GROWUPGROWOLD | Moffitt & Caspi | Genes Environment Health Behavior

HUMAN DEVELOPMENT, BIRTH TO DEATH

Concept Paper Form

Provisional Paper Title: Test-Retest Reliability of Common and Innovative Approaches to Network Neuroscience	
Proposing Author: Meriwether Morris	
Author's Email: meriwether.morris@duke.edu	
P.I. Sponsor: Ahmad Hariri (if the proposing author is a student or colleague of an original PI)	
Today's Date: 5/11/2020	

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The central goal in the proposed study is to determine the test-retest reliability of graph theoretical measures of functional brain connectivity. For a method to be a reliable measure for clinical application, subjects must compare consistently in a test-retest setting. However, recent findings suggest low test-retest reliability of many commonly used fMRI measures, limiting their ability to consistently identify individual differences between subjects. Last year, our team conducted a meta-analysis of the 90 studies examining the test-retest reliability of rest and task ROI-based fMRI and revealed poor test-retest reliability (mean ICC= 0.397) (Elliott et al, 2020, in press). This highlights a need for the use of more reliable methodologies in individual differences research.

A promising alternative approach to the analysis of fMRI data is graph theoretical analysis of fMRI functional connectivity data. This methodology has demonstrated encouraging rationale in methodological development as well as promising test-retest reliability (Andellini et al, 2015). There remains a need for both confirmation of the few test-retest studies of graph theoretical modeling of rest and task fMRI data that have been conducted, as well as evaluation of new, innovative methodologies that have the potential to improve reliability beyond that of today's common practices.

The proposed study will examine test-retest reliability of both common practices and novel methodologies employed to conduct graph theoretical analysis of fMRI functional connectivity data from both the Human Connectome Project and the Dunedin Brain Imaging Study.

In any analysis of functional connectivity using fMRI data, several methodological decisions must be made within a range of common selections; for example, the researcher must determine the length of scans, whether the subjects will be at rest or performing a task, the proportion of data they will retain after removing noise, and which graph theoretical measures they are going to use to represent the connectivity of the brain. Previous literature demonstrates conflicting evidence as to the comparative reliability of decisions in this case (Braun et al, 2013; Termenon et al, 2016; Wang et al, 2017; Andellini et al, 2015). Because the best practices remain unclear, we will first examine the comparative reliability of different choices within these commonplace approaches.

In addition, innovative approaches have the potential to improve reliability beyond common practices. Novel methodologies to be explored include the integration of both task and rest data within a singular analysis (general functional connectivity (GFC), previously described by Elliot et al. (2019)) as well as an alternative computation of one of the most widely used graph theoretical measures: small-worldness (Zanin, 2015).

Data analysis methods:

fMRI data both from a range of scan lengths (5-45 min) and at rest/performing tasks for each subject will be used to generate functional connectivity matrices for each subject at Time 1 and at Time 2. Matrices will then be thresholded at a range of preservation densities (10-40% in increments of 5%). Graph theoretical metrics (clustering coefficient, characteristic path length, efficiency, small worldness, modularity, betweenness centrality, and assortativity) will then be computed from each matrix. To measure test-retest reliability, ICCs will then be computed to determine the consistency of the graph theoretical metrics from each subject derived using identical methodologies and processing steps executed at Time 1 and Time 2 (Koo et al, 2016). These ICCs are the primary dependent variable. ICCs will be compared within methodological steps in both commonplace and innovative approaches.

Aim 1. *To investigate reliability of current best practices in graph theoretical analysis of brain networks in two new datasets.* ICCs will be compared across scan lengths, across thresholding densities and across graph theoretical measures.

Aim 2. *To investigate reliability of novel methodologies in graph theoretical analysis of brain networks.* ICCs will be compared between pure rest data and GFC data and between the two computations of small-worldness.

Variables needed at which ages:

DLS Age 45 variables:

- fMRI time course for the emotion / “Matching” task (targeting the amygdala)
- fMRI time course for the executive control / “Colours” task (targeting the dorsolateral prefrontal cortex and the dorsal anterior cingulate cortex)
- fMRI time course for the reward / “Quick-Strike” task (targeting the ventral striatum)
- fMRI time course for the episodic memory / “Face-name” task (targeting the hippocampus)
- fMRI time course for resting state

HCP variables:

- fMRI time course for the emotion task (targeting the amygdala)
- fMRI time course for the reward task (targeting the ventral striatum) o fMRI time course for the working memory task (targeting the dorsolateral prefrontal cortex)

- fMRI time course for the social / theory-of-mind task (targeting the lateral fusiform gyrus, superior temporal sulcus, and other “social-network” regions)
- fMRI time course for the relational task (targeting the rostrolateral prefrontal cortex)
- fMRI time course for the language task (targeting the anterior temporal lobe)
- fMRI time course for the motor task (targeting the motor cortex)
- fMRI time course for resting state

Significance of the Study (for theory, research methods or clinical practice):
This analysis of reliability of commonplace and innovative approaches to graph theoretical analysis of fMRI promises to: (1) contribute insights to a core debate central to our understanding of the human brain and its functional organization (how reliable is connectionist modeling in fMRI?), (2) rigorously evaluate reliability of current best practices in graph theoretical analysis of fMRI to help researchers maximize their ability to detect meaningful individual differences (how reliable is this graph theoretical methodology across various scan lengths, in task or rest data, and across various matrix preprocessing steps?), and (3) introduce and evaluate novel methodologies to graph theoretical connectionist work that may improve experimental reliability (how might integration of task and rest data modify this connectionist methodological reliability?).

References cited:

Andellini, M., Cannatà, V., Gazzellini, S., Bernardi, B., & Napolitano, A. (2015). Test-retest reliability of graph metrics of resting state MRI functional brain networks: A review. Journal of Neuroscience Methods, 253, 183-192. doi:10.1016/j.jneumeth.2015.05.020

Braun, U., Plichta, M. M., Esslinger, C., Sauer, C., Haddad, L., Grimm, O., . . . Meyer-Lindenberg, A. (2012). Test–retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. Neuroimage, 59(2), 1404-1412. doi:10.1016/j.neuroimage.2011.08.044

Elliott, M. L., Knodt, A. R., Ireland, D., Morris, M. L., Poulton, R., Ramrakha, S., … Hariri, A. R. (2020). What is the test-retest reliability of common task-fMRI measures? New empirical evidence and a meta-analysis. *Psychological Science (in press)*. https://doi.org/10.1101/681700

Elliott, M. L., Knodt, A. R., Cooke, M., Kim, M. J., Melzer, T. R., Keenan, R., . . . Hariri, A. R. (2019). General functional connectivity: Shared features of resting-state and task fMRI drive reliable and heritable individual differences in functional brain networks. Neuroimage, 189, 516-532. doi:10.1016/j.neuroimage.2019.01.068

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*, 15(2), 155–163. https://doi.org/10.1016/j.jcm.2016.02.012

Termenon, M., Jaillard, A., Delon-Martin, C., & Achard, S. (2016). Reliability of graph analysis of resting state fMRI using test-retest dataset from the human connectome project. Neuroimage, 142, 172-187. doi:10.1016/j.neuroimage.2016.05.062

Wang, J., Zuo, X., Gohel, S., Milham, M. P., Biswal, B. B., & He, Y. (2011). Graph theoretical analysis of functional brain networks: Test-retest evaluation on short- and long-term resting-state functional MRI data. PloS One, 6(7), e21976. doi:10.1371/journal.pone.0021976

Zanin, M. On alternative formulations of the small-world metric in complex networks. *arXiv* 5, 38 (2015).