# Stable, Dynamic & Variable Functional Networks

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**Introduction:** Differences of neuronal origin in resting state (rs) functional connectivity (FC) may arise due to disease, personality traits and state of mind. Typically, only one of these causes is investigated at a time and the other two act as confounds. Previous studies have focused mostly on inter-subject reproducibility but not intra-subject repeatability [1-4]. Hence, it is of much interest to study both intra-subject variability (changes in state of mind) and inter-subject variability (differences in trait) of FC, in order to decouple such variabilities from FC changes due to disease.

**Methods:** Ten runs of 7-minute rs-fMRI scans (2D-EPI with TR/TE=2000/30 ms; Flip Angle = 75°; 3 x 3 mm in-plane resolution with 4 mm slice thickness, interpolated to 128x128 matrix with 36 slices) were obtained from 10 participants in two sessions of five runs each, from a 3T MRI scanner (GE Discovery MR750). A structural T1-weighted image was also obtained for registration to an atlas. rs-fMRI data were slice time corrected, motion corrected, registered to MNI atlas, nuisance removed using COMPCOR [5], spatially smoothed with 6 mm FWHM Gaussian filter and temporally filtered with 0.01 to 0.1 Hz zero-phase Butterworth band-pass filter.

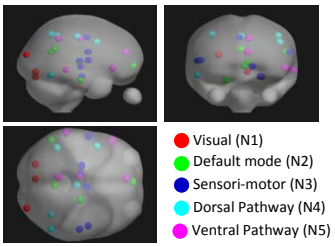


***Figure 1****: 24 seeds from five networks resting state networks to create FC*

Functional connectivity maps were computed as correlation between time courses of every voxel to the time course of seed regions. 6 mm radius spheres were placed on 24 seed regions based on 5 rs- networks' nodes from Deluca *et al* [6] (Fig. 1). One functional connectivity map was computed for each seed, each participant and each run. $\eta^2$ was used to compute similarity between two FC maps [7]. Let FC map for seed $i$, participant $j$ and session $k$ be $f_{ijk}$ and let $K$ be the number of runs. Mean of pairwise $\eta^2$ between run FC maps were computed (mean of 45 $\eta^2$) for each participant and each seed as $r(i,j) = \{\sum_{k=1}^{K}\sum_{l=(k+1)}^{K}\eta^2(f_{ijk}, f_{ijl})\}/\binom{K}{2}$. For each seed, the mean and SD of $r$ across participants were computed (shown in Fig. 2). In addition, mean FC map across sessions for each participant was computed as $\bar{f}_{ij}$. Mean and SD of pairwise $\eta^2$ between each participant's mean FC map is shown in Fig 3.

**Results:** Most FC maps show relatively high reproducibility (two-thirds of FC maps had $\eta^2 > 0.7$). Seeds from the Default Mode network and seeds from network 4 and network 5 showed high intra and inter-subject reproducibility (top-left quadrant of Figure 2, panel a). Hippocampal seed of the sensori-motor network showed consistently low intra-subject reproducibility in all subjects (lower-left quadrant). Other seeds showed low inter-subject reproducibility. In Fig. 3, seeds from network 2, 4 and 5 again showed high inter-subject reproducibility. No seeds show consistently low inter-subject reproducibility (lower left quadrant). All other seeds show low inter-subject reproducibility.

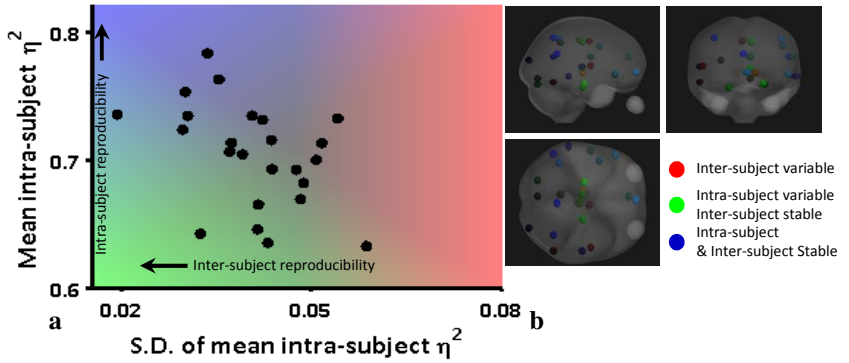


***Figure 2****: Mean intra-subject variability vs. standard deviation of intra-subject variability. Each point is measurement from 10 participants, 10 runs on one seed. Panel b shows intra and inter-subject stable and variable seed locations.*

**Discussion and conclusions**: Seeds found in the top left quadrant of Figure 2 and 3 (nodes of the default mode network, dorsal and ventral pathway), produced FC maps that were least variable across participants or runs and hence may be good candidates for changes associated with diseases but may not be good candidates to study state (intra-subject neuronal fluctuations) or trait (inter-subject neuronal fluctuations). The intra-subject variability of the hippocampal seed in the sensory motor network was consistently high in all subjects (green seeds in Fig. 2), which makes it a potential candidate for variability due to changes in state. Seeds in the lower left quadrant of Fig. 3 would have provided "signature" (unique) FC maps for each subject and not surprisingly, there are no primary network nodes of this nature. The right side of Fig. 3 shows networks that are variable across subjects and are potentially good candidates for associations with trait. Not all fluctuations in FC may arise from the interesting inter-subject and intra-subject neuronal variability. Observed FC variability may arise due to site/system differences, non-neuronal inter-subject differences (system fluctuations, physiology differences between participants, motion differences, functional registration differences, seed location, seed size) and intra-subject fluctuations (including system fluctuations, physiological fluctuations, motion, episodic disease, pre/post drug effects). Methods that account for fluctuations due to non-neuronal sources, such as accurate physiological nuisance regression, or additional methods such as concurrent EEG-fMRI will prove to be very useful to validate these results.

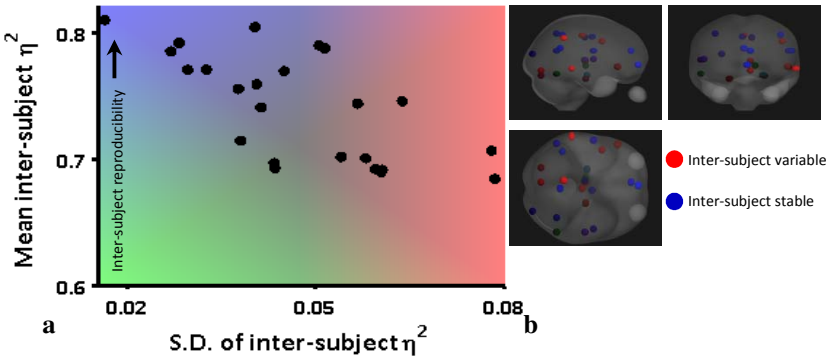


***Figure 3:*** *Inter-subject mean and standard deviation of eta-square. Each point is a measure from 10 participants, 10 runs on one seed. Panel B shows inter-subject stable and variable seed locations.*

**References:** 1. Guo CC et al., NI, 2012; 2. Chou YH et al., AJNR 2012; 3. Shehzad et al., NI 2009; 4. Zuo XN et al., NI 2010;5. Behzadi Y et al., NI 2008; 6. DeLuca M et al., NI 2006; 7. Cohen AL et al., NI 2008.