MOST AND LEAST TEMPORALLY STABLE BRAIN CONNECTIONS AS MEASUREDBY RESTING STATE fMRI

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INTRODUCTION

In recent years, the functional Magnetic Resonance Imaging (fMRI) research community has undertaken shift in attention from functional localization to functional connectivity. Today, it is well established that some brain regions are tuned primarily to perform specific tasks. Still, this one-to-one relationship soon diffuses as one moves beyond primary cortices into association cortex to understand the neuronal correlates of higher cognitive functions such as emotions, speech or attention. Moreover, it is increasingly common to discover anomalies in functional connectivity that seem to be at the origin of complex mental conditions.

In this resting state fMRI (rsfMRI), the spatial co-fluctuation of Blood Oxygenation Level Dependent (BOLD) signals recorded while subjects rest quietly in the scanner, in the absence of any specific task demands, is used to explore patterns of functional connectivity at the system level. Although overall patterns of rs-fMRI-based functional connectivity have proven to be reliable across scans, subjects, and even institutions, quantitative measures with the potential to become biomarkers are not yet sufficiently reliable, as they depend on factors such as scan condition, scan duration, and pre-processing pipelines. One additional factor that poses interesting questions regarding how to best record and quantify rsfMRI-based metrics is the recently observed dynamic behavior of resting-state connectivity patterns (Chang and Glover, 2010).

Several recent studies have shown how patterns of rsfMRI connectivity vary substantially even over the duration of a single scan (Chang and Glover, 2010;Handwerker et al., 2012;Hutchison et al., 2013), thereby calling into question the assumption of temporal stationarity even over short timescales. Similarly, other studies have explored how scan duration affects the reproducibility of rsfMRI connectivity patterns (Van Dijk et al., 2010;Birn et al., 2013). However, most of these studies have focused their analysis on a handful of representative connections and networks. Given the large variability of functional roles and connection strengths across the human brain connectome, it can be expected that optimal scan acquisition strategies and reliability of biomarker measurements will depend greatly on the connections of interest.

The purpose of the current study is to further explore and characterize rsfMRI connectivity dynamics under resting conditions. To overcome the limitations derived from short scan durations, in this study rsfMRI data were collected in 12 participants, who were scanned continuously for 60 minutes at a temporal resolution of 1s. Using these data, we evaluated pair-wise connections over the scale of minutes, investigating their polarity, strength, and variability. We evaluated the spatial distribution of three categories of connections and whether assignment of connections to these three groups was consistent across subjects. We also evaluated how window length, as a proxy for scan duration, affects the degree of similarity in whole-brain, within-subject connectivity patterns.

DATA ACQUISITION

DATA COLLECTION
- 12 subjects
- 3T fMRI
- 60 minutes rest
- Eyes closed
- 32 channel head coil
- T1 gradient echo
- Gradient-recalled EPI
- TR = 1 second
- 3.75mm x 3.75mm x 4mm
- Cardio and respiraton

PREPROCESSING
- Discard first 10 volumes
- Despiking
- Physio noise correction
  - RETROICOR
  - RVT and RHR
- Slice time correction
- Head motion correction
- Spatial smoothing
- ANAICOR
- Bandpass filtering

METHODS

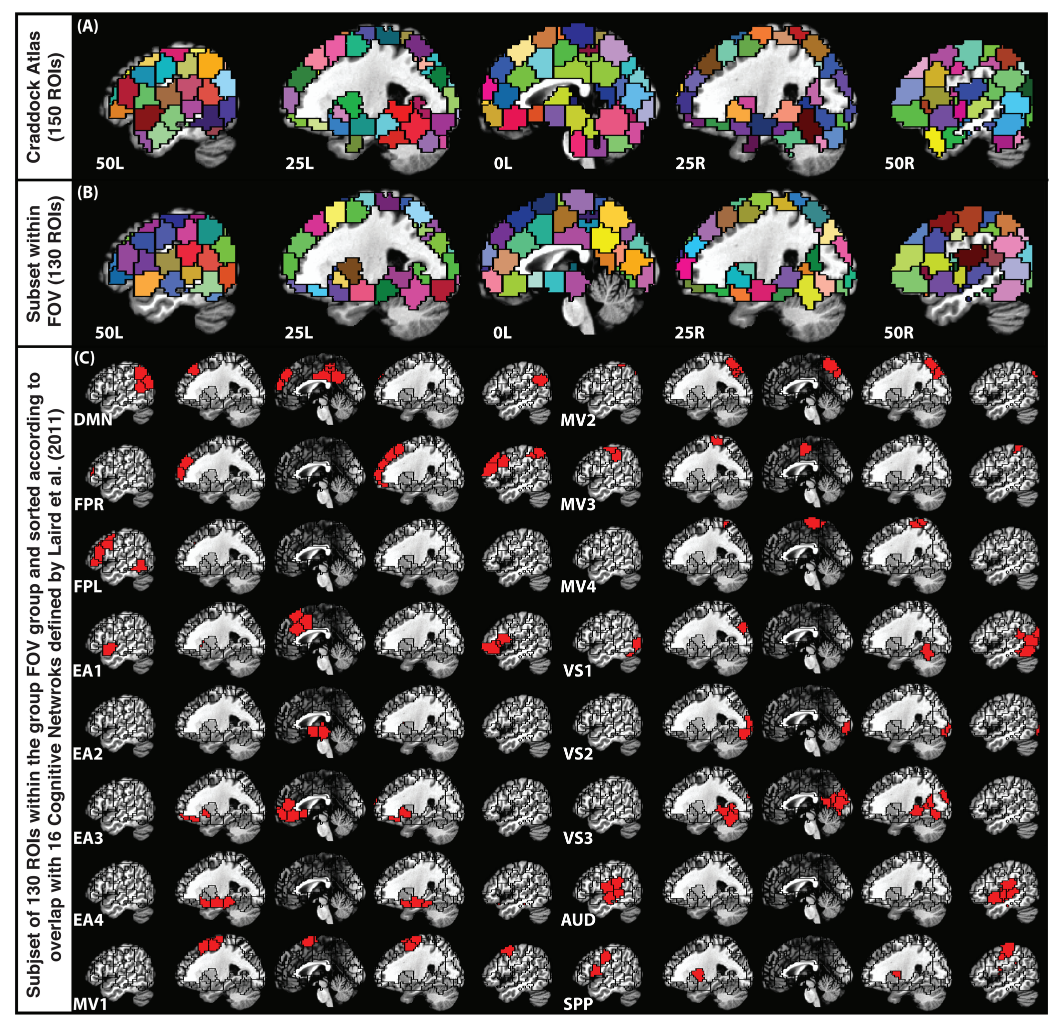

Figure 1. (A) 150-ROI Craddock Atlas (Craddock et al. (2012)) on top of 5 sagittal slices in MNI space. (B) 130 ROIs considered in this study. ROIs eliminated from the original atlas correspond to regions that were not part of the imaging FOV for all 12 participants. (3) Grouping of the remaining ROIs according to the Laird et al. (2011) functional network templates.

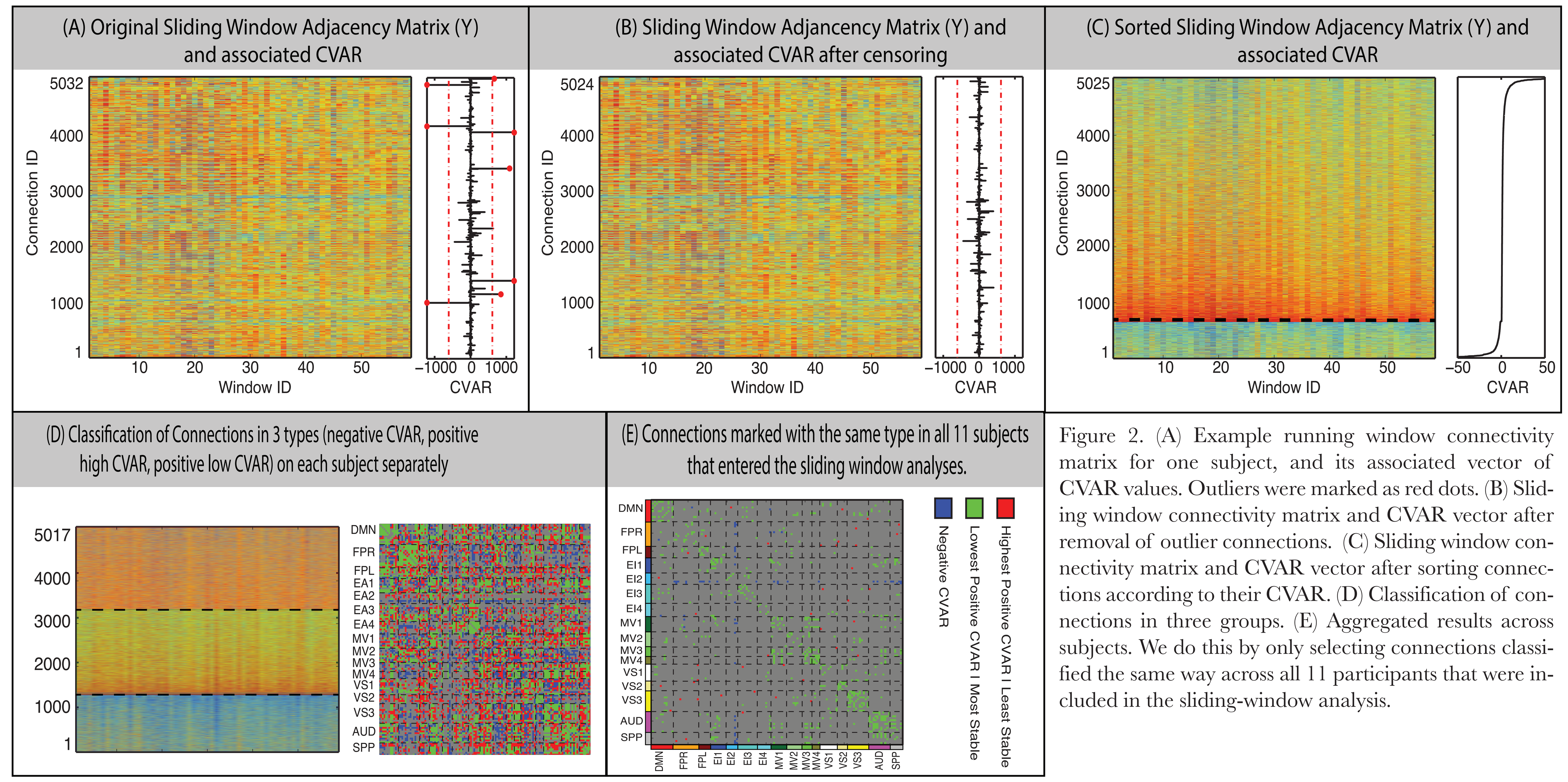

Figure 2. (A) Example running window connectivity matrix for one subject, and its associated vector of CVAR values. Outliers were marked as red dots. (B) Sliding window connectivity matrix and CVAR vector after removal of outlier connections. (C) Sliding window connectivity matrix and CVAR vector after sorting connections according to their CVAR. (D) Classification of connections in three groups. (E) Aggregated results across subjects. We do this by only selecting connections classified the same way across all 11 participants that were included in the sliding-window analysis.

RESULTS

Most Stable

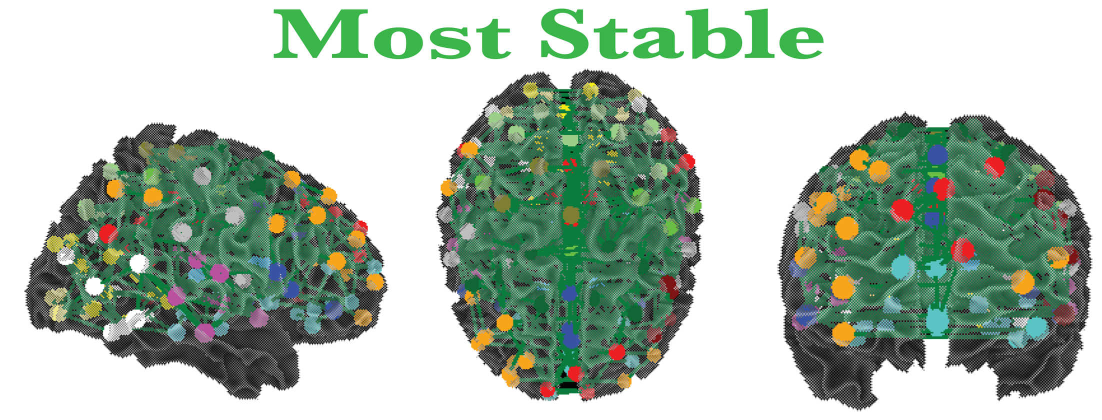

Figure 3. Most Stable Connections. These connection connections correspond mainly to symmetric, inter-hemispheric within- and across-network connections. 364 connections fell into this group, with148 corresponding to within-network connections and 216 corresponding to across-network connections. These connections may have an anatomical basis.

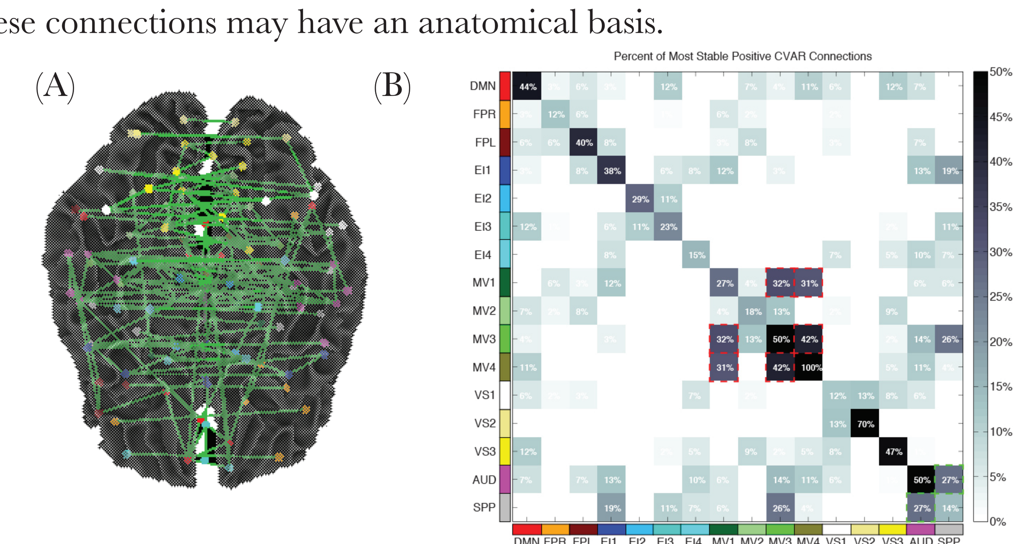

Figure 6. (A) 25% Most stable connections. When we (arbitrarily) sparsify the number of connections, we can better see the patterns that arise in this group. (B) Stable inter-network connections. The first is highlighted in red and the second in green. These reported agreements between network groupings suggest that those connections share a common functional space.

Least Stable

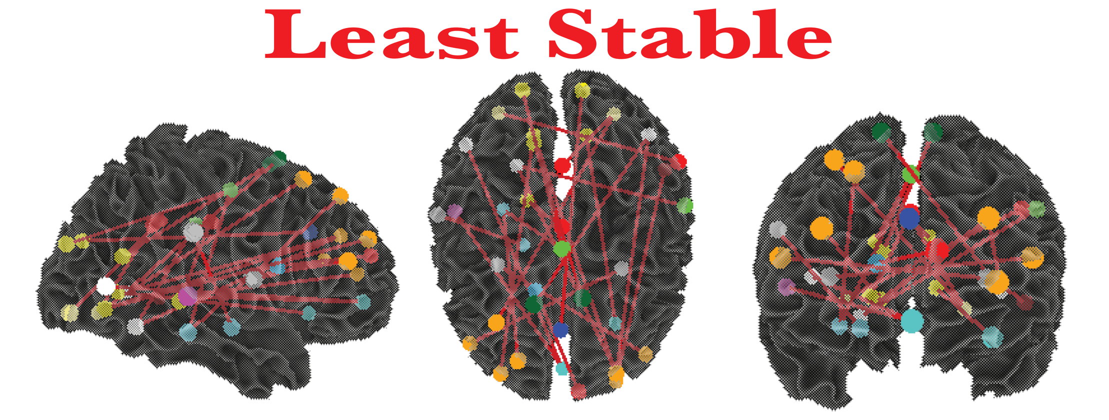

Figure 4. Least Stable Connections. These connections correspond primarily to inter- and intra-hemispheric, across-network connections between occipital and frontal regions. 23 connections fell into this group. The fronto-parietal network is composed of flexible hub regions that can reconfigure their functional connectivity to participate in a great variety of externally driven tasks

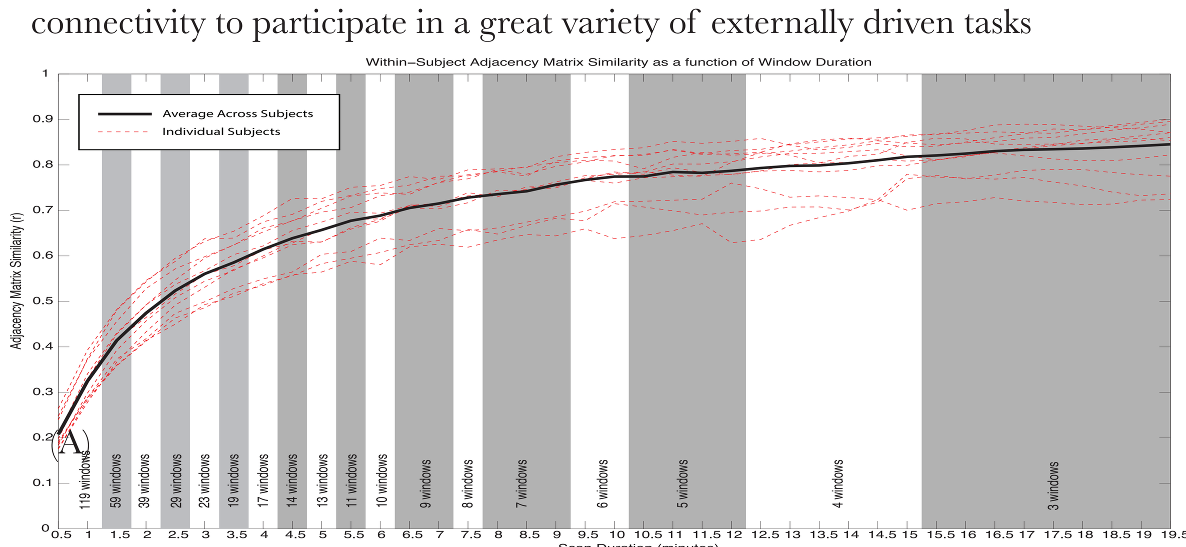

Figure 7. Similarity changes with scan duration. For short scan durations (approximately less than 10 minutes) similarity of whole-brain connectivity patterns decreases fast as scan duration shortens. For longer durations, although similarity keeps increasing with scan length, it does so at a much lower rate.

Negative CVAR

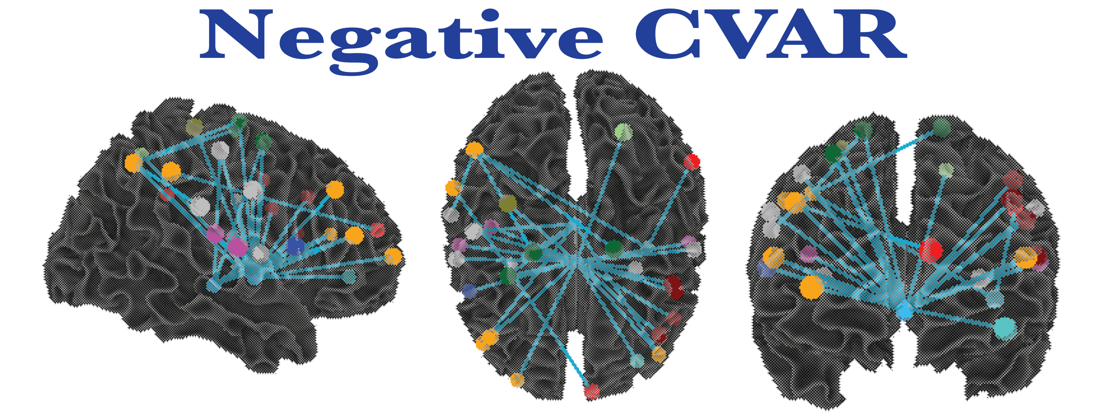

Figure 5. Negative connections correspond primarily to those between two medial subcortical regions and fronto-parietal regions. 32 connections fell into this group. Connections that show temporary negative behavior in a consistent manner across subjects involve the IPL hub region, or are artifacts from CSF regression (see Figure 8).

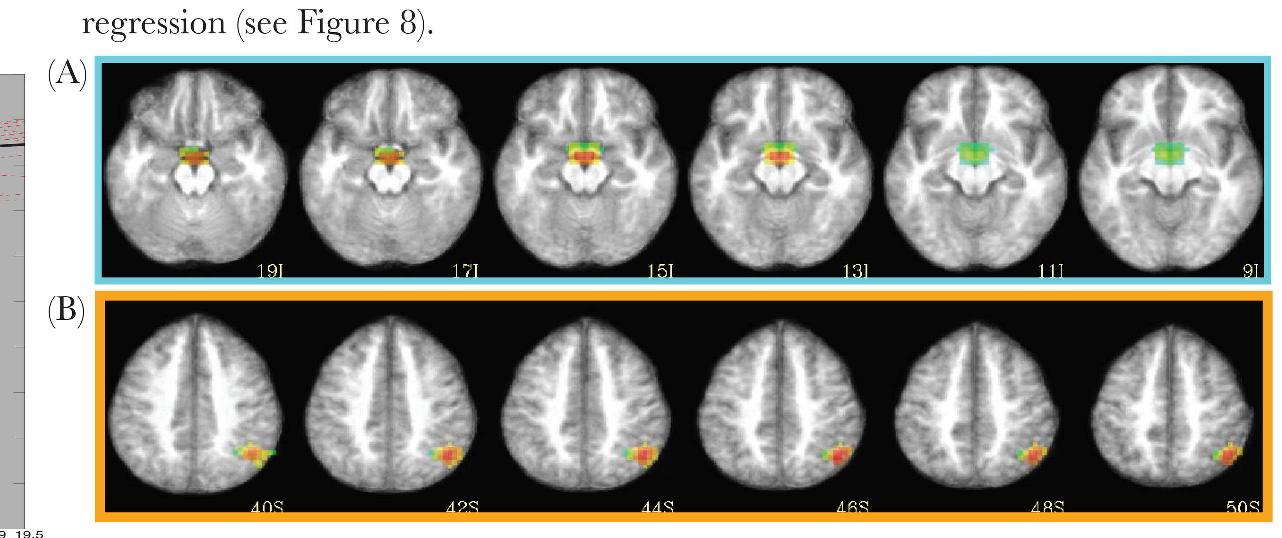

Figure 8. (A) ROI with 21 negative CVAR connections. The highest contributing voxels to the representative time series fall primarily within or around the third ventricle, indicating artifactual signal from CFS regression. (B) 6 negative CVAR connections involve ROIs within the bilateral inferior parietal lobule (IPL), with legitamate negatively fluctuating connections.

CONCLUSIONS

We found **3 well-differentiated sets of connections**, whose temporal variability patterns were reproducible across all participants and have distinct spatial patterns.

- First, **most stable connections** were found to correspond to **symmetric, inter-hemispheric** connections both **within and across networks**. **Primary sensory-motor networks** seem to be more temporally stable in their connectivity patterns that those more heavily involved in higher order cognitive processes.
- Second, **most variable connections** were found to correspond to **non-symmetric, inter-hemispheric, across-network connections** between **occipital and frontal regions**. The number of connections among the most variable group was much lower than the number of connections among the most stable, suggesting **subject-dependent** on-going cognition has a strong effect on the configuration of flexible connections in the brain.
- Finally, a small set of connections was found to have a **negative average connectivity**. A large percentage of these were identified as **potential artifacts**.

We also used the current dataset to evaluate how **whole-brain, within-subject similarity of connectivity patterns** varies as a function of window duration. In order to maximize similarity of overall whole-brain connectivity, rest scans should last as long as possible, with a lower bound of approximately 10 minutes.

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Research supported by the NIMH Intramural Program.