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Assessing functional connectivity beyond Pearson's correlation

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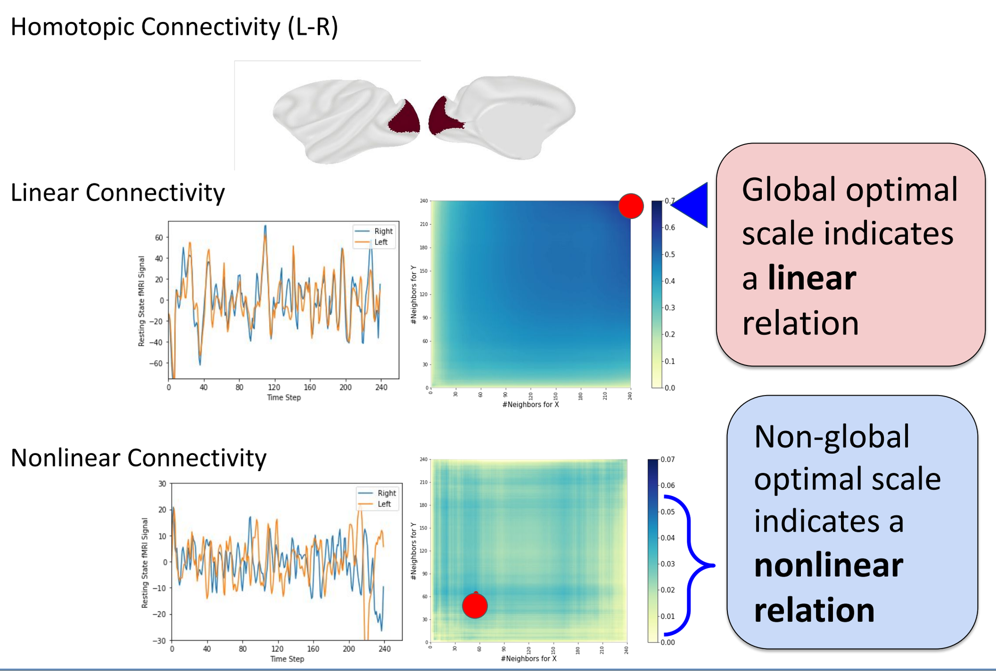
Introduction

Functional connectivity (FC) is defined as the temporal coincidence among neurophysiological events (Friston, 1994), which can be measured by the statistical dependency of recorded signals between two regions. In fMRI studies, Pearson's correlation is commonly used to measure the FC. In fact, it appears to have become the "synonym" of FC in the field. However, it is worth noting that Pearson's r is only one of many statistical dependency measures, and it limits its ability to a linear relationship. Recently, a statistical model - Multiscale Graph Correlation (MGC) was developed for testing the dependency of time series (Vogelstein et al., 2019). Unlike Pearson's r, MGC enables characterization of both linear and nonlinear relationships between two time series, and provides a novel 'optimal scale' metric to differentiate between linear and nonlinear dependence. Here, we used MGC as our dependency measurement to assess the FC and to examine the linear and nonlinear relations of fMRI signals in humans and macaque.

Methods

We selected 30 participants from the Human Connectome Projects (HCP, resting-state fMRI, 2 sessions x 200 volumes) and two macaque samples including awake and various anesthetized states (13, 15, 16, 16, 16 sessions in the awake state, anesthetized at 0.75%, 1.00%, 1.50%, 2.00% isoflurane concentration, 200 volumes per session). Data were processed using "HCP-style" surface based processing for both species. We first averaged the human and macaque data using the Glasser et al. (2016) and Markov et al. (2014) parcellations, respectively. Functional networks were defined by the Yeo et. al., (2011) and Bezgin et. al., (2012) parcellations. We calculated MGC statistics and Pearson's r to measure the functional connectivity. Finally, we computed the optimal scale to examine the linear and nonlinear nature of FC in macaque across multiple states and FC in humans. The optimal scale suggests the best fMRI signal range during a period of time that achieves the maximal local correlation. **Global optimal scale indicates an approximately linear or monotonic relationship, and non-global (i.e. local) optimal scale implies a nonlinear dependency.**



Results

- In general, MGC-based FC showed similar spatial pattern with Pearson'r FC in the human and macaque data. However, MGC-based FC includes both linear and nonlinear relationships (Fig 1).
- In human awake data, both inter- and intra-hemispheres MGC-FC exhibited more linear relationships within network than those between networks. Intriguingly, the optimal scale in high-order network appears to be lower than primary network (Fig 3A), indicates nonlinear dependency in high-order networks.
- Across awake and anesthetized states in macaques, the homotopic MGC-FC showed a shift from global to local optimal scales as the isoflurane concentration increased, indicating increased nonlinear homotopic connection in the anesthetized state. (Fig 2)
- Compared to awake state, the strength of MGC connectivity decreased in deep anesthetized states while the optimal scale increased (Fig. 4).

Conclusion

Using MGC, we characterized linear and nonlinear functional connectivity in both the human and macaque. Similar to Pearson's r, the MGC statistics captured dominant linear fMRI signal dependencies in the awake state. Beyond Pearson's r, the MGC optimal scale captures the nonlinear dependency in the anesthetized state, as well as scale differences in functional connectivity between networks. Our results open up new directions to measure the FC and infer linear and nonlinear relationships, facilitating our understanding of brain organization across different states and species.

Functional Connectivity

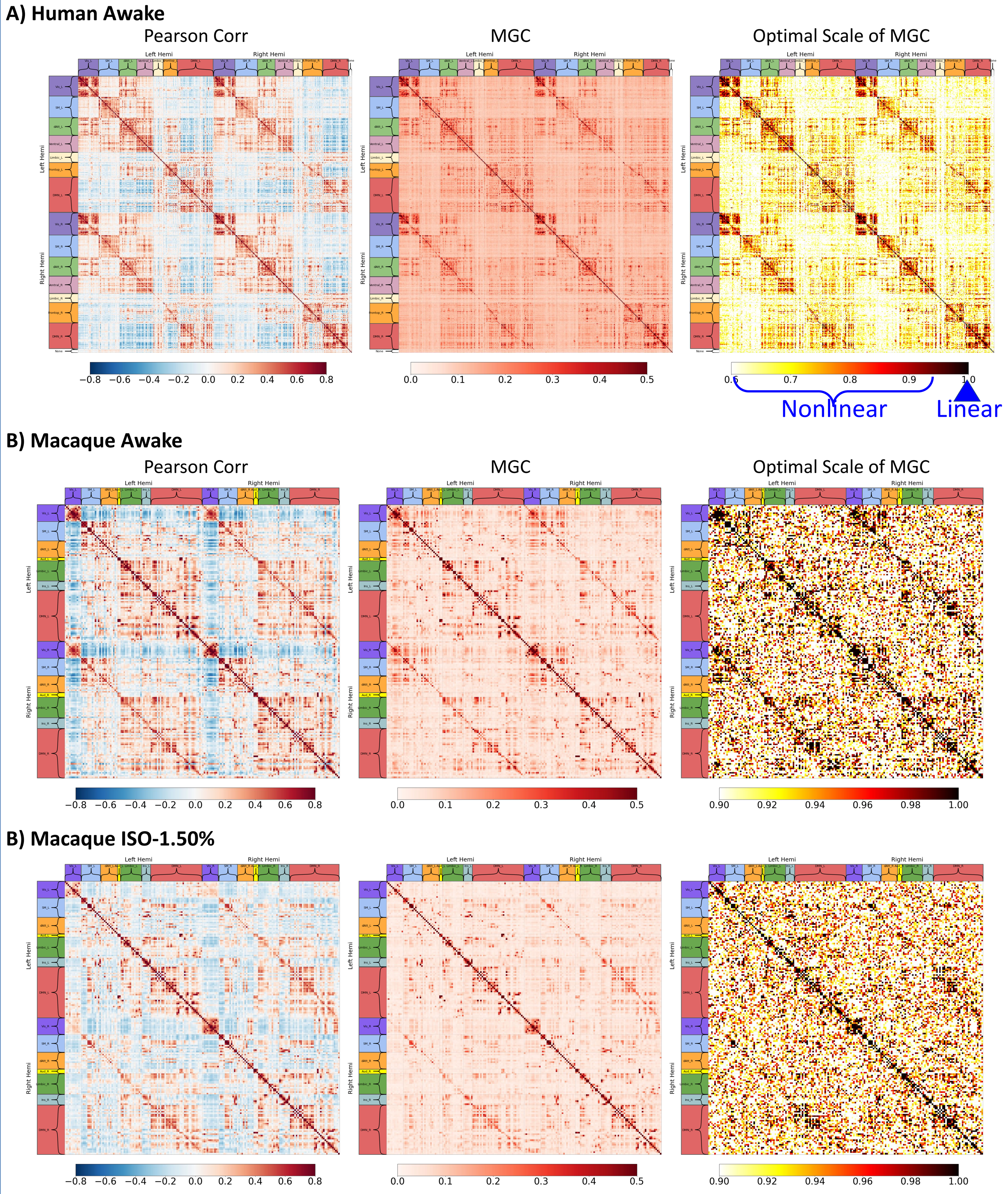


Figure 1. Functional Connectivity
A) Human (30 subjects, 2 sessions x 200 volumes) functional connectivity measured by Pearson's r, optimal scale of MGC and MGC test statistics. B -C) Macaque (13, 16 sessions x 200 volumes) in the awake state or anesthetized at 1.50% isoflurane concentration functional connectivity measured by Pearson's r, MGC test statistics and optimal scale of MGC.

Homotopic Connectivity

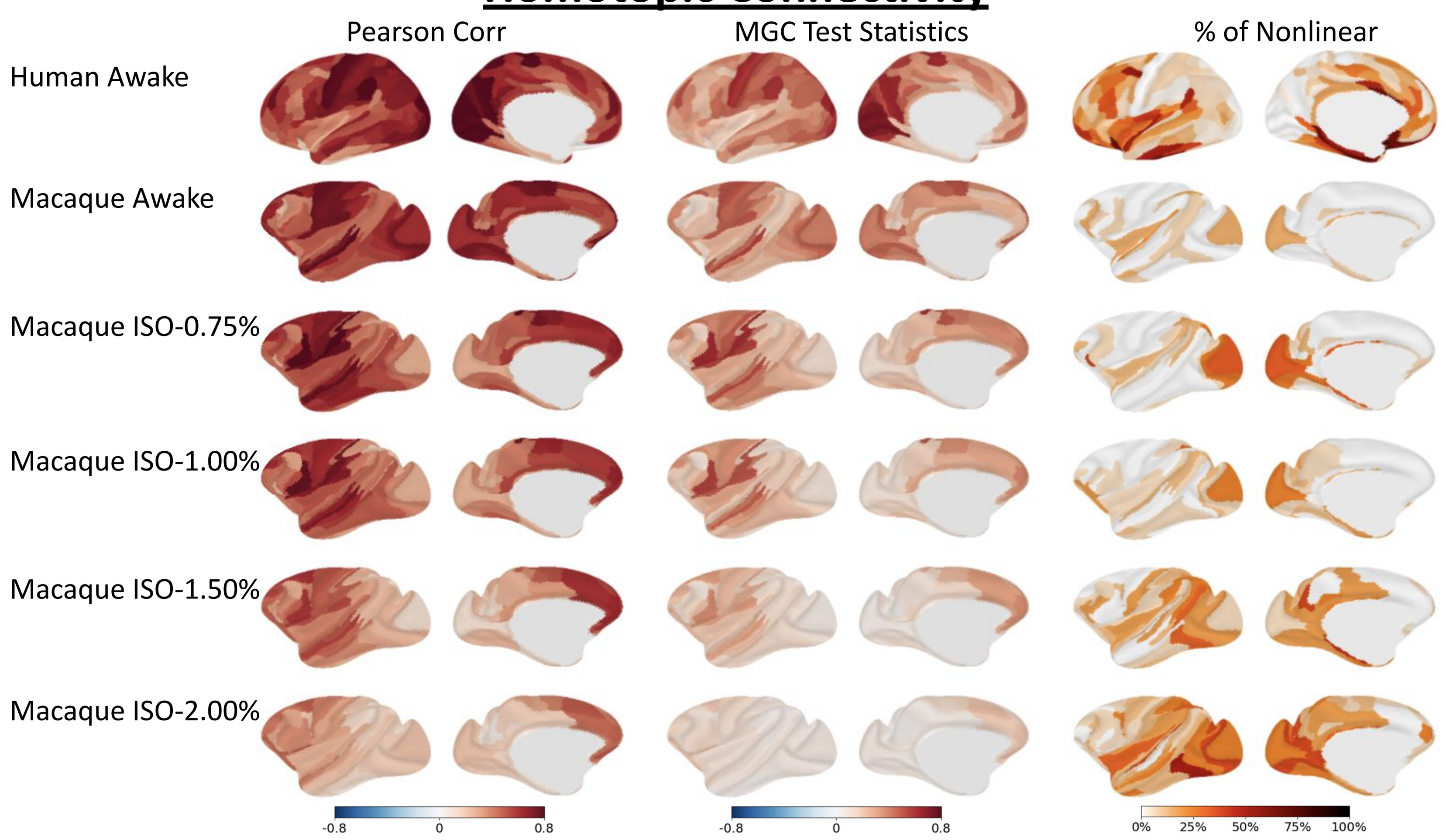


Figure 2. Homotopic Connectivity
Homotopic connectivity measured by Pearson's r, MGC, and MGC optimal scale in human (awake) and macaque (awake, and anesthetized at 0.75%, 1.00%, 1.50%, 2.00% isoflurane concentration). The optimal scale of MGC in the macaque showed a shift from global to local optimal scales as the isoflurane concentration increased.

Optimal Scales of MGC in 7 Networks

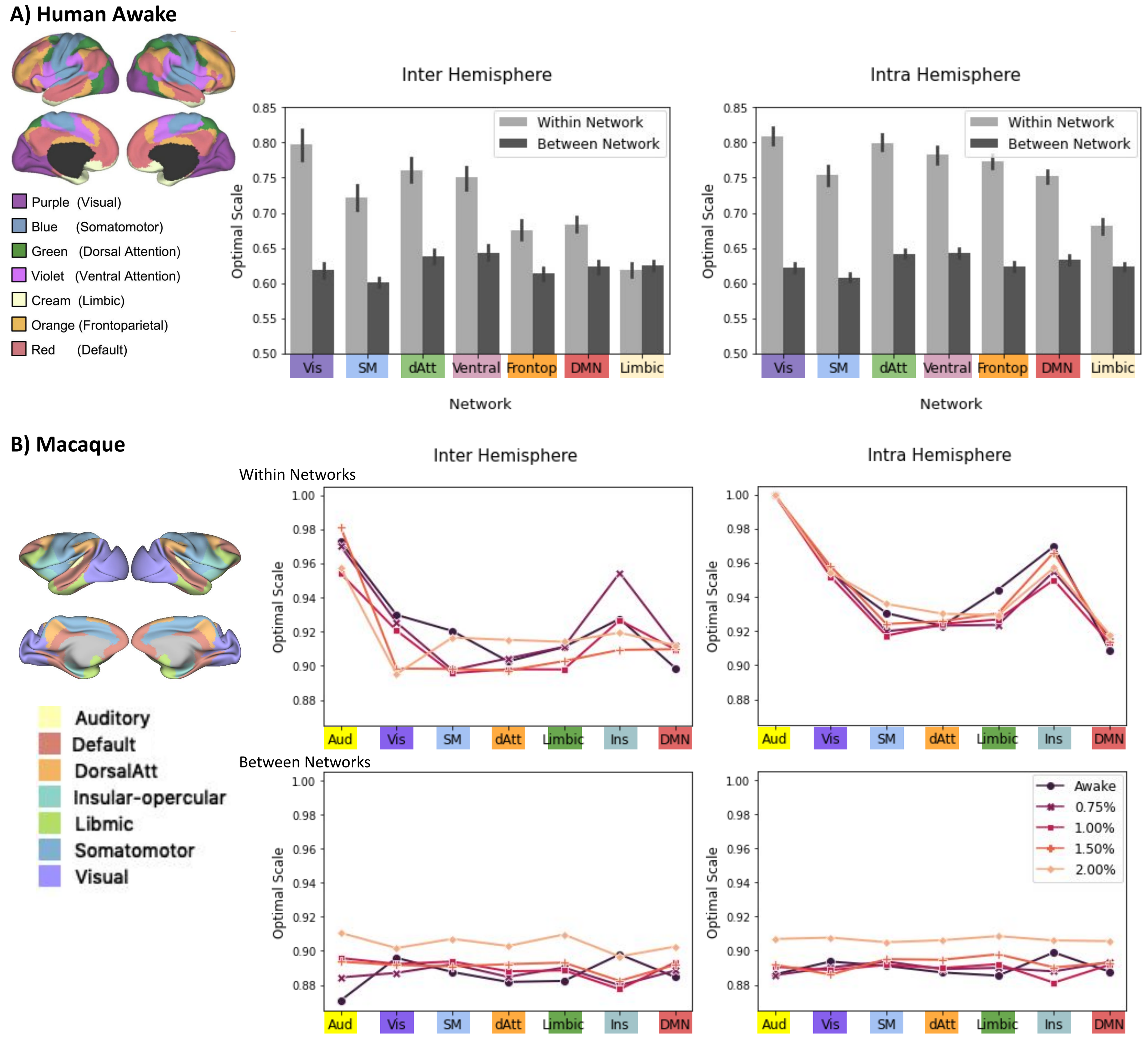


Figure 3. Optimal scales in 7 Networks.
A) Human awake optimal scales in Yeo's 7 Networks. B) Macaque optimal scales in 7 Networks defined in the Bezgin et. al., 2012 Parcellation, in the awake state or anesthetized at 0.75%, 1.00%, 1.50%, 2.00% isoflurane concentration.

Significant Changes Across States

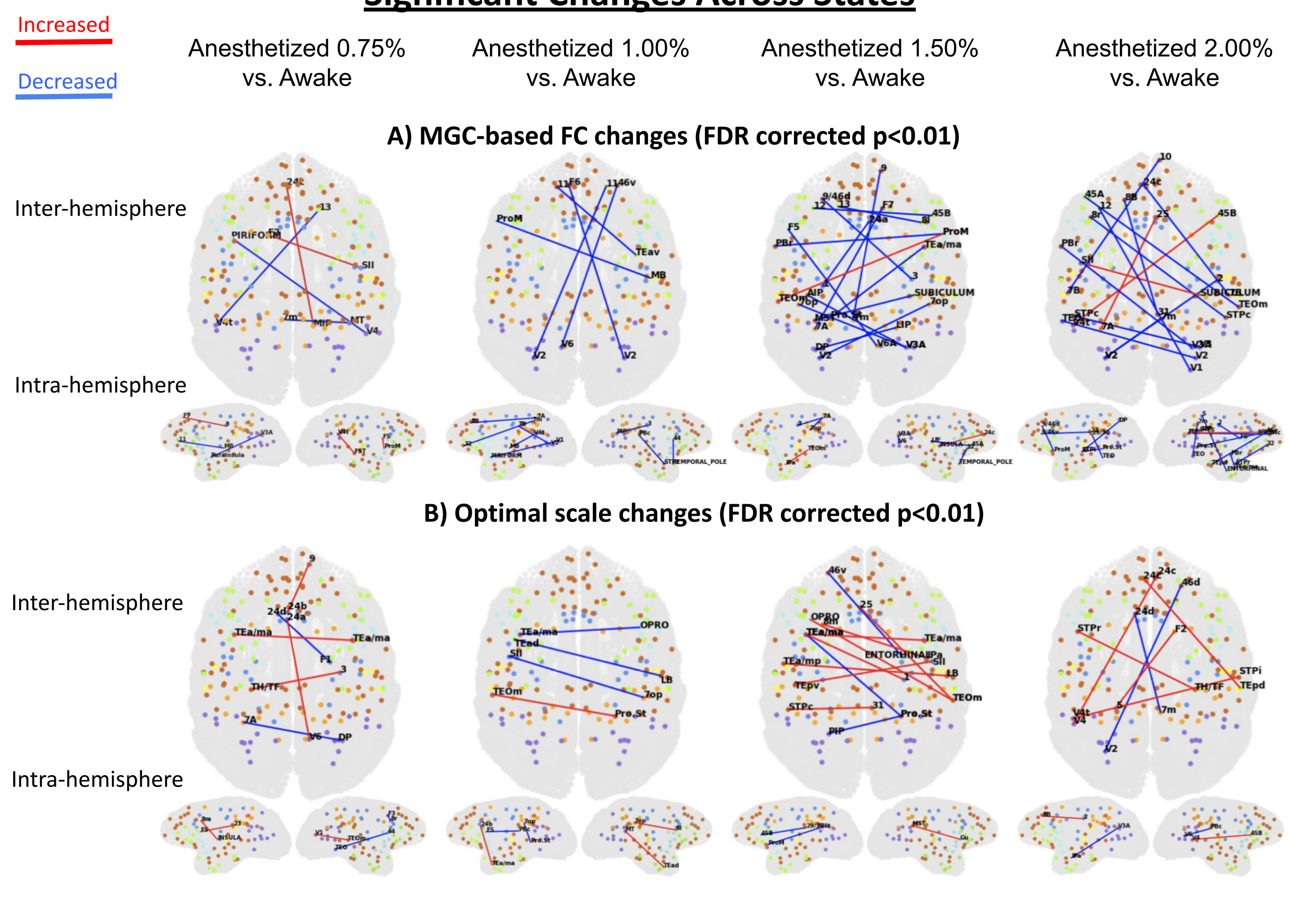


Figure 4. Significant (FDR corrected p<0.01) changes of MGC FC (A) and optimal scale (B) across states