

I've been thinking about the human brain for as long as I can remember.

As a young child growing up in the curiously-named town of Braintree, Massachusetts, I had a hypothesis – that people's minds grew among the branches of special brain-trees, and that each person's brain was specially harvested just for them. Like most ideas that three-year-olds have, it was highly imaginative and not physically possible. But the flawed logic in my strange idea is remarkably similar to some of the current leading theories about how the brain works. The philosopher John Searle writes, "The philosophy of the mind is unique among contemporary philosophical subjects in that all of the most famous and influential theories are false." To date, no theory can fully explain the intricacies of human cognition. I believe that through the application of neuroimaging technologies, the scientific community is moving ever closer towards a concrete explanation of the mind's inner workings. During my undergraduate research, I've had the opportunity to explore the brain through both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Through graduate school and a career in research, I plan to find creative new uses for neuroimaging technologies, with the hope that someday we will fully understand how neural mechanisms give rise to complex subjective experiences, emotions, and consciousness.

Having the opportunity to run experiments solidified my passion for research.

As an undergraduate research assistant in Dr. Richard Chechile's Memory and Cognition Lab at Tufts University, I worked with a team of researchers to decipher the mechanisms by which memory is encoded. I specifically chose to work in this lab because Dr. Chechile shared my interdisciplinary interests in both psychology and mathematics. As a double major in Computer Science and Cognitive & Brain Science, I was eager to learn about the potential uses of STEM research methods for studying the human mind. As my introduction to hands on experiments, the research in Dr. Chechile's lab inspired me to think more deeply about how memory works. I left lab meetings pondering how mathematical models could be used as evidence in support of models of cognition and was inspired to spend my free time searching the web for related research articles. Still, I yearned for a link not only from behavior to mathematics, but also to the biochemical signals and neural underpinnings present in the human brain.

Through neuroimaging research, I built an interdisciplinary knowledge base.

In search of such a connection, I sought to gain research experience in neuroimaging. I was attracted to neuroimaging research because of its interdisciplinary requirements. When studying something as complex as the brain, it is imperative to approach problems from multiple angles. During my first summer working at Massachusetts General Hospital (MGH) in Boston in the lab of Dr. Jacob Hooker, I learned the value of working in a diverse scientific group. While Dr. Hooker is primarily interested in developing new radiotracers for PET imaging of the brain, his lab includes researchers with expertise in multiple fields, and from a diverse array of academic and cultural backgrounds. As a part of such a diverse team, I valued not only the variety of scientific perspectives that an interdisciplinary team can offer, but also the wide range of viewpoints on academia, science, and life that a culturally diverse team brings to the table.

My first few projects with Dr. Hooker's group involved improving an existing software tool for kinetic modeling of PET radiotracers. Through these projects, I quickly learned new computer programming skills, built scientific connections in the neuroimaging community, and immersed myself in a new field of literature previously unknown to me. Additionally, I gained

valuable experience sharing my work with colleagues during short lab-meeting presentations and published my first scientific journal article¹. It became clear to me that a strong background in imaging *methodology* was essential to making proper conclusions about human psychology from imaging studies. I was eager to share my work and newfound imaging-knowledge with colleagues in Psychology at Tufts and did so through a presentation at Tufts' Annual Undergraduate Research Symposium.

With a solid foundation in PET imaging after that first summer, I continued working in Dr. Hooker's Lab a few days each week during the school year. During this time, I continued to work on several kinetic modeling projects, but also developed an interest in fMRI. Under the guidance of a fantastic mentor, I readily completed small projects using image-analysis software like FSL and became obsessed with the literature related to resting state fMRI (rs-fMRI). I was captivated by the possibility of exploring the inner workings of the mind through intrinsic, low frequency signals that permeate resting brain activity.

I am always searching for new technologies to utilize in brain research.

When tasked with completing a term-project in my computational biology course at Tufts, my mind immediately turned to my prior research in Dr. Hooker's lab. Although our computational biology course focused on genetics, I believed that similar computational methods could be applied to brain imaging research. After all, whether it's a genetic sequence or a brain image being analyzed, a computer only sees information stored as bits. Using machine-learning techniques from my computational biology class and image-processing skills I had developed in Dr. Hooker's lab, I created a computer program that can differentiate between the resting state scans of brains with schizophrenia and those of matched controls. By capitalizing on open-source rs-fMRI data I found freely available online and the interdisciplinary connections I had made across institutions, I built a unique and exciting research opportunity, and explored new ways for computer science to be applied to brain research.

Earlier this year, I chose to continue my work with Dr. Hooker's group for a second summer, and again during the school year. My previous projects with PET and fMRI allowed me to mature as a researcher. I now routinely generate independent hypotheses and design my own small experiments. Other lab members trust me to analyze their imaging data and we are working on several collaborative projects that should result in future publications. Moreover, I am pursuing a year-long independent project that will culminate in a Senior Honors Thesis. This project is specifically tailored to my research background. It capitalizes on resources available through both MGH and Tufts, and makes use of MGH's simultaneous MR/PET scanner. I am excited to conduct research with this state of the art imaging modality and plan to continue this line of work in graduate school.

I am committed to the art of making science accessible.

In addition to contributing to the development of neuroscience through research, I am committed to helping this field grow on a societal level. One of my favorite things about conducting brain research is that it is so relatable to the general public. Even though my parents and many friends from home are not scientists, I find that through the right metaphors and careful explanations, I can still get them excited about brain research. In Dr. Hooker's lab last summer, I volunteered to help with an open house event. In collaboration with the Alzheimer's Association, this event offered the general public the opportunity to hear from researchers first-hand and to see the research facilities up-close and personal. Paired with a blog and Twitter account that lab members regularly contribute to, Dr. Hooker encourages all lab members to

engage with their research outside of the lab and in the context of society as a whole. During my future research career, I plan to take the same “outside-in” approach to research. I believe that sharing science with the public and with people from other disciplines allows one to engage with research questions from new perspectives, and to ask more innovative, deeper questions.

To increase the number of people who can engage with science, I am an advocate for increased access to higher education. I believe that bringing diverse perspectives into science helps us to consider empirical questions from different points of view. As a contributing author for *Enigma: Tufts Independent Data Journal*, I worked with a group of computer scientists, graphic designers, and journalists to conduct a study examining student attitudes surrounding financial aid. We found that financial aid status and socioeconomic status are strongly associated with Tufts students’ job status, involvement in clubs, choice of academic major, and many of the social perceptions students have on campus. We shared our findings in an online publication, at our club’s biannual symposium, and plan to meet with the Chief Diversity Officer here at Tufts. Personally, I am thankful for the financial aid and scholarships I have received that made my educational and research experiences possible. In the future, I plan to continue advocating for increased financial aid in higher education, and to recruit more students from disadvantaged backgrounds.

By increasing diversity in STEM fields, we can ensure that STEM research has a greater positive societal impact. In some respects, brain science has suffered from a dark history – from the classification of homosexuality as a mental disorder in the DSM III to the performance of lobotomies on transgender individuals. I believe that increasing STEM diversity can help to avoid many of the negative impacts science can inadvertently have. Recently, I was one of 100 LGBTQ individuals selected from an international pool of applicants to attend a conference at Stanford University. The meeting aimed to increase the diversity of individuals in STEM fields and to form a network of individuals committed to this cause. I had the opportunity to present some of my brain imaging research to attendees in the form of a TED-style talk and started some great conversations about LGBTQ representation in the field of neuroscience. I walked away from this event with a renewed passion for increasing diversity in and access to STEM education. Many of the conference organizers are graduate students in STEM fields, and I plan to stay involved in the future.

I am passionate about finding creative solutions for science’s most difficult problems.

In graduate school, I plan to dedicate the next phase of my career to pursuing answers to questions about the human mind and brain. With funding from the NSF GRFP, I will be able to ask novel neuroscience questions and to challenge standard ways of thinking. Throughout my career, I plan to bring my own unique perspective to the table and to share my research with people outside of my field as well as the general public. Eventually, I hope to become a professor in neuroscience with my own neuroimaging lab. Through a diverse team of researchers from various scientific fields and cultural backgrounds, I hope to produce sound scientific research with positive societal implications. By taking advantage of multiple imaging modalities and the latest computational methods, I hope to start answering questions about the mind that philosophers have posed for centuries. With luck, I’ll someday explain to my own child that although brains don’t grow on trees, we do know how they work.

Works Cited: [1] Placzek, M. S., Zhao, W., Wey, H. Y., Morin, T. M., & Hooker, J. M. (2015). PET neurochemical imaging modes. *Seminars in Nuclear Medicine*, 46(1), 20-27.

Mapping Effective Connectivity During Reward Expectation with Simultaneous MR/PET

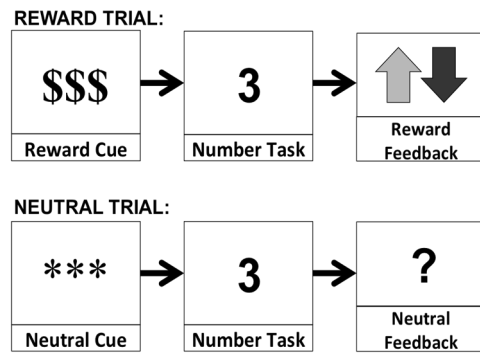
Introduction: When humans expect to receive a reward, their behavior and cognitive performance can be affected [1,2]. Recent neuroimaging research has identified specific brain regions often associated with reward, including frontal regions such as the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC), limbic regions such as the striatum and amygdala, and other connected regions such as the insula and anterior cingulate cortex (ACC) [1,2,3]. While the activity of these regions is correlated with reward expectation, little is known about how these regions interact causally. Neuroscientists often colloquially refer to the frontal lobe as the “control center” of the brain, but there is debate about the top-down influence that regions such as the OFC, mPFC and ACC may or may not have [2]. Mathematical models of fMRI data attempt to draw causal links about the direction of activity between different brain regions, but have little basis in actual biology [4,2]. With the unique perspective offered by simultaneous MR/PET imaging we may be able to make such inferences [4]. I propose a study utilizing simultaneous MR/PET imaging to investigate whether regions including OFC, mPFC, and ACC directly influence limbic and other connected regions during reward expectation.

Background/Rationale: With positron emission tomography (PET), researchers can examine changes in brain *chemistry*, and with fMRI, researchers can see changes in brain *activity*. When regions show highly correlated fMRI signal changes, we say they exhibit functional connectivity (FC). Neuroscientists use FC measures to make inferences about the architecture of brain networks and to learn how different brain regions interact.

However with mere correlations, we cannot draw conclusions about the causal influence that one brain region might have over another. When we do have evidence of a *directed* connection between brain regions, we say they exhibit effective connectivity (EC). Currently the most popular methods for deriving EC signals from fMRI data include Granger Causality (GC), Dynamic Causal Modeling (DCM), and other graph theoretical models. While these mathematical and statistical techniques can unearth exciting metrics about potential brain networks, they rely solely on fMRI signal and can suffer from confounds such as varying hemodynamic response curves between different experimental groups [4].

With the addition of chemical information, such as glucose metabolism from simultaneous PET imaging, we can discern directionality in the FC networks acquired with fMRI. This new method is known as Metabolic Connectivity Mapping (MCM), and relies on information about the brain’s consumption of glucose [4]. We know that most of the brain’s energy-use is dedicated to sending and receiving signals, and that most of the energy used in signaling is consumed postsynaptically [4]. With PET, we can use a radiotracer called [^{18}F] fluorodeoxyglucose ([^{18}F]FDG) to track changes in glucose metabolism, and measure the brain’s varied energy use between regions [4,1]. PET imaging can reveal the regions with higher rates of glucose metabolism: the “target” regions of neural signals. When we overlap the PET images of energy use with simultaneously acquired fMRI images of brain activity, we can visualize the overall direction of neural signaling. In other words, MCM provides a powerful means of deriving information about EC in the brain.

Experimental Methods: Previously, MCM has been used in an “eyes-open/eyes-closed” task to examine EC between the visual and sensory cortices [4]. I propose using the MCM method to examine the possible top-down influence of frontal regions over limbic and connected regions during a reward-expectation task. Subjects will undergo a one-hour simultaneous MR/PET scan while completing a modified version of the delayed monetary incentive task [5,3]. During the scan subjects will complete trials where they quickly judge whether a number is greater than or



less than 5 with a button press. Before each trial, subjects will see either a reward cue (\$\$\$), indicating the possibility of receiving a monetary reward for successful completion of the upcoming trial, or a neutral cue (***), indicating no possibility of reward for this trial. Subjects will receive feedback after reward-cued trials in the form of a green upward-pointing arrow (for correct/fast answers), or a red downward-pointing arrow (for incorrect/slow answers). After a neutral trial, subjects will receive feedback in the form of a neutral question mark. The paradigm is illustrated at left.

To account for the poor temporal resolution of simultaneous PET imaging, I will examine long-term changes in glucose metabolism by biasing the trials to which subjects are exposed [5]. For thirty minutes of the scan, 80% of the trials will be reward-cued trials, and for the other thirty minutes, only 20% of the trials will be reward-cued trials. This will allow us to compare long-term changes in glucose metabolism between reward and neutral conditions.

By comparing fMRI signal during reward-cued and neutral trials, we can examine differences in brain activity and FC due to expectation of a reward. I expect to see increased activity in all areas associated with reward-expectation, and hypothesize that OFC and mPFC may exhibit a top-down influence on limbic and other connected structures. With the fMRI data alone, I plan to first derive EC using DCM. In a subsequent analysis, I will use measures of glucose metabolism to derive EC from MCM, and compare to the DCM math modeling results. **Broader Impacts:** By using MCM to examine EC in more complex cognitive tasks, we can start to create a “circuit diagram” of how the brain’s many functional regions influence each other. With a better understanding of reward circuits, we can develop new cognitive models to explain how the human brain is affected by reward expectation. This is an important consideration for psychological studies, many of which compensate participants monetarily. Additionally, MCM can be used in future studies to discover new EC networks, and to validate networks hypothesized by GC and DCM. Once published, I plan to make all of the imaging data fully available upon request. Access to this data could be important to other researchers seeking to develop better mathematical models for examining EC. It is conceivable that future math models of this nature may even incorporate PET signal. Altogether combined MR/PET imaging allows us to consider the brain as a complete biochemical system, and to make new discoveries about the interactions between brain activity and brain chemistry.

Feasibility and Support: This study will require a combined MR/PET scanner for human imaging. The Martinos Center for Biomedical Imaging at Mass. General Hospital in Boston has the necessary infrastructure for the proposed study. During my past research experience, I have completed necessary training and obtained access to the simultaneous MR/PET scanner and computing resources for data analysis. Through this study, I will broaden my experience and training with multimodal brain imaging through a creative application of MR/PET.

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