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# STATE-DEPENDENT VARIABILITY OF DYNAMIC FUNCTIONAL CONNECTIVITY BETWEEN FRONTOPARIETAL AND DEFAULT NETWORKS RELATES TO COGNITIVE FLEXIBILITY

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**Abstract—The brain is a dynamic, flexible network that continuously reconfigures. However, the neural underpinnings of how state-dependent variability of dynamic functional connectivity (vdFC) relates to cognitive flexibility, are unclear. We therefore investigated flexible functional connectivity during resting-state and task-state functional magnetic resonance imaging (rs-fMRI and t-fMRI, resp.) and performed separate, out-of-scanner neuropsychological testing. We hypothesize that state-dependent vdFC between the frontoparietal network (FPN) and the default mode network (DMN) relates to cognitive flexibility. Seventeen healthy subjects performed the Stroop color word test and underwent t-fMRI (Stroop computerized version) and rs-fMRI. Time series were extracted from a cortical atlas, and a sliding window approach was used to obtain a number of correlation matrices per subject. vdFC was defined as the standard deviation of connectivity strengths over these windows. Higher task-state FPN–DMN vdFC was associated with greater out-of-scanner cognitive flexibility, while the opposite relationship was present for resting-state FPN–DMN vdFC. Moreover, greater contrast between task-state and resting-state vdFC related to better cognitive performance. In conclusion, our results suggest that not only the dynamics of connectivity between these networks is seminal for optimal functioning, but also that the contrast between dynamics across states reflects cognitive performance. © 2016 Published by Elsevier Ltd on behalf of IBRO.**

**Key words: brain dynamics, cognition, resting-state fMRI.**

## INTRODUCTION

The exploration of spatial patterns of functional connectivity in the brain as a correlate of cognitive functioning has become a staple in modern neuroscience. Most studies assume that this connectivity is stationary, using averaged values of connectivity during either resting-state or task-state functional magnetic resonance imaging (rs-fMRI and t-fMRI, resp.). The interaction between the default mode network (DMN) and frontoparietal network (FPN) has been shown to control executive functions such as cognitive flexibility, attention, and working memory (Kehagia et al., 2010; Chadick and Gazzaley, 2011; Cole et al., 2012; Fornito et al., 2012; Bray et al., 2014; Beaty et al., 2015; Dajani and Uddin, 2015; Hearne et al., 2015; Takeuchi et al., 2015; Vatansever et al., 2015a). The DMN is most active at rest and is down-regulated during many tasks, and consists of the posterior cingulate cortex (PCC), medial frontal areas, lateral inferior parietal cortex, and medial and lateral temporal areas (Gusnard and Raichle, 2001). It has mostly been related to internal processes, self-generated thought, and mind wandering (Raichle et al., 2001; Buckner and Vincent, 2007; Anticevic et al., 2012). In contrast, the FPN spans the lateral frontal and parietal cortices adjacent to the classical default mode areas and is particularly active during cognitive tasks (Rosazza and Minati, 2011). It is sometimes termed the executive control network, and is thought to relate most to top-down cognition and attentional control, including task switching and cognitive flexibility (Sauseng et al., 2005; He et al., 2007; Rosazza and Minati, 2011; Spreng et al., 2013).

DMN activity is negatively correlated with FPN activity during task performance (Anticevic et al., 2012; Cole et al., 2012). Therefore, the DMN and FPN have previously been thought to operate in opposite functional directions, with greater anticorrelation being associated with better cognitive performance (see for instance this review (Anticevic et al., 2012)). Other studies, however, show the opposite, with increased internetwork correlation underlying cognitive performance (Spreng et al., 2013; Hellyer et al., 2014; Hearne et al., 2015; Piccoli et al., 2015). These results indicate that the flexible interactions

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*Abbreviations:* DMN, default mode network; EPI, echo planar imaging; FDR, false discovery rate; FPN, frontoparietal network; PCC, posterior cingulate cortex; vdFC, variability of dynamic functional connectivity.

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between the DMN and FPN under different task conditions may underpin the brains' ability to cope with changing environmental demands.

The non-stationary properties of functional connectivity have only recently started to garner attention (Hutchison et al., 2013; Liu and Duyn, 2013). Functional connectivity operates dynamically on both spatial and temporal scales, which is thought to promote adaptation to changing neural demands and allow for network reconfiguration across behavioral states (Cole et al., 2013; Allen et al., 2014; Alavash et al., 2015; Davison et al., 2015). Task-state fMRI studies investigating learning, memory, and working memory have shown that more dynamic connectivity during task execution, particularly of the FPN and DMN, relates to better cognitive performance (Bassett et al., 2011; Fornito et al., 2012; Spreng and Schacter, 2012; Cole et al., 2013; Monti et al., 2014; Beaty et al., 2015; Braun et al., 2015; Vatansever et al., 2015b). This body of literature suggests that task-state dynamic connectivity reflects an active cognitive control process.

Less is known about resting-state (FPN–DMN) dynamic connectivity, particularly with respect to cognitive functioning, although it does seem to outperform stationary connectivity in the prediction of cognitive functioning (Jia et al., 2014; Kucyi and Davis, 2014). However, both positive and negative correlations between resting-state dynamic connectivity and cognitive performance have been reported (Jia et al., 2014; Kucyi and Davis, 2014; Lin et al., 2015; Sadaghiani et al., 2015), leaving the precise role of resting-state dynamics in cognitive flexibility to be elucidated.

In summary, cognitive flexibility seems to depend on the functional interactions between the DMN and FPN, but it is unclear how dynamics and state come into play. We report that higher task-state dynamics of connectivity between the FPN and DMN are predictive of greater cognitive flexibility, while the opposite is true for the resting-state.

## EXPERIMENTAL PROCEDURES

### Subjects

A cohort of healthy controls was recruited at the Athinoula A. Martinos Center for Biomedical Imaging (Massachusetts General Hospital, Boston, USA). All subjects were highly educated, relatively young healthy volunteers. Exclusion criteria were (1) history of psychiatric or neurological disease, (2) age < 18 or > 65 years, (3) more than 2 mm absolute movement during either t-fMRI or rs-fMRI and/or more than one movement larger than 0.2 mm between two subsequent time points (frame-to-frame displacement) during either scanning session. In the main analyses, we retained all datasets satisfying these motion criteria, since our measure of variability in dynamic functional connectivity depends on the temporal ordering of connectivity patterns. However, in order to exclude the possible confounding effect of frame-to-frame motion on our measures of vdFC, we replicated all significant results after scrubbing time points showing more than 0.2-mm movement from the previous time point, as well as the time points preceding and following these high motion time points.

This study was approved by the MGH institutional review board, and was performed in accordance with the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written consent of the subjects.

### Out-of-scanner cognitive flexibility

Upon participation, subjects were first cognitively tested by a trained neuropsychologist [LD] before scanning using a clinically validated English version of the Stroop color word test (Stroop, 1935). This test consists of three timed conditions: (1) subjects read color words out loud as fast as possible, (2) subjects name color blocks as fast as possible, (3) subjects name ink colors of color names, which are incongruent with the written color name. For each of the conditions, the subject is asked to finish an entire page of stimuli as fast as possible, with the time from start to finish being recorded. If a mistake is made, the subject is allowed to correct himself/herself, which generally leads to healthy subjects not having any remaining incorrect responses (although corrections do lead to increased total time).

Total times to complete each condition were converted to a z-score based on the group mean and standard deviation and averaged to obtain a single measure of relative cognitive flexibility. Although each condition assesses a specific aspect of cognitive flexibility, we chose to combine all three into a composite score by averaging the three z-scores, in order to assess the most general aspects of cognitive flexibility.

### MRI acquisition

Subsequently, subjects underwent MR scanning in the 3T Siemens Connectom scanner (Erlangen, Germany) with a 64-channel head coil (Keil et al., 2013; Setsompop et al., 2013). Anatomical images were collected with magnetization-prepared rapid acquisition with gradient echo (MPRAGE; repetition time = 2530 ms, echo time = 1.15 ms, flip angle = 7°, field of view = 256, voxel size = 1mm$^3$ isotropic).

RS-fMRI was collected using an echo planar imaging (EPI) sequence (repetition time = 3000 ms, echo time = 30 ms, flip angle = 85°, field of view = 220, voxel size = $2 \times 2 \times 2.4$ mm$^3$, 160 volumes, 8-min acquisition). During rs-fMRI, subjects fixated their gaze and were instructed to stay awake without thinking about anything in particular.

T-fMRI was collected during a block design Stroop task, using largely the same imaging parameters as during the resting-state to facilitate comparison (repetition time = 3000 ms, echo time = 30 ms, flip angle = 85°, field of view = 220, voxel size = $2 \times 2 \times 2.4$ mm$^3$, 148 volumes, 7.4-min acquisition). Subjects were first familiarized with this version of the task, in which one color name was presented on the screen at a time. After discarding five dummy scans to achieve field equilibrium, and 8 s of

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