Structural support for brain state transitions that contribute to working memory

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In the healthy brain, large-scale white matter architecture and local neuronal membrane properties facilitate seamless transitions between cognitive states. However, the manner in which white matter supports the brain's recurrent spatial patterns of activity, or states, remains unknown. Here, we ask whether structural connectivity predicts trajectories of brain states in the resting state, and whether those predictions are conserved as participants engage in a cognitively demanding task. Using a large (n = 690) community-based sample of healthy youths from the Philadelphia Neurodevelopmental Cohort, we identify common brain states by applying unsupervised clustering to functional neuroimaging data acquired during the resting state and during the performance of an n-back working memory task to classify each time point as a discrete state.

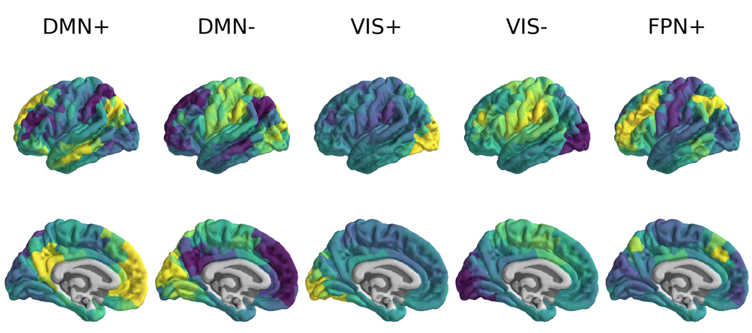

Figure 1. Brain states identified through unsupervised clustering of fMRI BOLD data. We applied *k*-means clustering to concatenated time series from resting state and n-back task BOLD time series. We selected $k = 5$ as the optimal number of clusters through a stability analysis using the z-scored Rand index. The cluster centroids for $k = 5$ are shown above, with classification based on similarity to *a priori* definitions of resting state functional networks.

In order to determine the optimal number of clusters, we assessed the stability of partitions generated through *k*-means clustering of BOLD time series by calculating the coefficient of variation of the z-scored Rand index between 100 repetitions of *k*-means with random initialization. All subsequent analyses were performed with the lowest mean-squared error partition.

Highly active regions in the cluster centroids closely mirror resting state functional networks (Fig. 1), with larger dwell times in visual and frontoparietal (FPN) states during task and default mode network (FPN) states during rest. States were assigned based on similarity to binary vectors corresponding to *a priori* definitions of resting state functional networks. Furthermore, state transition probabilities differ between rest and n-back and change over the course of normative neurodevelopment. We found that older subjects have higher FPN state probabilities during the n-back task and decreased DMN state probabilities at rest. Using diffusion-weighted imaging acquired from the same subjects, we show that increasing structural connectivity between highly active regions in each state positively correlates with the probability of transitioning between the respective states. These trends are similar for resting state and n-back task data, persist when accounting for spatial distance, and are robust to the choice of cluster number. State probabilities and state transition probabilities also predict working memory performance: decreased FPN state probabilities and increased transitions between VIS+ and VIS- states at rest positively predict working memory performance. These results suggest that both spatial and temporal properties of resting state brain activity are predictive of working memory. Overall, these findings shed new light on the relationship between brain structure and brain activity, as well as the role of regional coactivation in cognition.