Stability of resting state functional connectivity within intensive longitudinal designs

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Background

Traditional group-based neuroimaging studies often lack the power to detect brain–behavior associations[1]. Recent perspectives[2,3] emphasized two complementary strategies to address these limitations:

1. **Intensive longitudinal designs (Fig. 1)** - Derives statistical power from repeated measurements within individuals, enabling detection of within-subject effects over time
2. **Precision neuroimaging** - Improves measurement reliability through high-quality, individualised data acquisition.

Together, these approaches make the investigation of within-subject brain-behaviour associations possible.

To inform these goals, here we investigate naturally occurring between-person and within-person (i.e. session-to-session) variance of functional connectivity to evaluate how powered precision intensive longitudinal designs actually are

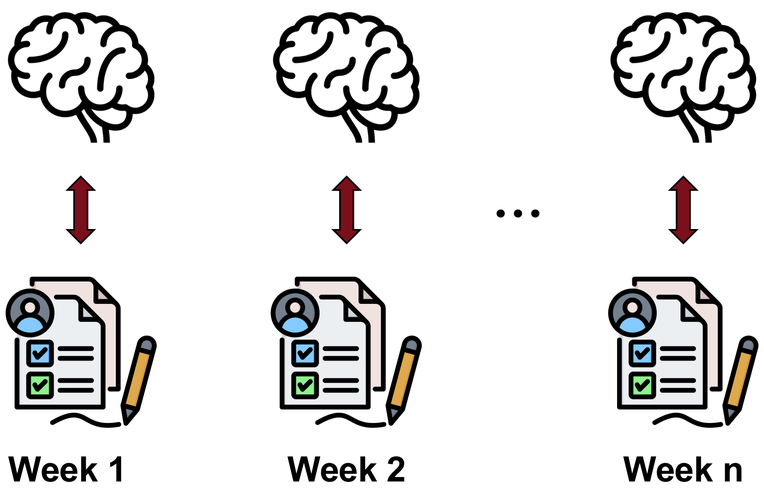

Figure 1. Dense longitudinal neuroimaging design

Methods

Dataset

- N = 14 participants (5 males, ages = 9-11), each scanned 3-4 times in 1-to-8-week intervals
  - Minimum of **30 minutes** of **low motion** resting-state fMRI acquired using **multi-echo** (ME) multi-band sequence (echo = 4,TR = 1761ms, 2.0 mm isotropic voxels) per session
- All preprocessing was performed using fMRIprep[4] and XCPd[5]. Data were parcellated with Glasser[6] atlas

Analysis

- Linear mixed effects model with random intercepts for each subject fitted for every edge
- Edgewise interclass correlation coefficient (ICC) reliability calculated as the ratio of between and total variance
- Disaggregated within-subject power was calculated using simulated data with variance components from empirical data.
  - Effect sizes of brain-behaviour associations set to: r = 0.1 and r = 0.2
  - Behavioural variance components were taken from previous work[7]

$$Y_{ij} = \beta_0 + \beta_B \bar{X}_i + \beta_W \left(X_{ij} - \bar{X}_i\right) + u_i + \varepsilon_{ij}$$

Results

1. **Natural occurring within-subject variance in functional connectivity is very low (Fig. 2)**

   Between-subject variance (i.e., stable individual differences between participants) in higher-order networks was up to an order of magnitude higher than within-subject variance (i.e., session-to-session changes).

2. **Functional connectivity is most stable (highest ICC) within and between higher order and attention networks (Fig 3). Sensory networks should most variability**

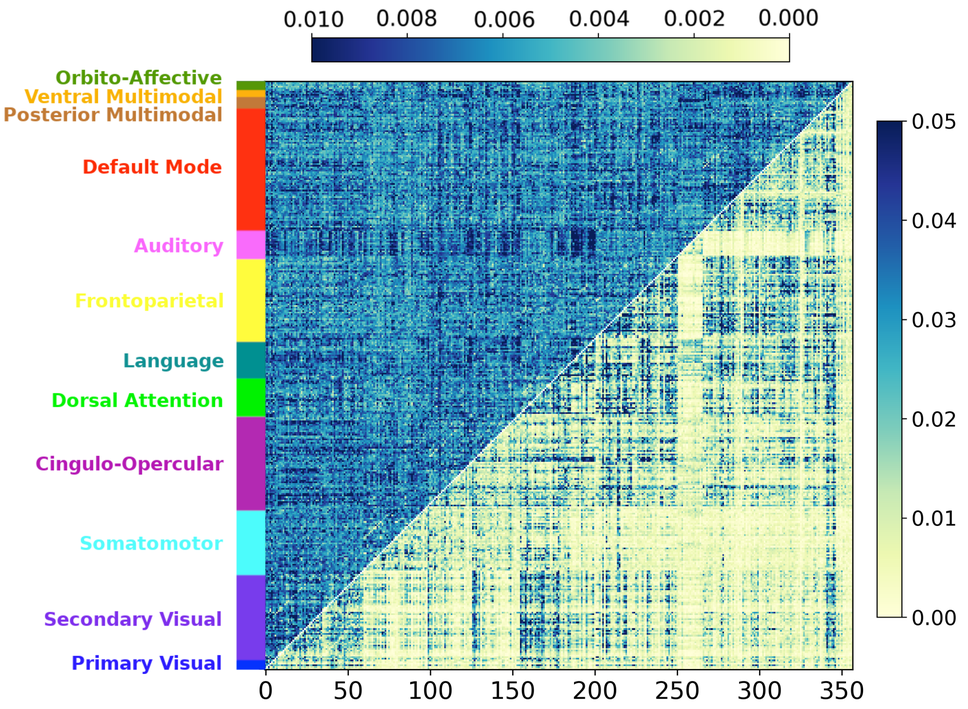

Figure 2. Edgewise between and within subject variance

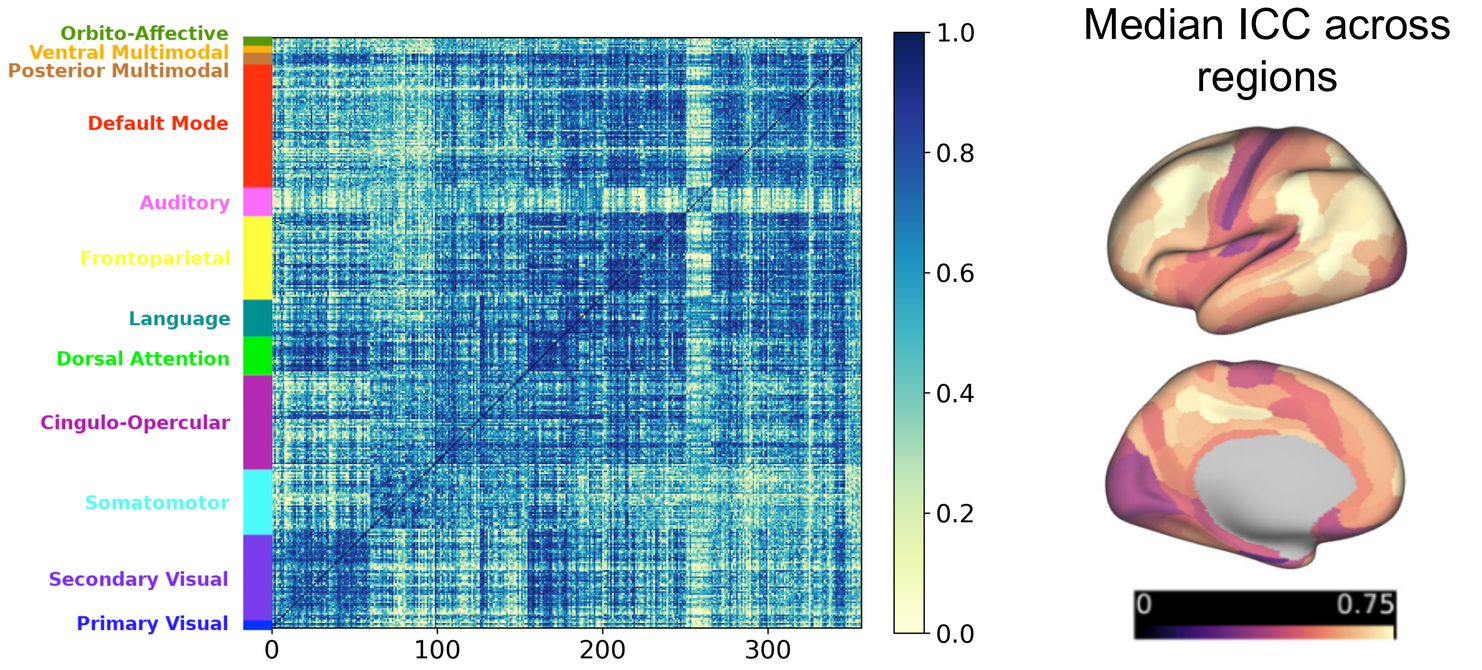

Figure 3. Edgewise and nodewise stability (ICC) of functional connectivity

3. **Within-subject brain-behaviour associations likely require modest sample sizes and large number of repeat sessions (Fig. 3)**

   Figure 3 displays statistical power for a range of sample sizes and within-subject sessions to identify a weak association between the connectivity of frontoparietal and dorsal attention networks and a reliable phenotype (ICC = 0.75)

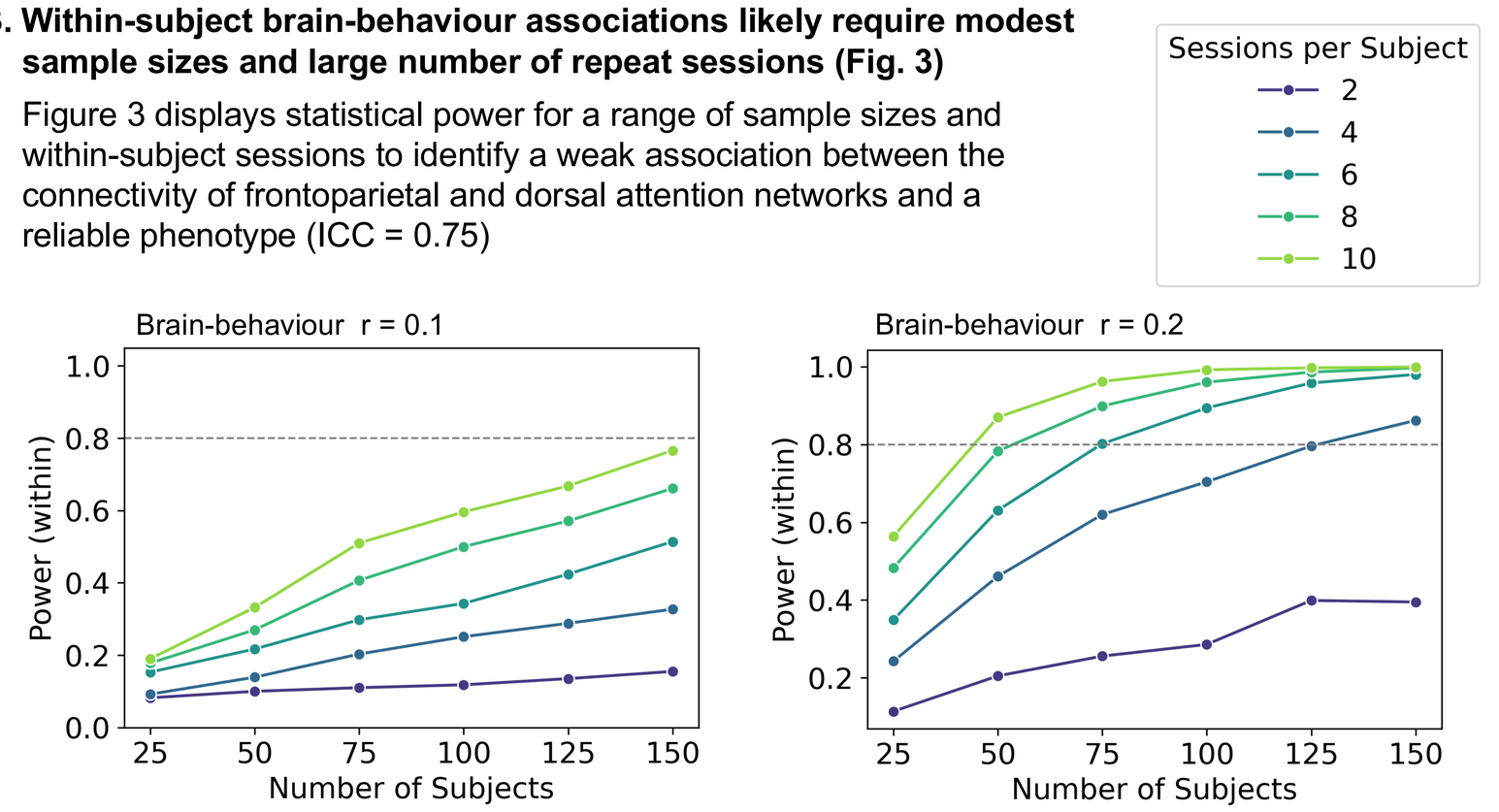

Figure 3. Statistical power to identify small effect size within-subject brain-behaviour associations

Conclusions

These findings strongly support "trait-like" stability of the functional connectome across scanning sessions
Unstructured, naturally occurring within-person changes in functional connectivity over weeks to months are minimal

Tracking brain-behavior associations in densely sampled individuals will likely require large associations, sizable samples, or perturbations (e.g., task paradigm) to amplify within-subject variability.

References: 1. Marek, S., Tervo-Clemmens, B., et al., (2022). Reproducible brain-wide association studies require thousands of individuals. Nature; 2. Gratton, C., et al., (2022). Brain-behavior correlations: Two paths toward reliability. Neuron; 3. Kraus, B., et al., (2023). Insights from personalized models of brain and behavior for identifying biomarkers in psychiatry. Neuroscience & Biobehavioral Reviews; 4. Esteban, O., et al., (2019). fMRIPrep: A robust preprocessing pipeline for functional MRI. Nature Methods; 5. Mehta, K., et al., (2023). XCP-D: A Robust Pipeline for the post-processing of fMRI data. bioRxiv; 6. Glasser, M. F., et al., (2016). A multi-modal parcellation of human cerebral cortex. Nature; 7. Voelkle, M. C., et al., (2014). Toward a Unified Framework for the Study of Between-Person and Within-Person Structures: Building a Bridge Between Two Research Paradigms. Multivariate Behavioral Research.