Title: Using Neural Synchrony to Predict Social and Non-Social Decision-Making Under Uncertainty

Abstract (249 / 250 words): Uncertainty is an often pervasive, stressful experience that arises when making judgments about others' beliefs, intentions, or emotions (i.e., ambiguous social situations). Excessive uncertainty can have pernicious effects upon memory, mood, and physical and mental outcomes. Yet, we understand little of how decisions of social certainty form over time, the neural circuitry underlying these decisions, and how these decisions meaningfully differ from non-social uncertainty sources (e.g., calculations, perceptions). Traditional univariate neuroimaging analyses, which compare average magnitudes of activation across broad neural regions, are unresponsive to the subtle pattern differences that characterize complex social cognition. Novel multivariate techniques, such as intersubject correlations (ISC), applied to dynamic, feature-rich, and ecologically-valid sources of social ambiguity are crucial for understanding fundamental aspects of social cognition but have not yet been applied to answer these important questions. My proposed doctoral project uses a novel study design in which adult participants continuously rate their certainty of a given social (e.g., a character's innocence or guilt) and non-social (e.g., frame luminance) outcome while observing long-form narrative video stimuli (i.e., 45 min crime drama) during fMRI. This yields a continuous time course of concurrently-recorded neural and behavioral data which can be analyzed via ISC to determine the neural circuitry commonly implicated in uncertainty judgment formation among normative adult populations. Interdomain neural-behavioral synchrony can underscore how social and non-social certainty judgment formation mechanisms differ. Defining normative adult neural uncertainty responses provides a crucial comparison to vulnerable populations with pronounced uncertainty responses, including autism spectrum, anxiety, and mood disorders.

1. Theoretical & Practical Significance

1.1. Social situations can produce pervasive and aversive feelings of uncertainty [1,2]. Increased uncertainty and/or difficulty tolerating it are hallmarks of negative psychological conditions like anxiety and depression [1,3,4]. However, dealing with uncertain situations and outcomes is an unavoidable reality of daily life. Uncertainty can manifest in both social contexts (e.g., "Am I being told the truth?") [5] and non-social contexts (i.e., "Was the traffic light yellow or red?") [6,7]. Many clinical disorders are characterized by issues with evaluating and regulating responses to uncertainty, including schizophrenia [8], autism spectrum [3], and anxiety disorders [3], moreover, high uncertainty intolerance predicts emotion dysregulation [9]. This speaks to the clinical and public health importance of understanding the neural and behavior bases of social and non-social uncertainty, and identifying strategies that can be used to regulate the negative states that it elicits. Prior work has found that assessing social and non-social ambiguity recruits unique neural circuitry [6,10], which may stem from differences in cognition underlying social and non-social ambiguity assessments. That is, non-social assessments may demand greater focus on unimodal sensory details and calculations while social assessments may instead demand greater focus on heuristics, schemas, and prior experiences [10,11]. Thus, social uncertainty may be especially difficult to manage [5] but *few studies have differentiated how social versus non-social uncertainty judgments form using complex, dynamic, and ambiguous social stimuli.*

1.2. Complex, feature-rich stimuli are an ecologically valid means of studying context-dependent social phenomena [12–15]. Social uncertainty has typically been studied in the context of economic games (e.g., Trust Game, Ultimatum game) [16] in which a participant collaborates with a real or fictitious participant to make economic decisions. These interactions, while offering a great deal of experimental control, are not faithful representations of how these kinds of decisions are made in the real world [17,18], in which our representations about others is accrued gradually, across multiple situations, and updated based on new information. [5,19]. Video narratives offer a well-validated, feature-rich, socially-relevant alternative to traditional stimuli while incorporating greater ecological validity and comparable experimenter control [20,21]. Using video stimuli in neuroimaging research to study context-sensitive phenomena is growing rapidly [22], but *demands specialized data collection approaches and analytic techniques sensitive to the multivariate nature of the complicated neural patterns they elicit.*

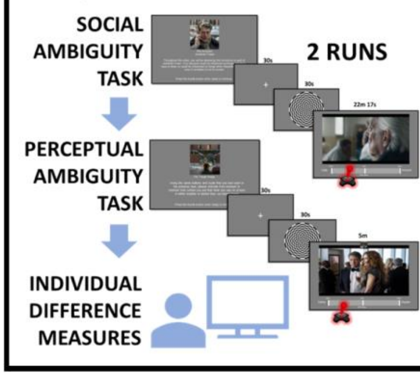
<u>1.3. Intersubject neural synchrony is a multivariate measure of intersubject overlap in social cognition</u>. Synchrony, or the correlative strength in activity between two or more individuals across a time series, differ from univariate methodologies, which are sensitive to changes in activation magnitude but not activation patterns within a region [23,24]. High intersubject neural synchrony in response to the same information suggests similar processing of that information and provides evidence of neural signatures, or regions that definitively contribute to a specific neural mechanism [25]. Complex social and cognitive phenomena are often represented at the voxel level and analyses sensitive to patterns, such as Intersubject Correlations (ISC), are required to quantify these representations [25]. Different psychiatric disorders are associated with dysfunction in neural synchrony, including ASD [26] and anxiety disorders [27]. *This speaks to the importance of using synchrony and other multivariate approaches when examining neural data in normative and clinical populations.*

<u>1.4. Intersubject neural synchrony predicts downstream decision-making.</u> For example, intersubject neural synchrony as calculated by ISC positively predicts cooperation, agreement, communication, coordination, empathy, and perspective-taking [27–29]. <u>However, these studies only examine how neural synchrony predicts decision-making outcomes rather than the decision-making process</u> [17]. Time series analyses of continuous behavioral measurements have precedence in the social and affective literature [17,30], but have not yet been applied to paradigms using dynamic, feature-rich stimuli examining intersubject neural synchrony. Using dynamic narratives to elicit and continuously sample judgments of

uncertainty and neuroimaging data concurrently could use neural intersubject synchrony to predict intersubject synchronization in subjective downstream behavioral assessments of uncertainty [17]. *This approach could identify associations between the role that specific neural regions play in generating subjective assessments of social and non-social certainty judgments.*

2. Methodological Approach

Figure 1. fMRI task. Participants receive background information and view one minute of visual baseline (fixation cross, rotating checked pattern). Participants continuously indicate their certainty as events occur.

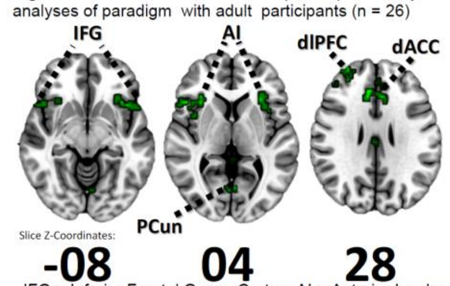


<u>2.1. Task Design</u>. The fMRI task (**Fig 1**) has been pilot tested and is currently being used to capture data from adult participants. Participants first complete a training exercise to ensure comfortably using a handheld device (i.e., button box/joystick) and assess ability to clearly hear audio. During the primary (social) uncertainty task, participants are introduced to the target and supporting characters by reviewing necessary background information (e.g., character's names, general roles, and relationships to other characters). Participants then watch video (i.e., *The Undoing*, HBO Television) while continuously rating how certain they are of a given outcome (i.e., a character's innocence or guilt) using their handheld device. Behavioral certainty ratings are sampled at the stimulus's average framerate (24 Hz). A rotating checkered pattern precedes and follows each stimulus for 30 seconds, which is standard practice to assess responses from the visual system when using dynamic video stimuli [13]. The stimulus is split into two 22 minute 17 second components and presented to participants across two sequential runs. The first 17 seconds of each run is ignored to account for initial scanner lag. Participants are randomly assigned to rate one of the halves and to passively watch the other half, but to engage with the stimulus and form uncertainty judgments as if they were providing ratings. Following the primary task, participants watch 5 minutes of video from a different episode of the source show, but containing the same characters, and rate how certain they are that the luminance of each frame

is lighter or darker than a target image. The luma value (i.e., luminance) of each frame is calculated using a standard formula [31] adapted into an R function built by the applicant. The target image is displayed during the task and is the frame closest to the median luminance of all frames contained within the stimulus, such that an approximately even number of frames are lighter and darker than the target image. This measures the formation of perceptual certainty judgments. Participants then complete individual differences measures outside of the scanner to assess including character assessments (e.g. "How agreeable was character X?") based upon a validated measure of person perception dimensions [32], task engagement and difficulties, and how their personal theories of which character committed the crime evolved over time.

2.2. Task Validation. To validate our task, we ran a preliminary sample (*n* = 26). Based upon extant literature [6,10], we hypothesized that the orbitofrontal (OFC), dorsolateral prefrontal (dlPFC), anterior insula (AI), precuneus, dorsal anterior cingulate (dACC), and inferior frontal gyrus (IFG) activation during social uncertainty tasks specifically would be associated with periods of increased uncertainty in the social uncertainty task, which also matched Neurosynth [33] queries using the terms "social cognition", "ambiguous", and "uncertainty". We then used FSL's FEAT [34] to conduct a parametric analysis using data from 26 adult subjects that have completed the outlined paradigm. Subjects' certainty ratings from moment to moment were detrended (resulting in a time course of only rating inflections), demeaned, and z-standardized, to reduce spurious correlative influences and lagged by 10 seconds to capture the decision-making cognitive processes that precede rating changes – analogous to standard practices in the memory event-segmentation literature [12,14]. We found strong activation within each of the previously outlined regions during our social task (**Fig 2**), suggesting our task is

Figure 2. Thresholded Z-statistic map from preliminary analyses of paradigm with adult participants (n = 26)



IFG = Inferior Frontal Gyrus; Cortex; AI = Anterior Insula; dlPFC = Dorsolateral Prefrontal Cortex; PCun = Precuneus dACC = Dorsal Anterior Cingulate Cortex successfully targeting social ambiguity-related cognitions.

2.3. Participants and Power Analysis. Participants will be healthy individuals, ages 18 to 85. Using Stanford's Neuropower [35] Toolkit with pilot data collected in our lab suggested that 53 subjects would be required for 1 - β = 0.80, as indicated by the random field theory parameter.

2.4. Image Acquisition and Pre-processing. Scanning will be performed on a 3T Siemens Tim Trio MRI system at Temple University. Acquisition parameters for the T2* EPI BOLD sequence includes 3 mm slice thickness, a TR = 2000 ms; TE = 25 ms; flip angle of 75°, and a FOV = 1680 x 1680 mm. Neuroimaging data will be preprocessed with the standard fMRIPrep pipeline [36] to maintain generalizability. It should be noted that MVPA analyses like ISC, which are sensitive to the voxel-level patterns that spatial smoothing could distort, are robust to the standard gaussian kernel size that fMRIPrep applies during spatial smoothing [37]. Behavioral rating data will be averaged across 2 second periods to match the TR. Motion outliers will be assessed using the FSL Motion Outlier Tool [34], which defines outlier thresholds as the 75th percentile plus 1.5 times the interquartile range. If greater than 15% of TRs that compose a trial are outliers, the TR will not be used for analyses.

2.4 Analyses. ***Intersubject Neural Synchrony Within and Across Domains.*** Intersubject correlations will be calculated using the voxel-wise approach that nltool's ISC function [38] employs in Python. The ISC function correlates the time series of each voxel's activity within each participant with the average time series of that same voxel across all other participants, yielding a coefficient representing how similar neural activity patterns are in that voxel among people on average. To adjust for autoregression (i.e., a statistical relationship between prior and subsequent datapoints; violating the assumption of observation independence), temporal smoothing, voxel-wise detrending, and nuisance regression functions from the nltools package will be applied to our data. The ISC-generated coefficients of each voxel contained within each of the discrete functionally-defined regions from Schaefer's 2018 cortical atlas [39] will be averaged to compute a region-level value of intersubject synchrony. Nonparametric permutation analyses will test for significance by generating correlations of randomly permutated activity within each subject iteratively ($n \geq 5000$) and comparing confidence intervals for our observed against a null distribution, as has been applied in previous examples of ISC analyses [20]. The degree of synchrony across participants will be visualized using cortical heat maps to highlight which specific regions are involved in either social or non-social uncertainty judgments while processing complex, feature-rich stimuli across individuals. ***Neural Synchrony Predicting Behavioral Synchrony.*** We will also the explore the link between neural signals of certainty judgments and subjective behavioral indicators of uncertainty by using the neural synchrony exhibited between subjects for a given parcel to predict the behavioral synchrony they exhibit. Intersubject correlations among behavioral ratings will be generated using generalized estimating equations (GEEs), which do not assume normality or observation independence, in R via the gee package [40]. Intersubject neural correlation values within a given region will be used to predict correlation between subjects among lagged behavioral values using mixed effects hierarchical linear modeling (HLM) via the lme4 package [41] in R. To address spontaneous fluctuations in functional activity which often limit our ability to generate reliable correlations of neural activity over long continuously-measured time courses [42], associations between behavioral and neural data will be examined within tapered sliding windows, using the same approach as has been applied in other video stimuli ISC paradigms [15]. We will employ an information theoretic approach by comparing Bayesian Information Criteria (BIC) values for competing models in chi square comparisons. Our initial null model will include a random intercept for the correlated subject pair in each observation. We will iteratively add fixed effects of neural ISC values, the region which generated the ISC value, and covariates as appropriate (e.g., visual contrast, etc. [21,43]) until a model of best fit is determined. We will also take a data-driven approach to determine the appropriate lag between our neural and behavioral activity by incrementally varying lag magnitude and adopting the model of best fit.

2.5. Predicted Results. We anticipate increased neural synchrony across participants within parcels containing the dlPFC and components of the OFC during the non-social certainty task. We also anticipate seeing increased synchrony from the PCun, IFG, dACC, AI, and dlPFC when performing the social uncertainty task. We hypothesize that synchronization across these regions will predict increased synchronization of behavioral certainty ratings. The degree of synchrony will likely vary depending upon which character a subject hypothesizes had committed the crime during the social task. We theorized that subject hypotheses should be divided into two groups: subjects suspecting our target character and subjects suspecting another character. A confirmatory factor analysis conducted using the lavaan package [44] in R applied to the time series of behavioral ratings collected thus far supports this data structure (*rmsea* = 0.07, $p > 0.05$) across both video halves. As such, subject hypothesis at the time of rating will be a moderator in our analyses such that individuals entertaining similar hypotheses will be expected to demonstrate greater neural synchrony than individuals entertaining different hypotheses.

3. References

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