Systemic Low-Frequency Oscillations (sLFOs) and Global Signal [Regression]

2024/05/21

Global signal regression is a common denoising step

After preprocessing, postprocessing workflows often include global signal regression:

1. Average BOLD signal within brain mask.
    a. Cortical gray matter is often used as a surrogate (Power et al., 2018).
2. Regress mean brain signal from preprocessed BOLD data.

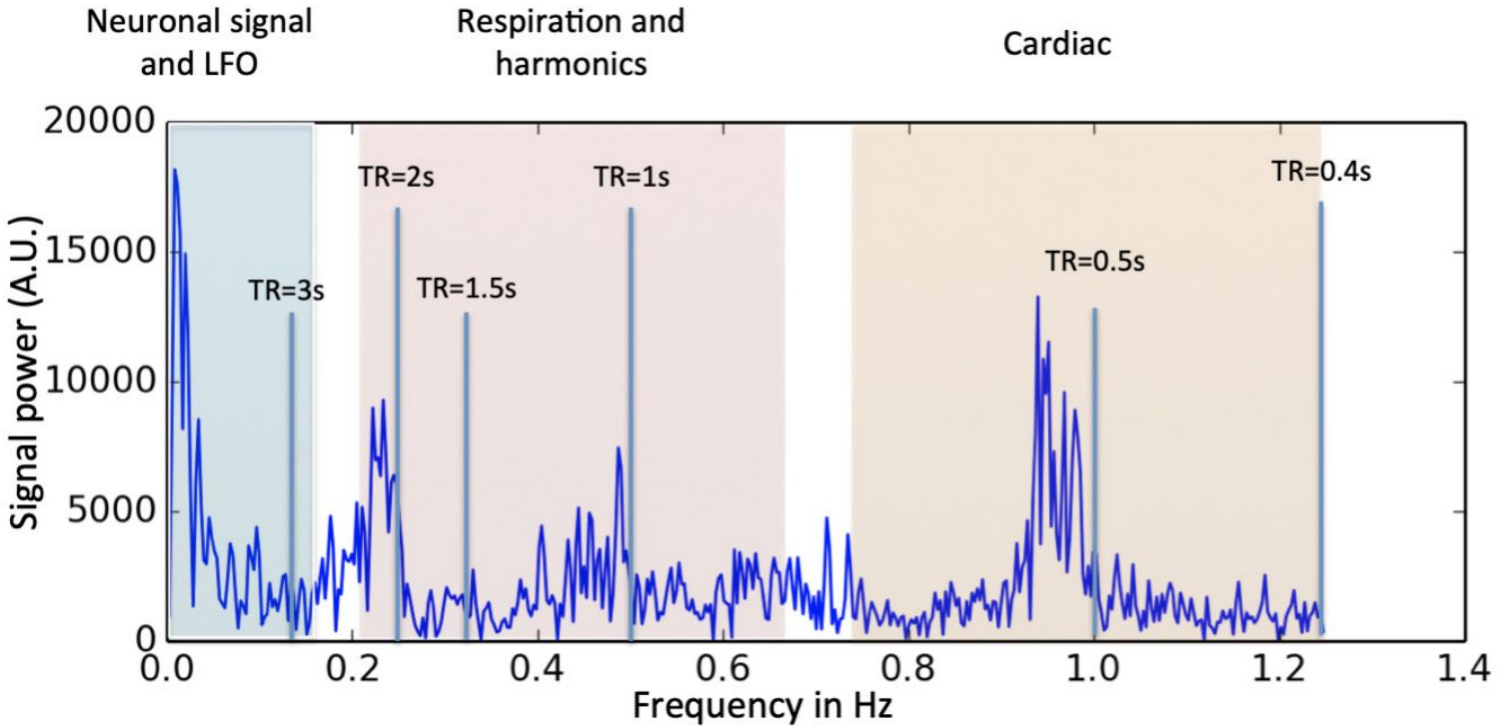
This approach assumes (1) the global BOLD signal reflects noise and (2) the noise captured by the global signal affects the whole brain at the same time.

Systemic low-frequency oscillations in fMRI data

Tong, Locke, & Frederick (2019)

What are low-frequency oscillations?

- **Low-frequency content**: Brain LFOs have frequencies from ~0.01 to 0.2 Hz.
- **Dynamic noise signals**: *Systemic* LFOs (sLFOs) can be modeled as a single signal with different delay times across the brain.
- **Hemodynamic timescale**: sLFOs travel through the brain at the speed of blood flow, not at the speed of neuronal activity.
- **Following the vasculature**: The spatial pattern of sLFO propagation follows the vasculature. First, it appears in the center of the brain, then moves out through the parenchyma, and ends up in the superior sagittal sinus.
- **From outside the brain**: Early studies using peripheral NIRS found the LFO signal in the brings and toes preceded its appearance in the brain.



Low-frequency oscillations occur in same frequency band as neurogenic BOLD

et al., 2007; Brookes et al., 2011; Ma et al., 2016). Moreover, while we have shown that up to 30% of the low frequency gray matter variance (13% of the total variance across *all* frequency bands, Hocke et al., 2016) is due to non-neuronal sLFOs (Frederick et al., 2012a), this means, necessarily, that 70% of the variance *is not* due to sLFOs, and likely represents neuronal signal. However, it is clear that there are both vascular and neuronal "connectivity" networks, with significant spatial overlap.

Tong, Locke, & Frederick (2019)

Resting-state network signals correlate with peripheral NIRS data at delays

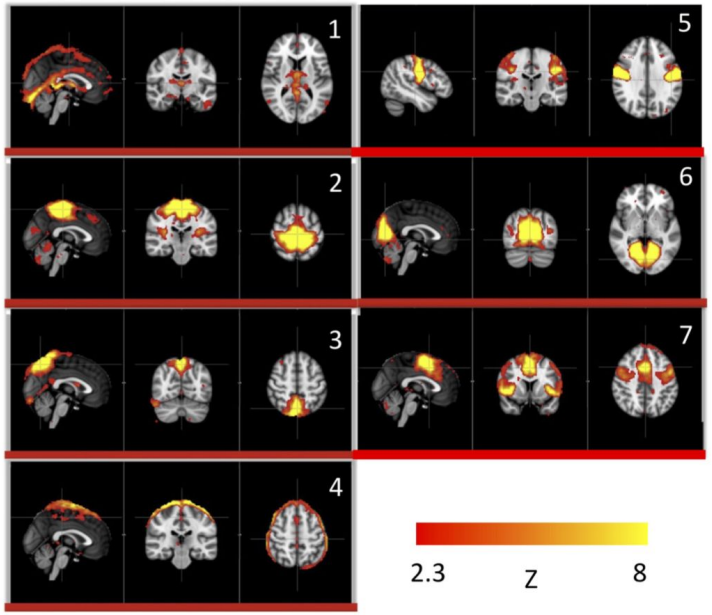
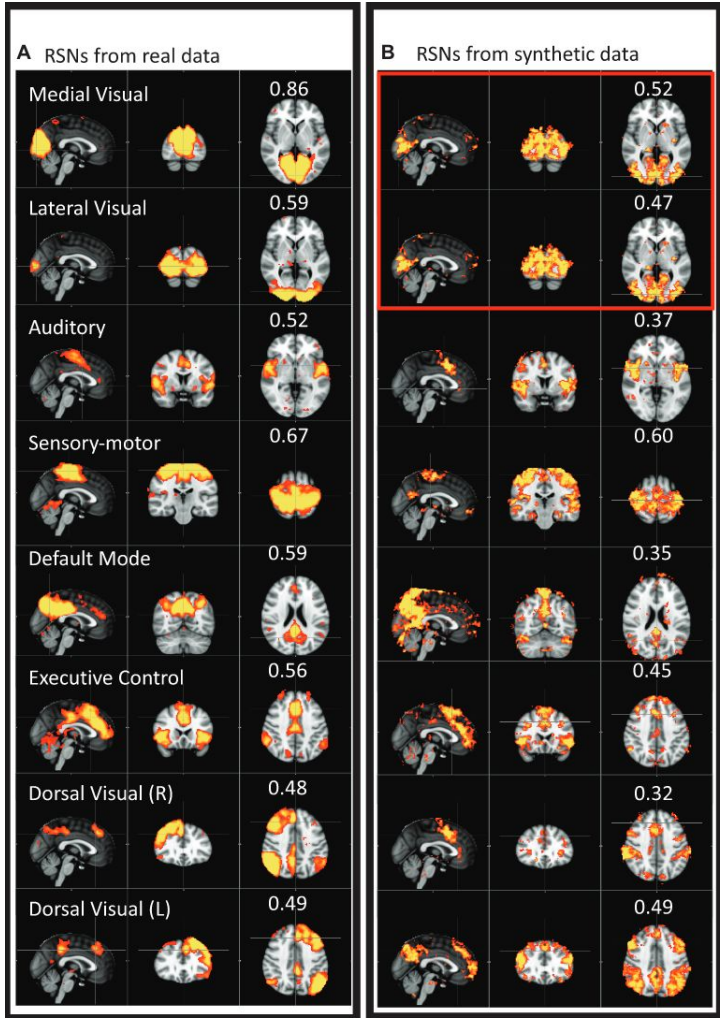


FIGURE 2 | Independent components (1–7) from a group analysis of 10 subjects' resting state data that have high, significant positive correlations with simultaneously recorded peripheral NIRS data (Figure adapted from Tong et al., 2015).

Simulations show the same finding

1. Use peripheral NIRS and fMRI to extract LFO signal.
2. Calculate delay brain map from real data.
3. Simulate an LFO signal.
4. Simulate BOLD time series using *just* the delay and simulated LFO signal.
5. Run group ICA on set of synthetic BOLD runs.
6. Compare to group ICA results from the corresponding real data.

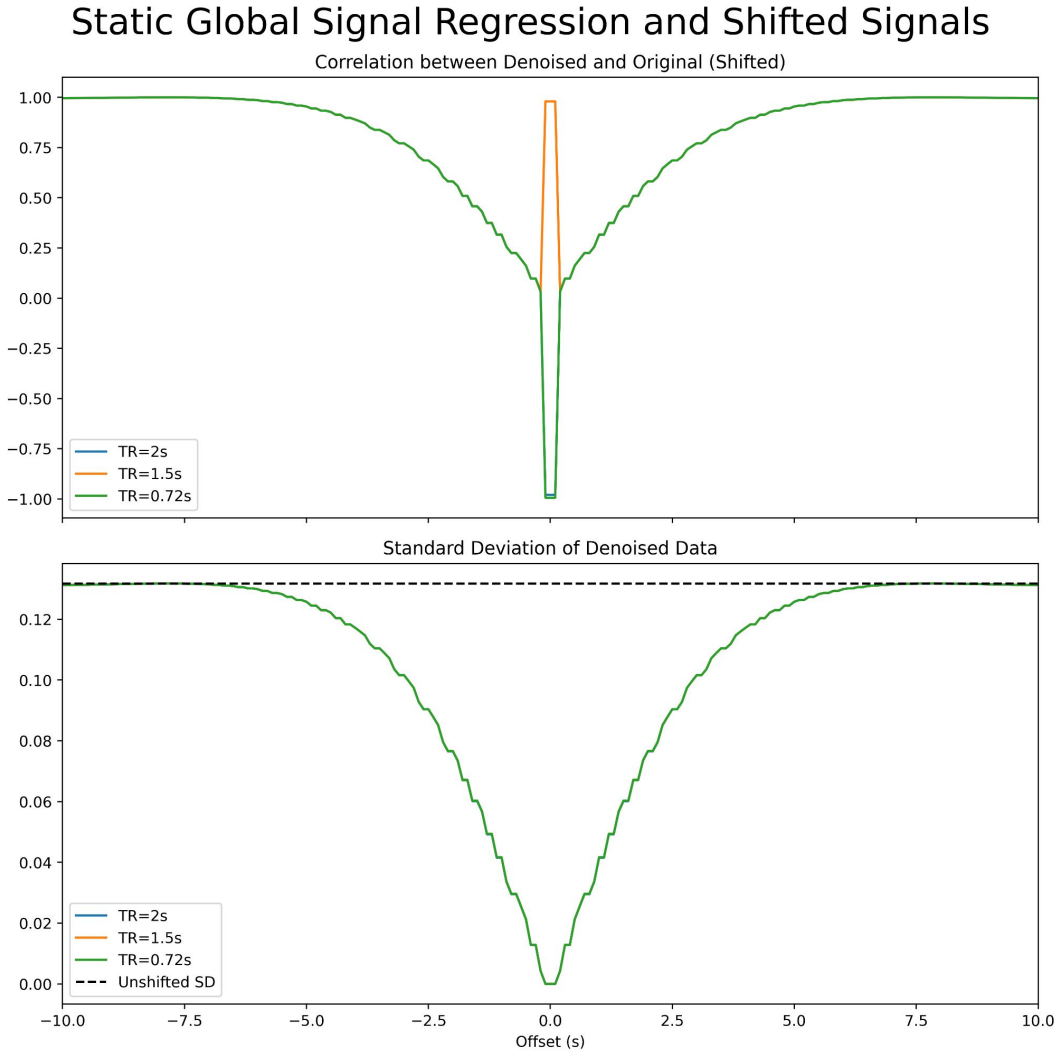


Global signal regression and sLFOs

1. In an extreme case, where sLFOs dominate global BOLD signal, mean global signal is averaging a traveling signal over time.
2. The mean global signal will be similar to the traveling signal, but they will not be temporally aligned.
3. Thus, each voxel's correlation with the global signal will be relatively high.
4. Regressing out the global signal at the wrong delay will add noise to the data.

Ad hoc simulations support this

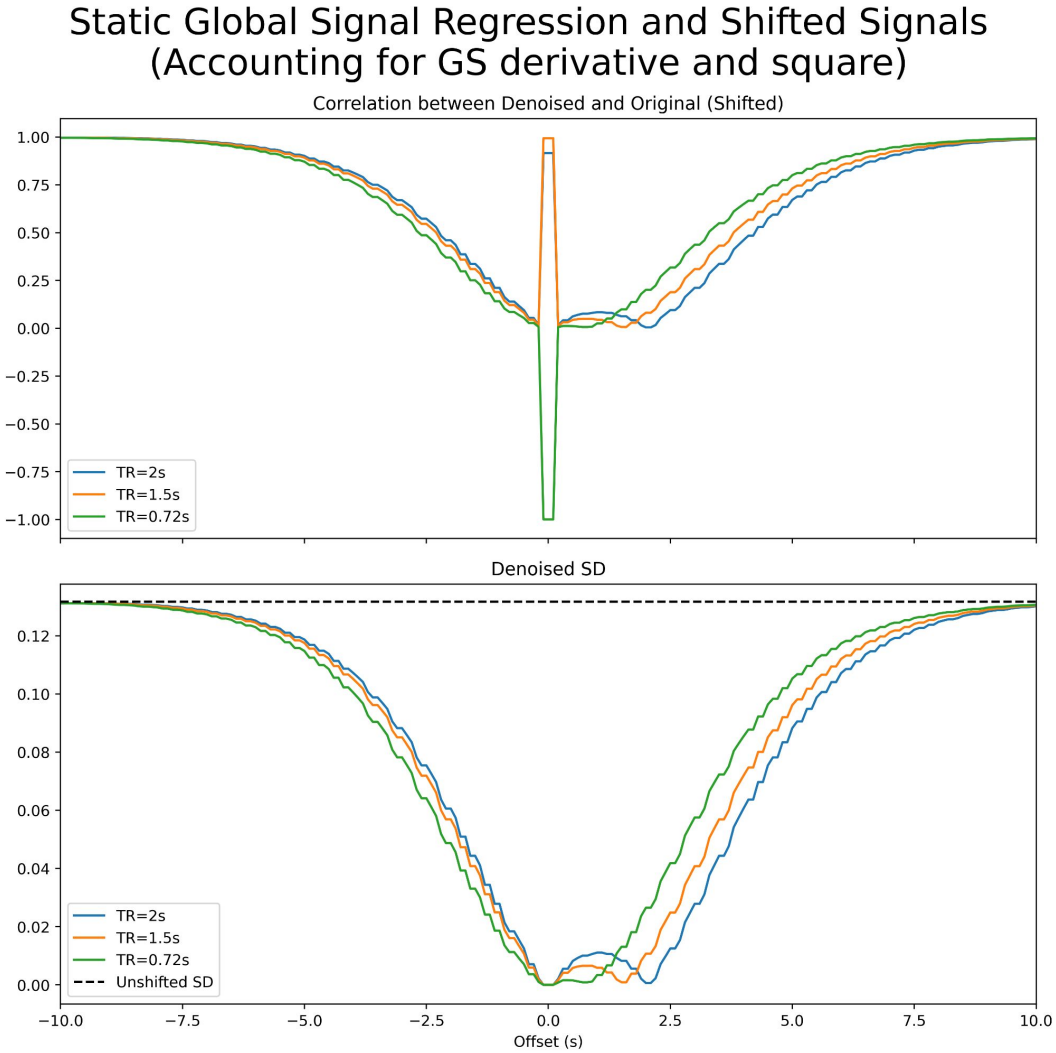
Static global signal regression does not remove lagged signals.



36P doesn't solve the problem

We often include derivatives of confounds to account for lags, so I added that to my simulation.

The problem persists.



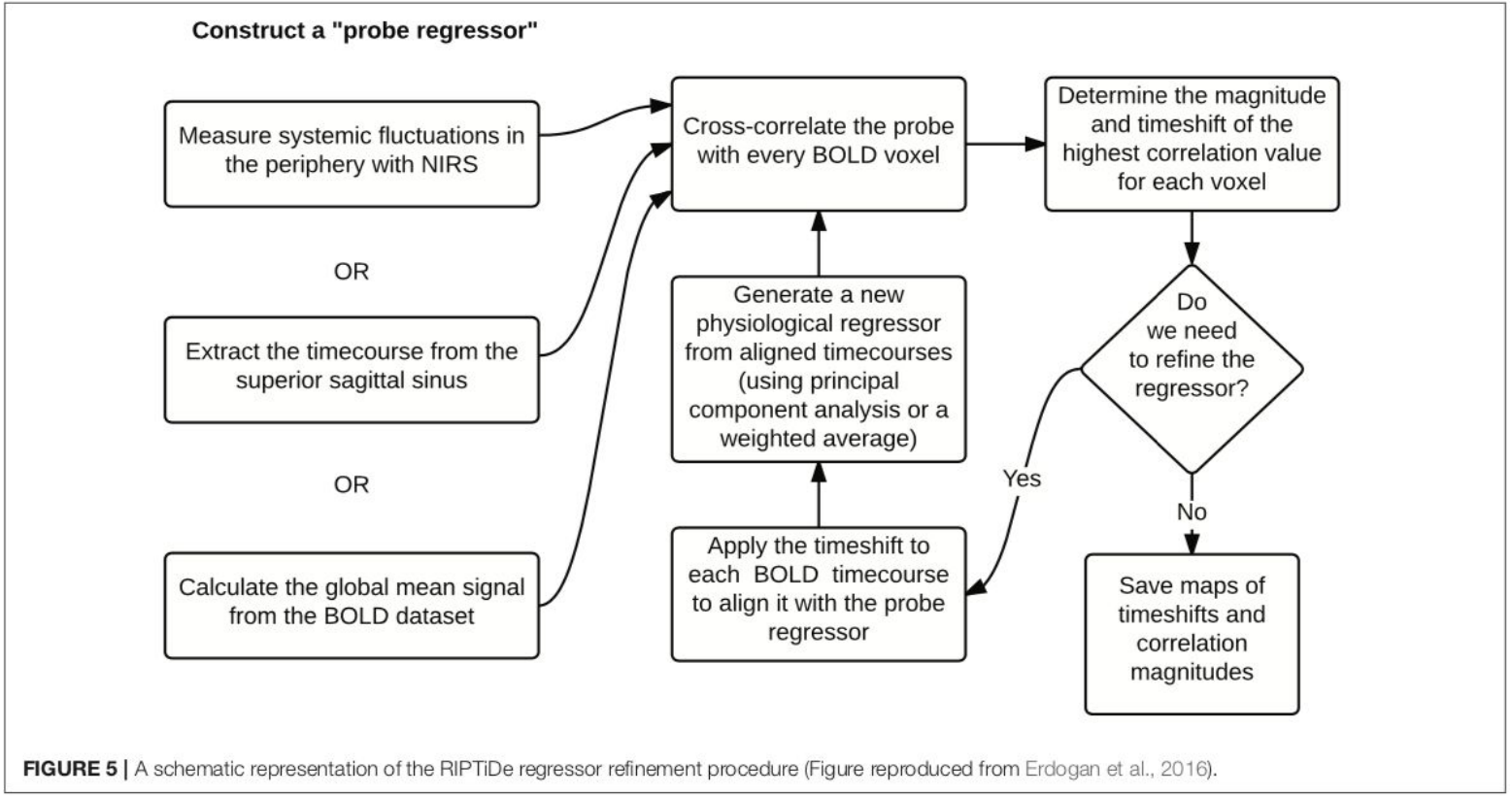
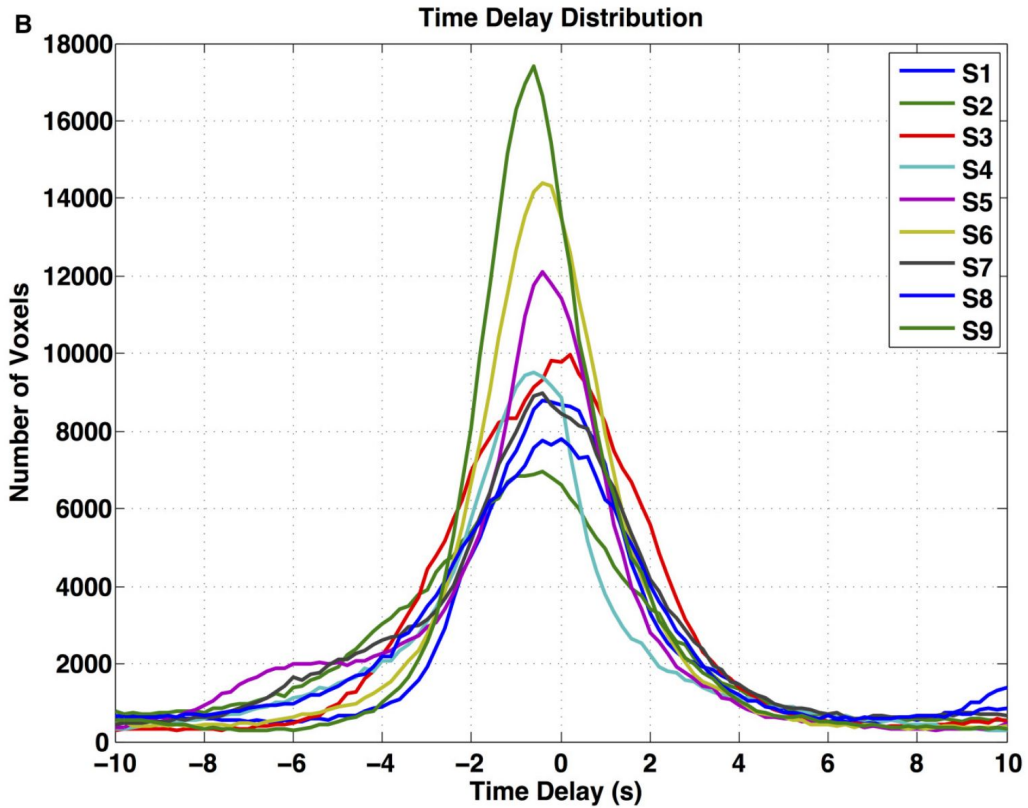


FIGURE 5 | A schematic representation of the RIPTiDe regressor refinement procedure (Figure reproduced from Erdogan et al., 2016).

Dynamic global signal regression with RIPTiDe



A sampling of dGSR regressor delays

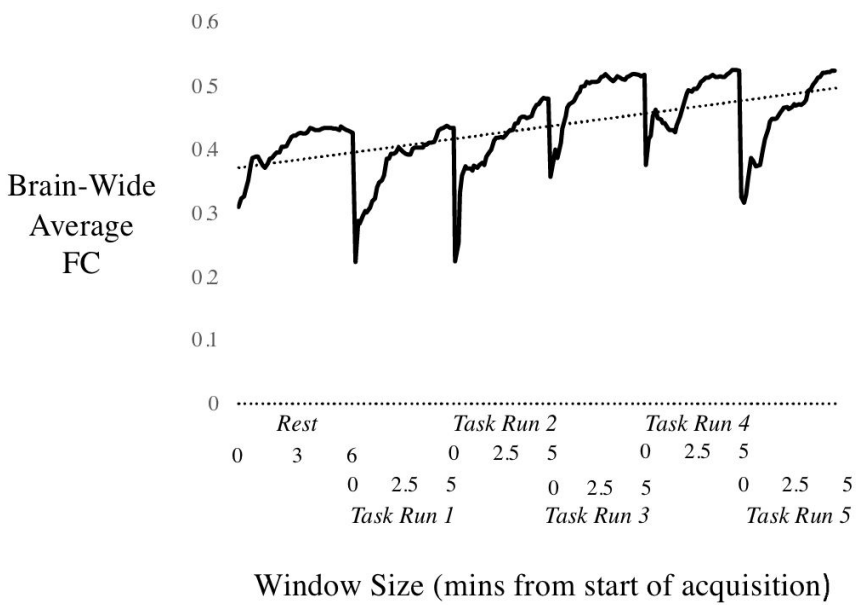
To summarize...

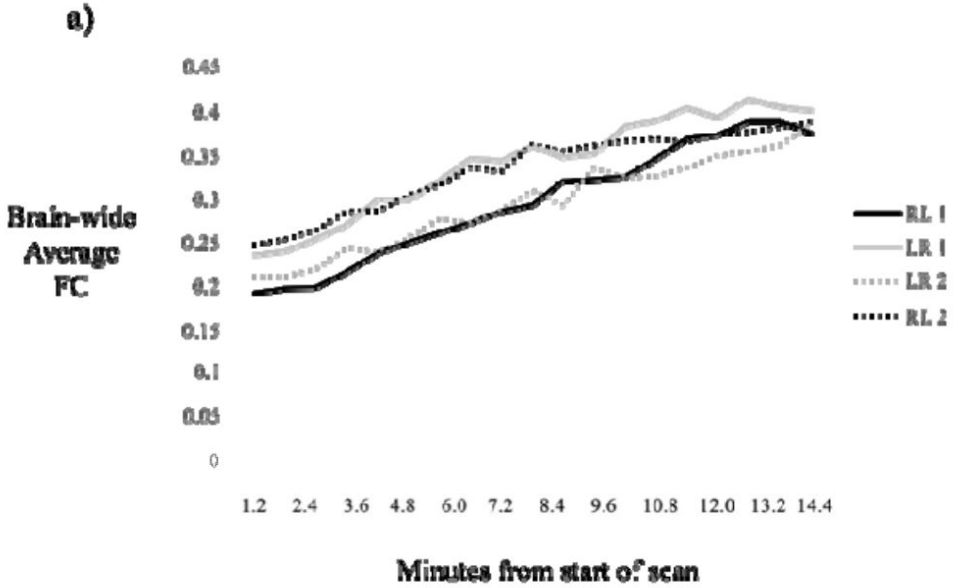
- "[S]ignificant low frequency physiological oscillation (~0.01–0.15 Hz) remains in the signal [after removing respiratory and cardiac fluctuations]." - Tong & Frederick (2019)
- sLFOs account for ~30% of low-frequency BOLD signal variance in gray matter!
- sLFOs, when delay isn’t accounted for, decompose into patterns like established RSNs.
- Static GSR does not remove lagged signals.

Functional connectivity inflation and sLFOs

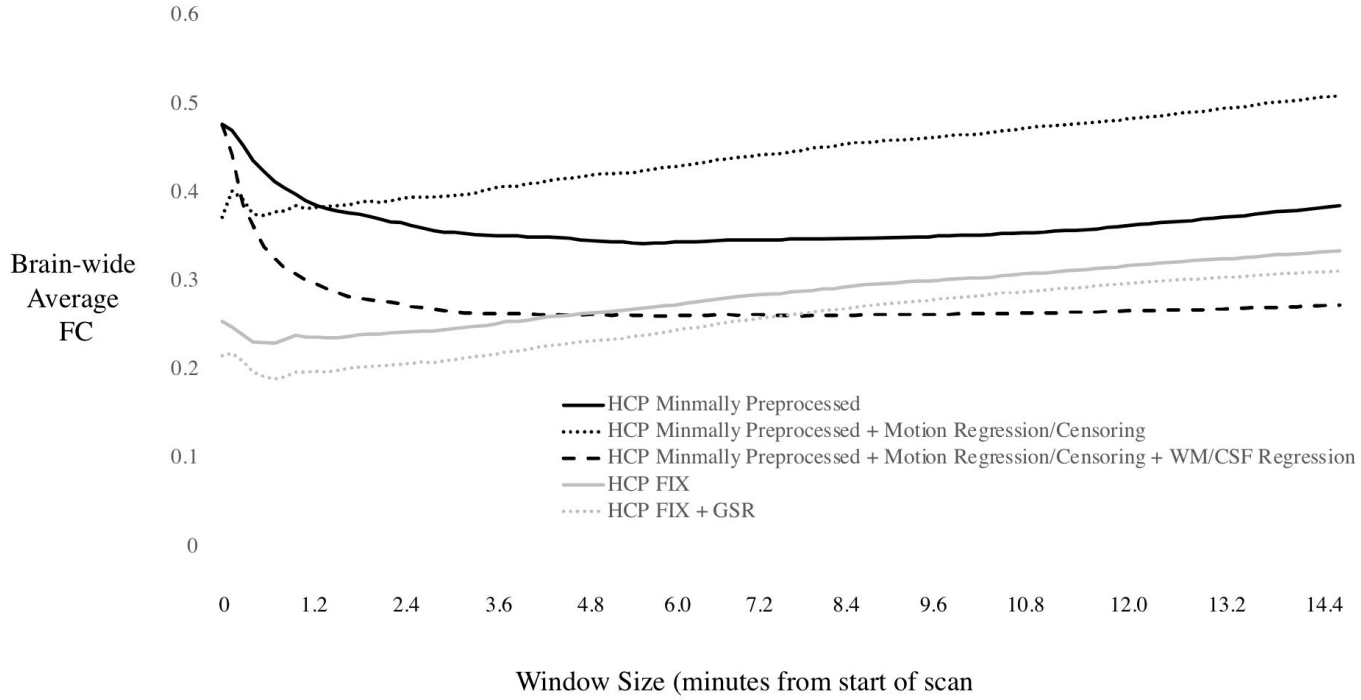
Korponay et al. (2023)

Global functional connectivity increases over scan time

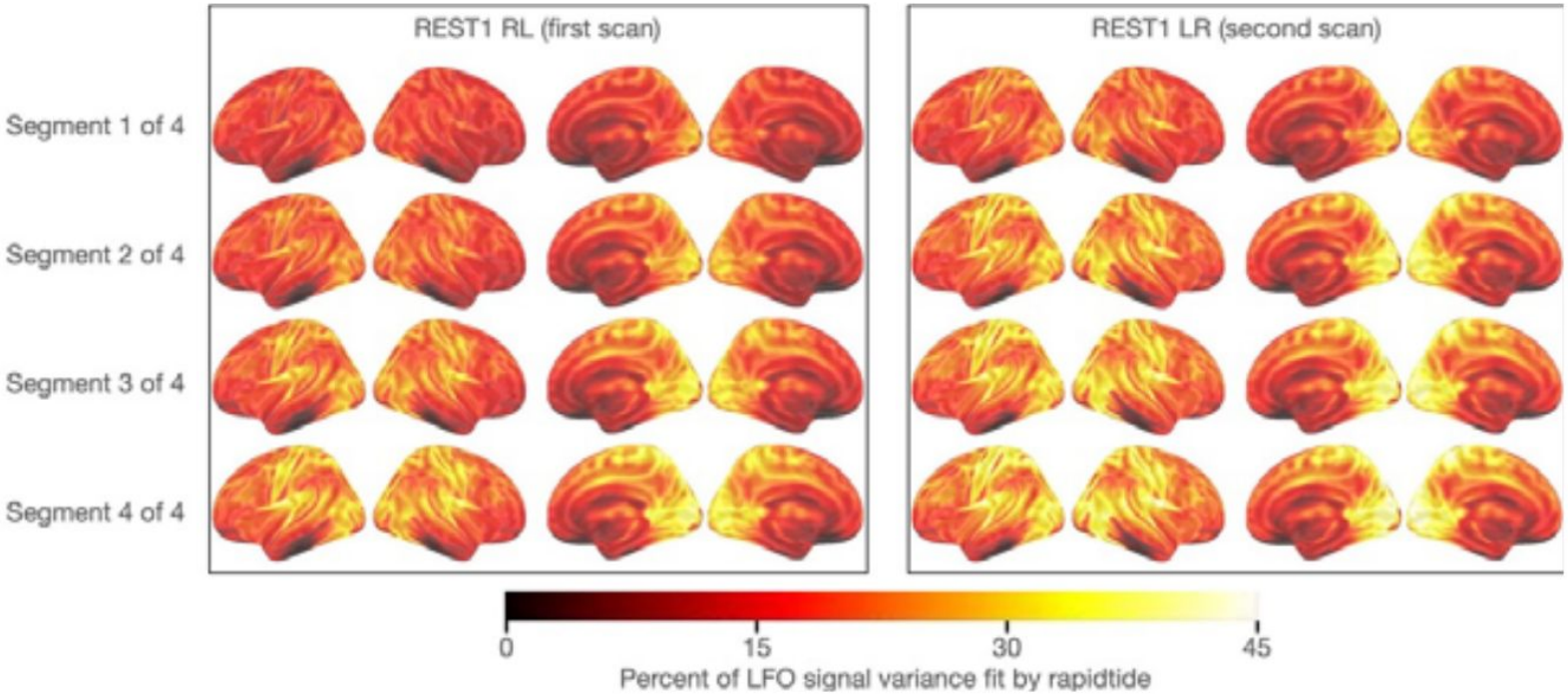




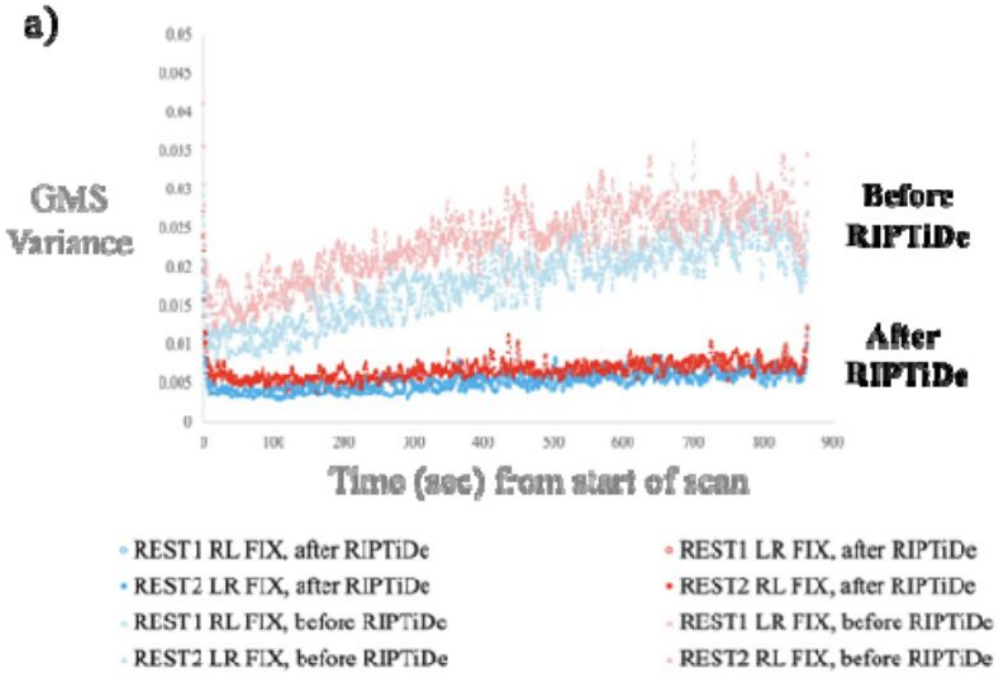
Neither FIX nor GSR mitigates FC inflation

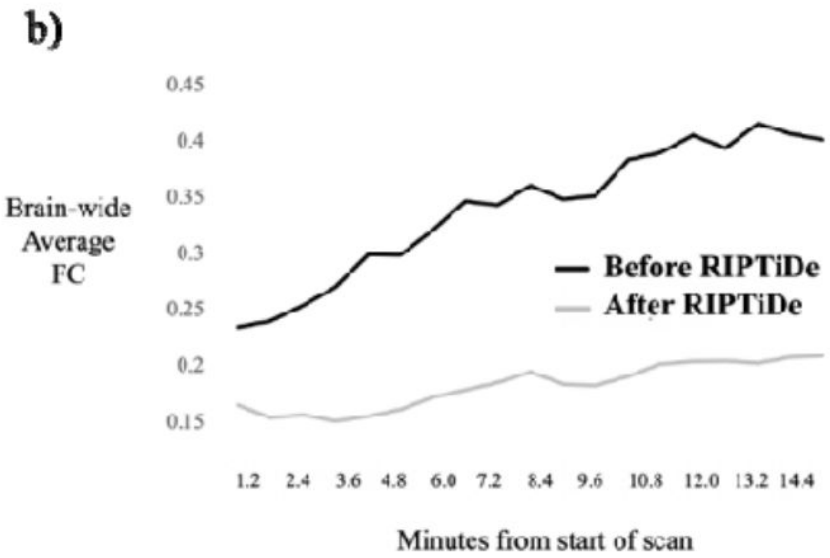


Variance explained by sLFO increases over time



Dynamic GSR mitigates (but does not eliminate) FC inflation





And now the bad news...

1. Almost no one deals with sLFOs in their processing pipelines.
2. Rapidtide has certain limitations:
    a. It assumes that the sLFO signal is (1) truly random and (2) sufficiently "white" within the band of interest. Assumption 1 appears generally true, but assumption 2 does not.
    b. Inhomogeneous time delays in the sLFO regressor. Refinement helps with this.
3. The rapidtide code is in rough shape.
    a. ~50k lines of code
    b. ~37% test coverage
    c. 51 command-line interfaces

There are also some cool applications

Cerebrovascular reactivity mapping from rsfMRI

Golestani et al. (2016)

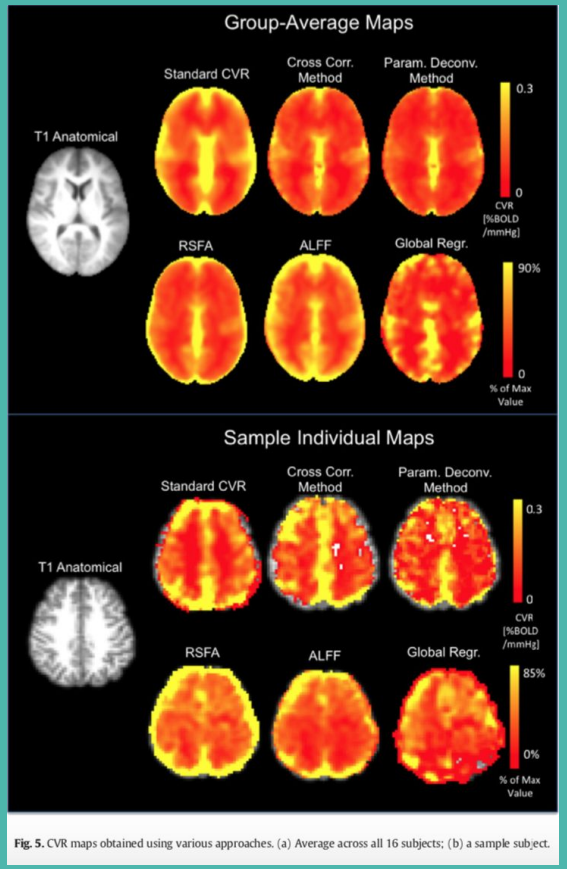


Fig. 5. CVR maps obtained using various approaches. (a) Average across all 16 subjects; (b) a sample subject.

Quantitative blood flow imaging

Tong, Locke, & Frederick (2019)

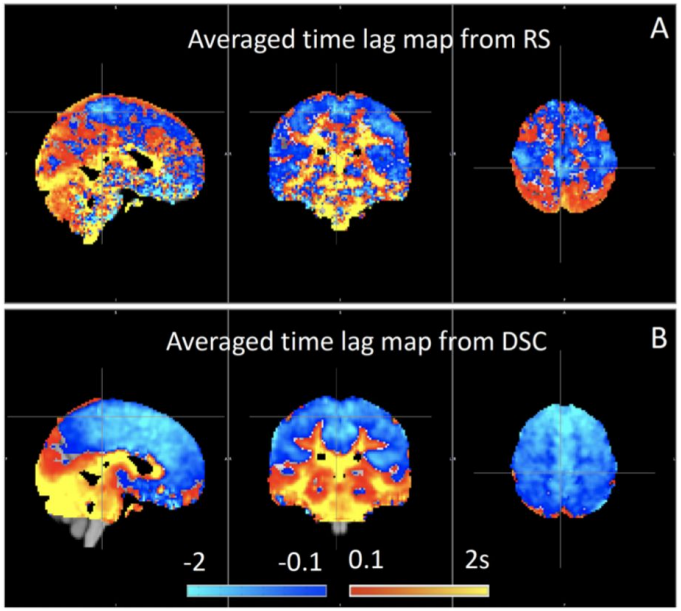


FIGURE 7 | Blood arrival time delay values (in seconds) obtained from rapidtide analysis of **(A)** resting state fMRI data and from **(B)** dynamic susceptibility contrast imaging during the same imaging session in healthy controls (N = 8) (Figure adapted from Tong et al., 2017).

References

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A (sort of) timeline

2004: Wise et al. find that slow changes in arterial CO2 are related to low-frequency BOLD variations.

2010: Tong & Frederick acquire fMRI with simultaneous functional NIRS in brain and find widespread spatial correlations between brain fNIRS and BOLD signal that change with time lag.

2012: Tong et al. acquire fMRI with simultaneous *peripheral* fNIRS (on the fingers and toes). Toes and fingers have similar patterns to brain, *but with different lags*!

2014: Tong & Frederick test it out on ultrafast fMRI to see if aliased cardiac or respiratory signals cause the low-frequency oscillations. They don't!

2015: Tong et al. flip the process by synthesizing sLFO-based data and comparing to real fMRI data. Resulting "networks" are very similar.

2016: Erdoğan et al. show that the RIPTIDE approach works with global signal too! No need for NIRS or a special ventricle seed.