

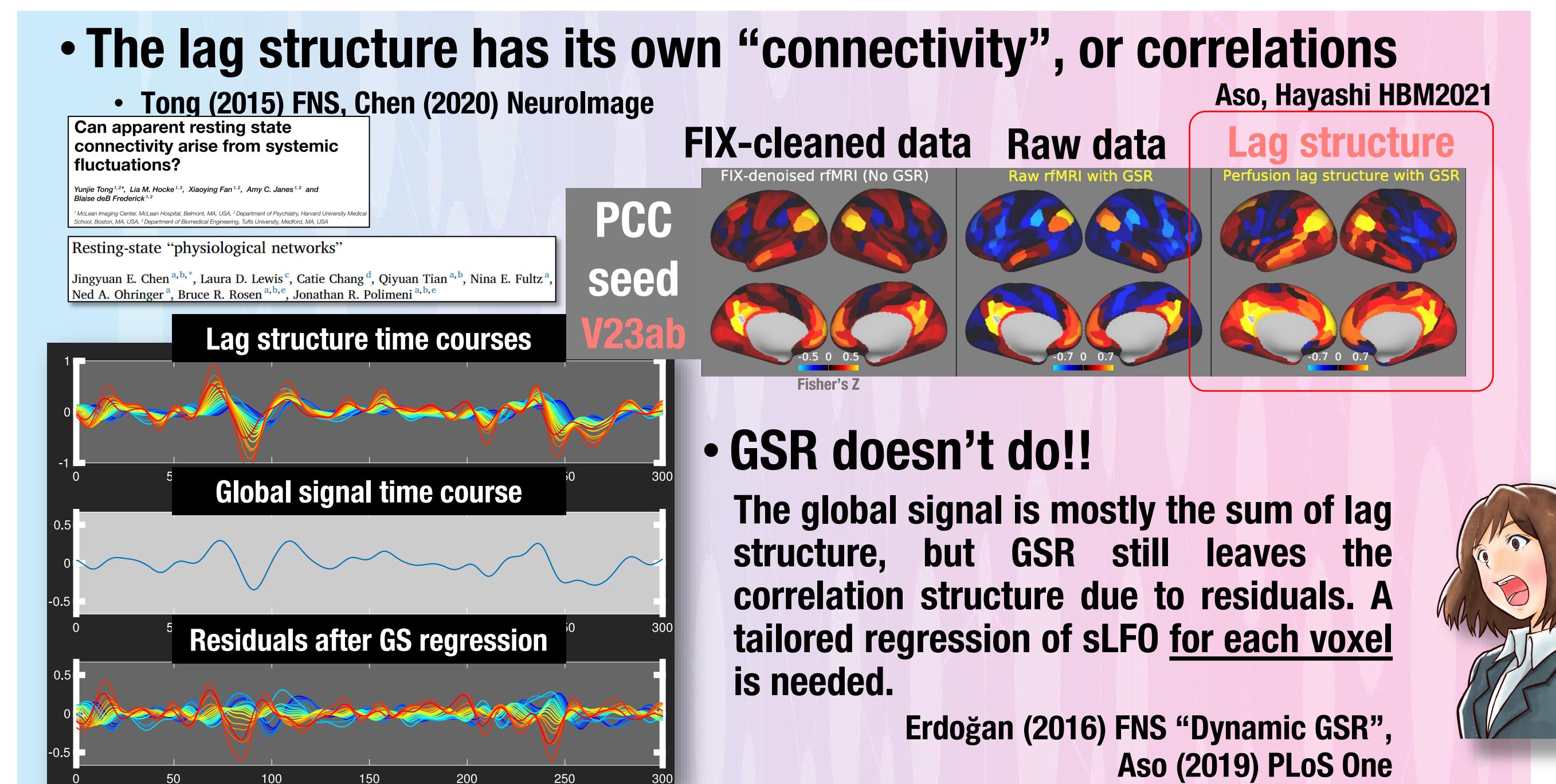
Reliability of BOLD perfusion lag mapping depends on global signal amplitude

Toshihiko ASO, Akiko UEMATSU and Takuya HAYASHI
 RIKEN Center for Biosystems Dynamics Research toshihiko.aso@riken.jp

Functional magnetic resonance imaging (fMRI) signal contains systemic and spontaneous low-frequency oscillation (sLFO). This slow fluctuation moves with the blood creating a phase variation according to blood arrival/drainage timing which should confound resting-state fMRI because the “lag map” varies with age and disease conditions. In the course of demonstrating sufficient reliability and individuality (fingerprint specificity) of the lag map to affect functional connectivity, we also found the net global signal amplitude determining those quality measures presumably by reflecting the sLFO power in the global signal.

Functional connectivity analyses based on correlation of blood oxygen level-dependent (BOLD) signals are susceptible to synchronized variations such as motion or physiological artifact. This has led to the widespread use of global signal (GS) regression that was once a common practice in fMRI with tasks, although not on a solid scientific basis in either case [1]. It would be valid if the GS is representing a “noise” that is uniform across voxels.

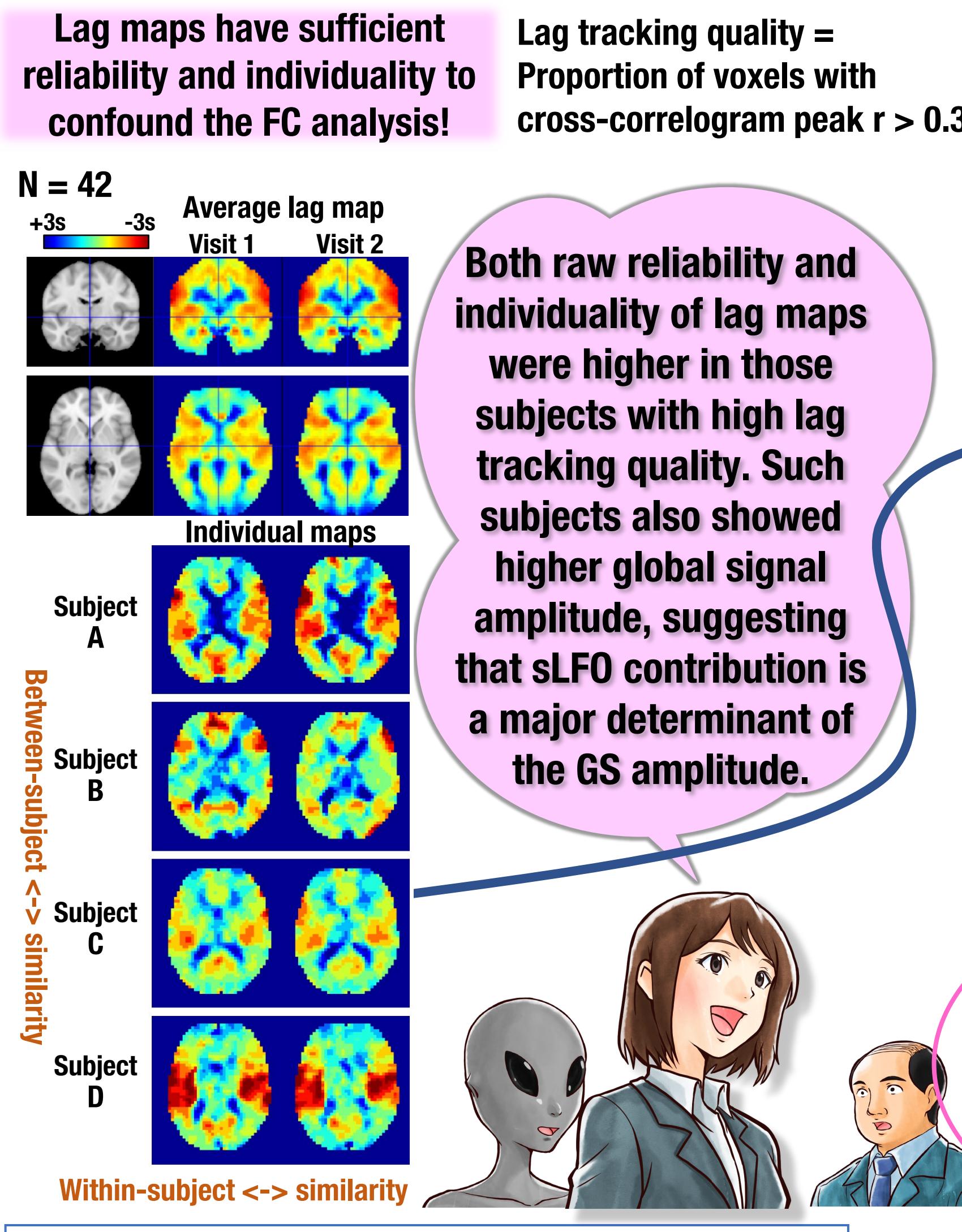
Perfusion lag structure is a global, non-neural component created by the spontaneous low-frequency oscillation (sLFO) that appears to be fluctuating deoxyhemoglobin density in the blood [4,5], because it is detectable in other body parts with different lags [6,11].



The sum of this component over the brain accounts for up to 40% of the GS variance. Since such a global component has its own correlation structure creating network-like patterns (left figure) [2,7,10], its removal has been proposed for fMRI data cleaning [4,7] (“deperfusioning”). This treatment has been shown to improve specificity of task fMRI without spurious deactivations [5].

However, less is known about reliability and robustness of lag mapping itself [3]. In this study, we explore the lag map’s reliability and fingerprint specificity using high quality resting-state fMRI data from HCP young-adult test-retest sessions ($N = 42$).

Result #1: Reliability and quality of lag map depend on GS amplitude



Discussion

Reportedly, 40% of slow GS variance is removed by regressing out the lag structure. The present results indicate that a higher contribution of sLFO to GS directly affects the GS amplitude, because it also improves lag tracking quality by better estimation and fitting of the sLFO waveform. The tight relationship of this lag tracking quality with its reliability and individuality in turn supports the validity of the lag map as a surrogate of individual perfusion pattern, a confound of FC analyses. The fingerprint specificity of the FC (Result #3) in the raw data should hence, in part, be that of the lag structures. Finally, the relationship of the GS amplitude with pulse and respiration rates further supports a non-brain origin of the sLFO (Result #2).

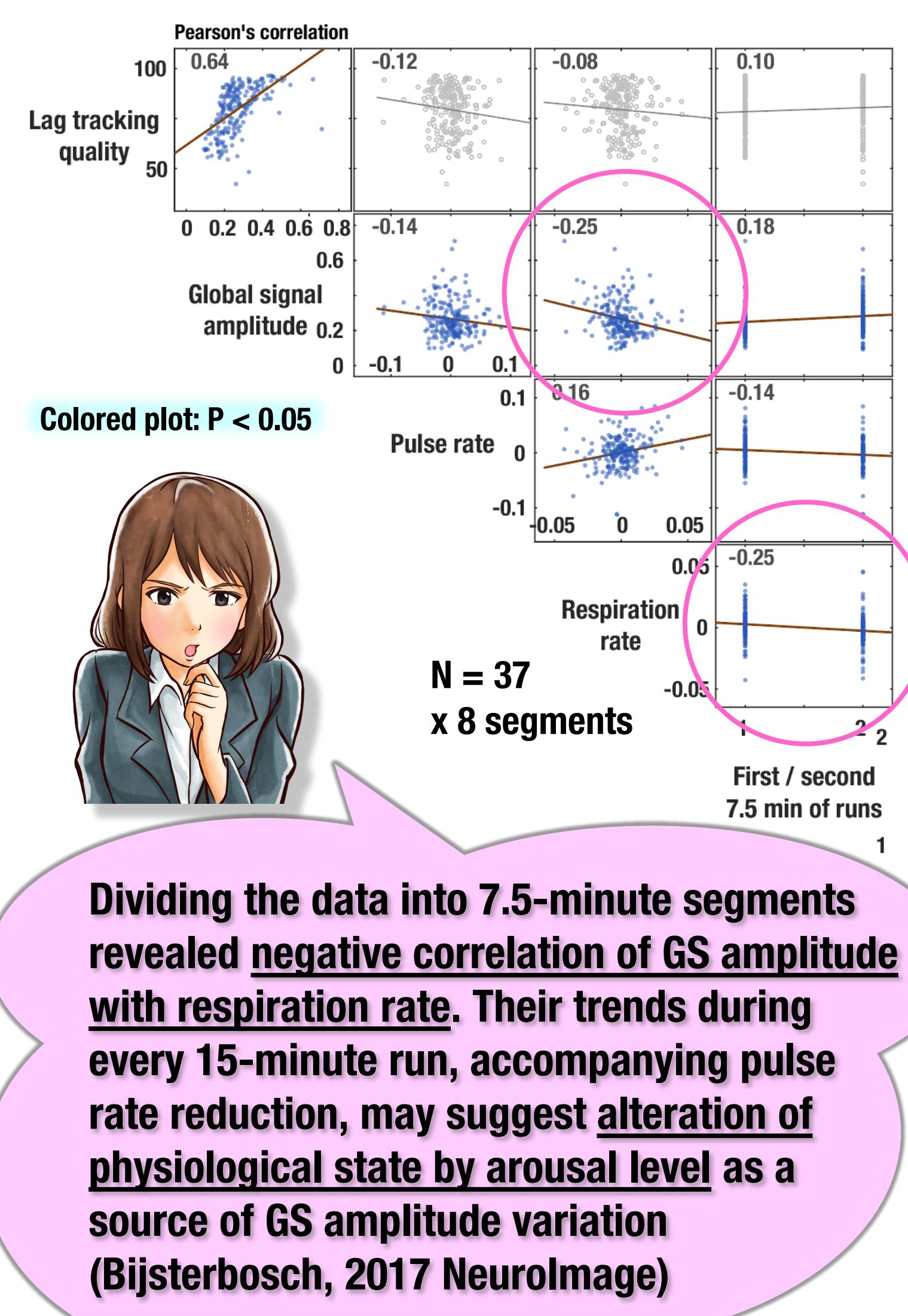
Methods

HCP test-retest dataset from 42 young-adult subjects with two visits each with a 1-hour resting fMRI scan was used. Preprocessed volume data were fed into the in-house lag mapping pipeline (<https://github.com/RIKEN-BCIL/HCPstyle-BOLDLagMappingAndCleaning>) in which brain voxels were grouped by their phase of spontaneous low-frequency oscillation (sLFO, below 0.1 Hz) at 0.72-s step. The sLFO was extracted by finding the zero-lag voxels with precisely the same phase as global signal (GS) using cross-correlogram and obtaining their average time series. The rest of the voxels were then given the lag values by the cross-correlogram peak with the sLFO.

Analysis #1. Lag maps from the 2 visits were compared using voxel-wise cosine similarity (or Spearman's rho, with similar results) to create a similarity matrix where diagonal elements represent within-subject raw reliability. Fingerprint specificity (FS) is a measure of individuality obtained by subtracting the mean between-subject similarity from the diagonal element for each subject [9].

- Lag tracking quality: proportion of reliably tracked voxels (cross-correlogram peak $r > 0.3$) in lag mapping
- GS amplitude: standard deviation of the global mean percent signal change

Result #2: GS amplitude changed with pulse and respiratory rates



Dividing the data into 7.5-minute segments revealed negative correlation of GS amplitude with respiration rate. Their trends during every 15-minute run, accompanying pulse rate reduction, may suggest alteration of physiological state by arousal level as a source of GS amplitude variation (Bijsterbosch, 2017 Neuroimage)

Overall, the perfusion lag structure can be a major source of confound for brain-wide association studies with rs-fMRI via its sensitivity to aging or some disease conditions [12]. Its removal should contribute to more accurate FC evaluation through fundamental SNR improvement.

Systemic slow oscillation

determines the global signal amplitude emerging from circulatory & respiratory circuits

Inter- and intra-individual fluctuation

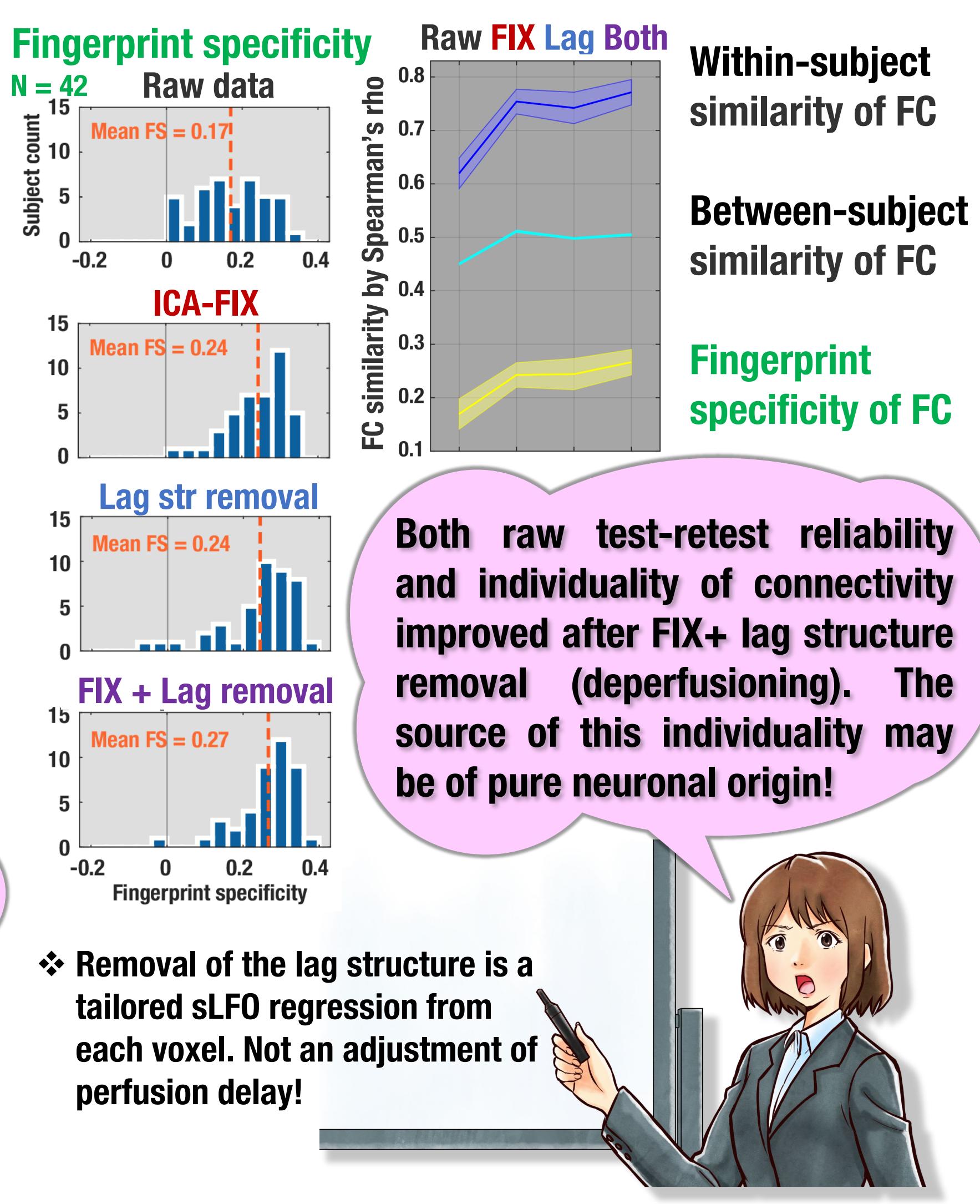
Neural activity
Global sum of local neurovascular coupling

Global mean signal amplitude

Analysis #2. From those subjects with complete physiology data, pulse & respiratory rate fluctuations for every 7.5-minute epoch were measured and fed into correlation analysis.

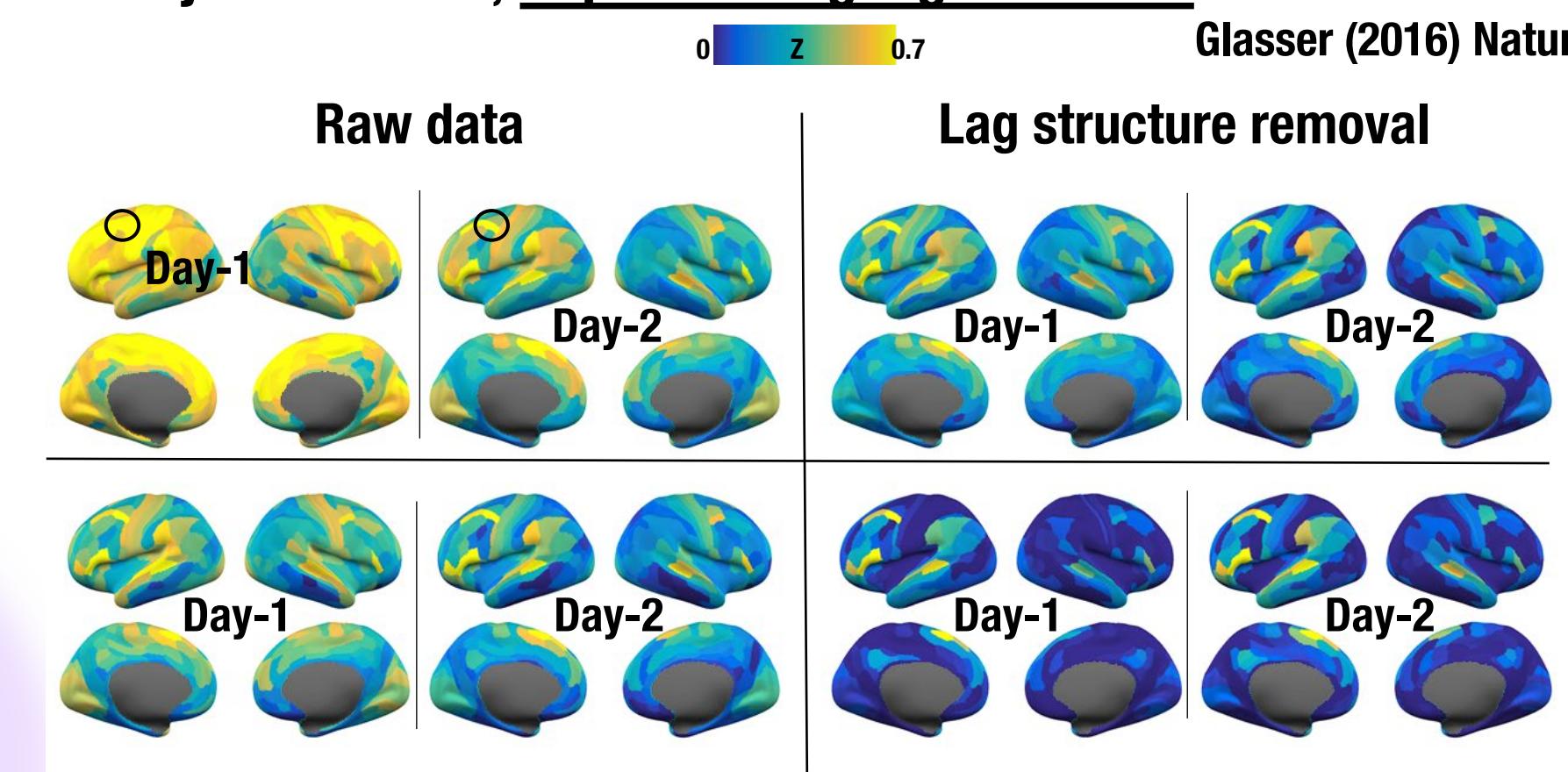
Analysis #3. The whole lag structure was removed from the individual rsfMRI data by regressing out the sLFO with the corresponding lag for each lag map regions [5]. ICA-FIX was applied to both the raw and this “deperfused” data to see their effects on reliability of functional connectivity. Mean fingerprint specificity was calculated from the 360 FC patterns using Spearman's rho as the similarity measure.

Result #3: Removing the lag structure enhanced reliability & individuality of FC



From Aso & Hayashi, ISMRM2022

Subject #599671, Superior Language Network/Area 55b seed



References

- Aguirre GK, Zarahn E, D'Esposito M (1998) The Inferential Impact of Global Signal Covariates in Functional Neuroimaging Analyses. *Neuroimage* 8(3):302–306
- Aso T. et al. (2021) Seed-based Correlation Analysis on Isolated Perfusion Lag Structure in the Resting-state fMRI Signal. *Human Brain Mapping Meeting 2021*
- Aso T. et al. (2017) A Resilient, Non-neuronal Source of the Spatiotemporal Lag Structure Detected by BOLD Signal-Based Blood Flow Tracking. *Front Neurosci* 11:256
- Das, A., Murphy, K., & Drew, P. J. (2021). Rude mechanics in brain haemodynamics: non-neuronal actors that influence blood flow. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences*, 376(1815), 20190635.
- Aso T. et al. (2019) Axial variation of deoxyhemoglobin density as a source of the low-frequency time lag structure in blood oxygenation level-dependent signals. *PLoS One* 14(9):e0222787
- Chang C. et al. (2009) Relationship between respiration, end-tidal CO₂, and BOLD signals in resting-state fMRI. *Neuroimage* 47(4):1381–1393
- Erdogán SB. et al. (2016) Correcting for Blood Arrival Time in Global Mean Regression Enhances Functional Connectivity Analysis of Resting State fMRI-BOLD Signals. *Frontiers Human Neuroscience*. doi: 10.3389/fnhum.2016.00311
- Harrison SJ. et al. (2020) Modelling subject variability in the spatial and temporal characteristics of functional modes. *Neuroimage* 222:117226
- Tong Y. et al. (2015) Can apparent resting state connectivity arise from systemic fluctuations? *Frontiers in Human Neuroscience*. doi: 10.3389/fnhum.2015.00285
- Tong Y. et al. (2011) Partitioning of Physiological Noise Signals in the Brain with Concurrent Near-Infrared Spectroscopy and fMRI. *J Cereb Blood Flow Metab* 31(12):2352–2362
- Aso, T. et al. (2020). A venous mechanism of ventriculomegaly shared between traumatic brain injury and normal ageing. *Brain: A Journal of Neurology*, 143(6), 1843–1856.