**Concept Paper**

**Provisional Paper Title:** Optimizing Measurement of Intrinsic Connectivity for Individual Differences Neuroscience: Rest, Task or Both?

**Proposing Author:** Maxwell L. Elliott

**Author's Email:** maxwell.elliott@duke.edu

**P.I. Sponsor:** Terrie Moffitt, Ahmad Hariri
(if the proposing author is a student or colleague of an original PI)

**Today's Date:** 05/03/18

---

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

This is a methodological project to improve the reliability of connectivity measurement, primarily using data from the Human Connectome Project, but with a small validation analysis using the 600 Dunedin Study Members who have been seen to date. Full cohort not needed because there are no epidemiological inferences to be made in the paper.

## Objective of the study:

Functional magnetic resonance imaging has played a pivotal role in our understanding of the functional organization of the human brain[1–3]. Functional connectivity, often measured using resting-state fMRI, has been favored in many studies that aim to measure stable, trait-like phenotypes because it does not require task demands, has no practice-effects and is relatively easy to collect in children, aging and psychiatric populations[4–8]. While functional connectivity has revealed many insights about average, group level effects in the brain, there has been much slower progress in finding reliable links between individual differences in brain function and human traits, behaviors or diseases[1,3]. The low reliability of fMRI measures likely contributes to this lack of progress. In general task fMRI and resting state phenotypes have ICCs below .5[9,10], placing them in the poor range of reliability[11]. In order to build a cumulative neuroscience of individual differences and more efficiently discover biomarkers for aging and psychiatric disease, the reliability of fMRI must be improved, as reliability fundamentally limits the validity of a measure and its ability to predict individual differences.

Recent work has shown that high levels of reliability are achievable if you collect enough fMRI data on individual subjects[12]. Functional connectivity may simply be a noisy measure of stable traits that require aggregating many measurements to accurately estimate[9]. However, these studies suggest that close to an hour of resting state fMRI is needed to achieve high levels of stability. Due to the high cost of scan-time and the limited ability of many children and patient populations to lie still without falling asleep for an hour, this depth of measurement has been unfeasible for many large clinical and population-based studies. Instead, large-scale imaging datasets focused on predicting individual differences in health and disease (UK biobank, 1000 Functional Connectomes, PING) have collected less than 10 minutes of resting-state data, likely leading low test-retest reliability and predictive validity.

While few datasets collect enough resting-state data to achieve high levels of reliability, many datasets have subjects complete multiple task-fMRI scans in addition to resting-state. While it has historically been taken for granted that task and resting-state fMRI are two separate measure of brain function, to be analyzed independently, a growing body of evidence suggest that the intrinsic functional connectivity measured in each may have substantial overlap, sharing over 80% of the same variance[13,14]. Functional connectivity from task-fMRI has even been suggested as a method that may more reliably emphasize individual differences[15,16].

If task and resting state fMRI overwhelmingly converge on the same individual differences in intrinsic functional connectivity and resting-state has poor reliability because of inadequate length of acquisition, then task and resting-state fMRI may be able to be combined to achieve a more reliable measure of intrinsic functional connectivity. We propose 3 analyses to test this hypothesis.

**Data analysis methods:**

1) W**hat are the upper limits of reliability that can be achieved from task, resting-state and their combination in their measurement of individual differences of intrinsic connectivity**?

   Analysis will use the publicly available myConnectome datasets that includes hundreds of minutes of resting-state and task-fMRI, all collected on a single individual. We will recreate the reliability curve in Laumann et al., 2015[12], by sampling increasing amounts of data and testing reliability with a large amount of left out data. We will sample from all resting state data, then increasingly amounts task data, to test the feasibility of adding task to resting state data in order to boost reliability.

2) **Can the effects found above be replicated in a test-retest dataset that represents acquisition parameters of a typical large-scale neuroimaging study?**

   Analysis will calculate ICCs of intrinsic connectivity using the 40 subjects with test retest data from the human connectome project. This data set has 1 hour of resting state and 1 hour of task data in each subject. We will test the reliance of ICCs on the amount of data and the type of data by computing correlation matrices from increasing amounts of data and an increasing proportion of task data. While aim 1 tested the limits of reliability in a single subject, aim 2 will measure the reliability of individual differences across subjects, a better measure of performance in studies of individual differences.

3) **Is intrinsic connectivity estimated from rest and task together better at predicting individual differences than rest alone?**

   Analysis will test the relationship between behavioral prediction from intrinsic connectivity on the reliability of the data. We will predict individual differences (intelligence, depression, p-factor) in the Dunedin and HCP study from intrinsic connectivity derived from rest alone and compare the effect size to a prediction from rest combined with task across a range of scan lengths.

**Variables needed from the Dunedin Study at which ages:**

IQ at 38 and 45
P factor at 38 and 45
Depression diagnosis status at each age
Connectivity measures from MRI scan (to be supplied by Annchen)

**Significance of the Study (for theory, research methods or clinical practice):**

The primary significance of this study is for functional connectivity methods in fMRI. If functional connectivity is more reliably measured by adding task data to rest, then all researchers with access to rest and task data should combining these measures to achieve higher reliability. More reliable measurement promises to lead to stronger predictions of psychopathology and behavior. In addition, this study will contribute to our understanding of the brain during "resting-state" and "task-states". This holds the potential to give researchers practical solutions to improving reliability in existing archival data as well as guiding future imaging protocol design.

**References cited:**


1 Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M *et al.* The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 2011; **106**: 1125–1165.

2 Buckner RL, Andrews-Hanna JR, Schacter DL. The Brain's Default Network. *Ann N Y Acad Sci* 2008; **1124**: 1–38.

3 Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA *et al.* Functional Network Organization of the Human Brain. *Neuron* 2011; **72**: 665–678.

4 Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA *et al.* Genetic control over the resting brain. *Proc Natl Acad Sci U S A* 2010; **107**: 1223–1228.

5 Shehzad Z, Kelly AMC, Reiss PT, Gee DG, Gotimer K, Uddin LQ *et al.* The resting brain: Unconstrained yet reliable. *Cereb Cortex* 2009; **19**: 2209–2229.

6 Ge T, Holmes AJ, Buckner RL, Smoller JW, Sabuncu MR. Heritability analysis with repeat measurements and its application to resting-state functional connectivity. *Proc Natl Acad Sci* 2017; **114**: 5521–5526.

7 Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol* 2008; **21**: 424–30.

8 Fox MD. Clinical applications of resting state functional connectivity. *Front Syst Neurosci* 2010; **4**. doi:10.3389/fnsys.2010.00019.

9 Birn RM, Molloy EK, Patriat R, Parker T, Meier TB, Kirk GR *et al.* The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage* 2013; **83**: 550–558.

10 Luking KR, Nelson BD, Infantolino ZP, Sauder CL, Hajcak G. Internal Consistency of Functional Magnetic Resonance Imaging and Electroencephalography Measures of Reward in Late Childhood and Early Adolescence. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2017; **2**: 289–297.

11 Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016; **15**: 155–163.
12 Laumann TO, Gordon EM, Adeyemo B, Snyder AZ, Joo SJ, Chen MY *et al.* Functional System and Areal Organization of a Highly Sampled Individual Human Brain. *Neuron* 2015; **87**: 658–671.
13 Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE. Intrinsic and task-evoked network architectures of the human brain. *Neuron* 2014; **83**: 238–251.
14 Geerligs L, Rubinov M, Cam-CAN, Henson RN. State and Trait Components of Functional Connectivity: Individual Differences Vary with Mental State. *J Neurosci* 2015; **35**: 13949–13961.
15 Finn ES, Scheinost D, Finn DM, Shen X, Papademetris X, Constable RT. Can brain state be manipulated to emphasize individual differences in functional connectivity? *Neuroimage* 2017; **160**: 140–151.
16 Gratton C, Laumann TO, Nielsen AN, Greene DJ, Gordon EM, Gilmore AW *et al.* Functional Brain Networks Are Dominated by Stable Group and Individual Factors, Not Cognitive or Daily Variation. *Neuron* 2018; : 439–452.

**Data Security Agreement**

| | |
|---|---|
| Provisional Paper Title | Task fMRI improves the reliability of resting state as a measure of intrinsic connectivity in fMRI |
| Proposing Author | Maxwell Elliott |
| Today's Date | 04/09/17 |

***Please keep one copy for your records and return one to the PI Sponsor***

Please initial your agreement

| | |
|---|---|
| ME | I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent) |
| ME | My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution. |
| ME | I will treat all data as "restricted" and store in a secure fashion.<br>My computer or laptop is:<br>a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines)<br>b) password-protected<br>c) configured to lock-out after 15 minutes of inactivity AND<br>d) has an antivirus client installed as well as being patched regularly. |
| ME | I will not "sync" the data to a mobile device. |
| ME | In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu) |
| ME | I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper. |
| ME | I will not post data online or submit the data file to a journal for them to post.<br><br>*Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.* |

| | |
|---|---|
| ME | I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office.<br><br>The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses. |

**Signature:** 

**CONCEPT PAPER RESPONSE FORM**

**A**

| | |
|---|---|
| Provisional Paper Title | Task fMRI improves the reliability of resting state as a measure of intrinsic connectivity in fMRI |
| Proposing Author | Maxwell Elliott |
| Other Contributors | Annchen Knodt, Tracy Melzer, Ross Keenan, David Ireland, Richie Poulton, Sandhya Ramrakha, Avshalom Caspi, Ahmad Hariri, Terrie Moffitt |
| Potential Journals | Nature Neuroscience, Neuron, Cerebral Cortex, Neuroimage |
| Today's Date | 05/03/18 |
| Intended Submission Date | ASAP, summer 2018 if all goes well |

***Please keep one copy for your records and return one to the proposing author***

**B.** To be completed by potential co-authors:

| | |
|---|---|
| | Approved |
| | Not Approved |
| | Let's discuss, I have concerns |

Comments:

Please check your contribution(s) for authorship:

| | |
|---|---|
| | Conceptualizing and designing the longitudinal study |
| | Conceptualizing and collecting one or more variables |
| | Data collection |
| | Conceptualizing and designing this specific paper project |
| | Statistical analyses |
| | Writing |
| | Reviewing manuscript drafts |
| | Final approval before submission for publication |
| | Acknowledgment only, I will not be a co-author |

**Signature:**

_____