Understanding the Limits and Potential of fMRI Motion Correction

Motivation: Functional magnetic resonance imaging (fMRI) allows non-invasive measurement of real-time brain activity in humans. The success of this technology has been evidenced by its rapid growth in popularity in the 25 years of its existence, resulting in nearly 40,000 research papers[1]. A large portion of these studies investigates the correlational structure of the brain signal, known as functional connectivity (FC). FC studies are most often implemented in resting state fMRI (RS-fMRI). Historically RS-fMRI has been especially useful in clinical and developmental imaging because it requires no task demands, avoids performance confounds and measures network connectivity in largely the same way that task fMRI does[2]. These methods have led to many groundbreaking findings in brain science that were previously inaccessible.

Recent evidence[3] has shown that many of these findings may be spurious and insidiously riddled with artifactual patterns of connectivity created by head motion. This is most often evident in clinical and developmental populations because head motion is confounded with the group effect of interest. Even small movements, on the scale of .1 mm, have been shown to cause structured patterns of spurious variance, enhancing short-range connectivity and decreasing long-range connectivity[3]. These findings have caused many groups to entirely reevaluate previous FC findings[3] and attempt to develop ways of overcoming this major problem.

Current motion correction methods summarize head motion as a rigid body transform with 6 parameters (motion in the 3 spatial dimensions as well as rotations along each of these axes). The amount of motion at any single time point can be estimated by the change in each of these 6 motion parameters from the previous time point. Many methods have been developed to characterize and correct for motion-related signal. Common motion correction pipelines model the relationship between each direction of motion and fMRI signal changes linearly in confound regression. However, this linear assumption may be inadequate[4]. Higher order expansions of this model[4] that allow for temporal offset and nonlinear relationships between motion and fMRI signals have been shown to perform better than standard methods in high motion populations, however, these models still fail to entirely remove motion related signal. To remove the remaining nuisance signal it is common practice to censor the problematic timepoints[5]. While this method works, it requires removal of valuable time points and often removal of entire subjects from an analysis. Regularly these removed subjects are patients whose data collection cost thousands of dollars and many person-hours. This leaves the field in a tenuous position in which previous findings require reevaluation and future studies must employ burdensome censoring techniques. If lasting, valid progress will be made with FC-fMRI a thorough understanding of motion and better motion correction techniques are required. The proposed research will apply established methodologies to a unique dataset, which will shine light on this important issue in fMRI.

Aim 1: Characterize and model head motion artifacts in a single highly sampled subject. The proposed project will begin by thoroughly characterizing motion related signal changes in the MyConnectome dataset[6]. This publicly available dataset consists of 88 ten minute RS-fMRI scans of a single healthy adult male, resulting in over 45,000 whole brain images. Originally collected to establish the reliability of FC-fMRI methods, this dataset provides a unique opportunity to understand fMRI signals related to motion, an endeavor previously overlooked. Compared to a typical RS-fMRI dataset this sample has no variance related to individual differences or sex effects, and minimal variance related to age, brain size, or vasculature.

From the wealth of time points in this dataset, I will construct smaller datasets out of time points that have motion primarily in a single direction and/or magnitude. Each will be the size of

a typical RS-fMRI analysis. I will then apply previously described methods[5] to characterize the influence of this highly controlled motion on fMRI signal change and FC. The unique flexibility of the MyConnectome dataset will allow me to further describe the nonlinearity and heterogeneity of motion related signal changes. To do this I will use established multiple regression methods [4], testing models of the linear and nonlinear effects of motion on the fMRI signal and time-course while penalizing for model complexity to avoid overfitting. I hypothesize that this approach will allow a precise description of the influence of directionality, magnitude and the time-course of head motion on fMRI signal and connectivity that will surpass current models in the amount of motion related variance explained.

Aim 2: Determine generalizability of head-motion model. A major issue with this model may be that its utility is specific to a single subject's brain and lacks generalizability to developmental or clinical populations with a larger amount of movement. I will use another unique and publicly available dataset, the Philadelphia Neurodevelopmental Cohort (PNC), to overcome this limitation. Since the PNC consists of a pediatric, demographically diverse, developing population, it is well suited to test the performance of the model defined in Aim 1 with a dataset most prone to the previously identified motion confounds of FC-fMRI. I hypothesize that the model identified will significantly outperform current state-of-the art processing methods, significantly reducing measurable motion related confounds[5] and the reliance on censoring.

Broader Impacts: This research has the potential to contribute crucial information to the growing discussion of motion in FC-fMRI. In depth investigation and rigorous control of motion in a single highly sampled subject has not previously been achieved and will demonstrate the upper limit of our ability to describe and correct motion artifact. With this information, generalizable gains in fMRI processing will follow, especially in mental illness and developmental research where human fMRI is especially important. Following the global push for openness in research and collaborative science, I will use data that is publically available and openly share all analytic programming code necessary to complete these analyses on GitHub so that the entire neuroimaging community may use and expand upon this work. This type of detailed fMRI artifact investigation is crucial for its validity and without it, progress may be dampened and slowed by confounds that are not adequately managed by current processing methods. Receiving support from NSF would allow me to develop these important motion correction methods during graduate school.

Feasibility and Support: The proposed research is to be completed with Dr. Satterthwaite, a leader in the fMRI literature relating to motion artifacts and an investigator for the PNC[4] .This will streamline access to the PNC data and its growing longitudinal child dataset. My experience with motion correction in a high motion population (see personal statement) and the tools I have previously developed to do this will immediately lend itself to this project. Access to NSF's XSEDE computing resources, made possible by this fellowship, will be indispensable for parallelizing the computationally-intensive analysis of the large datasets in this proposal.

References: (1) PubMed Search "fMRI OR functional MRI OR functional magnetic resonance imaging". **(2)** Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE (2014) Intrinsic and task-evoked network architectures of the human brain. Neuron 83: 238 –251. **(3)** Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59, 2142–2154. **(4)** Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., Wolf, D.H., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. NeuroImage 64, 240–256. **(5)** Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341. **(6)** http://myconnectome.org/