Characterizing the inter-subject variability of physiological response functions

Shiyu Wang[1], Roza G Bayrak[2], Jingyuan E Chen[3], Catie Chang[1,2,4]
[1]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA, [2]Department of Computer Science, Vanderbilt University, Nashville, TN, USA, [3]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA, [4]Department of Electrical and Computer Engineering, Vanderbilt University, Nashville, TN, USA

Introduction

- Low-frequency fluctuations in respiration volume and heart rate have been associated with functional magnetic resonance imaging (fMRI) blood-oxygen level dependent (BOLD) signals across the brain[1]. Understanding the variability of how low-frequency physiological factors are coupled with BOLD signals could help us better model their relationship.
- People have studied the inter-regional variability of the physiological response functions (PRFs) averaged across young adults [1] and the inter-subject differences of PRFs fitted to the global signal [2], but inter-subject differences in the full spatiotemporal pattern of PRFs remain to be quantified.
- Here, we characterized the range of whole-brain physiological response patterns that can be obtained across resting-state autonomic activities.

Method

- 1500 3T resting-state fMRI scans (375 subjects, each with 4 scans) from the Human Connectome Project (HCP) under the HCP FIX Preprocessing pipeline (TR=720ms; 1200 frames; voxel size=2mm isotropic) were included in the study.
- The fMRI time courses were detrended, band-pass filtered (0.01–0.15Hz), downsampled by a factor of 2, extracted 497 cortical and subcortical ROIs using 4 atlases [3–6], and z-normalized.
- Respiratory variation (RV) was defined as the standard deviation of a 6 s window of the respiratory belt recording centered at each downsampled time point. Heart rate (HR) was 1/(mean inter-beat-interval) of the pulse oximeter signal within the same windows. RV and HR were z-normalized, detrended, each convolved with 5 pre-defined basis functions [1], and fitted to each ROI's time course to obtain PRFs. Specifically, RRFs (respiratory response functions) and CRFs (cardiac response functions) were defined by multiplying the convolved RV or HR with their fitted βs.
- Modularity detection was used to obtain whole-brain PRF patterns across scans by 1) concatenating the 497×2 PRFs (both RRFs and CRFs) for each scan and correlated the concatenated PRFs, forming a 1500×1500 correlational matrix, 2) applying modularity detection on the correlational matrix using the brain connectivity toolbox[7].
  - The goal was to derive modules that maximize the within-cluster similarity while minimizing the across-cluster similarity [8].
  - A resolution parameter γ was introduced to overcome the resolution limit of modularity [9]. We tested γ values ranging from 0.9 to 1.2 with an increment of 0.01, with $\gamma > 1$ encouraging smaller clusters. The optimal γ was decided by selecting the most stable clustering results across all γ, where stability was measured by mean normalized mutual information [10].

Reference

1. Chen, J. E., et al.. (2020). *NeuroImage*, *213*, 116707.
2. Kassinopoulos, M., & Mitsis, G. D. (2019). *NeuroImage*, *202*, 116150.
3. Schaefer, A., et al.. (2018). *Cerebral Cortex*, *28*(9), 3095–3114.
4. Tian, Y., et al.. (2020). *Nature Neuroscience*, *23*(11), 1421–1432.
5. Hansen, C. B., et al.. (2021). *Neuroinformatics*, *19*(3), 447–460.
6. Edlow, B. L., et al.. (2012). *Journal of Neuropathology & Experimental Neurology*, *71*(6), 531–546.
7. Rubinov, M., & Sporns, O. (2010). *NeuroImage*, *52*(3), 1059–1069.
8. Sporns, O., & Betzel, R. F. (2016). *Annual Review of Psychology*, *67*(1), 613–640.
9. Fortunato, S., & Barthélemy, M. (2007). *Proceedings of the National Academy of Sciences*, *104*(1), 36–41.
10. Bassett, D. S., et al.. (2013). *Chaos: An Interdisciplinary Journal of Nonlinear Science*, *23*(1).

Results

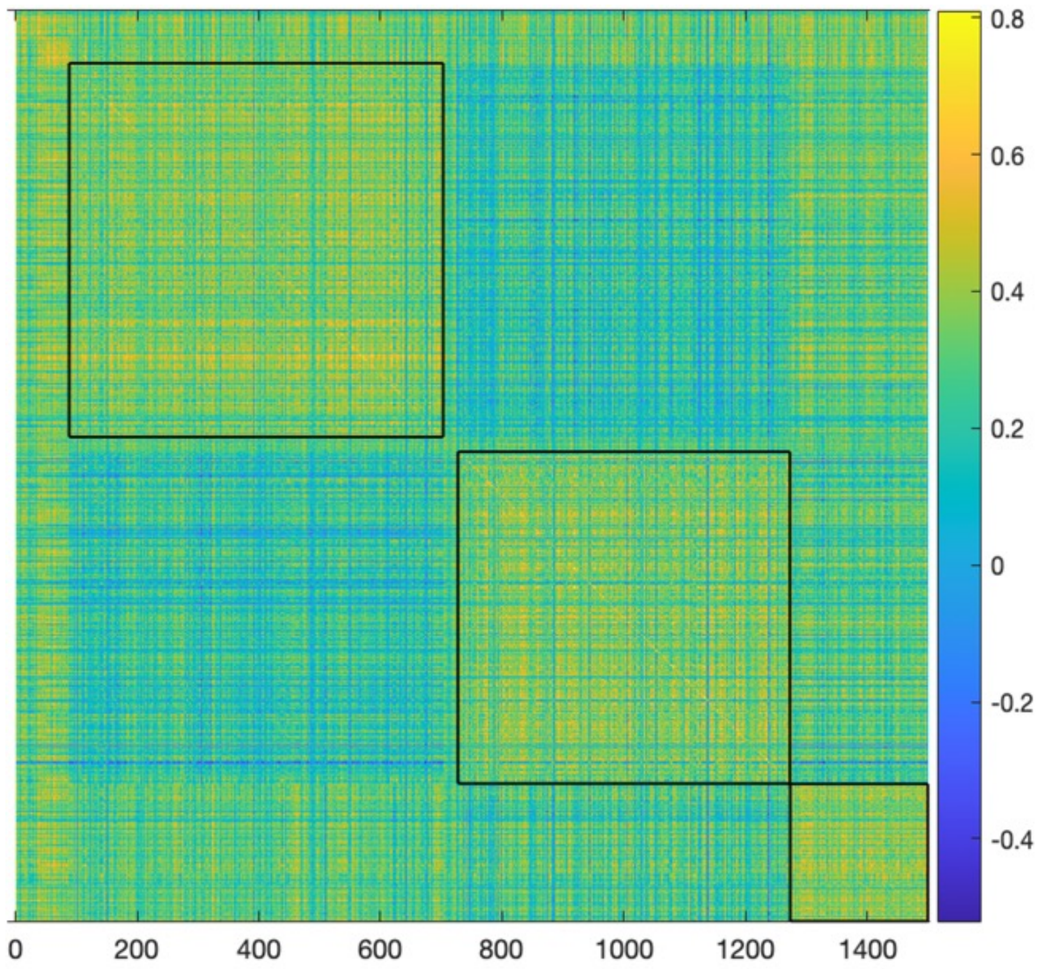

Figure 1. Correlational matrix among 375*4 scans (correlation was calculated between the PRFs concatenated among all ROIs). The matrix is ordered by cluster index and the 3 large clusters are marked.

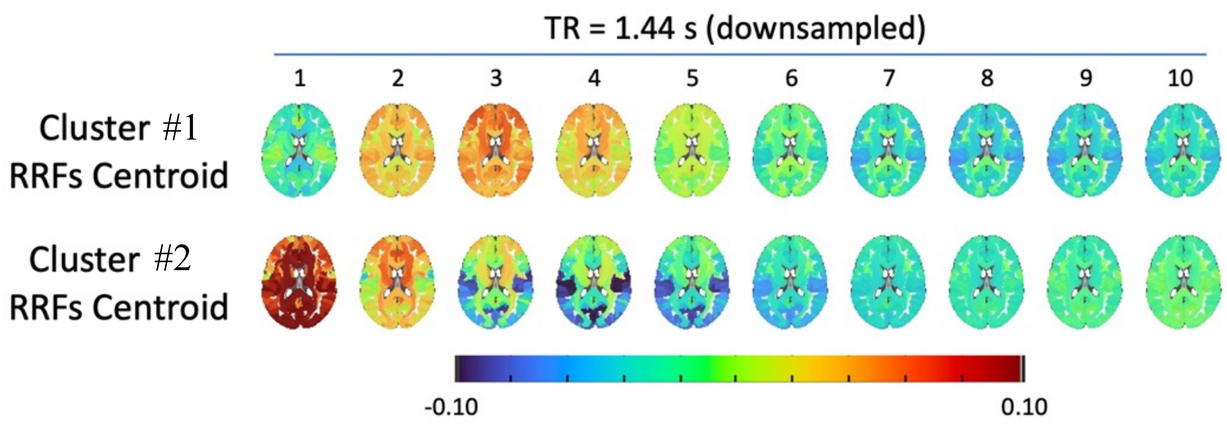

Figure 2. The centroids of the whole-brain RRFs from 2 of the biggest clusters. Cluster #8 had an initial dip and then response started to go up, whereas the cluster #10 peaked directly after the RV onset.

- The correlational matrix among the 1500 scans' PRFs reordered by modularity detection index were shown in Fig 1.
  - 11 clusters were found with an optimal $\gamma = 1.05$.
  - There were 3 large clusters (highlighted in the Fig 1), 3 medium-sized clusters and 5 small clusters.
  - Among the 375 subjects, at least 3 out of 4 PRFs from 4 scans were assigned the same cluster for 252 subjects, with only 12 subjects for whom all 4 PRFs were assigned to different clusters.
- The centroids of the whole-brain RRFs from 2 of the biggest clusters were shown in Fig 2. The major difference between them was that cluster #1 had an initial dip before an increase in the RRFs, whereas cluster #2 peaked immediately after the physiological onset, which was more consistent with the previous population-level spatiotemporal dynamics of RRFs [1].

Conclusions

- We observed several whole-brain PRF patterns that were shared across groups of subjects. Further, the cluster assignment of different scans within a given subject was relatively consistent.
- The observed inter-subject differences may arise, to some extent, from differences in subjects' breathing patterns during the scans.
- Our future steps include comparing PRFs across scans with matched breathing patterns, modeling respiratory and cardiac effects separately, and examining different physiological basis sets.