Characterizing Brain Entropy During a Face-Name Paired Association Task

by

Mackenzie Joel Leavitt

A thesis submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Master of Science

Auburn, Alabama
August 6, 2022

Keywords: brain entropy,
face-name paired association, hippocampus

Approved by

Jennifer L. Robinson, Ph.D., Chair, Alumni Professor of Psychological Sciences
Sara K. Blaine, Ph.D., Committee Member, Assistant Professor of Psychological Sciences
Jeffrey S. Katz, Ph.D., Committee Member, Professor of Psychological Sciences

Abstract

Brain entropy analysis – a measure of the unpredictability of a physiological time series - has gained attention as a measure of the complexity of brain activity in functional neuroimaging research. Investigations of neuropsychiatric and neurodevelopmental conditions have consistently demonstrated significant alterations in brain entropy compared to healthy controls. Additional work in healthy participants has found a gradient of brain entropy differences across the functional connectome associated with the resting state, as well as brain entropy differences in task-based neuroimaging experiments. In this study, I examined whole brain entropy at rest and whole brain entropy during a face-name paired association task. Region of interest (ROI) analyses were employed to examine hippocampal activity during different phases of the face-name paired association task (e.g., encoding versus recognition). Results revealed no significant differences in whole brain entropy between the resting state and the task state. Further, no significant entropy differences were observed between separate phases of the task state, both at the whole brain level and within the hippocampal regions. Limitations such as sample size, task length, and study design may potentially account for null results; however, these results may also suggest that entropy may be a less robust measure when applied to a within-subjects design in healthy participants.

Acknowledgments

It is difficult to convey how profoundly this project is the consequence of the labor, commitment, and support of so many individuals besides myself. First and foremost, I want to thank my advisor, Dr. Jennifer L. Robinson, for allowing me the freedom to explore a terrain of research beyond her domain and for her encouragement and support as we struggled together to bring the project to fruition; her patience and perseverance have been an indispensable aid throughout this process. Secondly, I would like to thank Dr. Ze Wang, associate professor in the Diagnostic Radiology and Nuclear Medicine department at University of Maryland. In addition to pioneering the use of sample entropy for functional brain imaging research, Dr. Ze Wang spent many months having patient e-mail conversations as we worked together to apply his method to the data for my project. Without his assistance, this project could not have been completed. I would like to thank Dr. Blaine and Dr. Katz, both of whom have served as mentors for me in my development as an instructor of psychology. Lastly, and most importantly, I would like to thank my angel mother, whose support, encouragement, and gentle patience and compassion have given me the strength to endure through trials and tribulations long after I wanted to give up.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BEN = Brain Entropy

BENtbx = Brain Entropy Mapping Toolbox

fMRI= Functional Magnetic Resonance Imaging

FSL=FMRIB Software Library

HCP=Human Connectome Project

ROI=Region of Interest

RsfMRI= Resting-state Functional Magnetic Resonance Imaging

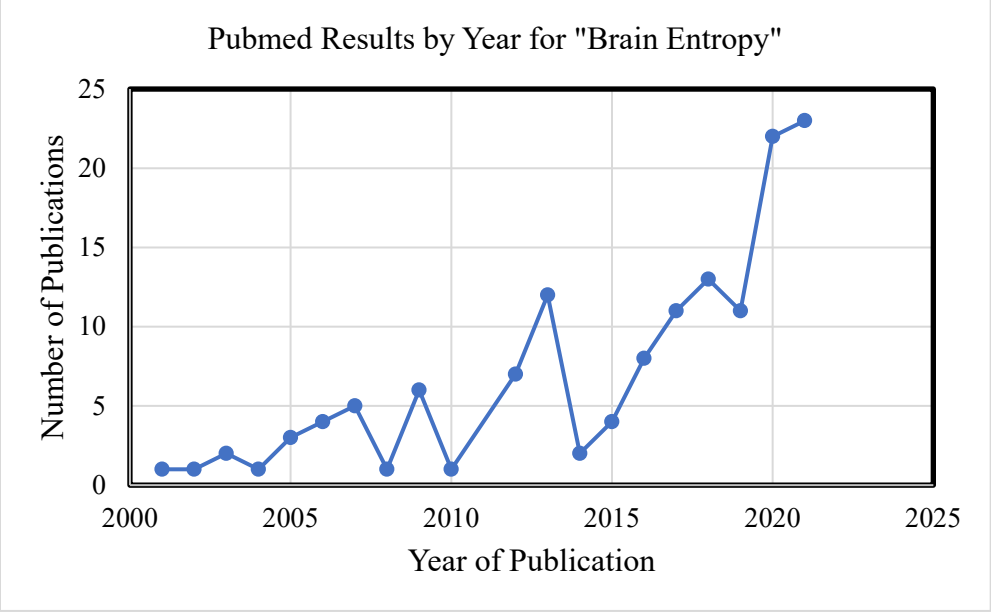
SPM12= Statistical Parametric Mapping version 12

TfMRI=Task-based Functional Magnetic Resonance Imaging

Introduction

Functional magnetic resonance imaging (fMRI) analysis has grown in popularity as a method for analyzing human brain function *in vivo* (Poldrack et al., 2011). Consequently, there has been a significant increase in analytic techniques probing the resultant functional neuroimaging data (Friston, 2009). One such technique, brain entropy (BEN), has gained popularity in the last 15 years, with the first paper utilizing this technique on fMRI data published in 2003 (De Araujo et al., 2003). A recent PubMed search (see Figure 1) reveals a broad increase in papers on the subject of brain entropy; applications of brain entropy analysis to functional neuroimaging data continue to rise, especially since publication of a brain entropy analysis of participants from the Human Connectome Project (HCP) (Z. Wang et al., 2014). Increasingly, this technique has been applied as a method for studying group differences in neural functioning and differences in task performance and engagement.

Figure 1. PubMed results returned for "Brain Entropy", years 2000-2021.



Brain Entropy

BEN is typically defined as a measure of complexity, predictability, regularity, and stochasticity of neural activity in the brain. Multiple methods exist for calculating BEN, each based on a different mathematical formulation of entropy. A variety of mathematical approaches to entropy analysis have been used in functional neuroimaging research; the most common techniques include Multiscale Entropy, Permutation Entropy, Sample Entropy, and Differential Entropy (Keshmiri, 2020). Each of these analytic techniques employs a measure that assesses variability in neural activity, but each accomplishes this assessment through different analytic procedures. Historically, the term entropy has been widely applied in the context of physics (as a means to quantify thermodynamic irreversibility (Landi & Paternostro, 2021); however, it has also been used to define information mathematically (Shannon, 1948). The methods of assessing entropy that have been applied to brain imaging research have their intellectual roots in Shannon entropy, which determines entropy by assessing the degree of uncertainty of the state of a given variable with respect to all its possible states (e.g., a variable with only 3 possible states has reduced Shannon entropy compared to a variable with 100 possible states). Existing methods for analyzing BEN build on this concept, assessing the entropy of neural activity using probability statistics.

For the purpose of this project, I used a measure of entropy called sample entropy, which is an algorithm designed to measure the regularity (or conversely, irregularity, or randomness) of a series of data based on the existence of patterns (Delgado-Bonal & Marshak, 2019). Sample entropy is designed to assess the randomness of a dataset without any assumptions about the source the dataset is derived from. Sample entropy is one of several measures to assess BEN, or neural complexity, terms which are frequently used interchangeably in the scientific literature. However, sample entropy is less dependent on researcher degrees of freedom and the length of

the time series being assessed (Richman et al., 2004). Furthermore, sample entropy has been widely used to analyze time-series data from a variety of physiological systems in the human body (Lake et al., 2002; Nezafati et al., 2020; Yentes et al., 2013) Thus, it represents a robust and effective technique to assess the complexity of biological time-series.

Sample entropy is mathematically defined as the negative natural logarithm of a conditional probability that a pattern length of *m* points will repeat itself without including self-matches, for *m*+1 within a tolerance of *r* in a time series of length *N* (Richman & Moorman, 2000). More specifically, it is a measure of a conditional probability that two similar sequences of points will remain similar at the next point (Richman et al., 2004). When calculating sample entropy, investigators must choose values for *m* and *r*. In the context of the above definition, *m* represents the pattern length of data vectors compared against one another for matches at the next timepoint within a tolerance interval, similar to a confidence interval known as *r.* Research identifying optimal values for *m* and *r* remains in its infancy but will be discussed in further detail in the methods section.

Specifically, when applied to fMRI data, sample entropy is calculated for each voxel in the time series. The entropy of a given voxel is determined mathematically by analyzing the probability that the BOLD signal from that voxel will repeat itself for a given pattern length, known as an embedding dimension (*m*) within a given tolerance window I. By comparing sequences of data from a time series, this analytic technique can measure the relative order/stability based on similarity/dissimilarity of data from the same participant. Entropy can thus be understood as a measure of predictability or regularity in the neuroimaging timeseries. The more predictable or regular the pattern, the less entropic it is. Importantly, since this measure

relies on the timeseries of individual voxels, it is an indirect measure of neural entropy since the time series of each voxel only indirectly reflects neuronal activity**.**

Brain Entropy in Healthy Subjects

Brain entropy has been examined in the context of resting state and task paradigms in healthy participants. As previously noted, (Z. Wang et al., 2014) researchers published a study analyzing healthy functional connectomes from the HCP dataset. Using spectral clustering, they found seven major clusters of differing entropy values across the functional connectome at rest (Z. Wang et al., 2014). These results revealed that brain entropy differs meaningfully across different brain regions, suggesting a relationship between regional functional specialization and brain entropy. Similarly, researchers (Nezafati et al., 2020) found important functional networks of brain entropy associated with task and resting conditions. Specifically, they (Nezafati et al., 2020) found differing entropy values based on task related functional networks that differed as task demands changed. During task, the dorsal attention network of the brain had increased brain entropy relative to the resting state, while the entropy of the limbic system was reduced during task. Additionally, whole brain entropy was higher during the resting state than during task conditions. This experimental paradigm is notable because it demonstrates a method by which the relationship between task/rest, task performance, and brain entropy can be probed. Identifying brain entropy as a marker of neural function is only possible after understanding how entropy is related to specific psychological functions.

Notably, several studies have examined human intelligence and its relationship to brain entropy (Menon & Krishnamurthy, 2019; Omidvarnia et al., 2021; Saxe et al., 2018; Z. Wang, 2021). Broadly, these studies observed a relationship between increased brain entropy and higher fluid intelligence. However, in a larger sample comprised of the human connectome project,

researchers (Z. Wang, 2021) observed that reduced entropy of the default mode network actually corresponded to higher fluid intelligence and better task performance. Once again, these patterns suggest that global brain entropy is related positively to psychological function, but the entropy of specific brain regions and functional networks does not necessarily follow those broad patterns. Brain entropy varies across the brain and these variations are largely unknown, especially in the context of different brain functions.

Brain Entropy and Brain Function

The above findings point to general theories of brain function that can be understood through the lens of neural complexity. A recent paper (Hager et al., 2017) argues that the existing literature comparing brain entropy in diseased patients relative to healthy controls point to neural complexity as a potential biomarker for psychosis. Yang and colleagues (2015) observed patterns of decreased complexity towards regularity and decreased complexity towards randomness in schizophrenia patients; specifically, they found these patterns were related to positive and negative symptoms of schizophrenia, respectively (2015). Based on Yang and colleagues (2015) results', Hager and colleagues (2017) argue that altered resting state brain dynamics reflected by entropy differences in severe mental illness could be subject to similar dynamics observed in cardiovascular disease, such as reduced heart rate variability or irregularity in atrial fibrillation (2017).

Furthermore, some researchers have attempted to use machine learning techniques to predict clinical status using entropy analyses of functional imaging data (Bosl et al., 2011; Song et al., 2019; Spuhler et al., 2018; Wu et al., 2021); most frequently, these techniques have been most successful in differentiating healthy controls and patients in various stages of cognitive decline and dementia (Sun et al., 2020). Although these investigations have yielded interesting

patterns of results, to fruitfully use BEN as a biosignature of abnormal neural function, additional research is needed to understand neural complexity in healthy participants, particularly in task-related contexts given that the bulk of the literature on BEN has been applied to resting state data. Specifically, the existing literature in clinical populations does not inform investigators on the mechanisms that cause BEN to differ in pathological states, nor does it indicate the ways in which BEN facilitates behavioral function in healthy participants. Even if BEN could reliably predict specific symptoms of neuropsychiatric dysfunction, these predictions could not clarify the causal relationship between BEN and neuropsychiatric symptoms. Thus, the mechanisms by which BEN facilitates brain function must be better understood if brain entropy is to be considered a viable biosignature of unhealthy brain dynamics.

Another theory of global brain function, the entropic brain hypothesis, attempts to integrate the existing empirical research on brain entropy (Carhart-Harris, 2014; Carhart-Harris et al., 2018; Carhart-Harris & Friston, 2019). Based on findings from neuroimaging experiments with healthy participants under the influence of psychedelic drugs, this theory proposes that entropy plays a critical role in the dynamics of consciousness. In particular, entropy analyses in these experiments show a significant increase in brain entropy once participants have ingested psychedelic drugs (Tagliazucchi et al., 2014; Viol et al., 2017; Varley et al., 2020). The entropic brain hypothesis suggests that in normal conscious states, brain activity occupies a state of 'criticality'- a transition point between order and disord–r - which shifts under the influence of psychedelic drugs (Carhart-Harris et al., 2014). The argument points to a spectrum of conscious states that can be understood through the ways in which brain entropy changes as conscious states change. This theory of criticality, if correct, would suggest brain activity functions at a precise balance between complexity and regularity under optimal brain function performance.

Thus, entropy is suppressed in waking consciousness to constrain neural activity to task demands. One study in healthy participants observed that increased brain entropy under the influence of lysergic acid diethylamide (LSD) actually predicted subsequent increases in the personality trait openness to experience more than six months after the psychedelic experience (Lebedev et al., 2016), suggesting a connection between resting brain entropy and personality differences. This research is critical because it may contextualize existing findings that task demands constrain global entropy values differentially.

Investigators have also paid attention to the relationship between information processing, brain connectivity, and entropy. A notable study combined findings from electroencephalography (EEG) entropy, fMRI entropy, and network connectivity analysis to argue that there is a significant relationship between measures of functional connectivity and brain entropy (D. J. J. Wang et al., 2018). They observed that increased regional entropy predicted higher functional connectivity of a given region with the rest of the brain. They argue that the complexity of regional neural signals could be understood as an index of the brain's information processing capacity. In this case, increased complexity might indicate greater transition between different states of brain networks, indicating a greater propensity for information processing (D. J. J. Wang et al., 2018). However, it is unclear whether increased complexity within a given region may aid that region in the performance of a behavioral function relative to increased complexity across the whole brain.

The Hippocampus and Face-Name Paired Association

Much existing research has examined the functional connectivity of the limbic system and its constituent elements, particularly the amygdala and hippocampus (Dalton et al., 2019; De Voogd et al., 2016; Fastenrath et al., 2014; Robinson et al., 2015, 2016; C. N. Smith et al., 2006;

Zeidman & Maguire, 2016). The hippocampus is involved in stages of memory encoding and consolidation (Raynal et al., 2020). Relevant to the present proposal, research on face-name paired association has demonstrated the importance of hippocampal function for face encoding and association (Sperling et al., 2003a; Sperling, 2003b; Sperling et al., 2001). Functional neuroimaging studies of face-name paired association tasks have shown strongly correlated activity between the right and left hippocampus during successful encoding (Sperling et al., 2003b). Other research supports the idea that functional connectivity of the hippocampus may subserve successful memory encoding (Grady et al., 2003). Particularly, tasks such as these robustly activate the anterior hippocampus, which suggests that this region is especially important for associative encoding, a finding supported by meta-analytic techniques (Robinson et al., 2015).

The hippocampal formation primarily consists of cornu ammonis (CA1-4), the dentate gyrus, and the subiculum (Wible, 2013). Different subregions of the hippocampi are involved in different phases of face-name association tasks (Zeineh, 2003). Further research (Tsukiura & Cabeza, 2008) demonstrates that successful recall on face-name paired associate tasks depends on the strength of functional connectivity between the hippocampus and other regions of the cortex. Given the argument that regional complexity may be related to functional connectivity such that increased regional complexity increases the likelihood of greater functional connectivity with other brain regions (D. J. J. Wang et al., 2018), the above results may support a connection between changes in the entropy of the hippocampal region and increased functional connectivity between the hippocampus and other brain regions. However, little is currently known about the entropy of the BOLD signal in the hippocampal region due to difficulties in image resolution at lower magnetic field strengths. If changes in entropy are observed in between

task and rest, this may suggest that the face-name paired association task is increasing functional connectivity between the hippocampus and other brain regions.

Regional Brain Entropy vs Whole Brain Entropy

Most research on brain entropy tends to either employ whole brain entropy or regional brain entropy, with the latter being performed through ROI analyses or through clustering techniques (Keshmiri, 2020). Consequently, there are limited empirical observations directly comparing whole brain and regional entropy in the same participants engaged in the same task. In this study, I propose to compare differences in brain entropy between task and rest conditions, both at the whole brain and regional levels. Such analyses may reveal that the entropy of different brain regions may vary in unexpected ways; for example, during a task state, it may be the case that whole brain entropy decreases compared to rest, but that the entropy of specific regions increases during rest. Such evidence might support the notion that the distribution of neural complexity may be as significant as the magnitude of neural complexity. Furthermore, recent work suggests variables such as stimulus type, task type, and participant state cause significant differences in the pattern of functional activation in the hippocampus (Robinson et al., 2021). Given the direct relationship between entropy and functional connectivity, further work will be necessary to elucidate task, state-, and trait-related differences in neural complexity.

Hypotheses and Pre-Registration

Despite a surge of published studies, BEN is a relatively under-utilized analytic technique in the functional neuroimaging community. The bulk of the existing literature has examined group differences between healthy controls and diseased patients. While this work is certainly useful for understanding neuropathology associated with disease states, it is equally critical to understand the principles by which entropy is modulated in the healthy brain. To this end, I

examined the entropy of the left and right hippocampus separately at rest and during a face-name paired association task. I posited that the entropy of the hippocampus should change meaningfully in response to interrogation via a face-name paired association task, and that different phase of the task would demonstrate differential effects on entropy. Methods for analyzing neural complexity have grown in abundance, but little is known about the specific relationship between neural complexity of individual brain regions and neuropsychological function. This research is important for understanding the relationship between entropy and brain function and will contribute to our understanding of how the neural complexity of the hippocampus subserves memory function. As such, I proposed the following hypotheses:

H1: Sample entropy of the whole brain will be higher during rest relative to sample entropy of the whole brain during the face-name paired association task.

H2: Sample entropy of the whole brain will be higher during the encoding phase of the face-name paired association task relative to sample entropy of the whole brain during the recognition phase of the face-name paired association task.

H3: Sample entropy across the bilateral hippocampus will be higher during the encoding phase of the face-name paired association task relative to the recognition phase of the face-name paired association task.

These hypotheses and the analytic plan described in the methods were pre-registered on the Open Science Framework (https://osf.io/4tkp2/).

Methods

Participants

Participants (between 19 and 25 years old) were volunteers recruited from the Auburn University community with no contradictions for magnetic resonance imaging. Contradictions for magnetic resonance imaging included the following: the presence of pacemakers, implanted cardioverter defibrillators, any metal implanted in the body, some dental work, prior injury to the eye involving a metal object or fragment, any implanted medical device or non-removable device, breathing problems or disorders, claustrophobia, inner ear disorders, vertigo or dizziness, tattoos or permanent makeup that contains metal, and body piercing jewelry that cannot be removed. Participants were recruited as part of a research study investigating hippocampal function. Recruitment primarily occurred through the Auburn University Department of Psychological Sciences online participant recruitment system (https://auburn.sona-systems.com). In total, 35 participants were recruited, with useable data from 31 participants (4 participants were excluded due to claustrophobia, cramps, inability to follow instructions, and scanner issues, respectively; see Table 1). This study employed a within-subjects design: all participants were required to complete all tasks. However, not all participants that completed the tasks had available data for each imaging condition; therefore, this document only reports on participants with usable data for all scans. In total, twenty-four participants had usable data for the scans relevant to this project.

Table 1

Participant Demographics

Characteristic	Sample
Gender	
n	24
Male	10
Female	14
Age	
M	21.1
SD	1.5
Handedness	
Left	2
Right	22

Prescreening Measures

Participants in this study filled out several pre-screening measures. Specifically, they filled out a demographic and medical history questionnaire in preparation to complete the functional neuroimaging portion of the experiment (see Appendix 1), including a handedness questionnaire (see Appendix 2). Participants recruited to this study were also pre-screened for symptoms of depression and excluded if they met diagnostic criteria for depression via the Beck Depression Inventory (BDI) (Beck et al., 1961). The BDI (21 items) is a self-report assessment that measures depressive symptoms and asks subjects to consider their thoughts/feelings of the previous two weeks. Scores range from low depression (1-16) to moderate depression (17-30) to significant depression (> 31) (see Appendix 3). Participants with moderate depression and significant depression were not considered beyond pre-recruitment. Participants were also pre-screened for symptoms of Posttraumatic Stress Disorder (PTSD) using the PTSD Checklist (PCL) Civilian Version (Weathers et al., 1993) and excluded if they met diagnostic criteria. This

checklist (17 items) is a self-report assessment that measures PTSD symptoms that asks participants to consider their thoughts/feelings of the previous month. Items are scored into types B, C, and D, and diagnostic criteria are based on a response to at least one B item, three C items, and two D items (see Appendix 4). Personal attitudes and traits were also briefly assessed using a shortened 10-item version of the Marlow-Crowne social desirability scale, to assess participants' self-reported social desirability bias (Strahan & Gerbasi, 1972) (see Appendix 5). No other psychiatric or mental health conditions were screened for in this study.

Magnetic Resonance Imaging Prescreening Measures

Following the completion of the above prescreening measures, each participant was verbally interviewed either in person or over the phone using the MRI Subject Recruitment/Advance Screening Form (see Appendix 6). If a participant answered yes to any of questions 4-13 on the MRI Subject Recruitment/Advance Screening Form or had any of the implanted devices at the bottom of the form, the participant was informed that they did not meet qualifications for the study. Participants that met qualifications were invited to schedule a time to participate in the research study.

Upon arrival to the Auburn University Magnetic Resonance Imaging Center, an investigator met participants in the reception area on the first floor. Participants were presented an Informed Consent form and asked to fill it out and return it to the investigator. After clarifying participant understanding of the informed consent form, participants filled out the MRI Pre-Entry Screening from (see Appendix 6). The investigator then asked participants if they were feeling well that day. Upon confirming this, both the participant and investigator signed the MRI Pre-Entry Screening Form.

Participants were then asked to change into surgical scrubs provided by the Auburn University MRI Research Center. Participants were then weighed facing outwards from the scale (no comment was made on participant weight). Participants were then shown the neurocognitive tasks they would later complete in the scanner. Participants were able to practice the tasks on the computer monitor to increase familiarity with the task procedure. Following a brief practice period, participants were then scanned by an operator with Level 3 MRI safety training. Upon completion of the study, participants received $25 as compensation for their time. Further, participants also received two hours of SONA credit to be applied as extra credit in their psychology courses.

Functional Neuroimaging

All neuroimaging data were acquired on the Auburn University MRI Research Center (AUMRIRC) 7T Siemens MAGNETOM outfitted with a 32-channel head coil by Nova Medical (Wilmington, MA). A whole-brain high-resolution 3D image utilizing an MPRAGE sequence was collected (256 slices, 0.63mm x 0.63mm x 0.60mm, TR/TE: 2200/2.8, flip angle = 7°, base/phase resolution = 384/100%, collected in an ascending fashion, TA = 14:06) for registration purposes.

All functional neuroimaging measures were captured during one experimental session. Participants performed a memory task encoding faces/words/scenes (a task unrelated to the present document), followed by a face-name paired associate task, a face matching task, a resting state fMRI scan, a diffusion tensor imaging scan, and a recognition of faces/words/scenes. The relevant imaging scans for completion of this project were the face-name paired associate task, the resting state scan, and the MPRAGE structural scan.

Resting-State Functional Magnetic Resonance Imaging (rs-fMRI)

High resolution, submillimeter rs-fMRI was performed. Specifically, participants were scanned with an echoplanar imaging (EPI) sequence, optimized in-house for the hippocampus (37 slices acquired parallel to the AC-PC line, 100 volumes, interleaved acquisition, voxel size = 0.85mm x 0.85mm x 1.5mm, TR/TE = 3000/28ms, flip angle = 70°, base/phase resolution = 234/100%, A>P phase encode direction, iPAT GRAPPA acceleration factor = 3, TA = 5:00). Participants were asked to lie in the scanner with their eyes closed and to not think about anything in particular for the resting state portion of the scan. The use of the 7T MAGNETOM, with its improved spatial resolution and sensitivity, affords a more precise characterization of blood oxygen level dependent (BOLD) signals from the hippocampus, a region which is especially hard to image precisely and reliably at lower magnetic strengths (Springer et al., 2016). The same imaging parameters were utilized to perform task-based functional imaging.

Task-based Functional Magnetic Resonance Imaging

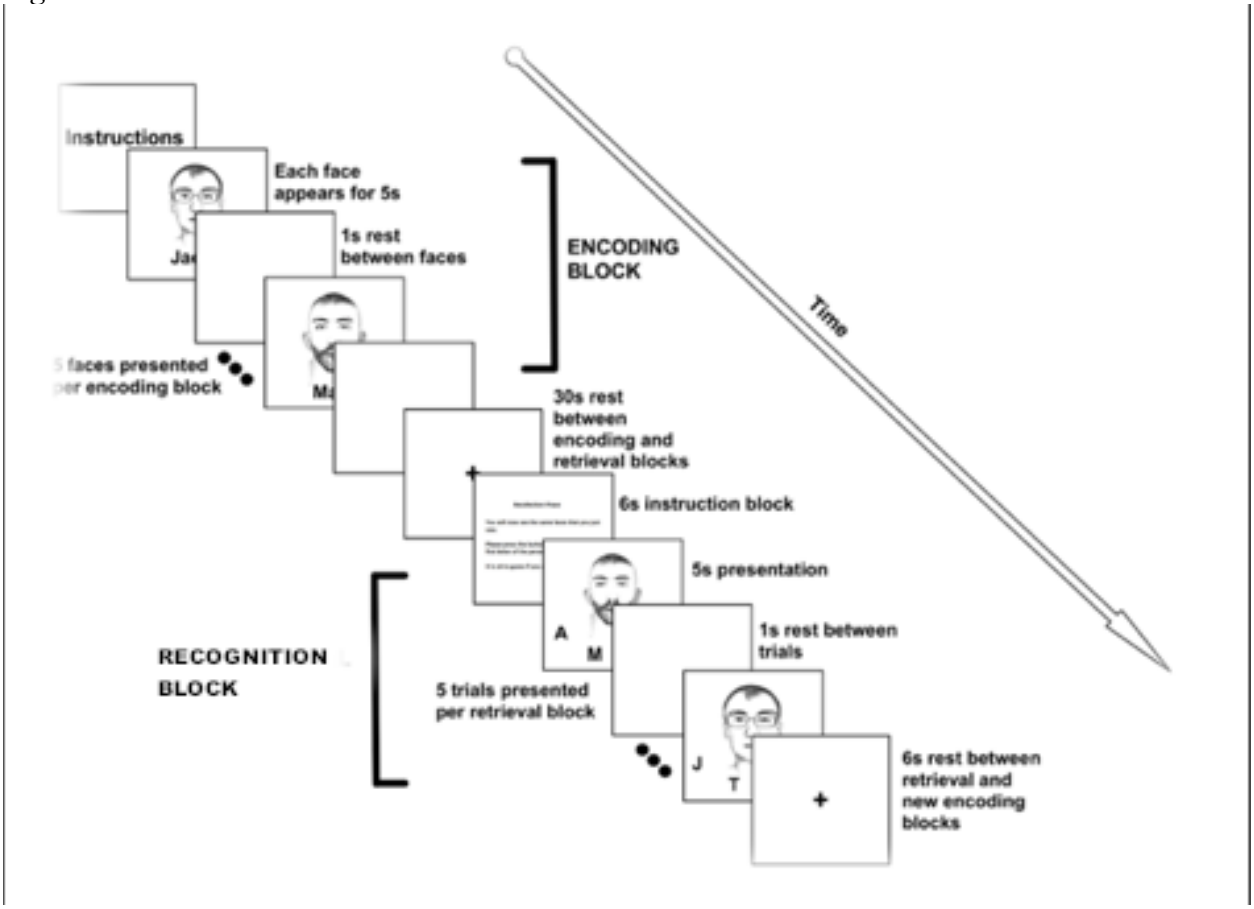
High resolution, submillimeter task-based fMRI was also performed as well. Total acquisition time for the task-based imaging was 10 minutes and 6 seconds. While in the scanner, participants completed a face-name paired associate task, known to reliably elicit hippocampal activation (Tsukiura & Cabeza, 2008). Briefly, this task consisted of an encoding phase, in which participants were shown faces with names listed underneath, and a recognition phase, in which participants were shown the same faces and were required to indicate with a button box which letter corresponded to the name associated with that face. The task was programmed using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). Images of faces were gray scaled with the same dimensions for each image.

Face/name pairings for this task were presented in blocks (6 encoding blocks and 6 recognition blocks). Blocks alternated back and forth (one encoding block, one recognition block, followed by a rest period, and then the beginning of a new encoding/recognition series of blocks). Novel faces were presented in each encoding block, for a total of 30 faces over the task period. At the beginning of the task, participants viewed an instruction screen for 6000ms informing them of the instructions for the following encoding block. Following a brief rest period, they were shown a face with a name underneath. Participants viewed faces for five seconds with a one second rest period (where participants viewed a black fixation cross in the center of a white background) between faces. Following the presentation of five faces, there was a thirty second rest period where participants viewed a black fixation cross in the center of a white background. The 30 second rest period was completed between each block.

Next, an instruction screen appeared for 6000ms prior to the recognition phase. In the recognition block, participants viewed the five faces previously displayed in the encoding block for five seconds, only with letters under the image of each face. Participants were required to indicate (using an in-scanner button box) which initial displayed at the bottom of the screen corresponded to the first letter of the name associated with the previously displayed face. Images of faces were gray scaled with the same dimensions (see Figure 2 for an example of encoding and recognition blocks; see Appendix 7 for a time chart of the task protocol).

During data collection, there was a communication issue between the in-scanner button box and E-prime 2.0, which prevented participant responses on the button box from being properly recorded. As a consequence, I was unable to assess participant accuracy in correctly pairing faces to names. Thus, no behavioral data are presented in this study.

Figure 2. Task-Protocol for Face-Name Paired Associate Task



Functional Magnetic Resonance Imaging Preprocessing

Preprocessing was performed using the sample entropy toolbox on the task and resting state fMRI data (Z. Wang et al., 2014). This toolbox runs preprocessing analyses via MATLAB scripts utilizing both Statistical Parametric Mapping 12 (SPM12) along with the FMRIB software Library (FSL) version 6.0. All preprocessing steps described in this section were completed for both RsfMRI data and TfMRI data.

To begin, the image origin was reset at the anterior commissure in order to ensure proper alignment of functional images to structural images in SPM12. Following this, the structural images were segmented in SPM12 for each subject; gray matter, white matter, and cerebrospinal fluid (CSF) were each segmented, and a deformation field was generated to be used for

normalization. Afterwards, slice timing correction was completed in SPM12. Following slice timing correction, realignment and motion correction was performed in SPM12. Then, calculation of signal to noise ratio was performed in SPM 12, and each functional image was then co-registered to its anatomical counterpart. Temporal nuisance filtering was performed using a bandpass filter; this script implemented CompCor, a component based method for noise reduction in blood oxygenation level dependent (BOLD and perfusion-based (fMRI) (Behzadi et al., 2007). The last preprocessing step performed before calculation of BEN was spatial smoothing. All functional images were smoothed at a 4 mm Gaussian kernel.

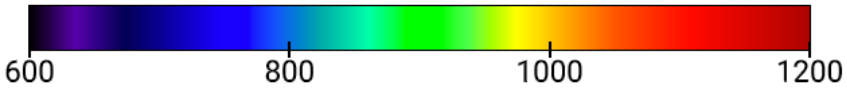
BEN maps were then calculated for each subject (more detail on this process is provided in the next subsection). After entropy maps were calculated, co-registration was performed; BEN maps were co-registered to the preprocessed functional images, and they were each co-registered to their respective anatomical images. This ensured that BEN maps were properly aligned with both their functional and structural images to afford more precise comparison of entropy maps within subjects. Then, spatial normalization was performed on the preprocessed BEN maps, aligning the BEN maps into MNI space. Finally, spatial smoothing was performed on the BEN maps themselves with a 9mm Gaussian kernel to reduce signal to noise ratio in the entropy calculation.

Measuring Brain Entropy

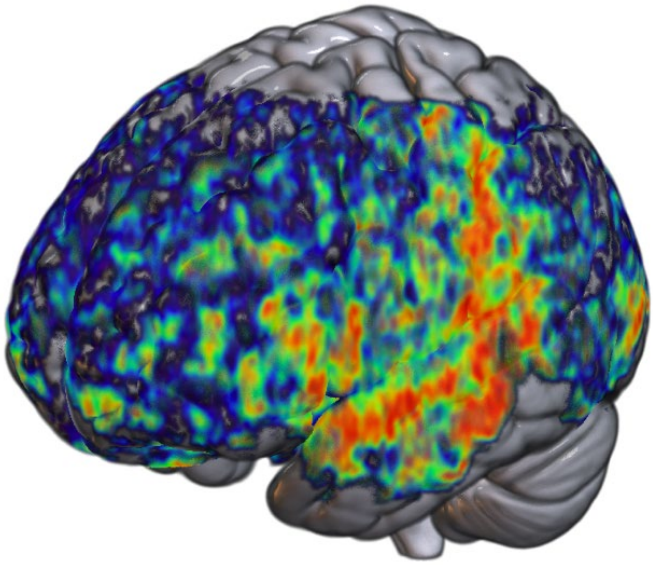
The Brain Entropy Toolbox (BENtbx) was used to calculate the entropy for both task and resting state neuroimaging data (Z. Wang et al., 2008 Z. Wang et al., 2014). Brain entropy calculations were performed with a binary code that runs a sample entropy calculation on an fMRI time-series. This tool treats each voxel as its own time-series, computing the sample entropy for every brain voxel. Upon calculating entropy, the file generates a BEN map

containing a spatial distribution of entropy values across the whole brain (see Figure 3 for an example of a resting-state whole BEN map and Figure 4 for a mosaic of resting state BEN maps for all participants).

Figure 3. Example of a Single Participant Whole Brain Entropy Map for the Resting-state



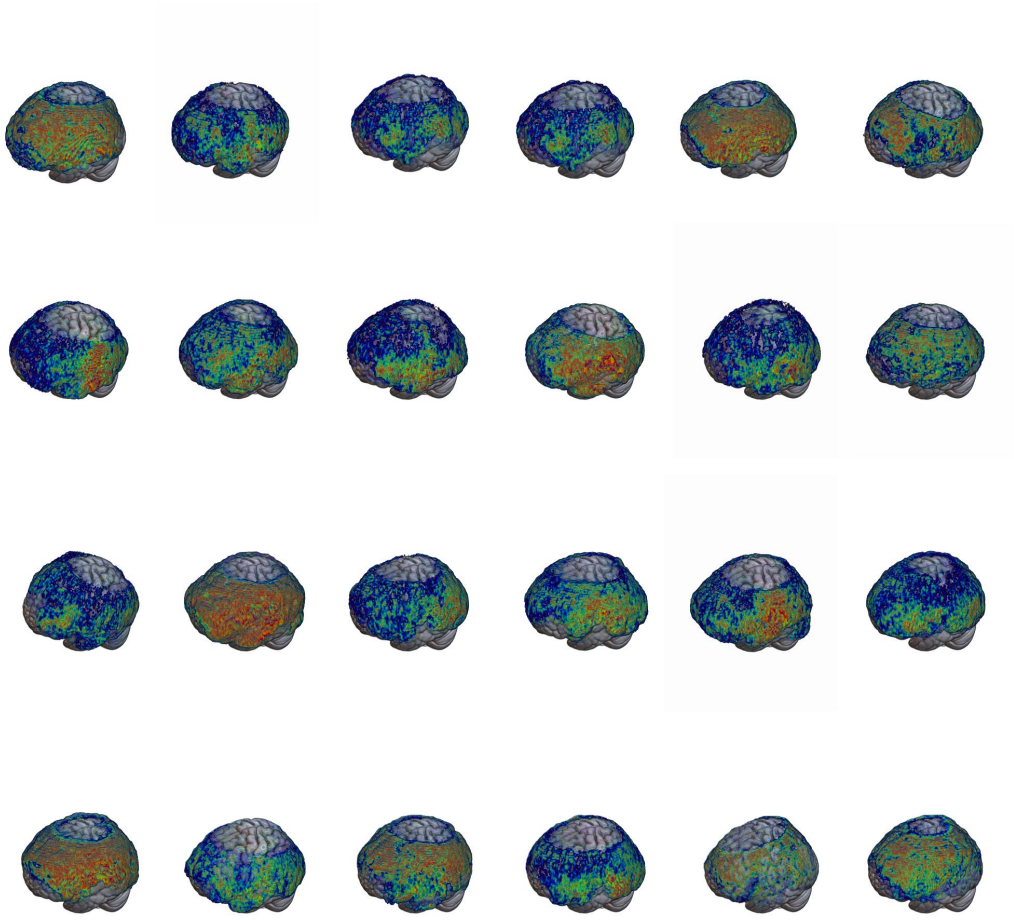
The values on the color bar represent signal intensity at each voxel



Note. Darker colors represent lower entropy, brighter colors represent higher entropy values.

Figure 4. Resting-state Whole Brain Entropy Maps for all Participants

The values on the color bar represent signal intensity at each voxel



Note. Darker colors represent lower entropy, brighter colors represent higher entropy values.

As described in the introduction, the values for *m* and *r* in the formula for sample entropy must be chosen by the investigator. Prior literature has compared differing values of *m* and *r* for fMRI experiments. (Z. Wang et al., 2014). The general consensus for the value *m* is 3, and the

consensus for the value *r* is 0.6 multiplied by the standard deviation of the time series (Mikoláš et al., 2012; Z. Wang et al., 2014; Yang et al., 2018). Sample entropy was chosen over other methods for analyzing brain entropy because it is less dependent on the length of the time series, and it demonstrates relative consistency compared to other methods such as approximate entropy (Menon & Krishnamurthy, 2019). The results obtained from entropy analysis methods are sensitive to both the parameters one chooses and the time series length in question, so it is important to use methods that are less sensitive to shorter time series given the current data set. For a review of the existing algorithms used to analyze brain entropy and relative advantages and disadvantages, see (Mikoláš et al., 2012).

In brief, sample entropy is defined as the negative natural logarithm of the probability that if two simultaneous data points of a given subset have a certain distance from one another, then two simultaneous data points of a similar subset with an extra data point will also have a similar distance from one another. To simplify the mathematics, take voxel *X.* Suppose voxe*l X* has a time series of 100 timepoints. Take one subset of timepoints from voxel *X* (say 5 timepoints) and refer to the length of that subset as *m*. Now, take a second subset of timepoints of the same length *m* with one extra timepoint (6 timepoints) from voxel *X* and compare it to the first subset. These two subsets are defined as matching if and only if the absolute distance between them is less than *r*, which as previously described is a value chosen by the investigator, typically chosen as a multiple of the standard deviation of the time series (in our case, 0.6). In other words, sample entropy assesses the negative probability that different subsets of timepoints of similar length from a given time series will match each other within a given interval defined by *r.* If a given time series has few matching sets, the entropy of that time series is higher relative

to a time series with more matching sets. The formulas used to calculate sample entropy are documented in Appendix 8.

Whole brain entropy was calculated for the resting state scans and the task scans. Four whole brain entropy maps were generated for each participant: one for the resting state scan, one for the task-based scan, and two for the encoding and recognition phases of the task scan, respectively. Further, Dr. Ze Wang built a revision to the BENtbx toolbox, allowing me to use a text file to indicate which timepoints in an imaging file will be analyzed together into a single entropy map. Using this revised toolbox, I analyzed the entropy of each encoding block as one block by collating the time series data into a single entropy map using the BENtbx, despite the encoding blocks being separated in time from one another. I performed the same analysis for each participant for the recognition block. In total, this yielded 48 whole brain entropy maps: 24 for the encoding block and 24 for the recognition block.

While developing this project, an important limitation had to be addressed, namely that the task protocol and the resting protocol were not the same length, and sample entropy is sensitive to data length, which may possibly bias comparisons between the task and resting state. However, this sensitivity can be adjusted by reducing the value of *m* (the sliding window which determines the size of the vectors that are compared in an entropy analysis) for the task scans for comparison to the resting state scans. Consequently, we calculated entropy maps using the standard in the field of 3 for the *m* value and 0.6SD for the *r* value; however, we also calculated entropy maps using 2 and 1 for the *m* value for the task scans. This was done to partially account for the additional length of the task scan compared to the resting state scan. Thus, we calculated a total of 72 task state brain entropy maps at each *m* value, which were separately compared against the resting state scans during statistical analysis.

Statistical Analysis

Statistical analyses for this project were performed in SPM12 (SPM12 http://fil.ion.ucl.ac.uk/spm/). All within-subject comparisons of brain entropy were performed using paired *t*-tests in SPM12. FSL neuroimaging analysis software (Jenkinson et al., 2012) was utilized to extract summary statistics from entropy maps.

Hypothesis 1: Whole Brain Resting-state Entropy vs. Task Entropy

Differences in the whole brain entropy of the resting state were compared to the whole brain task state. Whole brain entropy maps for the resting state and the task state were compared using a directional paired *t*-test in SPM12, hypothesizing that whole brain entropy would be greater in the resting state period relative to the task state period. Three separate paired *t*-tests were run, comparing whole brain resting state entropy and task state entropy at each value of *m* (3, 2, and 1, respectively).

Hypothesis 2: Encoding Entropy vs. Recognition Entropy across the whole brain

Whole brain entropy maps for the encoding portion of the task scan and the recognition portion of the task scan were compared using a directional paired *t*-test in SPM12, hypothesizing that whole brain entropy would be greater in the encoding phase relative to the recognition phase. Because the timeseries were equivalent lengths for each condition, the whole brain entropy map calculations were performed with the *m* value set to 3.

Hypothesis 3: Encoding Entropy vs. Recognition Entropy in the Hippocampus

ROI analyses were performed comparing the entropy of the bilateral hippocampi between the encoding and recognition phases of the task. The Harvard-Oxford Structural Probability Atlas distributed with FSL neuroimaging software (Smith et al., 2004; Jenkinson et al., 2012) was used to define right and left hippocampal ROI's for entropy analyses. Each ROI was

thresholded at 75% to yield a conservative anatomical representation. ROIs were extracted, binarized, and registered to each participant. A directional paired *t*-test was performed in SPM12, to test the hypothesis that the entropy of the left hippocampus during the encoding phase would be greater relative to the entropy of the left hippocampus during the recognition phase. Likewise, an identical paired *t*-test was performed comparing the entropy of the right hippocampus between the encoding and recognition phases of the task.

Entropy Statistics

Entropy values were extracted using FSL 6.0 (Jenkinson et al., 2012). Specifically, the *fslmeants* function in FSL was used to generate summary statistics, which generates a mean value for the 'timeseries' of a functional image (but in this case the 'timeseries' is the actual entropy calculation). This step was performed for each whole brain entropy map in each condition (task, rest, encoding, and recognition) for all participants in the sample. Additionally, entropy statistics were extracted for each ROI (left and right hippocampi) for both conditions (encoding and recognition).

Results

Hypothesis 1: Whole Brain Task Entropy vs. Rest Entropy

Whole brain BEN maps were compared within-subjects using a paired *t*-test in SPM12 between the task and resting state conditions. Three paired *t*-tests were performed, comparing BEN maps calculated at each value of *m* (3, 2, and 1, respectively) for the task-based scans.

A paired *t*-test with a family-wise error (FWE) corrected value of .05 comparing BEN maps with an *m* value of 3 in the resting state (M = 318.03, SD = 47.16) and task states (M = 294.59, SD = 85.98 showed no significant differences in entropy between the two conditions. No significant voxels were observed at or below a *p*-value of .05; therefore, no statistical maps are reported here.

Likewise, a paired *t*-test with a FWE corrected value of .05 comparing the resting state BEN maps (M = 318.03, SD = 47.16) at an m value of 3 and the task-based BEN maps at an m value of 2 (M = 299.58, SD = 84.79) also failed to yield significant differences between the conditions. No significant voxels were observed at or below a *p*-value of .05; therefore, no statistical maps are reported here.

The third paired *t*-test with a FWE corrected value of .05 comparing resting state BEN maps (M = 318.03, SD = 47.16) at an *m* value of 3 to task-based scans (M = 310.17, SD = 82.81) utilizing an *m* value of 1 did not yield significant differences. No significant voxels were observed at or below a *p*-value of .05; therefore, no statistical maps are reported here.

Given the significant difference in acquisition time between the resting state period and the task state period, it is possible that the absence of significant results may reflect diminished reliability in comparing time series of different lengths. Although adjusting the *m* value can

adjust for this impact, existing research does not offer clear guidelines on how significant this effect may be when comparing time series of different lengths.

Mean whole brain entropy values for each condition and entropy calculation can be found in Table 2. Although there were no statistically significant differences, the mean entropy for the resting state scans was qualitatively higher than the mean entropy for the task scans, in line with the hypothesized direction of the effects. Interestingly, for each reduction in the m value (3 to 2 to 1), the mean entropy for the task scans rose to match the resting state mean entropy more closely, perhaps further corroborating the lack of a significant difference between task conditions.

Table 2

BEN for the Resting State and Task State

	M* ± *SD		***M* ± *SD***
Rest (*m* = 3)	318.03 ± 47.16	**Task (*m* = 3)**	294.59 ± 85.98
Rest (*m* = 3)	318.03 ± 47.16	**Task (*m* = 2)**	299.58 ± 84.79
Rest (*m* = 3)	318.03 ± 47.16	**Task (*m* = 1)**	310.17 ± 82.81

Note. m refers to the embedding dimension in the sample entropy calculation. Mean entropy values are multiplied by 1000 to yield whole number estimates

Hypothesis 2: Whole Brain Encoding Entropy vs Whole Brain Recognition Entropy

BEN maps were calculated for the aggregated BOLD activity of the encoding and recognition blocks of the task protocol separately. To address whether there were significant entropy differences between the encoding and recognition blocks, a directional paired *t*-test was performed comparing whole brain BEN maps between the encoding ($M = 332.38$, $SD = 64.38$) and recognition ($M = 338.9$, $SD = 60.39$) phases of the task. No significant differences were observed at the whole brain level between the encoding and recognition phases of the task. No significant voxels were observed at or below a *p*-value of .05; therefore, no activation maps are

reported here. Although there were no statistically significant differences between the conditions, the mean entropy for the recognition blocks was higher than the mean entropy for the encoding blocks, in line with the direction of the hypothesized effects. Results can be found in Table 3.

Table 3

BEN for the Whole Brain During Encoding and Recognition

	M* ± *SD
Encoding (*m* = 3)	332.38 ± 64.38
Recognition (*m* = 3)	318.03 ± 60.39

Note. m refers to the embedding dimension in the sample entropy calculation. Mean entropy values are multiplied by 1000 to yield whole number estimates.

Hypothesis 3: Encoding Entropy vs. Recognition Entropy in the Hippocampus

An ROI analysis was performed to examine if entropy significantly changed within the hippocampus between the encoding phase and the recognition phase of the task period. Two one-tailed paired samples *t*-tests were performed in SPM12 with a FWE corrected value of .05 to compare entropy differences between the right and left hippocampus entropy in the encoding phase against the recognition phase of the task, respectively. No significant differences were observed in the left hippocampus between the encoding (M = 918.19, SD = 174.16) and recognition (M = 935.32, SD = 158.89) phases, nor were any significant differences observed in the right hippocampus between the encoding (M = 911.89, SD = 181.14) and recognition (M = 930.07, SD = 167.63) phases of the task. No significant voxels were observed at or below a *p*-value of .05 between conditions in either ROI; therefore, no activation maps are reported here. Although no statistically significant differences emerged, results followed a similar pattern as above; mean entropy was slightly higher in both the left and right hippocampi in the recognition phase compared to the mean entropy of the left and right hippocampi in the encoding phase. Interestingly, mean entropy values for the hippocampal regions were higher (although not to a

level of statistical significance) than mean entropy values for the whole brain estimates, both at task and rest. The implications of this finding are discussed in further detail in the discussion section. Mean entropy values for comparisons between the encoding and recognition phases can be found below in Table 4.

Table 4

BEN for the Hippocampus during Encoding and Recognition

	M* ± *SD
Left Hippocampi Encoding (*m* = 3)	918.19 ± 174.16
Right Hippocampi Encoding (*m* = 3)	911.89 ± 181.14
Left Hippocampi Recognition (*m* = 3)	935.32 ± 159.89
Right Hippocampi Recognition (*m* =3)	930.07 ± 167.63

Note. M refers to the embedding dimension in the sample entropy calculation. Mean entropy values are multiplied by 1000 to yield whole number estimates

Discussion

Brain entropy represents an emerging application of complexity science to our understanding of the distribution of BOLD signaling in the human brain. It has been primarily used to advance our understanding of healthy and unhealthy brain dynamics, altered states of consciousness, and some limited examination of neurocognitive functions. In this document, I present evidence that brain entropy may not meaningfully change within-subjects as a consequence of condition, both at the whole brain and regional level, within the hippocampus specifically. Importantly, the bulk of the literature on brain entropy has used between-subjects approaches, typically between patients and healthy controls. Much less evidence has examined differences in brain entropy in within-subjects designs; thus, one contribution of this piece is evidence that brain entropy may not differ meaningfully within-subjects, particularly healthy ones, but only between-subjects.

Brain Entropy and Brain Function

In order to contextualize these results in terms of brain function, it is helpful to examine existing theoretical frameworks for understanding the role of entropy in brain function. Most existing theories are informed by observations about the dynamics of brain entropy in pathological states. For example, a well-known theory of complexity in biological function suggests that diminished complexity is a biomarker for eventual system dysfunction (Lipsitz & Goldberger, 1992). This work has influenced suggestions by other researchers that contend that mental illness can be primarily understood as a loss of neural complexity (Yang & Tsai, 2013). In particular, they argue that multiscale entropy should be utilized as a measure of neural complexity in order to quantify patterns of entropy towards randomness and towards regularity. They claim that this provides a more meaningful measure of neural complexity because it

indicates a directionality that is more clinically meaningful in schizophrenia particularly, which is characterized by wide scale variations in neural complexity that are differentially related to positive and negative symptoms of schizophrenia, respectively. Broadly, neural complexity, whether measured by multiscale approaches or sample entropy does demonstrate a pattern of reductions in numerous pathological states, which are highly variable between diseases, tasks, and brain areas.

Another contending theoretical perspective on brain entropy and brain function is referred to as the entropic brain hypothesis (Carhart-Harris, 2018; Carhart-Harris et al., 2014), proposed by researchers examining the influence of psychedelic drugs on neural function. In brief, this hypothesis proposes that the brain dynamics subserving conscious experience operate at a function termed self-organized criticality, a transitory state maximizing the degree of chaos in a neural system up to a tipping point before the system falls into entirely chaotic dynamics (Beggs, 2008). When participants are under the influence of psychedelic substances, brain entropy massively increases, tipping neural dynamics into a state of super-criticality; however, when participants are unconscious, depressed, or suffering from neurodegeneration, brain dynamics tilt towards sub-criticality, or more ordered and regular states of activity. The entropic brain hypothesis proposes that ordinary conscious experience and behavioral function is best maintained when neural systems are in a state of self-organized criticality. In other words, the appropriate balance of chaotic and orderly brain dynamics is necessary for adaptive behavioral function.

Brain Entropy: Whole Brain Rest vs Whole Brain Task

Contrary to my expectations, there were no significant differences in whole brain entropy between the task-state and resting-state scans in this study. Prior literature (Nezafati et al., 2020)

examined distributions in entropy across the brain corresponding to functional brain networks; namely, this work observed that the dorsal attention network had higher entropy during task states and the frontoparietal network had higher entropy during the resting state. Furthermore, subcortical regions had reduced entropy during a task state compared to a resting state in their study; however, the subcortical regions showed the widest distribution of entropy during the task state. These results are interesting in light of our observation that the hippocampal entropy during task trended higher than whole brain entropy at rest. Further analyses should be done to assess if hippocampal entropy during a face-name paired association task is significantly different than whole brain entropy during task and during rest

Furthermore, at rest, in the work by Nezafati and colleagues (2020), the limbic network had the lowest brain entropy, which may partly explain the trend towards differences between task hippocampal entropy and whole brain resting state entropy; however, our results may suggest an opposite effect, entropy in the hippocampus trended higher than mean whole brain entropy. Several possible explanations could account for this discrepancy between existing work: namely, the sample size in this study was small, especially in comparison to Nezafati & colleague's investigation, which used a large sample from the HCP dataset. Task-related differences may also play an important role; my investigation examined a face-name paired associate task, while Nezafati and colleagues (2020) analyzed data from an n-back task. Additionally, Nezafati and colleagues (2020) were also able to truncate their resting state scans for analysis so that they were the same length as the task scans; however, due to design limitations, scans of different lengths had to be compared. This may also play a role in explaining the discrepancy between my results and those observed in a much larger sample.

This finding might support evidence that local increases in regional neural complexity may be necessary to perform functions closely associated with a given set of brain regions. Previous work supports the idea that increases in regional entropy are strongly associated with stronger functional connectivity between a given region and the rest of the brain (D. J. J. Wang et al., 2018). I hypothesize that the trend towards increased hippocampal entropy during task may be related to increased functional connectivity between the hippocampus and other brain regions caused by task-related activation. Future work should examine the relationship between entropy in the hippocampus during task and entropy in the hippocampus during rest as well as the relationship between entropy and functional connectivity. However, that work is beyond the scope of this document.

Brain Entropy and the Hippocampus

As described in the introduction, the hippocampus is a brain structure that reliably activates during face-name paired associative tasks (Tsukiura & Cabeza, 2008), and its connectivity with surrounding brain regions (Grady et al., 2003) with other brain regions during memory encoding is predictive of successful recall of encoded memories. In context, the existing literature on brain entropy has observed increased regional brain entropy is predictive of increased functional connectivity to other brain regions (D. J. J. Wang et al., 2018).

In this investigation, we failed to observe any significant change in entropy between encoding and recognition phases of a task in brain entropy within the hippocampus. However, we did observe that the brain entropy of the hippocampus during both task phases trended higher compared to the whole brain entropy of either the task or resting state condition. As referenced above, existing evidence supports the idea that increased regional entropy may be related to greater functional connectivity of that region to other areas of the brain. The observation that

mean hippocampal entropy trended higher during the task than mean whole brain resting state entropy might suggest indirect evidence that hippocampal functional connectivity with other brain regions was also increased, a finding well supported for the hippocampus in memory based tasks (Grady et al., 2003; Hahn et al., 2010; L. Wang et al., 2010; Zeineh, 2003). Thus, it may be the case that the degree to which neural activity in the hippocampus is functionally correlated with activity in other brain regions, the entropy of the hippocampus is increased; further work needs to examine how hippocampal entropy at rest changes compared to task states.

Further, hippocampal entropy in both task phases trended higher than resting state whole brain entropy. In other words, it may be that the hippocampus has a higher resting state brain entropy than the whole brain, which may corroborate its role in driving brain wide functional connectivity patterns at rest (Chan et al., 2017). More specifically, if regional brain entropy is a direct index of the functional connectivity between that region and the rest of the brain, this investigation provides corroborating evidence of this observation given that the hippocampus displays widespread patterns of functional connectivity across the brain, especially between cortical areas (Schott et al., 2013). Recent work has identified a set of three distinct functional brain networks that interact along the long-axis of the hippocampus and subserve different streams of information processing during memory-guided decision making (Barnett et al., 2021). Thus, my investigation provides limited support for the observation that the entropy of the hippocampus may increase as a consequence of activation related to a face-name paired associate task.

Contrary to my expectations, no significant difference in hippocampal entropy was observed between the encoding and recognition blocks of the memory task. Although existing work does support the fact that functional connectivity between the hippocampus and other brain

regions can predict successful memory recall (Grady et al., 2003), the work by Grady and colleagues (2003) did not suggest that the magnitude or degree of functional connectivity is predictive; rather, their research suggested that successful recall depends on the brain regions involved rather than the strength of the correlations. It is plausible that entropy (and the strength of hippocampal connectivity with other brain regions) may not differ significantly between memory encoding and memory recognition. However, given that in our sample, the mean entropy of the hippocampus trended higher during the task phase relative to mean whole brain entropy in the resting state, this would suggest that a fruitful future approach may involve performing ROI analyses of entropy at the within-subjects level in multiple states and conditions.

As described previously (D.J.J Wang, 2018), regional entropy is most directly associated with the strength of the functional connectivity between a given brain region and other brain regions. Thus, it may not be possible to elucidate what role entropy may play in a given region without understanding the functional connectivity of that region with the rest of the brain. This may in part explain why many studies of brain entropy comparing patient populations and healthy controls see many different patterns of results; the nature of the symptoms of any given patient group are likely to be associated with a complex interaction of multiple patterns in the fluctuation of neural activity. In other words, entropy calculations alone may be insufficient to understand the relationship between entropy and neuropsychological function. Further, some other evidence suggests that the ability to recall recently learned information is specific to the strength of interhemispheric connectivity between the two hippocampi (L. Wang et al., 2010). Future work should more clearly examine entropy and functional connectivity in the same participants as they engage in a variety of neurocognitive tasks; this would confirm previous

findings discussed above and would help shed light on the relationship between functional connectivity and regional brain entropy.

Limitations

There are limitations in this investigation that may influence the generalizability of its results. Only twenty-four participants were analyzed in this study, which represents a relatively low sample size for neuroimaging studies. Recent research suggests that reproducible association studies between brain activation patterns and mental/behavioral phenotypes typically require sample sizes well into the thousands (Marek et al., 2022). Existing work examining differences in brain entropy as a context of task condition employ much larger sample sizes using the Human Connectome Project dataset (Nezafati et al., 2020; Z. Wang, 2021). Within-subjects' differences in brain entropy may not be statistically significant at smaller sample sizes. Thus, future work should investigate similar memory-based task paradigms with larger sample sizes.

To my knowledge, this is the first investigation to apply brain entropy as an analytic technique to neuroimaging data derived from a 7T MRI scanner. The higher spatial resolution afforded by 7T imaging has proved useful in multiple neuroimaging contexts. However, more precise characterization of BOLD signaling may reveal that estimates of entropy, based on the predictability of the time series, may be partly biased; although the test-retest reliability of functional connectivity networks is substantially increased in 7T imaging studies (Nemani & Lowe, 2021), sensitivity to physiological and imaging artifacts are increased at 7T (Xue Yang et al., 2012), which may influence entropy estimates of the BOLD signal. Future research should utilize a within-subjects approach to compare entropy estimates between different magnetic field strengths. In particular, the HCP dataset, which has subjects scanned at both 3T and 7T magnetic field strength could be a useful resource for making such comparisons. Such research would

inform investigators what degree of variability in entropy estimates is a consequence of magnetic field strength.

Furthermore, entropy estimates were compared between task and resting state protocols with significantly different acquisition times, namely the task protocol was much longer than the resting state protocol. Sample entropy is an analytic technique that is partially dependent on the length of the time series. Although it is less dependent on time series length than other measures of entropy (Richman et al., 2004), estimates of entropy at a within subjects level of different data lengths may not be statistically reliable. Although changes to the embedding dimension *m* were made to address this issue (which did result in changes to entropy calculations), these changes did not significantly alter results. Although this study could not compare scan lengths of equal times, future work should employ that method whenever possible.

Lastly, the relationship between the entropy of the BOLD signal and the hemodynamic response function (HRF) is currently understudied. In this study, entropy analyses of the entire task blocks (encoding vs recognition) were aggregated together; however each encoding and recognition block in this experiment was relatively short (no more than 30 seconds), while existing research suggests the hemodynamic response function has a 12 second cycle (Voss, 2016). Since estimates of entropy were derived from the entire block period; BOLD signal response was included that had not yet changed fully in response to the task condition. Future work should examine entropy estimates at different time lengths in the HRF cycle. Furthermore, the BOLD signal is an indirect index of neural activity, so the entropy of this signal is not a direct measure of the entropy of neural activity; it is also unknown to what degree the entropy of the time series represented by the BOLD signal is sensitive to physiological artifacts and confounds, which should be kept in mind when interpreting the results of this research.

Conclusion

Complexity represents a recent frontier in physics, biology, and neuroscience. Neuroscience research utilizing complexity measures is gaining increasing traction for its ability to capture nonlinear dynamics of brain function and their relationship to behavior and health outcomes. Here, I have presented countervailing evidence that entropy may not change meaningfully from task to resting states at the within-subjects level. However, future studies with much larger samples would be needed to determine whether these results are robust. Nonetheless, understanding how complexity manifests across the brain at different scales and in different regions across subjects will help further elucidate the mechanisms by which entropy facilitates adaptive neural function. The remarkable order in nature has long fascinated scientists, philosophers, and theologians alike; nonetheless, nature's disorder may yet have much to say about the mystery of its inner workings as its order.

References

Barnett, A. J., Reilly, W., Dimsdale-Zucker, H. R., Mizrak, E., Reagh, Z., & Ranganath, C. (2021). Intrinsic connectivity reveals functionally distinct cortico-hippocampal networks in the human brain. *PLOS Biology*, *19*(6), e3001275. https://doi.org/10.1371/journal.pbio.3001275

Beck, A. T., Steer, R.A., & Brown, G. (1996). *Beck Depression Inventory-II (BDI II)* [Database Record]. APA Psyc Tests. https://doi.org/10.1037/t00742-000

Beggs, J. M. (2008). The criticality hypothesis: How local cortical networks might optimize information processing. *Philos Trans A Math Phys Eng Sci*, *366*(1864), 329–343. https://doi.org/10.1098/rsta.2007.2092

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Bosl, W., Tierney, A., Tager-Flusberg, H., & Nelson, C. (2011). EEG complexity as a biomarker for autism spectrum disorder risk. *BMC Medicine*, *9*(1), 18. https://doi.org/10.1186/1741-7015-9-18

Carhart-Harris, R. L. (2018). The entropic brain—Revisited. *Neuropharmacology*, *142*, 167–178. https://doi.org/10.1016/j.neuropharm.2018.03.010

Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacological Reviews*, *71*(3), 316–344. https://doi.org/10.1124/pr.118.017160

Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., & Nutt, D. (2014). The entropic brain: A theory of conscious states

informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00020

Chan Russell W., Leong Alex T. L., Ho Leon C., Gao Patrick P., Wong Eddie C., Dong Celia M., Wang Xunda, He Jufang, Chan Ying-Shing, Lim Lee Wei, & Wu Ed X. (2017). Low-frequency hippocampal–cortical activity drives brain-wide resting-state functional MRI connectivity. *Proceedings of the National Academy of Sciences*, *114*(33), E6972–E6981. https://doi.org/10.1073/pnas.1703309114

Dalton, M. A., Mccormick, C., De Luca, F., Clark, I. A., & Maguire, E. A. (2019). Functional connectivity along the anterior–posterior axis of hippocampal subfields in the ageing human brain. *Hippocampus*, *29*(11), 1049–1062. https://doi.org/10.1002/hipo.23097

De Araujo, D. B., Tedeschi, W., Santos, A. C., Elias, J., Neves, U. P. C., & Baffa, O. (2003). Shannon entropy applied to the analysis of event-related fMRI time series. *NeuroImage*, *20*(1), 311–317. https://doi.org/10.1016/s1053-8119(03)00306-9

De Voogd, L. D., Fernández, G., & Hermans, E. J. (2016). Awake reactivation of emotional memory traces through hippocampal–neocortical interactions. *NeuroImage*, *134*, 563–572. https://doi.org/10.1016/j.neuroimage.2016.04.026

Delgado-Bonal, A., & Marshak, A. (2019). Approximate Entropy and Sample Entropy: A Comprehensive Tutorial. *Entropy*, *21*(6), 541. https://doi.org/10.3390/e21060541

Fastenrath, M., Coynel, D., Spalek, K., Milnik, A., Gschwind, L., Roozendaal, B., Papassotiropoulos, A., & De Quervain, D. J. F. (2014). Dynamic Modulation of Amygdala-Hippocampal Connectivity by Emotional Arousal. *Journal of Neuroscience*, *34*(42), 13935–13947. https://doi.org/10.1523/jneurosci.0786-14.2014

Friston, K. J. (2009). Modalities, Modes, and Models in Functional Neuroimaging. *Science*, *326*(5951), 399–403. https://doi.org/10.1126/science.1174521

Grady, C. L., Mcintosh, A. R., & Craik, F. I. M. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. *Hippocampus*, *13*(5), 572–586. https://doi.org/10.1002/hipo.10114

Hager, B., Yang, A. C., Brady, R., Meda, S., Clementz, B., Pearlson, G. D., Sweeney, J. A., Tamminga, C., & Keshavan, M. (2017). Neural complexity as a potential translational biomarker for psychosis. *Journal of Affective Disorders*, *216*, 89–99. https://doi.org/10.1016/j.jad.2016.10.016

Hahn, T., Dresler, T., Plichta, M. M., Ehlis, A.-C., Ernst, L. H., Markulin, F., Polak, T., Blaimer, M., Deckert, J., Lesch, K.-P., Jakob, P. M., & Fallgatter, A. J. (2010). Functional Amygdala-Hippocampus Connectivity During Anticipation of Aversive Events is Associated with Gray's Trait "Sensitivity to Punishment." *Biological Psychiatry*, *68*(5), 459–464. https://doi.org/10.1016/j.biopsych.2010.04.033

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Keshmiri, S. (2020). Entropy and the Brain: An Overview. *Entropy*, *22*(9), 917. https://doi.org/10.3390/e22090917

Lake, D. E., Richman, J. S., Griffin, M. P., & Moorman, J. R. (2002). Sample entropy analysis of neonatal heart rate variability. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *283*(3), R789–R797. https://doi.org/10.1152/ajpregu.00069.2002

Landi, G. T., & Paternostro, M. (2021). Irreversible entropy production: From classical to quantum. *Reviews of Modern Physics*, *93*(3). https://doi.org/10.1103/revmodphys.93.035008

Lebedev, A. V., Kaelen, M., Lövdén, M., Nilsson, J., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2016). LSD-induced entropic brain activity predicts subsequent personality change. *Human Brain Mapping*, *37*(9), 3203–3213. https://doi.org/10.1002/hbm.23234

Lipsitz, L. A., & Goldberger, A. L. (1992). Loss of "complexity" and aging. Potential applications of fractals and chaos theory to senescence. *JAMA*, *267*(13), 1806–1809.

Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., Donohue, M. R., Foran, W., Miller, R. L., Hendrickson, T. J., Malone, S. M., Kandala, S., Feczko, E., Miranda-Dominguez, O., Graham, A. M., Earl, E. A., Perrone, A. J., Cordova, M., Doyle, O., … Dosenbach, N. U. F. (2022). Reproducible brain-wide association studies require thousands of individuals. *Nature*, *603*(7902), 654–660. https://doi.org/10.1038/s41586-022-04492-9

Menon, S. S., & Krishnamurthy, K. (2019). A Study of Brain Neuronal and Functional Complexities Estimated Using Multiscale Entropy in Healthy Young Adults. *Entropy*, *21*(10), 995. https://doi.org/10.3390/e21100995

Mikoláš, P., Vyhnánek, J., Škoch, A., & Horáček, J. (2012). Analysis of FMRI time-series by entropy measures. *Neuroendocrinology Letters*, *33*(5).

Nemani, A., & Lowe, M. J. (2021). Seed-based test–retest reliability of resting state functional magnetic resonance imaging at 3T and 7T. *Medical Physics*, *48*(10), 5756–5764. https://doi.org/10.1002/mp.15210

Nezafati, M., Temmar, H., & Keilholz, S. D. (2020). Functional MRI Signal Complexity Analysis Using Sample Entropy. *Frontiers in Neuroscience*, *14*. https://doi.org/10.3389/fnins.2020.00700

Omidvarnia, A., Zalesky, A., Mansour L, S., Van De Ville, D., Jackson, G. D., & Pedersen, M. (2021). Temporal complexity of fMRI is reproducible and correlates with higher order cognition. *NeuroImage*, *230*, 117760. https://doi.org/10.1016/j.neuroimage.2021.117760

Poldrack, R. A., Mumford, J. A., & Nichols, T. E. (2011). *Handbook of Functional MRI Data Analysis*. Cambridge University Press; Cambridge Core. https://doi.org/10.1017/CBO9780511895029

Raynal, E., Schnider, A., & Manuel, A. L. (2020). Early signal from the hippocampus for memory encoding. *Hippocampus*, *30*(2), 114–120. https://doi.org/10.1002/hipo.23137

Richman, J. S., Lake, D. E., & Moorman, J. R. (2004). Sample Entropy. In *Methods in Enzymology* (pp. 172–184). Elsevier. https://doi.org/10.1016/s0076-6879(04)84011-4

Richman, J. S., & Moorman, J. R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology-Heart and Circulatory Physiology*, *278*(6), H2039–H2049. https://doi.org/10.1152/ajpheart.2000.278.6.h2039

Robinson, J. L., Barron, D. S., Kirby, L. A. J., Bottenhorn, K. L., Hill, A. C., Murphy, J. E., Katz, J. S., Salibi, N., Eickhoff, S. B., & Fox, P. T. (2015). Neurofunctional topography of the human hippocampus. *Human Brain Mapping*, *36*(12), 5018–5037. https://doi.org/10.1002/hbm.22987

Robinson, J. L., Salibi, N., & Deshpande, G. (2016). Functional connectivity of the left and right hippocampi: Evidence for functional lateralization along the long-axis using meta-

analytic approaches and ultra-high field functional neuroimaging. *NeuroImage*, *135*, 64–78. https://doi.org/10.1016/j.neuroimage.2016.04.022

Robinson, J. L., Zhou, X., Bird, R. T., Leavitt, M. J., Nichols, S. J., Blaine, S. K., & Deshpande, G. (2021). Neurofunctional Segmentation Shifts in the Hippocampus. *Frontiers in Human Neuroscience*, *15*, 632. https://doi.org/10.3389/fnhum.2021.729836

Saxe, G. N., Calderone, D., & Morales, L. J. (2018). Brain entropy and human intelligence: A resting-state fMRI study. *PLOS ONE*, *13*(2), e0191582. https://doi.org/10.1371/journal.pone.0191582

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). E-Prime (Version 2.0). [Computer software and manual]. Pittsburgh, PA: Psychology Software Tools Inc.

Schott, B. H., Wüstenberg, T., Wimber, M., Fenker, D. B., Zierhut, K. C., Seidenbecher, C. I., Heinze, H.-J., Walter, H., Düzel, E., & Richardson-Klavehn, A. (2013). The relationship between level of processing and hippocampal-cortical functional connectivity during episodic memory formation in humans. *Human Brain Mapping*, *34*(2), 407–424. https://doi.org/10.1002/hbm.21435

Shannon, C. E. (1948). A Mathematical Theory of Communication. *Bell System Technical Journal*, *27*(3), 379–423. https://doi.org/10.1002/j.1538-7305.1948.tb01338.x

Smith, C. N., Hopkins, R. O., & Squire, L. R. (2006). Experience-Dependent Eye Movements, Awareness, and Hippocampus-Dependent Memory. *Journal of Neuroscience*, *26*(44), 11304–11312. https://doi.org/10.1523/jneurosci.3071-06.2006

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M.

(2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Song, Z., Deng, B., Wang, J., & Wang, R. (2019). Biomarkers for Alzheimer's Disease Defined by a Novel Brain Functional Network Measure. *IEEE Transactions on Biomedical Engineering*, *66*(1), 41–49. https://doi.org/10.1109/tbme.2018.2834546

Sperling, R. A. (2003). FMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(1), 44–50. https://doi.org/10.1136/jnnp.74.1.44

Sperling, R. A., Bates, J. F., Cocchiarella, A. J., Schacter, D. L., Rosen, B. R., & Albert, M. S. (2001). Encoding novel face-name associations: A functional MRI study. *Human Brain Mapping*, *14*(3), 129–139. https://doi.org/10.1002/hbm.1047

Sperling, R., Chua, E., Cocchiarella, A., Rand-Giovannetti, E., Poldrack, R., Schacter, D. L., & Albert, M. (2003). Putting names to faces: *NeuroImage*, *20*(2), 1400–1410. https://doi.org/10.1016/s1053-8119(03)00391-4

SPM12. http://fil.ion.ucl.ac.uk/spm/

Springer, E., Dymerska, B., Cardoso, P. L., Robinson, S. D., Weisstanner, C., Wiest, R., Schmitt, B., & Trattnig, S. (2016). Comparison of Routine Brain Imaging at 3 T and 7 T. *Investigative Radiology*, *51*(8), 469–482. https://doi.org/10.1097/rli.0000000000000256

Spuhler, K., Bartlett, E., Ding, J., DeLorenzo, C., Parsey, R., & Huang, C. (2018). Diffusion Entropy: A Potential Neuroimaging Biomarker of Bipolar Disorder in the Temporal Pole. *Synapse*, *72*(2). https://doi.org/10.1002/syn.22015

Strahan, R., & Gerbasi, K. C. (1972). Short, homogeneous versions of the Marlow-Crowne Social Desirability Scale. *Journal of Clinical Psychology*, *28*(2), 191–193.

https://doi.org/10.1002/1097-4679(197204)28:2<191::AID-JCLP2270280220>3.0.CO;2-G

Sun, J., Wang, B., Niu, Y., Tan, Y., Fan, C., Zhang, N., Xue, J., Wei, J., & Xiang, J. (2020). Complexity Analysis of EEG, MEG, and fMRI in Mild Cognitive Impairment and Alzheimer's Disease: A Review. *Entropy*, *22*(2), 239. https://doi.org/10.3390/e22020239

Tagliazucchi, E., Carhart-Harris, R., Leech, R., Nutt, D., & Chialvo, D. R. (2014). Enhanced repertoire of brain dynamical states during the psychedelic experience. *Human Brain Mapping*, *35*(11), 5442–5456. https://doi.org/10.1002/hbm.22562

Tsukiura, T., & Cabeza, R. (2008). Orbitofrontal and hippocampal contributions to memory for face–name associations: The rewarding power of a smile. *Neuropsychologia*, *46*(9), 2310–2319. https://doi.org/10.1016/j.neuropsychologia.2008.03.013

Varley, T. F., Carhart-Harris, R., Roseman, L., Menon, D. K., & Stamatakis, E. A. (2020). Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains. *NeuroImage*, *220*, 117049. https://doi.org/10.1016/j.neuroimage.2020.117049

Viol, A., Palhano-Fontes, F., Onias, H., De Araujo, D. B., & Viswanathan, G. M. (2017). Shannon entropy of brain functional complex networks under the influence of the psychedelic Ayahuasca. *Scientific Reports*, *7*(1). https://doi.org/10.1038/s41598-017-06854-0

Voss, M. W. (2016). Chapter 9—The Chronic Exercise–Cognition Interaction: FMRI Research. In T. McMorris (Ed.), *Exercise-Cognition Interaction* (pp. 187–209). Academic Press. https://doi.org/10.1016/B978-0-12-800778-5.00009-8

Wang, D. J. J., Jann, K., Fan, C., Qiao, Y., Zang, Y.-F., Lu, H., & Yang, Y. (2018). Neurophysiological Basis of Multi-Scale Entropy of Brain Complexity and Its Relationship With Functional Connectivity. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00352

Wang, L., Negreira, A., Laviolette, P., Bakkour, A., Sperling, R. A., & Dickerson, B. C. (2010). Intrinsic interhemispheric hippocampal functional connectivity predicts individual differences in memory performance ability. *Hippocampus*, NA-NA. https://doi.org/10.1002/hipo.20771

Wang, Z. (2021). The neurocognitive correlates of brain entropy estimated by resting state fMRI. *NeuroImage*, *232*, 117893. https://doi.org/10.1016/j.neuroimage.2021.117893

Wang, Z., Aguirre, G. K., Rao, H., Wang, J., Fernández-Seara, M. A., Childress, A. R., & Detre, J. A. (2008). Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx. *Magnetic Resonance Imaging*, *26*(2), 261–269. https://doi.org/10.1016/j.mri.2007.07.003

Wang, Z., Li, Y., Childress, A. R., & Detre, J. A. (2014). Brain Entropy Mapping Using fMRI. *PLoS ONE*, *9*(3), e89948. https://doi.org/10.1371/journal.pone.0089948

Weathers, F., W., Litz, B., Herman, D., Juska, J., & Keane, T. (1993). PTSD Checklist- Civilian Version (PLC-C). *APA PsycTests*. https://doi.org/10.1037/t02622-000

Wible, C. (2013). Hippocampal Physiology, Structure and Function and the Neuroscience of Schizophrenia: A Unified Account of Declarative Memory Deficits, Working Memory Deficits and Schizophrenic Symptoms. *Behavioral Sciences*, *3*(2), 298–315. https://doi.org/10.3390/bs3020298

Wu, Y., Zhou, Y., & Song, M. (2021). Classification of patients with AD from healthy controls using entropy-based measures of causality brain networks. *Journal of Neuroscience Methods*, *361*.

Xue Yang, Martha J. Holmes, Allen T. Newton, Victoria L. Morgan, & Bennett A. Landman. (2012). *A comparison of distributional considerations with statistical analysis of resting state fMRI at 3T and 7T*. *8314*. https://doi.org/10.1117/12.911307

Yang, A. C., Hong, C.-J., Liou, Y.-J., Huang, K.-L., Huang, C.-C., Liu, M.-E., Lo, M.-T., Huang, N. E., Peng, C.-K., Lin, C.-P., & Tsai, S.-J. (2015). Decreased resting-state brain activity complexity in schizophrenia characterized by both increased regularity and randomness. *Human Brain Mapping*, *36*(6), 2174–2186. https://doi.org/10.1002/hbm.22763

Yang, A. C., & Tsai, S.-J. (2013). Is mental illness complex? From behavior to brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *45*, 253–257. https://doi.org/10.1016/j.pnpbp.2012.09.015

Yang, A. C., Tsai, S.-J., Lin, C.-P., & Peng, C.-K. (2018). A Strategy to Reduce Bias of Entropy Estimates in Resting-State fMRI Signals. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00398

Yentes, J. M., Hunt, N., Schmid, K. K., Kaipust, J. P., Mcgrath, D., & Stergiou, N. (2013). The Appropriate Use of Approximate Entropy and Sample Entropy with Short Data Sets. *Annals of Biomedical Engineering*, *41*(2), 349–365. https://doi.org/10.1007/s10439-012-0668-3

Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: The anatomy of perception, imagination and episodic memory. *Nature Reviews Neuroscience*, *17*(3), 173–182. https://doi.org/10.1038/nrn.2015.24

Zeineh, M. M. (2003). Dynamics of the Hippocampus During Encoding and Retrieval of Face-Name Pairs. *Science*, *299*(5606), 577–580. https://doi.org/10.1126/science.1077775

Appendix 1

Study _____ Date _____
Subject ID _____ Researcher _____

Functional Neuroimaging Demographic & Medical History Questionnaire

Gender: M F Current Medical Diagnoses: _____
Age: _____
Handedness: _____

"I'm going to read you a list of common health problems. For each problem, please answer YES if you've ever had it or NO if you haven't."

1. Arthritis? No Yes
   If yes: What are your symptoms? _____
   How long have you had these symptoms? _____

2. Chronic pain? No Yes
   If yes: What are your symptoms? _____
   How long have you had these symptoms? _____

3. Headaches? No Yes
   If yes: How often do you have them? _____
   How long has this been a problem for you? _____

4. High cholesterol? No Yes
   If yes: Do you take medication for it? _____
   How long have you had it? _____

5. High triglyceride levels? No Yes
   If yes: Do you take medication for it? _____
   How long have you had it? _____

6. Stroke? No Yes
   If yes: What were your symptoms? _____
   Were you hospitalized? How long? _____

7. A heart attack? No Yes
   If yes: What were your symptoms? _____
   Were you hospitalized? How long? _____

8. Heart disease? No Yes
   If yes: What are your symptoms? _____
   How long have you had these symptoms? _____

9. High blood pressure? No Yes
   If yes: Do you take medication for it? _____
   How long have you had it? _____

10. Diabetes (high blood sugar)? No Yes
    If yes: Do you take medication for it? _____

How long have you had it? _____

11. Asthma? No Yes
    If yes: What are your symptoms? _____
    How long have you had these symptoms? _____
12. Any lung disease? No Yes
    If yes: What are your symptoms? _____
    How long have you had these symptoms? _____

13. Thyroid disease? No Yes
    If yes: Do you take medication for it? _____
    How long have you had it? _____

14. Multiple sclerosis? No Yes
    If yes: What are your symptoms? _____
    How long have you had these symptoms? _____

15. Parkinson's Disease? No Yes
    If yes: What are your symptoms? _____
    How long have you had these symptoms? _____

16. Cancer? No Yes
    If yes: What type/stage? _____
    How long have you had it? _____

17. Neurosurgery or brain tumor? No Yes
    If yes: What were your symptoms? _____
    Were you hospitalized? How long? _____

18. Stuttering? No Yes
    If yes: How long have you had this problem? _____

"Next, I'm going to ask you some other general health questions. Please answer 'yes', or 'no'.

19. Wear glasses? Yes No
20. Seizure? Yes No
21. Convulsions? Yes No
22. Concussion? Yes No
23. Lost consciousness? Yes No
24. Learning disability? Yes No

"Now, I'm going to read you a list of conditions. Please indicate whether or not they run in your family."

_____ Alzheimer's Disease Which family members? _____
_____ Dementia _____
_____ Essential Tremor _____
_____ Memory loss _____
_____ Parkinson's Disease _____
_____ Stroke _____
_____ Epilepsy _____

"Please tell me about your consumption of the following substances."

	Type	Quantity	Frequency	Today?
Caffeine				
Nicotine				
Alcohol				
Exercise				
Social Interaction				

"Please tell me the names of all medications, both prescription and over-the-counter, that you are currently taking."

Name of Drug	Purpose	Dosage	# of Times/Day	Time of Last Dose

Method of ascertaining medications currently being taken:

____ Directly from drug bottles
____ Participant recollection
____ List brought in by patient
____ Combination

Appendix 2

Study _____ Date _____
Subject ID _____ Researcher _____

Handedness Questionnaire

Which hand do you prefer to use when:

	Left	Right	No preference	Do you ever use the other hand?
Writing	☐	☐	☐	☐yes
Drawing	☐	☐	☐	☐yes
Throwing	☐	☐	☐	☐yes
Using scissors	☐	☐	☐	☐yes
Using a toothbrush	☐	☐	☐	☐yes
Using a knife (without a fork)	☐	☐	☐	☐yes
Using a spoon	☐	☐	☐	☐yes
Using a broom (upper hand)	☐	☐	☐	☐yes
Striking a match	☐	☐	☐	☐yes
Opening a box (holding the lid)	☐	☐	☐	☐yes
Holding a computer mouse	☐	☐	☐	☐yes
Using a key to unlock a door	☐	☐	☐	☐yes
Holding a hammer	☐	☐	☐	☐yes
Holding a brush or comb	☐	☐	☐	☐yes
Holding a cup while drinking	☐	☐	☐	☐yes

Appendix 3

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

THE PSYCHOLOGICAL CORPORATION®
Harcourt Brace & Company
SAN ANTONIO
Orlando • Boston • New York • Chicago • San Francisco • Atlanta • Dallas
San Diego • Philadelphia • Austin • Fort Worth • Toronto • London • Sydney

0154018392

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

15 16 17 18 19 20 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

Appendix 4

PTSD Checklist – Civilian Version (PCL-C)

INSTRUCTIONS: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences NOT related to your military service. Please read each one carefully, and then select the answer to the right to indicate how much you have been bothered by that problem in the past month.

		Not at all	A little bit	Moderately	Quite a bit	Extremely
1.	Repeated, disturbing *memories, thoughts,* or *images* of a stressful experience from the past?	O	O	O	O	O
2.	Repeated, disturbing *dreams* of a stressful experience from the past?	O	O	O	O	O
3.	Suddenly *acting* or *feeling* as if a stressful experience *were happening again* (as if you were reliving it)?	O	O	O	O	O
4.	Feeling *very upset* when *something reminded you* of a stressful experience from the past?	O	O	O	O	O
5.	Having *physical reactions* (e.g., heart pounding, trouble breathing, sweating) when *something reminded you* of a stressful experience from the past?	O	O	O	O	O
6.	Avoiding *thinking about* or *talking about* a stressful experience from the past or avoiding *having feelings* related to it?	O	O	O	O	O
7.	Avoiding *activities* or *situations* because they *reminded you* of a stressful experience from the past?	O	O	O	O	O
8.	Trouble *remembering important parts* of a stressful experience from the past?	O	O	O	O	O
9.	*Loss of interest* in activities that you used to enjoy?	O	O	O	O	O
10.	Feeling *distant* or *cut off* from other people?	O	O	O	O	O
11.	Feeling *emotionally numb* or being unable to have loving feelings for those close to you?	O	O	O	O	O
12.	Feeling as if your *future* will somehow be cut short?	O	O	O	O	O
13.	Trouble *falling* or *staying asleep*?	O	O	O	O	O
14.	Feeling *irritable* or having *angry outbursts*?	O	O	O	O	O
15.	Having *difficulty concentrating*?	O	O	O	O	O
16.	Being *"super alert"* or watchful or on guard?	O	O	O	O	O
17.	Feeling *jumpy* or easily startled?	O	O	O	O	O

PCL-C for DSM-IV (11/1/94) Weathers, Litz, Huska, & Keane National Center for PTSD – Behavioral Science Division

Appendix 5

Study _____ Date _____
Subject ID _____ Researcher _____

INSTRUCTIONS: Listed below are a number of statements concerning personal attitudes and traits. Read each item and decide whether the statement is **TRUE** or **FALSE** as it pertains to you personally.

		False	**True**
1.	I like to gossip at times.	O	O
2.	There have been some occasions when I took advantage of someone.	O	O
3.	I'm always willing to admit it when I make a mistake.	O	O
4.	I always try to practice what I preach.	O	O
5.	I sometimes try to get even rather than forgive and forget.	O	O
6.	At times I have really insisted on having things my own way.	O	O
7.	There have been occasions when I felt like smashing things.	O	O
8.	I never resent being asked to return a favor.	O	O
9.	I have never been irked when people expressed ideas very different from my own.	O	O
10.	I have never deliberately said something that hurt someone's feelings.	O	O

Appendix 6

MRI Recruitment / Advance Screening Form	Auburn University MRI Research Center 560 Devall Drive Suite 202 Auburn, AL 36849 Tel: (334) 844-6747 Fax: (334) 844-0214
This form to be used for: Recruiting and initial screening of research subjects prior to arrival at the AU MRI Research Center	

1.	☐Yes ☐No	Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind where a device was implanted? If yes, please describe_____
2.	☐Yes ☐No	Have you had any medical condition that prevented you completing an MRI exam in the past or had any related to a previous MRI examination or procedure? If yes, please describe: _____
3.	☐Yes ☐No	Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, shrapnel, etc.)? If yes, please describe: _____

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the AU MRI Research Center staff BEFORE entering the MR system room. **The MR system magnet is ALWAYS on.**

Answering "Yes" to any of the following questions excludes the subject from the study

4.	☐Yes ☐No	Do you have a cardiac pacemaker or implanted cardioverter defibrillator (ICD)?
5.	☐Yes ☐No	Is there a possibility of metal in your head (for example aneurysm clips, do not include dental work)? If yes, please describe: _____
6.	☐Yes ☐No	Have you had an injury to the eye involving a metallic object or fragment (for example, metallic slivers, shavings, foreign body), or have you ever needed an eyewash having worked with metals? If yes, please describe: _____
7.	☐Yes ☐No	Do you have an implanted medical device that is electrically, magnetically, or mechanically controlled or activated (see examples below)? If yes, please describe: _____
8.	☐Yes ☐No	**Females Only**: Are you pregnant or is there any possibility that you may be pregnant?
9.	☐Yes ☐No	Do you have a permanent retainer or braces?

Protocol-Specific Questions (Answering "Yes" to any of the following questions excludes the subject from the study)

10.	☐Yes ☐No	Do you have a breathing problem or motion disorder?
11.	☐Yes ☐No	Are you claustrophobic?
12.	☐Yes ☐No	Do you have inner ear disorders or experience vertigo or dizziness?
13.	☐Yes ☐No	Do you have tattoos or permanent makeup that contains metal?
14.	☐Yes ☐No	Do you have body piercing jewelry that cannot be removed?

Examples of implanted medical devices	
Neurostimulation system *	Shunt (spinal or intraventricular)
Spinal cord stimulator *	Vascular access port and/or catheter
Internal electrodes or wires *	Radiation seeds or implants
Bone growth/bone fusion stimulator *	Swan-Ganz or thermodilution catheter
Cochlear, otologic, or other ear implant	Medication patch (Nicotine, Nitroglycerine)
Insulin or other infusion pump	Any metallic fragment or foreign body
Implanted drug infusion device	Wire mesh implant
Any type of prosthesis (eye, penile, etc.)	Tissue expander (e.g., breast)
Heart valve prosthesis	Surgical staples, clips, or metallic sutures
Eyelid spring or wire	Joint replacement (hip, knee, etc.)
Artificial or prosthetic limb	Bone/joint pin, screw, nail, wire, plate, etc.
Metallic stent, filter, or coil	IUD, diaphragm, or pessary
* If these implanted medical devices are present, the subject cannot be scanned	

Appendix 7

Task Design for Face-Name Paired Associate task (far left column is task time in milliseconds, second left column is the time of each task phase indicated by 1).

		encoding	recognition	rest	instruct
0	5000	1	0	0	0
5000	1000	0	0	1	0
6000	5000	1	0	0	0
11000	1000	0	0	1	0
12000	5000	1	0	0	0
17000	1000	0	0	1	0
18000	5000	1	0	0	0
23000	1000	0	0	1	0
24000	5000	1	0	0	0
29000	1000	0	0	1	0
30000	30000	0	0	1	0
60000	6000	0	0	0	1
66000	5000	0	1	0	0
71000	1000	0	0	1	0
72000	5000	0	1	0	0
77000	1000	0	0	1	0
78000	5000	0	1	0	0
83000	1000	0	0	1	0
84000	5000	0	1	0	0
89000	1000	0	0	1	0
90000	5000	0	1	0	0
95000	1000	0	0	1	0
96000	6000	0	0	0	1
102000	5000	1	0	0	0
107000	1000	0	0	1	0
108000	5000	1	0	0	0
113000	1000	0	0	1	0
114000	5000	1	0	0	0
119000	1000	0	0	1	0
120000	5000	1	0	0	0
125000	1000	0	0	1	0
126000	5000	1	0	0	0
131000	1000	0	0	1	0
132000	30000	0	0	1	0
162000	6000	0	0	0	1
168000	5000	0	1	0	0
173000	1000	0	0	1	0

174000	5000	0	1	0	0
179000	1000	0	0	1	0
180000	5000	0	1	0	0
185000	1000	0	0	1	0
186000	5000	0	1	0	0
191000	1000	0	0	1	0
192000	5000	0	1	0	0
197000	1000	0	0	1	0
198000	6000	0	0	0	1
204000	5000	1	0	0	0
209000	1000	0	0	1	0
210000	5000	1	0	0	0
215000	1000	0	0	1	0
216000	5000	1	0	0	0
221000	1000	0	0	1	0
222000	5000	1	0	0	0
227000	1000	0	0	1	0
228000	5000	1	0	0	0
233000	1000	0	0	1	0
234000	30000	0	0	1	0
264000	6000	0	0	0	1
270000	5000	0	1	0	0
275000	1000	0	0	1	0
276000	5000	0	1	0	0
281000	1000	0	0	1	0
282000	5000	0	1	0	0
287000	1000	0	0	1	0
288000	5000	0	1	0	0
293000	1000	0	0	1	0
294000	5000	0	1	0	0
299000	1000	0	0	1	0
300000	6000	0	0	0	1
306000	5000	1	0	0	0
311000	1000	0	0	1	0
312000	5000	0	0	0	0
317000	1000	1	0	1	0
318000	5000	0	0	0	0
323000	1000	1	0	1	0
324000	5000	0	0	0	0
329000	1000	1	0	1	0
330000	5000	0	0	0	0
335000	1000	1	0	1	0
336000	30000	0	0	1	0

366000	6000	0	0	0	1
372000	5000	0	1	0	0
377000	1000	0	0	1	0
378000	5000	0	1	0	0
383000	1000	0	0	1	0
384000	5000	0	1	0	0
389000	1000	0	0	1	0
390000	5000	0	1	0	0
395000	1000	0	0	1	0
396000	5000	0	1	0	0
401000	1000	0	0	1	0
402000	6000	0	0	0	1
408000	5000	1	0	0	0
413000	1000	0	0	1	0
414000	5000	1	0	0	0
419000	1000	0	0	1	0
420000	5000	1	0	0	0
425000	1000	0	0	1	0
426000	5000	1	0	0	0
431000	1000	0	0	1	0
432000	5000	1	0	0	0
437000	1000	0	0	1	0
438000	30000	0	0	1	0
468000	6000	0	0	0	1
474000	5000	0	1	0	0
479000	1000	0	0	1	0
480000	5000	0	1	0	0
485000	1000	0	0	1	0
486000	5000	0	1	0	0
491000	1000	0	0	1	0
492000	5000	0	1	0	0
497000	1000	0	0	1	0
498000	5000	0	1	0	0
503000	1000	0	0	1	0
504000	6000	0	0	0	1
510000	5000	1	0	0	0
515000	1000	0	0	1	0
516000	5000	1	0	0	0
521000	1000	0	0	1	0
522000	5000	0	0	0	0
527000	1000	1	0	1	0
528000	5000	0	0	0	0
533000	1000	1	0	1	0

534000	5000	0	0	0	0
539000	1000	1	0	1	0
540000	30000	0	0	1	0
570000	6000	0	0	0	1
576000	5000	0	1	0	0
581000	1000	0	0	1	0
582000	5000	0	1	0	0
587000	1000	0	0	1	0
588000	5000	0	1	0	0
593000	1000	0	0	1	0
594000	5000	0	1	0	0
599000	1000	0	0	1	0
600000	5000	0	1	0	0
605000	1000	0	0	1	0

Appendix 8

Brain Entropy Calculation (Wang et al., 2014)

$$\mathrm{B}^{\mathrm{m}}(\mathrm{r}) = \frac{1}{(\mathrm{N}-\mathrm{m})(\mathrm{N}-\mathrm{m}-1)} \sum_{\mathrm{i}=1}^{\mathrm{N}-\mathrm{m}} \mathrm{B}_{\mathrm{i}}^{\mathrm{m}}(\mathrm{r})$$

$$A^{m}(r) = \frac{1}{(N-m)(N-m-1)} \sum_{i=1}^{N-m} \mathrm{B}_{i}^{m+1}(r)$$

Formulas A and B are both distance functions, calculated using the Chebyshev Distance formula; both A and B refer to the number of subset pairs less than or equal to the tolerance interval *r,* with the length of subset A being *m*+1 compared to the length of subset B as simply *m*. Hence, this formula calculates the negative logarithm of the empirical probability that subset A is a match for subset B at the next point of A within a tolerance interval *r.*

$$\mathrm{SampEn}(m,r,N,x) = -\ln\left[\frac{A^{m}(r)}{B^{m}(r)}\right]$$