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TOWARD A GRAPH THEORETICAL MODEL OF FUNCTIONAL CONNECTIVITY IN CHRONIC DEVELOPMENTAL TRAUMATIC STRESS DISORDERS

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ABSTRACT

Psychopathologies connected to traumatic stress have been a recognized phenomenon since the advent of psychotherapy. Efforts to characterize the symptomatology and to find neurological mechanisms of these disorders have been notoriously restricted by political motivation and technological limitations. At present, the medical community has not reached a formal consensus on whether psychopathology stemming from child abuse is a distinct entity from recognized disorders with similar symptom profiles (e.g. PTSD, see Herman 2012, Resick 2012) and does not appear to be making significant progress toward addressing this question. This thesis will examine the use of resting state functional Magnetic Resonance Imaging (rsfMRI) technology and graph theoretical modeling to investigate functional connectivity in brain. We will examine the fundamental challenges of combining rsfMRI with translational models of psychiatric conditions, and elaborate an awake animal imaging paradigm developed by the Translational Neuroimaging and Systems Neuroscience Lab at Penn State, where the author is a research assistant. We then propose a novel translational model to obtain the longitudinal data necessary to understand how sensory integration develops in the context of prolonged developmental abuse.

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1

Introduction

Psychopathologies connected to traumatic stress have been recognized phenomena since the advent of psychotherapy. Efforts to characterize the symptomatology and to find neurological mechanisms of these disorders have been notoriously restricted by political motivation and technological limitations. In the 1970's, the condition of traumatized Vietnam War veterans in the US lead to renewed political and scientific interest in stress-related psychopathology and to the medical diagnosis of Post Traumatic Stress Disorder (PTSD) (Herman, 1992). The Diagnostic and Statistic Manual of Mental Disorders, fifth edition (DSM-V) requires a PTSD diagnosis to include an initial traumatic stressor, intrusive symptoms (e.g. traumatic nightmares), avoidance (e.g. from reminders of the incident), negative alterations to mood and cognition, and alterations in arousal (e.g. hypervigilance) that persist for at least a month after the incident (APA 2013). However, clinicians and medical researchers have long argued that characterizing traumatic stress disorders only in terms of behavioral symptoms is reductionist and potentially harmful. One of the most compelling distinctions clinicians have argued for are between conditions stemming from a single traumatic incident (e.g. a natural disaster) and chronic exposure to a traumatic stimulus (e.g. relational abuse) and between conditions emerging from trauma sustained in adulthood and during childhood (Herman 1992, van der Kolk 2005). These two separate distinctions produce four subcategories of traumatic stress. This thesis will

focus on better understanding psychopathology related to developmental, chronic traumatic stress in the form of childhood maltreatment (CM).

Pathologies resulting from prolonged childhood abuse pose a unique challenge to modern psychiatry. While it is clear that personality formation and assimilation, attachment, and learning are all areas of development that are made vulnerable by chronic exposure to totalitarian violence (Herman 1992, van der Kolk 2005), it is unclear how to formally define a disorder arising from compromised child development if the same symptom profile can be observed in non-abused patients (Resick et al, 2012). In spite of this ambiguity, there is compelling neurological and clinical evidence that this issue must be pursued.

In 2011, 676,569 American children were determined to be victims of abuse and neglect by Child Protective Services. The number of CPS confirmed cases of child abuse, however, should not be confused with the number of abused children in the US. A study by Briere and Elliot (2003) examining the life experiences of 935 Americans found that 14.2% of men and 32.3% of women reported childhood sexual abuse; 22.2% of men and 19.5% of women reported physical abuse; and 21% of the sample reported experiences that met the criteria for both sexual and physical abuse. These results suggest that childhood abuse is much more pervasive in the population than the number of Child Protective Services confirmed cases may lead researchers to believe.

It is unclear that the DSM-V defines psychopathology stemming from child abuse in a way that facilitates research and successful treatment (Herman, 1992, 2012, Resick 2012,

van der Kolk 2005, Courtois & Ford, 2009). While there have been attempts to uniquely classify these pathologies in a clinical context (e.g. Herman 2012, van der Kolk 2005, Courtois & Ford, 2009), these proposals, taken together, are ill-defined (Resick 2012). At present, the medical community has not reached a formal consensus on whether psychopathology stemming from child abuse is a distinct entity from recognized disorders with similar symptom profiles (e.g. PTSD, Herman 2012, Resick 2012) and does not appear to be making significant progress toward addressing these questions.

New research methods present exciting opportunities to uncover the underlying neurological mechanisms of Developmental Traumatic Stress Disorders at the systems level, which may allow researchers to tackle this question in a meaningful way. The emergence of resting-state fMRI (rsfMRI) as a method for investigating the functional connectivity of neural networks (Biswal 1995) in particular has shown promise in elucidating the underlying neuropathology of psychiatric and neurological conditions (e.g. Schizophrenia, Li et al 2015). This approach allows the use of graph theoretical tools to quantify the strength of connections between neurological Regions of Interest (ROIs), which are represented as nodes on a graph, and allows at least a well-defined discussion of how information is trafficked in pathological and healthy brain.

This thesis will examine the fundamental challenges of combining rsfMRI with translational models of psychiatric conditions, and elaborate an awake animal imaging paradigm developed by the Translational Neuroimaging and Systems Neuroscience Lab at Penn State, where the author is a research assistant. We will then propose a novel

translational model to obtain the longitudinal data necessary to understand how sensory integration develops in the context of prolonged developmental abuse.

Chapter 2

Sensory Dysregulation in Abuse-Related Disorders

Particularly relevant to the question of appropriately characterizing developmental traumatic stress disorders is evidence that the neurobiological ramifications of Child Maltreatment (CM) on sensory learning are unique. If this is the case, then developmental traumatic stress disorders may be understood as biologically different from other anxiety disorders associated with the same behavioral symptoms. Perception of sensory information is clinically recognized to be impaired in Childhood Maltreatment-reporting patients (van der Kolk, 1995) and structural changes have been observed both in the grey and white matter of survivors. In spite of this, there is no clear understanding of the effects of child abuse on sensory perception and integration.

Prolonged cognitive dissociation from sensory stimuli is typical of child abuse survivors (Courtois & Ford, 2009) and under the stress-diathesis model dissociativity is generally assumed to be an adaptive response to traumatic stimulus. Dissociative disorders in general are common amongst abuse survivors (Courtois & Ford, 2009). Integration and processing of sensory information relevant to traumatic events is generally impaired and traumatic memories sustained during child abuse are often remembered only as sensory fragments (van der Kolk & Fisher, 1995). Trauma is also commonly associated with conversion disorder, a condition linked to abuse, which is characterized by impaired voluntary motor and sensory function (Roelofs et al, 2002). Evidence from Spinhoven et al.

demonstrates that in patients with Conversion Disorder, physical abuse predicts somatoform dissociation (i.e. the patient will not be able to perceive physical pain) more than level of psychopathology.

In disorders associated with child abuse there are many examples of dissociation between the sensory systems and executive neurological processes. First, abuse survivors show increased startle reactivity in adulthood, which might be explained by dysfunctional upstream (i.e. related to higher cognition) inhibition of fear response following unexpected sensory input (Jovanovich et al, 2009). Personality disorders, which are broadly associated with child abuse and neglect (Johnson et al, 1999), have been studied for abnormal sensory processing. Borderline Empathy, documented in Borderline Personality Disorder patients in Dinsdale and Crespi's 28-study review, is described as a phenomenon where an enhanced perception of social stimuli – constructed by multimodal sensory information -- is made pathological by dysfunctional upstream processing (2013). While this phenomenon is only understood in the context of Borderline Personality Disorder, enhanced perception of social stimuli has been observed in other personality disorders related to fear and anxiety (Arntz et al, 2009).

CM-related neurological changes have also been reported. These changes offer extremely compelling evidence that, on a network level, CM-related psychopathologies are unique in their pathophysiology. Reductions in Cortisostriatal-Limbic Grey Matter (GM) volume have been found in adult survivors of CM (e.g. Heim et al 2013), though in many studies it is often difficult to say whether those changes are due to CM or psychopathology in CM survivors. In CM-reporting adults who did not report psychiatric illness within a two

year span, Heim et al. have found maltreatment modality-specific reductions in cortical thickness that are evidence of reduced synapses to the relevant areas (e.g. genitalia mapping in the Primary Somatosensory Cortex has reduced thickness in survivors of childhood sexual abuse) (2013). In CM-reporting adolescents who were not diagnosed with psychiatric illness, Edmiston et al. found decreased GM volume in parietal, temporal and occipital association cortices. Because the adolescent and adult participants in these studies were not diagnosed with a psychiatric condition, it is possible that these reductions in GM volume aid in resiliency, and/or it also possible that they are indicative of impaired, though not necessarily pathological, sensory processing (2011, Heim et al 2013). While it is possible to attribute reductions in cortical thickness to reduced neuronal populations in effected areas, an alternate and preferred explanation attributes these findings to a reduction of synapses in the area (Heim et al 2013). Structural differences in white matter tracts relevant to sensory processing have also been discovered in CM vs. Healthy cases. Using Diffuse Tensor Imaging, Choi et al (2009, 2012) have observed reduced fractional anisotropy in white matter circuits related to the sensory modality of CM (the arcuate fasciculus in survivors of parental verbal abuse, and the inferior longitudinal fasciculus of adults who had witnessed domestic violence as children). Given the nature of Diffuse Tensor Imaging, it is not completely clear what physiological difference(s) are being measured, but reduced fractional anisotropy is evidence of abuse-related structural abnormalities in relevant sensory tracts. It may indeed point to abuse-related altered sensory integration in effected pathways.

While the literature frequently assumes that these structural changes relate strictly to dysfunctional higher order processing, the absoluteness of this assumption must be questioned. Reductions in GM volume have been observed in the sensory association cortices of CM-reporting adolescents with no confounding psychiatric illness, which may effect sensory processing well before the executive level. Reduced fractional anisotropy in fasciculi efferent to those primary sensory cortices implicated by abuse modality points to effected processing even further downstream than the association cortices. It is also worth bearing in mind that Fear Conditioning related plasticity has been observed in sensory tracts even at the sub-thalamic level[1] (Gonzalez-Lima et al 1989), with continued alterations seen on the neurological representation of sensory stimuli at the more upstream thalamocortical level, and so on.

There is compelling evidence that abnormal and pathological processing of sensory information is frequent in CM survivors. To aid clinicians in understanding how the ramifications of CM on sensory development and integration may complicate and effect the treatment of behavioral consequences, it is imperative to investigate the overall

[1] Subthalamic processing of sensory information is considered much less cognitively complex that upstream cortical processing and might involve, for example, neural bands, each responding to a different frequency, that tonotopically map sound frequencies as they stimulate signal transducers in the ear. Upstream processing, as an example, might involve integrating those sounds with visual information and deciding based on integrated audiovisual cues whether or not something is a threat.

neurological development of sensory pathways. It is worthwhile to note that the implications of this question stretch even further than aiding survivors. Here, the foundational logic of modern psychiatry is taken to task. If the same behavioral consequences associated with one disorder can be linked to different characteristic pathophysiologies, such as a difference in sensory functioning between CM cases of PTSD and others, then in what meaningful sense are clinicians treating the same disorder? While research is turning in this direction, this question still sits uncomfortably in the gap between clinical and research neuropsychiatry. To aggressively address it, we need researchers who are aware of clinical intuition surrounding psychiatric conditions and new tools with which to examine them. Having addressed clinical intuition and research, we will now examine two of those new tools in clinical application: graph theoretical modeling and resting state functional MRI.

Chapter 3

Graph Theoretical Modeling of Functional Connectivity

Mathematical tools allow researchers to investigate brain functional connectivity data in a well-defined sense. Specifically, graph theoretical tools may be used to model brain networks by placing regions of interest (ROIs) as connected nodes on a graph whose characteristics may be investigated using multiple network measures (Bullmore and Sporns, 2009). Topological characteristics particularly relevant to studies of functional connectivity will be discussed in more detail below, with their mathematical definitions stated explicitly when necessary.

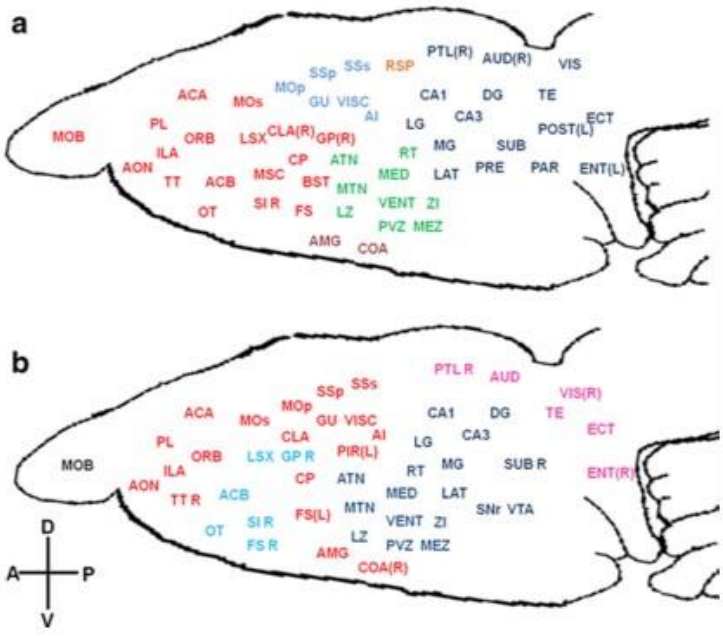

Figure 1 Anatomical labels of 114 ROIs in the rate brain (Liang et al 2011)

The origin of graph theory as a branch of mathematics is traced to Euler, who in 1736 demonstrated that it would be impossible to cross the 7 bridges of Königsberg exactly one time

and return to the starting point. The tools he developed to show this are accepted as the birth of graph theory, which has since been applied with considerable success to the life sciences, where the quantitative investigation of networks and network dynamics is exigent (Bullmore and Sporns, 2009).

A graph (typically written *G(E,V)*) is a collection of pathways or *edges* (i.e. *E*, in functional connectivity edges represent connections between neural regions) connected by a series of stops, vertices (hence the set lettering *V*) or in application to functional connectivity investigations, *nodes*. In the simplest case, edges between nodes of a graph may either exist or not, with each vertex granted equal importance. In the more complex case, the edges of the graph may assigned weights of different numerical value, often visualized as an edge width and intuitively thought of as the strength of that connection within the network. In the unweighted case especially, a graph may be described using many well-defined measures that allow quantitative investigation into the function of biological systems (Stam & Reijneveld 2007). Though this list should not be considered comprehensive by any means, neuroscientists working on functional connectivity frequently use the following standard measures to investigate graph topology:

> *Node Degree*: Number of connections to a node, in our specific case, number of functional connections to ROIs. It would thus be appropriate, for example, for a node representing the thalamus in a functional connectivity map to be of high degree.

The *betweenness centrality* of a node *n* is a measure of the importance of a node within the network and is explicitly defined to be the number of shortest pathways between node pairs $(j, i) \quad \forall j, i,\ i \neq j$ that pass through *n.*

Modularity ranges between -1 and 1 and is a measure that of how a graph can be divided into groups or communities, called modules. Graphs modeling functional connectivity in the animal brain exhibit high levels of modularity. Mathematically, a modularity measure *Q* for a graph of *n* nodes may be defined as

$$Q = \frac{1}{4n} \sum_{i,j} \left(a_{ii} - \frac{k_i k_j}{2n} \right) \delta(c_i, c_j)$$

where $a_{ij} = a_{ji} = 1$ if (i, j) ∈ E, 0 otherwise, k_i and k_j denote the degrees of the *ith* and *jth* nodes, and $\delta(\cdot,\cdot)$ is the Kronecker Delta Function and *c* refers to the community of the *ith* and *jth* nodes. *Hierarchical modularity* exists when modules may be decomposed into smaller modules, and is a recognized characteristic of functional brain networks (Meunier et al, 2010).

Hub: A node is said to be a *provincial hub* if is has a high number of connections within a module; It may be thought of as an important node within that module. A node is said to be a *connector hub* if it has a high number of connections to nodes outside its module. This language is very intuitively appealing to the study of brain networks: A unimodal region such as the primary auditory cortex may appear as a provincial hub, for example, while a multimodal association area, such as the rostral

superior temporal gyrus (anatomical region in the brain), would appear as a connector hub (Bullmore & Sporns 2012).

Clustering Coefficient: Interconnected nearest neighbors *i* and *j* (explicitly, $j \leftrightarrow i$) are said to form clusters. The *local* clustering coefficient *c* quantifies this notion by taking the ratio of the number of connections between the *jth* node and its neighbors, E_j, and the number of possible connections to the neighbors of *j*, V_j. Discounting the possibility of a node connecting to itself the number of possible connections can be expressed through a modified version of Gauss' formula: $\frac{1}{2} V_j(V_j - 1)$. This ratio thus becomes

$$c = \frac{2E_i}{V_i(V_i - 1)}$$

The *global* clustering coefficient *C* is the arithmetic average of the clustering coefficients for all nodes, or

$$C = \frac{1}{m} \sum_{j=1}^{m} c_j$$

(Liang et al, 2011).

Path Length: A path *d* between nodes *i* and *j* is of length *k* if the path contains *k* connected vertices $(V_1, \ldots, V_{k-1}, V_k)$. The *shortest path* between two nodes is the path that contains the fewest number of vertices. The *mean shortest path length L*, a

measure necessary to quantify the *small-worldness* of a network, is defined mathematically as the harmonic mean of the shortest paths between all nodes in the network. The harmonic mean is selected to address the problem of infinite path length between unconnected nodes (Liang et al 2012).

Local and global efficiency: The *efficiency* of a path between two nodes as the inverse of the shortest path length between those nodes. The *global efficiency* of a graph of *N* nodes is defined as the average over all pairwise efficiencies, i.e.

$$E_{glob} = \frac{1}{N(N-1)} \sum_{i,j \in N, i \neq j} \frac{1}{d_{i,j}}$$

where *d* is the shortest path length between the *ith* and *jth* nodes.The definition of efficiency can be localized to the neighborhood around a specific node G_i by taking the mean of the efficiencies of that node with *N* neighbors, i.e.

$$E_{loc} = \frac{1}{N} \sum_{i \in N} E(G_i)$$

.

Local efficiency of a node may be thought of as a measure of how well the graph could communicate information if that node were removed (Latora et al 2001).

Scale-free network properties: A network is said to be *scale free* if its node degree distribution at least asymptotically follows a power law, i.e. The proportion of nodes with *k* many connection $P(k) \sim k^{-\gamma}$ where $2 < \gamma < 3$. Some evidence suggests that

brain functional connectivity graphs are scale-free (Eguílez et al 2005). These properties suggest that different ROIs in the brain display considerably different centrality (Stam 2014).

Small-worldness: Watts and Strogatz define a class of small-world networks characterized by shortest path length and clustering coefficient that fall between a fully randomized graph and a lattice. These graphs exhibit both a large clustering coefficient and a relatively short average path length and have been found to appropriately characterize many real-world networks, including social networks, gene networks, and brain functional connectivity networks (1998). To ensure biorealism in graph theoretical models of functional connectivity, it is important that small-worldness be maintained (Liang, 2011). Small-worldness is measured as a ratio of global clustering coefficient and mean shortest path length.

Typically healthy brain functional connectivity is hierarchical and highly efficient, displaying scale-free and small world properties. It is also noteworthy that these graphs are undirected, i.e. there is no information from the models about the direction of information processing in the brain. Empirical studies on relevant networks (e.g. tracer studies) can be used to elucidate that information.

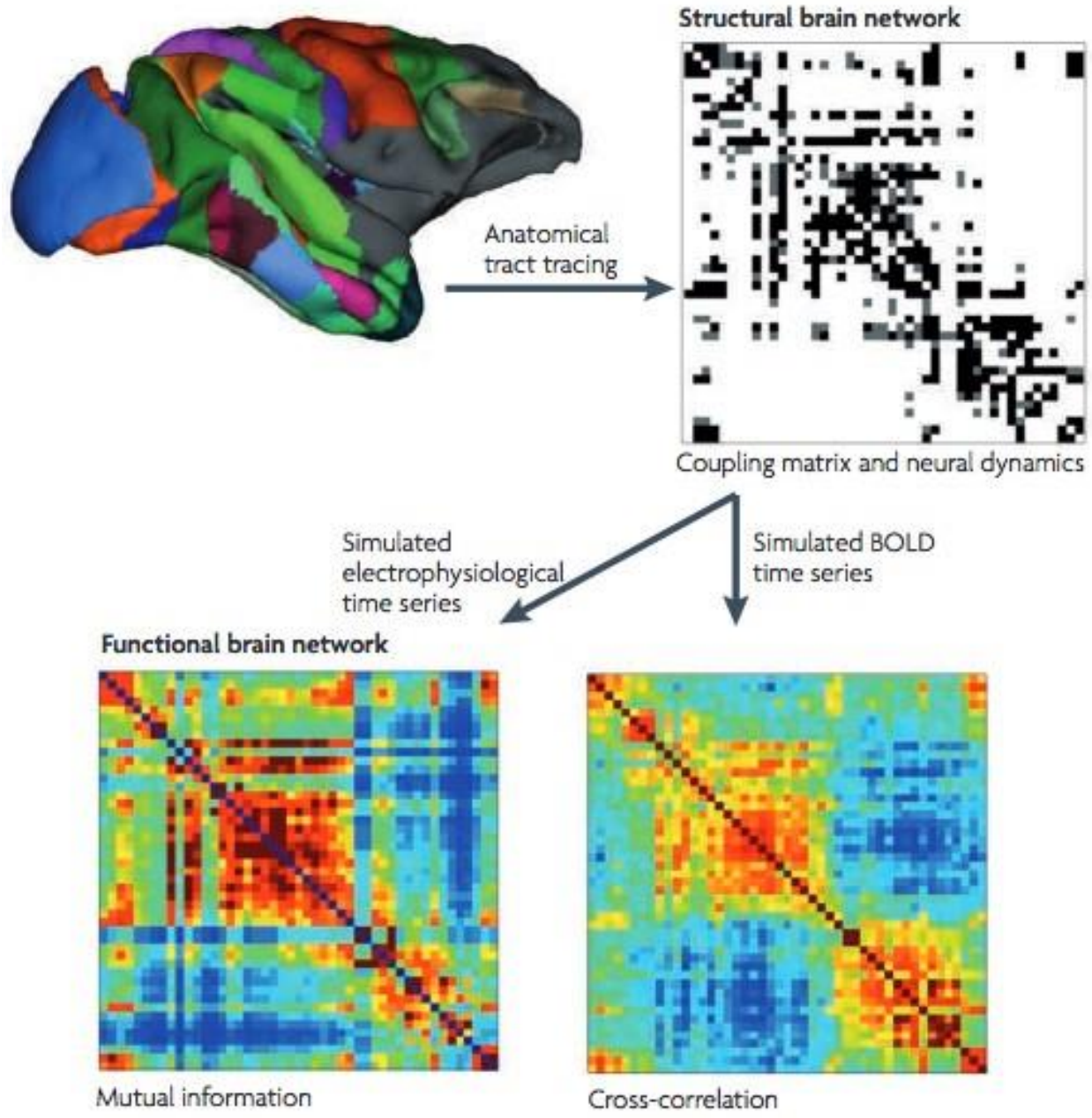

Figure 2 Matrices representing structural connections between ROIs (black and white) and functional connectivity between the same ROIs (colored, resting state associativity matrix on the right). (Bullmore & Sporns 2009).

Graph spectral analysis (GSA) is also be used to examine functional connectivity. To perform spectral analysis on functional data graph properties of the networks must be interpreted

in matrix form. To construct the *Adjacency matrix A* of a graph, each entry is 1 if there is a connection between the *ith* and *jth* nodes, 0 otherwise (Bullmore & Sporns 2009). In the weighted case, an *Association matrix* may quantify the strength of the connection between nodes on the graph (Figure 2). As we shall see in the case of rsfMRI, time series correlation between ROIs may be used as a continuously variable metric to measure connection strength. An association matrix constructed of time series correlation coefficients may be thresholded to produce a binary association matrix (Bullmore & Sporns 2009). Note that in the case of the undirected graph, both matrices will be symmetric. The *spectrum* of an undirected graph are the eigenvalues of its Adjacency matrix, here denoted

$$\{\lambda_1, \lambda_2, \ldots \lambda_n\}$$

for *n* ROIs or nodes.

We will examine one measure that arises from GSA in particular, *graph spectral entropy,* which will be formally defined in the following paragraphs. It is not a standard measure, unlike the measures discussed up until now, but will be of use in specific application to Attention-Deficit Hyperactivity Disorder as covered in Chapter 4. In Information Theory, entropy is a measure of the randomness of a communication channel (Takahashi et al 2012). In application to functional connectivity, graph spectral entropy can be related to randomness in the communication between ROIs, and can thus be related to their communication efficacy. The higher the entropy, the more randomness in the graph, the less meaningful neural network communication becomes.

For any family of random graphs *g* generated by some probability law, the eigenvalues of each graph form random vectors with respect to which we may take an expectation according to

the probability law we use, and for which we may derive a probability distribution. In this case, we define the spectral density function of the graph family as

$$P_g(\lambda) = \lim_{n \to +\infty} \left(\frac{1}{n} \sum_{i=1}^{n} \delta \left(\frac{\lambda - \lambda_i}{\sqrt{n}} \right) \right)$$

where we use the Dirac delta function and the sharp brackets indicate the expectation (Takahashi et al 2012). Takahashi et al. model functional connectivity graphs as families of random graphs. Taking this idea to the study of neuropsychiatric pathology, Sato et al. first compute the spectrum of each graph. They then calculate spectral density functions and measure spectral entropy. The eigenvalues' probability distribution is approximated using Gaussian kernel regression to achieve a smoother histogram and improve entropy *H* estimation, which is done using an integral of the probability distribution weighted with its log:

$$H(P_g) = -\int_{-\infty}^{+\infty} P_g(\lambda) \log(P_g(\lambda))\, d\lambda \quad .$$

As we will see in our subsequent examination of applications of rsfMRI and functional connectivity studies to neuropsychiatric illness, this measure of entropy is very intuitively appealing to the study of neuropsychiatric disorders where unfocused communication between ROIs is implicated and may be a measure of clinical value.

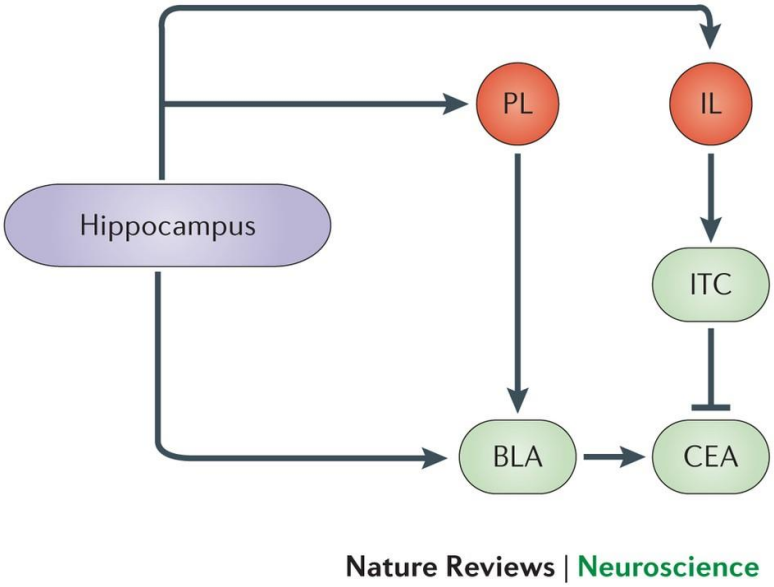

Figure 3 Contextual fear extinction circuit from Maren et al. showing excitatory (arrow) and inhibitory (line) connections (2013).

While a descriptive measure such as entropy is appealing in specific cases, it is possible that measures as simple as the association matrix will be of tremendous and more general value to clinical investigations. The pairwise correlation coefficient, while a simple measure, models a very powerful neurophysiological property: the amount of information being communicated between two brain regions. To illustrate, very simply, how meaningful this measure may be in application we will address a problem currently under investigation in my lab, the Translational Neuroimaging and Systems Neuroscience Lab (TN-SNL lab) at Penn State's Center for Neural Engineering (PI: Nanyin Zhang).

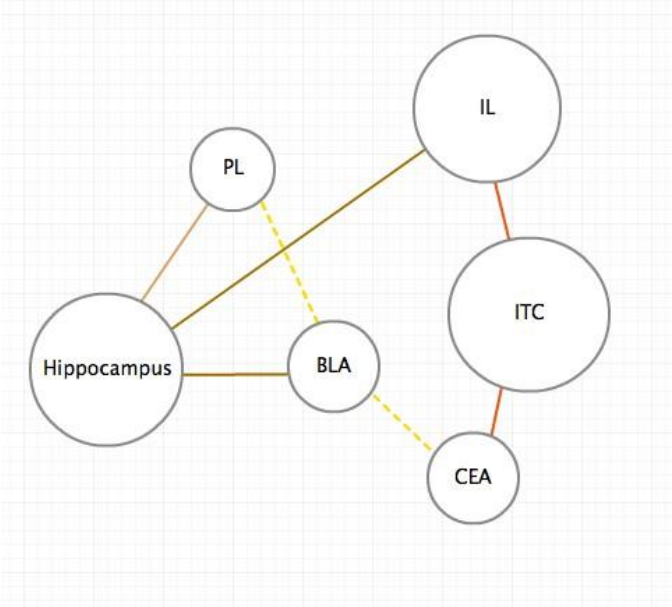

Figure 4 Mock undirected network diagram showing healthy function connectivity after fear extinction. Dashed lines represent decreased connectivity, solid lines represent increased connectivity. Enlarged regions are predicted to be more active by our hypothesis.

We are currently investigating the role of the medial prefrontal cortex, which is comprised of prelimbic (PL) and infralimbic (IL) cortices. It is suspected that dysfunctional communication between these regions and the amygdala prevents effective fear extinction in subjects with PTSD. Below, we present a highly cartooned graph of this neural circuit simplified to six main ROIs, which we will take as our nodes (Maren et al, 2013).

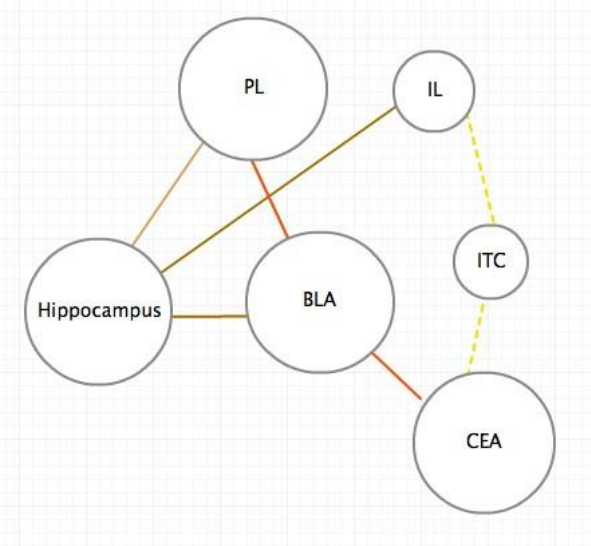

Figure 5 Mock undirected network diagram showing PTSD functional connectivity after fear extinction. Dashed lines represent decreased connectivity, solid lines represent increased connectivity. Enlarged regions are predicted to be more active by our hypothesis.

In this graph, it is thought that the excitatory connections between the PL and the basolateral amygdala (BLA), and the BLA and the Central Amygdala (CEA), are responsible for physiological fear response to a frightening stimulus. The excitatory connection between the IL and intercalated cells (ITC) in the amygdala inhibit the CEA, which then inhibits fear response. In a conventional fear conditioning paradigm, a fear-induced unconditioned stimulus (e.g. a shock) will be paired with an otherwise neutral stimulaus (e.g. a tone). Subjects will learn to respond fearfully to the conditioned stimulus through this association. If the conditioned stimulus is presented without the unconditioned stimulus enough times, the subject can "unlearn" the association through a process called fear extinction. In PTSD, it is hypothesized that the IL → ITC circuit is pathologically ineffective, resulting in impaired fear extinction.

To illustrate how simply a graph theoretic model may provide evidence for this hypothesis we present the following mock associativity matrices:

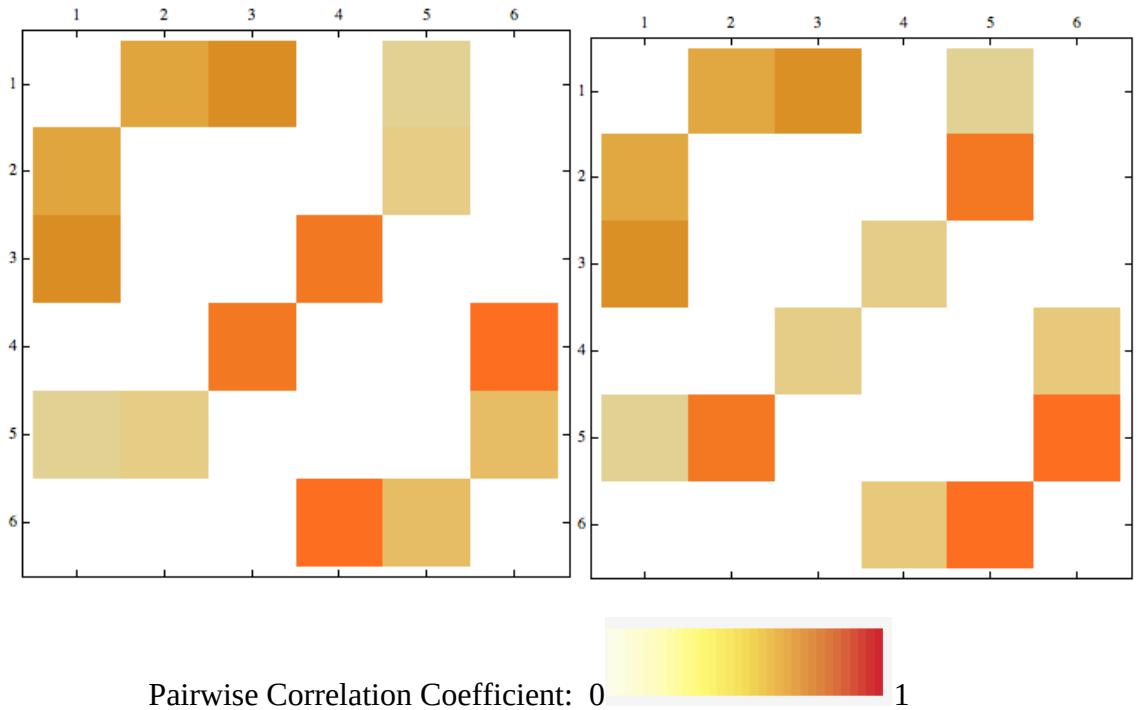

Figure 6: Comparison of mock associativity matrices between healthy control (left) and PTSD (right) test groups after a fear learning/extinction paradigm. We have labeled the hippocampus region 1, the PL region 2, the IL region 3, the ITC region 4, the BLA region 5 and the CEA region 6. Note that because the functional connectivity networks are undirected, the matrices are symmetric.

In Figure 6, on the left, is a mock associativity matrix for a healthy control after a fear learning and extinction paradigm. Given the above hypothesis, in healthy subjects we expect the IL → ITC and ITC → CEA connections (fear inhibition) to be stronger after successful fear extinction, while the PL→BLA and BLA → CEA connections (fear expression) should be weaker. The associativity matrix models this expected functional connectivity by increased correlation coefficients, or *r* values in the a34 and a46 entries (IL → ITC and ITC → CEA, respectively) and decreased *r* values in the a25 and a56 entries (PL→BLA and BLA → CEA, respectively). In accordance with our hypothesis, the PTSD associativity matrix on the right shows opposite *r* values in the Medial Prefront Cortex-Amygdala circuit, modeling what may be interpreted as a pathological dysfunction in IL → CEA communication. This is meant to be a

highly cartooned illustrative example of how a simple graph theoretic measure of functional connectivity, the associativity matrix, may allow quantifiable evaluation of a very complicated biological hypothesis. In the following chapter, we will see how this approach is actually applied and analyzed in an experiment on Schizophrenia out of the TN-SNL lab (Li et al 2015).

We have also calculated numerical values of descriptive measures detailed earlier in this chapter for the network illustrated in figures 4 and 5. While the graph has so few nodes that, in the context of brain, measures like modularity (Q, with two community structures subjectively defined as regions {1,2,5,6} and {1,3,4,6}) are not necessarily very meaningful because in our cartoon so much brain has been lost; Typically, we expect the number of ROIs in a human brain to number around 100, and the number of connections to be very large. Of particular interest here are local and global efficiency measures. We observe in Figure 7 that the network itself is highly efficient, which makes intuitive sense as each node can be reached by any other node in the network. The local efficiency values for each node, given in Figure 8, suggest that removing ROIs 3, 4 or in particular 6 would most disrupt successful communication in the network. This is also intuitively the case, particularly with ROI 6.

Graph Theoretical Measure	Value for Fear Extinction Network
Q	.03
C	.144
E_{glob}	.738

Figure 7

Node (ROI) Number	Local Efficiency
1	1.29
2	.5
3	.16
4	.16
5	.44
6	.125

Figure 8

Using the pairwise correlation coefficients *r* evented for Figures 4,5 and 6, we have constructed an Adjacency matrix for the healthy control by thresholding *r* at .5 (i.e. *r* >= .5 returns an Adjacency matrix entry of 1, 0 otherwise). The matrix can be seen in Figure 9, and its spectrum in Figure 10.

	1	2	3	4	5	6
1	0	1	1	0	1	0
2	1	0	0	0	0	0
3	1	0	0	1	0	0
4	0	0	1	0	0	1
5	1	0	0	0	0	0
6	0	0	0	1	0	0

Figure 9 Adjacency matrix for healthy controls

$\lambda_1 \approx -1.90211$
$\lambda_2 \approx 1.90211$
$\lambda_3 \approx -1.17557$
$\lambda_4 \approx 1.17557$
$\lambda_5 = 0$
$\lambda_6 = 0$

Figure 10 Spectrum of Figure 9

Chapter 4

rsfMRI Investigations into Neuropsychiatric Disorders

We have proposed that the right level of abstraction to investigate the neurological consequences of Childhood Maltreatment on sensory learning might be obtained using the experimental and mathematical tools made available by rsfMRI technology. These mathematical tools have been discussed in the previous chapter, and we may now examine their application in conjunction with rsfMRI technology to neuropsychiatric disorders.

In 1995 Biswal et al. remarked that the spontaneous fluctuations in fMRI signal observed when the brain was at rest (i.e., signals were not task-evoked) were temporally correlated between regions known to be functionally and anatomically connected. This observation was the beginning of a functional imaging fMRI paradigm, which we refer to here as resting state fMRI due to the lack of task expectation during imaging. Over time and in clinical application, rsfMRI has become an exciting technique in that it may allow researchers to better understand how changes in functional connectivity may characterize psychiatric disorders (Zhang & Raichle, 2010). Here, we will present published data from or in collaboration with the TN-SNL lab and will consider the use of graph spectral entropy.

Human studies

Because anesthesia interferes with functional connections in the brain (Liang et al 2011), subjects must be awake in the MRI scanner for the data to have value. As a consequence, most rsfMRI studies into psychopathology are conducted in human patients. Neurological disorders, such as Traumatic Brain Injury and Alzheimer's disease, have shows dysfunctional connectivity in hub ROIs, with severity of hub dysfunction associated with surgical outcomes in epilepsy (Stam et al 2014). While findings in the neuropsychiatric disorders have also been broad, we will consider two studies in depth here for illustrative purposes, examining changes in functional connectivity linked to Schizophrenia and Attention deficit/hyperactivity disorder (ADHD).

Schizophrenia is a psychiatric disorder initially classified as a "splitting of the brain" (Bleuler 1911). Indeed recent studies, including a study out of the TN-SNL lab (Li et al 2015) have suggested that functional dysconnectivity may be characteristic of the disorder. rsfMRI studies into pathophysiology related to Schizophrenia have found evidence of aberrant functional connectivity in many different networks and circuits, including the Default Mode Network (DMN, a network active when the brain is not participating in a directed task, Raichle 2001), in the attention network, the executive network and in the thalamocortical circuit (the thalamus processes and routes sensory information to the cortex, and the cortex projects feedback to the thalamus). This research is complicated, however, by confounding effects of psychotropic medication on functional connectivity (Tost et al. 2010) and by changes provoked by the chronicity of the disorder (Insel 2010).

To address this, Li M et al. investigated functional connectivity in first-episode, treatment naïve patients (n=136) in comparison to a group of healthy controls (n=113) (2015). Subjects

were scanned using a T2*(electromagnetic field inhomogeneity)-weighted Echo Planar Imaging sequence). Processing of raw EPI data will be covered in depth here and proceeded as follows: The first 10 time points of the time series were removed to allow measured BOLD signal to reach a steady state, raw images were slice corrected (images are frequently obtained in 2D, which results in a temporal offset between slices that must be corrected), realigned and corrected for movement-by-susceptibility based variance in the time series (time series variance caused by subject movement is typically much greater than intrinsic time series variance). The results were then motion corrected, spatially normalized to the Montreal Neurological Institute EPI image, and smoothed using a Gaussian kernel. To eliminate high-frequency physiological noise, results were linearly detrended and put through a band-pass (presumably low-pass) filter. Motion parameters, signals from cerebrospinal fluid and white matter were controlled for.

Independent Component Analysis (ICA) was then performed to parcellate the brain into 90 different components, which were then scaled into z-scores. The healthy controls were used to extract spatial information for each independent component, and the time series of each component in both the healthy control and schizophrenic groups was obtained by averaging the time series of each voxel with z-scores >2 ($p < 0.05$). For each subject, the pairwise correlation coefficient *r* between each component was calculated and transformed into a z-score using Fischer's z-transformation. These z-scores were used to construct an Association Matrix for each subject. 4 components were identified in the Cerebrospinal Fluid and were removed as artifacts, leaving 86 components for between group comparisons (Figure 3). The differences in functional connectivity between groups was evaluated using 2-subject t-tests with a threshold at $p < 0.05$.

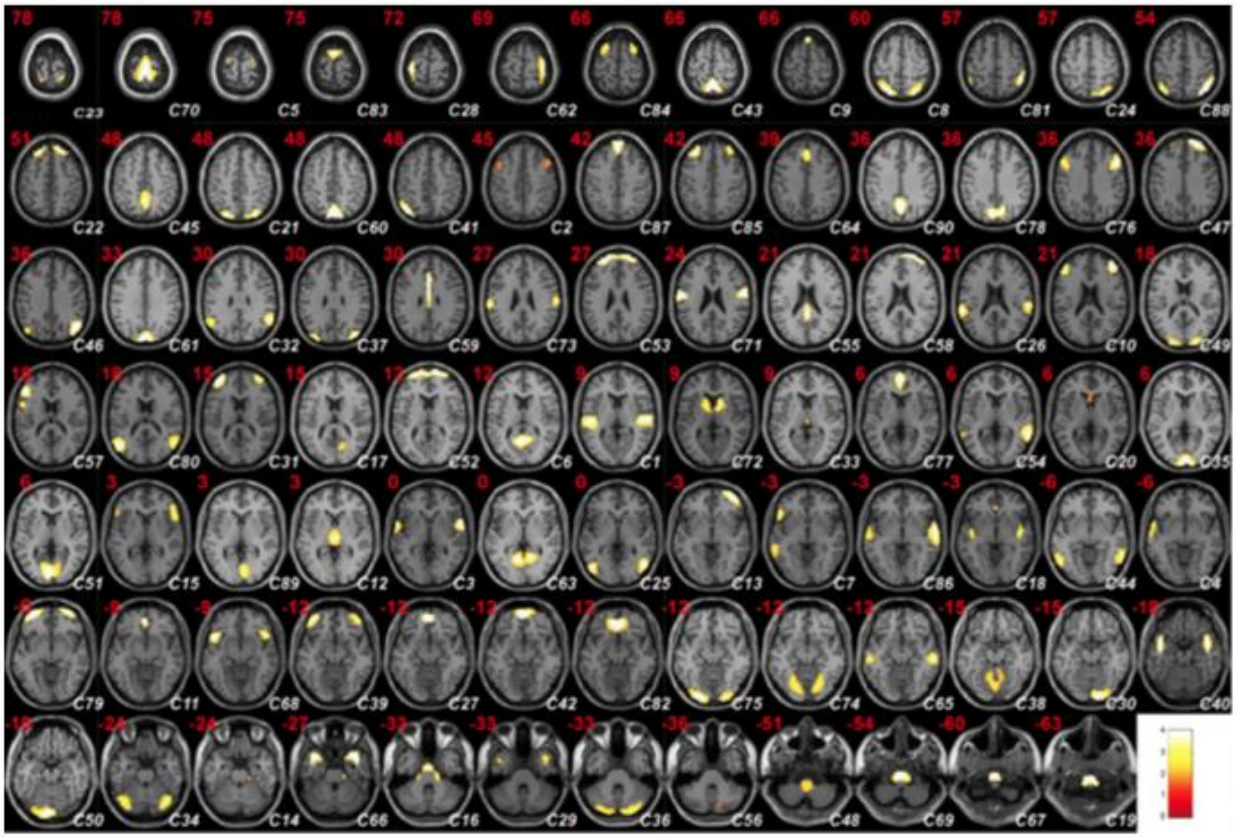

Figure 11 90 regions of interest as determined by Independent Component Analysis, before 4 were rejected as artifacts (Li M et al 2014)

Li M et al. associated each component with a functional network (e.g. the DMN) and were able to interpret between-group changes in between-component connectivity in terms of neural network function. The results showed widespread changes in connectivity following a comparison of association matrices between groups, where hyperconnectivity refers to increased correlation between relevant time series, and hypoconnectivity refers to decreased correlation (Figure 4). In particular, the study confirmed hyperconnectivity in the DMN (also detected in chronically schizophrenic patients), and for the first time was able to report additional hyperconnectibity between the DMN and the Dorsal attention network (DAN) and the DAN and Executive control and saliency network (ESN), whose anatomical features are given in Figure 4. Hypoconnectivity was observed in the Extrastriatal visual network (EVN) and between the

Auditory network and EVN. Hyperconnectivity between the DMN and DAN, as well at between the DMN and ESN, may result in pathological DMN interference during task performance, one hypothesized explanation for dysfunction neurocognitive function in schizophrenia. In addition, compromised thalamcortical function reflected in hypoconnectivity between the DMN and sensory networks was associated with increased severity of hallucinations, apathy and anhedonia. These results, in particular hypoconnectivity between prefrontal and sensory areas, may be limited by an age disparity between healthy control and schizophrenic groups (connections between prefrontal areas are believed to mature at around 25, the mean age of the schizophrenic group was 25.48 years while the healthy control mean age was 28.97 years). They are, however, very compelling. They paint a systems-level picture of brain dysfunction in schizophrenia that over the long term may prove very helpful for diagnosis and treatment in a clinical context. In particular, DMN dysfunction may come to be considered a characteristic pathophysiological marker of schizophrenia (Li M et al 2015).

Sato et al. used graph spectral entropy (see Chapter 3) to find descriptive differences between healthy (n=479 typically developing or TD controls, mean age 12.23 years) and ADHD (n=159 subjects, mean age 11.24) functional connectivity networks (2013). 351 ROIs were identified in the processed brain data and correlation coefficients between them (Spearman) were used to estimate functional neural networks. To identify coactivated networks, these were then clustered using a spectral clustering algorithm. The spectral clustering algorithm is used to cluster lowly interconnected sub-networks s.t. ROIs within the groups are highly connected. Sato et al. grouped the functional networks into 4 partitions of simultaneously-activitation clusters and in addition to betweeness centrality, clustering coefficient and shortest path length measures used

graph spectral entropy to look for topological differences in healthy and ADHD functional connectivity graphs.

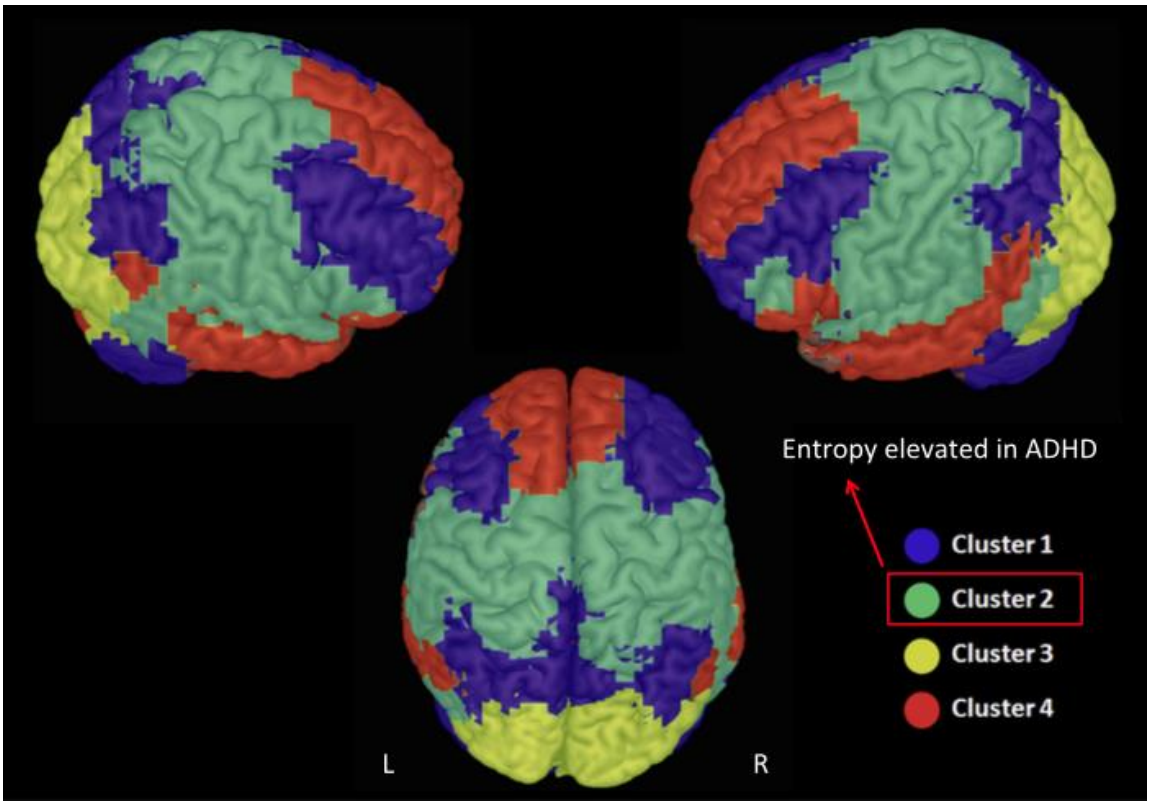

Figure 12 Cluster 2 in pale green, the only cluster with significantly increased entropy relative to healthy controls

In the cluster (Cluster 2) representing a partition of cortical areas immediately surrounding the central sulcus (including the primary motor and somatosensory cortices), the superior temporal gyrus and inferior frontal gyri (Figure 5), Sato et al. found significantly increased entropy vs. healthy controls (means -590.57 and -633.94, respectively). No other significant differences were found. For a complete description of results, see Figure 6. When interpreted in a neurophysiological context, increased randomness in communication between these regions suggests a relative lack of organizational coherence in neural firing, which may indeed contribute to attentional deficits in the disorder (2013).

Table 1
Descriptive measures and entropy measure obtained for each cluster of TD control samples and for each cluster of ADHD patients.

Cluster	Average betweenness centrality	Average clustering coefficient	Average path length	Entropy
#1	(0.115)	(0.926)	(0.121)	(0.025)
TD	19.27 ± 11.81	0.68 ± 0.07	1.40 ± 0.25	−661.68 ± 140.74
ADHD	22.10 ± 16.03	0.67 ± 0.09	1.46 ± 0.34	−640.27 ± 169.05
#2	(0.381)	(0.256)	(0.371)	**(0.002)**
TD	19.77 ± 11.09	0.68 ± 0.07	1.40 ± 0.23	**−633.94 ± 138.43**
ADHD	21.37 ± 14.10	0.69 ± 0.08	1.44 ± 0.29	**−590.57 ± 142n83**
#3	(0.722)	(0.457)	(0.716)	(0.353)
TD	4.91 ± 2.35	0.78 ± 0.08	1.27 ± 0.13	−313.00 ± 730.52
ADHD	5.25 ± 2.99	0.78 ± 0.08	1.28 ± 0.16	−272.68 ± 201.68
#4	(0.238)	(0.774)	(0.214)	(0.396)
TD	25.24 ± 15.41	0.65 ± 0.08	1.44 ± 0.27	−792.97 ± 234.16
ADHD	27.65 ± 20.14	0.65 ± 0.10	1.48 ± 0.36	−764.74 ± 467.69
All data	(0.092)	(0.395)	(0.092)	(0.026)
TD	68.97 ± 51.74	0.68 ± 0.09	1.39 ± 0.30	−5668.3 ± 5226.5
ADHD	79.51 ± 66.79	0.67 ± 0.12	1.45 ± 0.38	−5184.6 ± 8111.8

p-values (between brackets) and mean ± standard deviation for TD and ADHD. The descriptive measures are: average betweenness centrality, average clustering coefficient, average path length, and entropy. "All data" represents the p-values obtained when the neural network of the whole brain was analyzed, i.e., without partitioning into clusters. After Bonferroni correction for multiple comparisons, only the entropy of cluster 2 (in bold) presented statistical significance at a threshold of 5%.

Figure 13 Summary of Results for Sato et al. Note that graph spectral entropy is the only significantly different measure in the analysis.

Translational Study of Fear Response in Depression

There are significant challenges to overcome in combining translational (i.e. animal) models of neuropsychiatric disorders with rsfMRI technology. The most serious of these is that in order for rsfMRI to work at all, the subject must keep as still as possible while in the scanner. Most translational models of psychiatric disorders are done in rats and mice, animals that

obviously cannot be instructed to hold still for the scan duration. The benefits of combining animal research with rsfMRI are nonetheless incentivizing: The experiments are better controlled, invasive procedures can be used to confirm findings, and longitudinal research may be done that would be highly unethical in human subjects. Functional connectivity studies may also be used to confirm the translational validity of animal models. In general, when animals are required to hold still, they may be anesthetized. However, in rsfMRI, anesthesia interferes hugely with functional connectivity networks (Liang et al. 2011). To overcome this, Zhang et al. (i.e. the TN-SNL lab) propose an awake animal imagining paradigm that has allowed translational neuroimaging studies to further examine possible pathophysiological mechanisms of psychiatric illness (2010).

The awake animal imaging paradigm involves acclimating rats to restraints within the MRI environment, which is very noisy and initially very stressful. During acclimation, the rats are briefly anesthetized using isoflurane gas. While anesthetized, their forepaws and hindpaws are loosely taped to prevent self-injurious behavior within the scanner. They are secured in a plexiglass stereotaxic head holder through plastic ear bars with canines secured by a bite bar. Head restraints are now being 3D printed to improve comfort for the animals and EMLA cream is topically applied to alleviate discomfort. Their bodies are then inserted into a Plexiglas body tube and the entire unit is secured to a base. Secured and restrained rats are then taken off anesthesia (consciousness fully restored within 10-15 minutes) and placed in a black “mock MRI” box hooked up to audio from the MRI scanner with increasing duration over an 8 day period (+15 mins/day, from 15 to 90 mins on days 6,7 and 8) before imaging. This acclimation period greatly reduces motion artifacts and stress within the scanner (Zhang et al 2010).

Using this acclimation paradigm, Huang et al. were able to combine fMRI imaging with a translational model of depression to look at neuronal alterations in response to a fear-inducing stimulus (2011). Flinders sensitive line rats are bred as a well-validated genetic model of depression. They show many behavioral and neurochemical similarities with depressed humans (Overstreet et al 1998). Directed task neuroimaging experiments in humans have found hypo prefrontal activity and hyperactivity in the amygdala when clinical depression patients are shown negative emotional facial stimuli (Norbury et al 2009). Huang et al. used rsfMRI to examine network activity in FSL rats when they were exposed to predator odor (trimethylthiazoline) to see if these same ROIs would be implicated in any observed network dysfunction. They were compared to Flinders resistant line rats, which are their depression-resistant complement. Huang et al. indeed found hypoactivity the in PFC-Amygdala ROIs, which is (perhaps not) coincidentally the same circuit currently under translational model investigation by the TN-SNL lab for its involvement in fear extinction dysfunction in PTSD. As stated in Chapter 3, these studies are not yet finished, but this observation does call attention to possible pathophysiological overlap across what are clinically accepted to be distinct disorders.

Chapter 5

Translational model proposal

As we have seen, it is clear that a better understanding of the underlying pathophysiology will help clarify whether or not child abuse-related traumatic disorders are distinct entities (Goodman 2012). In their paper addressing the potential applications of computational methods to psychiatric research, Montague et al highlight the potential of new research approaches to address concerns regarding the treatments and classifications of DSM disorders (2012), including the graph theoretical and rsfMRI tools addressed in previous chapters. In that spirit, we propose the following investigation to explore the possibility of a neurological distinction between childhood and adult trauma-related psychopathologies.

rsfMRI data could provide insight into the functional ramifications of decreased Grey Matter volume, the clinically observed dysfunctional sensory processing, and the structural abnormalities Teicher et al have observed in the sensory white matter of child abuse survivors. By examining this question, rsfMRI and graph theoretical data analysis would be directly addressing the question of whether childhood trauma-related pathology is a distinct entity from adult trauma-related pathology. This question will indirectly challenge the assumptions and logic that have led clinicians to classify psychiatric disorders using behavioral criteria alone, and will provide much more meaningful characterizations of the conditions they wish to treat. In the case of CM, topologically different functional graphs along with similar symptom profiles would be sufficient to demonstrate an underlying neurological difference between pathologies in

prolonged child and adult trauma groups. It would be imperative for clinical care paradigms to evolve to address that evidence.

Elementary groundwork for this investigation is being laid in the TN-SNL lab at Penn State (where the author has been a research assistant since 2013) with concurrent translation investigations into functional connectivity in PTSD and the developmental trajectory of functional connectivity in rats. These studies are still in their infancy, but assuming success of pilot studies converging these two investigations, in a few years it should be possible to combine animal modeling, conscious animal rsfMRI (Zhang et al 2010) and graph theoretical modeling tools to derive profound insight into the effects of prolonged trauma on sensory learning adaptations and pathologies in the developing brain. It is true that rsfMRI and functional connectivity alone cannot paint a comprehensive picture of the effects of childhood maltreatment on the developing brain. However, given the overwhelming clinical and neurological evidence (see Chapter 2) of structural changes and dysfunctional information processing in psychiatric disorders associated with CM, it is almost certain that the systems level portrait of information trafficking that functional connectivity studies provide will transform our understanding of these conditions. While we cannot expect an animal model to reliably capture all forms of pathological learning associated with CM in humans, it may be possible to model the affects of CM on something as primitive as sensory learning. This would give us insight into how, at the most rudimentary level, the regions within the developing brain communicate in a prolonged traumatic environment. It may also allow us insight into how learning in childhood trauma-related pathologies is different on a functional network level than learning in adult trauma-related pathologies. Identifying learning differences specific to prolonged childhood trauma may inspire new and more effective therapeutic treatments for survivors.

To investigate the question of how a childhood environment of prolonged and repeated traumatic stress influences sensory processing relative to adult trauma, we propose the following traumatic fear conditioning paradigm. To investigate learned sensory pattern identification, we will use a paradigm of modified Pavlovian fear conditioning. Inspired by Artificial Language syntaxes (Gómez & Gerken, 2001), developed to test novel syntax recognition in preverbal infants, we will develop a series of tonal syntaxes whose iterations will be slightly more complex than auditory stimuli healthy adult rats have proved capable of recognizing[2] (Clark, 2000) and whose rules are more complex[3] (Murphy et al, 2008). One syntax will be paired to a shock conditioned stimulus (CS), and the rest will remain neutral (NS). The test group (TG) will be exposed to the paradigm throughout their adolescent period. A group of adult rats (AG) will be exposed to the same paradigm to test for learning differences between those rats traumatized as adolescents and those traumatized as adults. Healthy controls age-matched to the TG and AG will be used to confirm that the trauma rats show signs of chronic anxiety and enhanced arousal following the paradigm.

The trauma rats will be exposed to all syntaxes at random intervals, with random delays, and for random durations, in a variety of randomized contexts. The author expects that the sheer complexity of this learning environment will prevent any rats from being able to make the CS-

[2] Healthy rats should be able to identify two-tone oddball sequences within a repeating pattern (eg. Rats used to a hi-low repeating stimulus will startle at a low-hi oddball within that stimulus)

[3] Rats are able to distinguish XYX vs. XXY or YYX patterns when learning to associate one with a food reward.

Unconditioned Stimulus association immediately, and that this difficulty will be compounded by the presence of same-frequency tones in the NS patterns (i) and by randomized changes in context (ii). While (i) and (ii) will be easy to notice and to try to learn, they will not actually be associated with the shock and in that sense will function as red herrings. While the rats may make a CS-US association with time, the paradigm should be sufficiently complex and the association should be sufficiently difficult to allow for trauma in spite of any learning that takes place.

Sensory pattern learning will be measured by time spent in a freeze state when exposed to novel iterations of the CS, and not in a freeze when exposed to novel iterations of the NS. The rats will then be put through a generalized learning task, with the TG expected to perform worst relative the AG. The most interesting result would come if the TG showed enhanced tonal pattern recognition relative to the AG in spite of generalized learning deficits (similar to the Borderline Empathy phenomenon). To examine learning differences between trauma groups, it should be sufficient to compare learning between the TG and AG, and not with the healthy controls. Any such comparison would be nontrivial and outside the scope of our research question, at least for now.

rsfMRI could be used to look at the functional neural networks of all three groups, which would provide both further insight into overall graph organization and how that organization corresponds to diminished or enhanced learning ability. Because the paradigm investigates the brain as it developments in time, it would allow us to obtain rsfMRI data at time intervals throughout development. A dynamical model of development in abusive conditions, which for obvious ethical reasons is impossible to obtain using human data, would be an invaluable clinical

resource in that it would allow us to tease out the contributions of adaptive learning (modeled as Hebbian learning) and nonadaptive dysfunction to pathophysiological states.

A dynamic model, while appealing, is only one possibility here. As we have seen, part of the appeal of graph theory in functional connectivity investigations is the amount of information that can be gleaned using simple measures. As with the schizophrenia study presented in Chapter 4 and the mock PTSD fear extinction model presented in Chapter 3, we expect that a comparison of the pairwise correlation coefficients between ROI time series of the control and test groups will be an invaluable resource here. Decreased correlation coefficients between sensory cortices and higher order cortical areas would be evidence of decreased cognitive integration of sensory information. We might also observe overall decreased efficiency and shortest path length, decreased betweenness centrality in multimodal sensory areas (which connect different modalities of sensory information to higher order cognition), as well as an increase in overall network modularity. If these changes in graph topology prove unique to the CM model, their translation to the clinical case can significantly aid in CM-related pathology treatment and diagnosis. It will both allow and push clinical and legal paradigms to address underlying neurology in addition to behavioral and medical criteria. Improved protection and care is urgently needed for children affected by childhood maltreatment. This research, seated at the intersection of mathematics, engineering, medicine, and social justice, can direct that change.

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Eberly College of Science 2015 Student Climate and Diversity Award: *Awarded for the Everyday Sexism in STEM Project*

Women in Mathematics (WIM) Scholarship, 2013-14: $1000: *Awarded for mathematics research in Summer 2013.*

Schreyer Honors College Research Grant, Summer 2014: $1000

PI: Dr. Nanyin Zhang, Associate Professor, PSU

Lab: Translational Neuroimaging and Systems Neuroscience Lab

I assisted on a project examining the effects of traumatic stress on fear extinction and functional connectivity in the rat mPFC-amygdala circuit. I studied literature about the use of rsfMRI technology to study functional connectivity, studied an awake animal imaging paradigm and Pavlovian fear conditioning protocols, and learned about data processing. I was involved with the development and implementation a fear conditioning protocol, worked with rats before and after conditioning and helped maintain equipment. I was also trained to anesthetize the rats and administer basic medical aid.

Admission to the National French Honors Society (Pi Delta Phi): May 2012

Nominated and admitted in recognition of outstanding scholarship in French Language and Literature while at the University of Texas in Austin.

Diversity Work

Creator and Web Master, July 2014-present Everyday Sexism in STEM Project http://stemfeminist.com Media Coverage:

1. Baker, Kelly J. "Science Isn't the Problem, Scientists Are." https:// chroniclevitae.com/news/ 804-science-isn-t-the-problem-scientists-are.17November 2014. Web. 24 November 2014.

2. Blanda, Stephanie. "Everyday Sexism in STEM – A New Website" http:// blogs.ams.org/ mathgradblog/2014/09/29/sexism-stem/. 29 September 2014. Web. 24 November 2014.

Academic Work Experience

Instructor in Conversational English, Photography

September-December 2008

An-Najah National University

Nablus, West Bank,

Occupied Palestinian Territories.

Designed and taught a paid 30-hour Conversational English course and a volunteer photojournalism workshop to students at An-Najah National University.