Diving into the deep end: A personal reflection on the MyConnectome Study

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Abstract

In this reflection I discuss the factors that led me to undertake the MyConnectome study, in which I was scanned using MRI more than 100 times over the course of eighteen months along with many additional biological and psychological measurements. I describe the study from a personal standpoint, outline the major findings from the study, and discuss its implications for neuroimaging research.

Main Text

On September 24, 2012, I climbed into the Siemens Skyra MRI scanner at the University of Texas Imaging Research Center and began what would become one of the most scientifically interesting and personally challenging experiences of my life. In this reflection I will discuss what inspired this project, which became the MyConnectome Study, and the implications that it has for the field of cognitive neuroscience.

In the two years before I went into the scanner that day, several issues were on my mind that came together to inspire the MyConnectome Study. The first was the rapid ascendance of resting state fMRI. At that point, my career had been focused almost completely on task fMRI studies, and to be honest I was a bit skeptical that task-free measurements could inform our understanding of the neural organization of cognitive functions, which has always been my scientific goal. I'd been involved in at least one study that had collected resting state fMRI data [1], but I wasn't convinced that it would actually be useful for us. In part, this was because I wasn't even sure how reliable the measurements were. Before I could buy into the resting state juggernaut, I needed to be convinced that we could get reliable measurements, and at that point there were not yet compelling data to show this.

A second issue that had piqued my interest was the variability of brain function over time. This interest largely arose from thinking about the neural basis of neuropsychiatric disorders, largely inspired by my earlier collaboration with Robert Bilder and colleagues at UCLA [2]. At that point (and largely still), studies of individuals with these diagnoses would scan each individual once and assume that this single scan represented an accurate snapshot of whatever functional anomalies might exist in relation to their disorder. However, as someone who had previously struggled with an anxiety disorder, I knew that these problems varied greatly over time, and the data from other disorders including schizophrenia [3] and bipolar disorder [4] also have shown that symptoms vary greatly over the course of days and weeks. The fact that there were no longitudinal imaging studies at this time scale seemed to represent a true scientific lacuna --- as well as a prime scientific opportunity.

The question for me was how one could actually go about collecting sufficient data to assess variability over time. I considered trying to do this with a group of volunteer subjects, but there were just too many unknowns — in particular, would any volunteer subject really come back for repeated scans over such a long period? A confluence of two events drove me toward the decision to do it on myself. First, at this time the “Quantified Self” movement was in high gear. This movement was focused on collecting as much data as possible about oneself, and a friend who was deep in this movement was continually pushing me to consider using our MRI scanner to quantify my own brain. This seemed like a narcissistic folly until the second event, which was the publication of Michael Snyder’s landmark paper in *Cell* [5] in 2012. Snyder is a geneticist at Stanford whose lab developed the concept of “integrated personal -omics profiling” in which they deeply characterize the biology of an individual using genomic, transcriptomic, proteomic, and metabolomic methods. Snyder applied these methods to himself, collecting blood regularly across the span of a year, more frequently during periods when he was sick with respiratory illnesses. Fortuitously (for science, if not for Snyder himself), he developed Type II diabetes in the wake of one of these illnesses, and the study provided a deep biological picture into the onset of this disease. For me, the publication of this N-of-one study in the most prestigious journal in biology suggested that one could do serious science on oneself and was really the spark that led me to finally decide to start imaging myself.

Over many conversations in 2012, the plan for the study began to solidify. I first undertook a set of conversations and a literature review to determine whether it would actually be safe to scan myself regularly; although it’s never possible to prove that something will be safe, the research convinced me that there was no major risk of repeated MRI scanning. The study team and I decided to start with a schedule of three scans per week, keeping the time of day fixed, with scans on Tuesday and Thursday mornings and Monday afternoons. Each session would include a ten minute resting fMRI acquisition; in addition, different sessions included task fMRI (including n-back, stop signal, spatial and verbal working memory, visual object recognition, and retinotopic mapping), diffusion MRI, and structural MRI acquisitions.

In addition to scanning, I also wanted to track as many other psychological and biological variables as possible. We developed a platform through which I could complete questionnaires every morning and evening, which encompassed sleep, diet, and physical and mental health. We also developed a protocol in which I would have 20 ml of blood drawn once a week (while fasted, immediately after the Tuesday morning MRI scan), which would be processed by the UT Genome Sequencing Analysis Facility to extract white blood cells (from which RNA was extracted) and plasma, both of which were frozen for later analysis.

With all this in place, we started collecting data in September 2012. We treated the first month as a pilot period and made some adjustments to the protocol, beginning the “production” period on October 23, 2012. Soon thereafter it became clear that three sessions per week was just too much time for me to spend in the scanner, so we reduced it to two sessions per week, at 7:30 AM on Tuesday and Thursday mornings. I quickly settled into a routine, and over time these scans became a highly anticipated part of my life. I had always been rather anxious about getting into the MRI scanner, but over time the noises of the scanner became the soundtrack to an almost meditative morning break.

Even the weekly blood draws became a source of pleasure as I became friends with the technicians who searched for a vein every Tuesday morning.

However, one unanticipated complication appeared soon after we started the study. I have long suffered from tinnitus (ringing in the ears) due to too many hours spent playing and listening to loud music in my youth, but soon after I started the study I noticed that my tinnitus was increasing in its severity. To track this, I first visited the Audiology clinic at UT in October 2012, and the initial assessment showed that I had substantial high-frequency hearing loss. To ensure that I wasn't causing further damage, I continued to visit the clinic regularly for follow-up measurements. In March 2013, the assessment showed about a 10 db worsening at 6000 Hz, consistent with a subjective increase in tinnitus around the same time; for this reason (along with a spate of upcoming trips), I took a hiatus from most of March and April 2013. A followup audiology exam showed that the earlier worsening was probably a momentary blip, perhaps due to allergies, so we began scanning again on April 30, 2013. We did discontinue the use of several sequences, particularly the anatomical sequences, whose sounds were particularly grating to my ears. The study continued until March 11, 2014, after I had completed a total of 104 scanning sessions and 48 blood draws. The stopping criterion was two-fold. First, at that point I had accepted a position at Stanford and was planning to move within a couple of months, so my life was consumed with preparation for the move. Second, and more prosaically, the RNA sequencing analyses that we performed on my blood were done in batches of six, and given that I was unlikely to complete six more draws before moving, we decided to end at 48 draws.

The study left us with a large amount of data, and my group had no expertise in the analysis of resting fMRI data. Fortuitously, I received a message from Steve Petersen at Washington University in St. Louis, whose group is expert in the analysis of these data. Steve had heard about my study, and his group was interested in using the data to test the stability of the resting fMRI-based cortical parcellation techniques that they were developing. Tim Laumann, then a graduate student in Steve's lab, took the lead on processing the fMRI data and played a central role in the subsequent success of the project. By the end of 2014, he was ready to submit a paper, which was subsequently published in *Neuron* in 2015 [6]. This paper focused primarily on two questions: how reliable are the patterns of functional connectivity estimated using resting fMRI, and how do they relate to the patterns identified in group studies of resting connectivity? This paper demonstrated a result that has inspired a bevy of subsequent work: While my overall pattern of connectivity was broadly similar to that observed in the group studies, there were a number of fine-grained features that were unexpected. In particular, there were islands of connectivity ("network variants") in which the connectivity expected from group studies was violated within my brain. The analyses also showed that connectivity-based parcellations are highly reliable across sessions, providing a stronger basis for the use of those techniques more broadly. The results from these analyses also made me generally more confident that resting state fMRI can provide reliable measures of brain function, and paved the way for subsequent work on the dynamics of functional connectivity in collaboration with Mac Shine, including analyses of MyConnectome dataset [12].

I moved from Austin to the Bay Area in June 2014 and spent much of the summer of 2014 analyzing the data in parallel with Tim Laumann but from a broader perspective, inspired by the work I had done earlier with Robert Bilder on "phenome-wide" analysis. This involved combining the imaging data with

the RNA-seq and metabolomics data obtained from my blood along with all of the behavioral measures that I had collected. This experience was instrumental in the initial development of my interest in computational reproducibility, for a very practical reason. As the Petersen group continued to improve their parcellation methods, they would regularly send me updated versions of the resting fMRI data, which required me to rerun all of my analyses that were based on their summary data. For this reason, I developed a framework that allowed me to rerun the entire analysis workflow with a single command. I initially developed this on my Mac laptop, but before submitting the paper I wanted to make sure that it would run elsewhere, so I uploaded it to our cluster and tested it there. Once I got it running I was shocked to see that the results were substantially different! We ultimately tracked this down to differences in a particular R package between platforms, and the paper reporting these results was subsequently published in *Nature Communications* in 2015 [7]. The experience also cemented for me just how difficult computational reproducibility can be and inspired my subsequent efforts to develop the Stanford Center for Reproducible Neuroscience.

Around the time that I was planning the study, my group was also in the midst of launching the OpenfMRI project [8], which ultimately evolved into the OpenNeuro project. I made the decision early on that I would share all of the data that we collected in the MyConnectome study (save some very personal details, like my daily diary contents), in a completely open way (doi:10.18112/P2159B). These data have gone on to play a role in 27 publications, of which 24 are from groups other than my own. The data have been used for many different purposes including assessment of artifacts and quality control measures [9,10], modeling of dynamic functional connectivity [11–13], characterization of cerebral blood flow [14], and testing of a number of novel machine learning methods [15]. While there is some risk to sharing such detailed health-related data, I decided that the risk was worth it (especially given my privileged position as a tenured professor), and I think the payoff has been substantial.

I have been deeply heartened to see how other groups have sprinted forward carrying the torch that was lit in the MyConnectome study. The group led by Nico Dosenbach at Washington University in St. Louis has been remarkably successful with this deep phenotyping approach, in their Midnight Scan Club study [16]. They have demonstrated using this remarkable dataset (also openly shared: doi:10.18112/openneuro.ds000224.v1.0.3) that the unique connectivity features that we identified in the MyConnectome study were not unique to me but rather are present in nearly every individual and are remarkably stable within individuals [17,18]. Perhaps most impressively, they took the self-experimentation model one step further, casting their arms in order to assess the cortical plasticity that results from immobilization [19]. Another set of studies from Randy Buckner, Rodrigo Braga, and colleagues [20–22] has taken the deep phenotyping approach in a different direction, focusing on the presence of consistent substructures within large-scale networks that can be identified when sufficient data are collected from each individual but which were not evident from earlier group studies. Together these two lines of work highlight the scientific utility of the deep phenotyping approach, and I am sure that they are just the first of many such studies to come.

My experiences in the MyConnectome study fundamentally changed my approach to cognitive neuroscience. Foremost, it highlighted for me the need to precisely estimate signals within each individual. Within the community of researchers focused on reproducibility, there has long been a focus

on the need for larger sample sizes due to the effects of low statistical power on reproducibility [23]. The results from the emerging set of deep phenotyping studies highlight the complementary fact that previous approaches may have simply collected far too little data per individual, leading to estimates with a high degree of measurement error. There is of course a tradeoff: All else being equal, collecting more data per individual means collecting data from fewer individuals, which is particularly problematic when one is trying to detect relatively small associations between psychological measures and brain function (Marek et al., 2020, BioRxiv). The emerging work from deep phenotyping studies has highlighted the utility of trading sample size for sample depth; while there are certainly questions that will not be amenable to this approach (particularly those related to individual differences or genetics), going deep offers an important alternative to weakly powered group studies that have likely led to a high degree of irreproducibility in the neuroimaging literature [24]. As long as the implications for generalizability are kept squarely in mind, this approach can potentially provide researchers with an opportunity to perform rigorous and reproducible neuroimaging research without requiring the immense resources needed to run large-scale group studies.

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