus granting us sensitivity to both the dynamic features of and the complex, nuanced patterns of social affective processes and representations beyond that of univariate approaches. As such, the expectation should not be that this approach would highlight which systems are coming online or going offline, but rather which systems demonstrate greater homogeneity or greater heterogeneity in processing complex, dynamic feature-rich instances of social and non-social ambiguity.
2. **F99 Phase Conceptual Framework.** R1 and R2 expressed concerns regarding situating the conceptual framework within the broader social neuroscience literature and offered a number of helpful solutions to improve the design. In many cases, as the reviewers surmised, details were sacrificed in order to focus on the questions that reviewers cared about during the first submission. R2 highlighted that our preliminary data addressed only a small limited aspect of the proposal. Another preliminary analysis applying ISC to the data while dividing participants into groups based upon midpoint and endpoint theories (i.e., who they believe had committed the crime) found greater in-group synchrony than out-group synchrony within the Precuneus, dlPFC, dACC, and IFG for the social task during social processing. We are currently working through analyses contrasting univariate activity across our regions of interest during the social and non-social tasks. In response to R2’s concerns, we do capture measures of anxiety and intolerance of uncertainty as noted in section A.2.2. of the Research Strategy, which will inform our models and how our samples will be analyzed.
3. **Minor issues noted.**

*Limited Publications.* R2 and R4 noted the applicant’s limited publication history as a reasonable concern. While it may not alleviate the concern fully, we would like to note that the applicant is a middle author who had made significant contributions to task design and data collection on two additional manuscripts currently under review. The applicant is also the primary author of one behavioral empirical manuscript related to the proposal which is being submitted for review September 2023 and a second fMRI meta-analysis on emotion and self-regulation which is on target to be under review by the end of September 2023. The applicant has also made substantial contributions to a number of other manuscripts in varying stages of preparation.

*Sponsorship Concerns.* R3 expressed concern regarding Dr. Helion’s mentorship history as well as the role of Dr. Chein as a Sponsor. In addition to her 4 doctoral trainees, Dr. Helion has mentored dozens of undergraduate students, both in our lab but also as the director of Temple’s MINDS program which matches talented research-oriented undergraduates with specific labs and research projects across collaborating universities in Pennsylvania and Maryland. This proposal intentionally supplements Dr. Helion’s circumscribed experience mentoring NIH grant recipients (a consequence of her early-career status) with Dr. Chein’s considerable mentorship history and success producing doctorate recipients. Dr. Chein’s unique contributions are most directly addressed in the Respective Contributions section, which notes that Dr. Chein’s primary role has been to advise in the best use of available fMRI software (i.e., acquisition parameters, programs), hardware (e.g., head coil options, equipment, tools), and data collection (e.g., head motion considerations, mock-MRI usage) within the imaging center that he directs.

A graph showing a line

Description automatically generatedA diagram of a maze

Description automatically generated*Task Variability.* R1 expressed interest in the typical variability of the task which is a great question. I have included a visualization of overall variance in certainty ratings over time as well as the time course of individual ratings over time. We see high levels of variance even early in the task, with variance steadily increasing throughout as participants learn more about the narrative and move towards greater certainty in their hypotheses.

We would like to thank both you and the Council for consideration of our proposal. We believe that these changes will meaningfully improve the proposed research. Please contact us with any further questions or clarifications.

Warmly,

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