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

LINDA DOUW<sup>a,b\*</sup> DANIEL G. WAKEMAN<sup>a,c</sup>  
 NAOAKI TANAKA<sup>a,c</sup> HESHENG LIU<sup>a,c</sup> AND  
 STEVEN M. STUFFLEBEAM<sup>a,c</sup>

<sup>a</sup> Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 149 13th Street, Charlestown, MA 02129, USA

<sup>b</sup> Department of Anatomy and Neurosciences, VU University Medical Center, Van der Boeorchstraat 7, 1081 BT Amsterdam, The Netherlands

<sup>c</sup> Department of Radiology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA

**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 The Authors. Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**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 between the DMN and FPN under different task

\*Correspondence to: L. Douw, VU University Medical Center, Department of Anatomy & Neurosciences, O|2 Building, De Boelelaan 1108, 1081 HZ Amsterdam, The Netherlands.

E-mail address: [l.douw@vumc.nl](mailto:l.douw@vumc.nl) (L. Douw).

**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.

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<sup>3</sup> 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 × 2 × 2.4 mm<sup>3</sup>, 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 × 2 × 2.4 mm<sup>3</sup>, 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

fixation on a crosshair, 12 blocks consisting of six trials of congruent and six trials of incongruent stimuli were presented (presentation time 3 s, 144 trials total). Both the order of the blocks as well as the order of the trials were randomized.

In the congruent condition, a color word ('green', 'blue', 'red') was shown, written in the color of the written word. In the incongruent condition, the same color words were shown, this time in discordant colors (e.g. the word 'green' in red letters). Subjects were asked to press one of three buttons on a button box with the dominant hand (right in all subjects), corresponding to the color that the letters were written in, thus inhibiting reading the words.

### MRI analysis

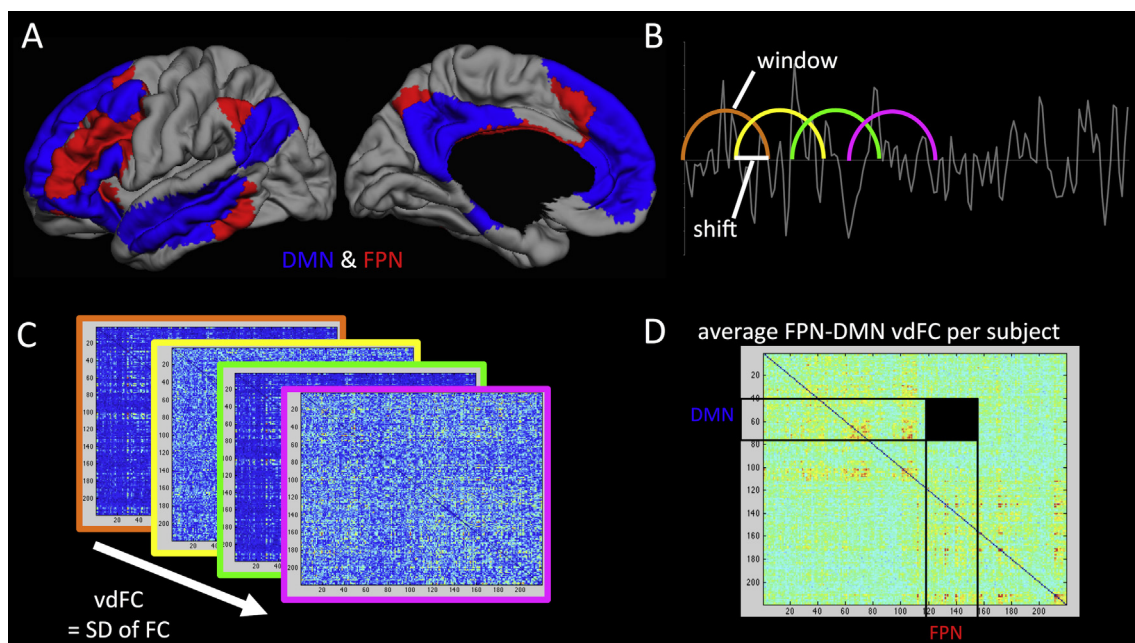
MPRAGE volumes were used to reconstruct cortical surfaces using FreeSurfer version 5.3.0 (Dale et al., 1999; Fischl et al., 2004). The t-fMRI data were analyzed using FreeSurfer's FsFast for resting-state MRI, in order to be able to look at variation of connectivity over the entire scan, and to be able to use identical analyses for t-fMRI and rs-fMRI. Preprocessing steps included (1) head motion correction, (2) slice timing correction, (3) registration to anatomical images, (4) intensity normalization, (5) low-pass filtering below 0.08 Hz, (6) regressing out six motion parameters and the average signals of the whole brain, ventricles, and white matter, (7) resampling of time series to a template cortical surface (fsaverage by FreeSurfer), and (8) spatial smoothing at 6-mm full-width half-maximum (FWHM). The Lausanne 2008 parcellation

scheme was used to first subdivide the brain into 219 parcels and extract time series from each (Gerhard et al., 2011; Daducci et al., 2012). Subsequently, seven subnetworks previously defined in the resting-state literature were used (Yeo et al., 2011). Yeo and colleagues used 1000 resting-state scans to achieve optimal and reproducible separation of the gray matter into subnetworks, yielding the DMN, FPN, visual network (VIS), somatomotor network (MOT), dorsal attention network (DA), ventral attention network (VA), and limbic network (LIM). This subnetwork decomposition in standard space was obtained, and each of the 219 parcels was assigned to a single subnetwork according to their maximum vertex overlap with each subnetwork.

### FPN–DMN variability of dynamic functional connectivity (vdFC)

The connectivity analysis is schematically depicted in Fig. 1 and was performed using Matlab (R2013b). First, stationary functional connectivity was determined by calculating Pearson's correlation coefficients between all parcels over the entire scan. These values were Fisher transformed to obtain normally distributed correlation values. In order to obtain network-specific stationary connectivity values, we normalized by average stationary connectivity over the entire brain.

A simple measure of vdFC requiring minimal choice of parameters is the standard deviation of functional connectivity between each parcel pair over a number of sliding windows (Cole et al., 2013). This means that from the  $n$  windowed connectivity matrices, one vdFC matrix



**Fig. 1.** Schematic representation of variability of dynamic functional connectivity calculation. *Note:* In (A), all cortical parcels from which time series are drawn are depicted. Shown in (B), is an exemplar time series, with the sliding window approach indicated. In (C), a connectivity matrix is calculated for each of these windows using Pearson's correlation coefficients. Variability of dynamic functional connectivity (vdFC) is then determined by calculating the standard deviation of connectivity over all windows, which yields one vdFC matrix per subject. In (D), vdFC between the default mode network (DMN) and frontoparietal network (FPN) is indicated, which is averaged and normalized to achieve a single measure of FPN–DMN vdFCv per subject.

per subject was created. In line with previous studies (Leonardi and Van De Ville, 2014; Leonardi et al., 2014), a window length of 60 s and a shift of 9 s were used for the main analyses, but we replicated results with different window lengths and shifts. After generation of this vdFC matrix per subject, values were averaged over all connections between the FPN and DMN. This average FPN–DMN vdFC was normalized to overall vdFC, by dividing it by the average vdFC of all other connections. Hereby, higher FPN–DMN vdFC reflects higher intra-individual dynamics between these networks than the rest of the brain, while controlling for overall level of within-subject vdFC.

### vdFC of other networks

In order to investigate the specificity of state-dependent FPN–DMN vdFC for cognitive flexibility, we also determined dynamic connectivity between all pairs of the seven previously described resting-state networks (Yeo et al., 2011). Additionally, we wanted to check whether dynamics within either of the two networks (FPN or DMN) determined the associations we might find, so we also calculated within-FPN and within-DMN dynamic connectivity by averaging vdFC of all connections within these networks and normalizing them for within-subject vdFC.

### Statistical analysis

Statistical analyses were performed using Matlab (R2013b, Natick (MA, USA)) and IBM SPSS Statistics for Macintosh (version 20.0, Chicago (IL, USA)). Correlations of confounders (motion, age, gender, educational level) with both cognitive flexibility and FPN–DMN vdFC were first explored using linear regression analyses using the confounders as predictors. Differences in FPN–DMN stationary and dynamic connectivity across states were tested using general linear models for repeated measures, with motion, age, and gender used as covariates.

Associations of out-of-scanner cognitive flexibility with both stationary and dynamic FPN–DMN connectivity were first tested using forward linear regression, with cognitive flexibility as the dependent variable. FPN–DMN vdFC, FPN–DMN stationary connectivity, as well as stationary and vdFC within both networks were used as possible predictors in a stepwise manner, in addition to motion, age, gender and educational level. Variables yielding significant results for vdFC indices were entered into the model with their covariates to check the confounding influences of the covariates on the associations between cognition and FPN–DMN vdFC. These analyses were performed for rs-fMRI and t-fMRI separately.

Statistical significance was set to  $p < 0.05$  for all tests. Where necessary, type II errors due to multiple comparisons were minimized using the false discovery rate (FDR (Benjamini and Hochberg, 1995)) with  $q < 0.05$ .

## RESULTS

### Subject characteristics

Seventeen subjects (mean age  $29 \pm$  SD 7.8 years; eight males; median education 16 years; all right-handed) were included. The confounders, including average in-scanner motion, age, gender, and educational level, showed no significant associations with our primary outcome measures of cognitive flexibility or resting-state and task-state FPN–DMN dynamic connectivity (see Table 1). However, stationary connectivity between the FPN and DMN during resting-state was significantly confounded by age, gender, and motion. In order to further ascertain that our results would not be due to these confounders, they were used as covariates in all subsequent (forward) regression analyses.

### FPN–DMN connectivity and vdFC across states

Heat maps of vdFC across both states can be seen in Fig. 2. There was no significant difference in normalized FPN–DMN vdFC between the resting-state ( $M = 1.01$ ,  $SD = 0.02$ ) and task-state ( $M = 1.01$ ,  $SD = 0.03$ ) at the group level, according to a repeated measures general linear model ( $F(1,12) = 0.003$ ,  $p = 0.955$ , corrected for task-state and resting-state motion, age, gender, and educational level) or paired t-test ( $t(16) = 0.238$ ,  $p = 0.815$ ). There was also no statistically significant correlation between vdFC in the two states (Pearson's correlation coefficient =  $-0.374$ ,  $p = 0.139$ ). When looking at stationary connectivity between these networks, there was a significant main effect of state ( $F(1,12) = 7.945$ ,  $p = 0.015$ ). This means that the FPN and DMN were more strongly anticorrelated during the task (normalized negative stationary connectivity  $M = 1.11$ ,  $SD = 0.31$ ) than during the resting-state ( $M = 0.94$ ,  $SD = 0.24$ ).

There was no significant association between FPN–DMN vdFC and stationary connectivity in either state (resting-state:  $\beta = -0.155$ ,  $t = -0.711$ ,  $p = 0.492$ ; task-state:  $\beta = -0.033$ ,  $t = -0.145$ ,  $p = 0.887$ , corrected for motion, age, gender, and educational level).

### Cognitive flexibility and task-state FPN–DMN vdFC

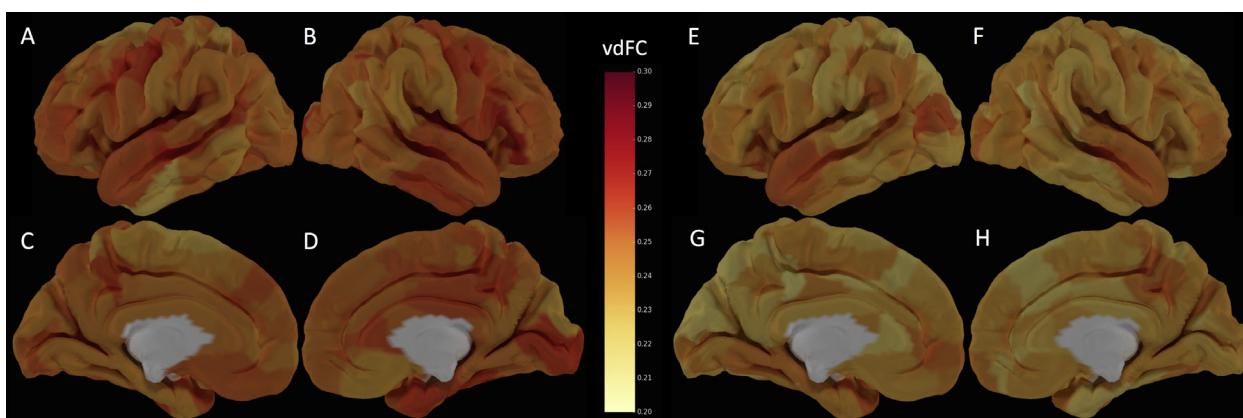
FPN–DMN vdFC during task performance was the single significant predictor of out-of-scanner cognitive flexibility (adj.  $R^2 = 0.342$ ;  $\beta = 0.619$ ,  $p = 0.008$ , significant after correction for multiple comparisons): higher FPN–DMN vdFC was related to better cognitive flexibility (see Fig. 3A). Stationary FPN–DMN connectivity during task performance was not significantly related to cognitive flexibility after correction for multiple testing ( $\beta = 0.052$ ,  $p = 0.809$ ), and neither were within-network FPN or DMN connectivity or the covariates (see Table 2 for all statistical results).

In order to investigate the specificity of this finding for vdFC between the FPN and DMN, we also show that vdFC between the other pairs of resting-state networks was not significantly related to cognitive flexibility using post hoc forward regression analyses, also taking age,

**Table 1.** Influence of confounding variables on primary outcome measures

Outcome measure	Confounder	Beta	t-value	p-value
Cognitive flexibility	Motion during t-fMRI	−0.349	−1.070	0.308
	Motion during rs-fMRI	0.025	0.069	0.946
	Age	−0.027	−0.074	0.942
	Gender	0.133	0.333	0.745
rs-fMRI vdFC	Education	−0.201	−0.679	0.511
	Motion	−0.094	−0.296	0.772
	Age	−0.187	−0.544	0.597
	Gender	−0.420	−1.177	0.262
t-fMRI vdFC	Education	0.064	0.230	0.822
	Motion	−0.057	−0.196	0.848
	Age	−0.097	−0.302	0.768
	Gender	0.139	0.431	0.674
rs-fMRI connectivity	Education	0.183	0.641	0.534
	Motion	0.607	2.578	0.024*
	Age	0.722	2.848	0.015*
	Gender	0.858	3.252	0.007**
t-fMRI connectivity	Education	−0.084	−0.410	0.689
	Motion	0.125	0.574	0.576
	Age	0.234	0.968	0.352
	Gender	0.608	2.497	0.028*
	Education	0.400	1.855	0.088

Note: \* $p < 0.05$ , \*\* $p < 0.01$ . rs-fMRI = resting-state fMRI, vdFC = variability of dynamic functional connectivity, t-fMRI task-state fMRI. Age and education in years. All vdFC and connectivity outcome measures are between the frontoparietal network and default mode network, normalized for vdFC/connectivity of the rest of the brain.



**Fig. 2.** Variability of dynamic functional connectivity across states. Note: The left panels show the average raw vdFC value per region during the resting-state from both lateral and medial views (panels A–D). On the right, task-state vdFC is shown in the same views (panels E–H). For comparison, all values are depicted in raw vdFC, which means that the resting-state shows slightly higher values than the task state, due to the slightly higher number of windows available for calculation. There were no significant differences nor correlations between vdFC in these states.

sex, motion, and educational level into account as possible covariates (see Table 3).

In order to assess the robustness of this result, we then tested the association between task-state FPN–DMN vdFC using the leave-one-out methodology, in which the regression analysis was repeated 17 times, each time leaving one of the subjects out. Indeed, the above-described results were replicated in every analysis (all  $p < 0.05$ ).

#### Associations with cognitive flexibility during resting-state

Similarly, FPN–DMN vdFC at rest was the sole significant predictor of cognitive flexibility (adj.  $R^2 = 0.366$ ,  $\beta = -0.637$ ,  $p = 0.006$ , significant after correction

for multiple testing), although the association was in the opposite direction: higher FPN–DMN dynamics correlated with poorer cognitive flexibility (see Fig. 3B). Stationary FPN–DMN connectivity was not significantly related to cognitive flexibility during resting-state ( $\beta = -0.171$ ,  $p = 0.433$ ), and neither were within-network connectivity, other network interactions, or the confounders (see Table 2).

When looking at Fig. 2B, we notice an outlier. Although there was no methodological or technical explanation found for this value, we also tested whether this result was robust using a leave-one-out methodology. Indeed, the above-described regression results were replicated (all  $p < 0.05$ ) in all 17 analyses, each time leaving one of the subjects out.

### Cognitive flexibility and FPN–DMN vdFC ratio across states

Since we found opposite correlations of cognitive flexibility with task-state versus resting-state vdFC, we next explored whether the ratio between task-state and resting-state FPN–DMN dynamics was more predictive of cognitive flexibility than vdFC during either state alone. Indeed, this proved to be the case (see Fig. 3C; beta = 0.748,  $p = 0.001$ ), indicating that higher FPN–DMN vdFC during task performance relative to resting-state is related to better cognitive flexibility. Moreover, a regression model containing only this ratio as the predictor explained more cognitive variance (adj.  $R^2 = 0.530$ ) than all previously mentioned models, or a model containing all three predictors (adj.  $R^2 = 0.486$ ). We again used a leave-one-out methodology on this association, which confirmed the regression results (all  $p < 0.05$ ).

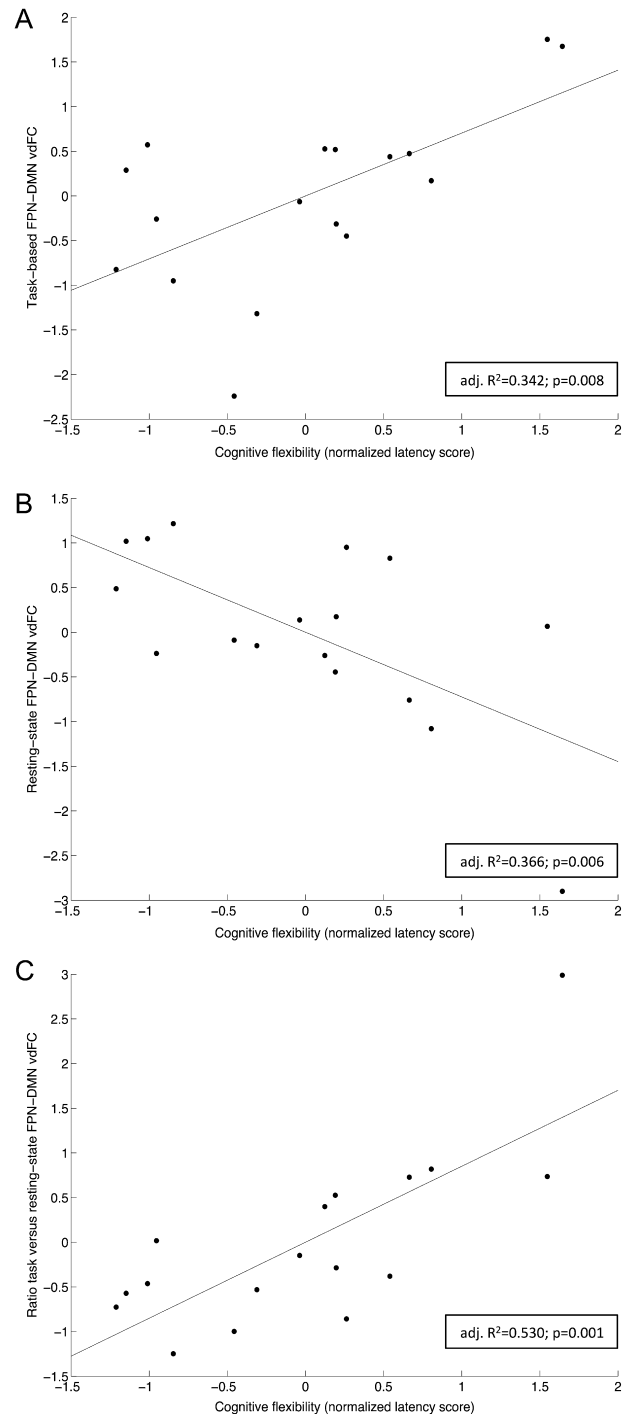
In order to further explore whether the association with state contrast vdFC held up for subjects' performance on all individual Stroop conditions, post hoc regression analyses per condition showed similar findings for the reading condition (adj.  $R^2 = 0.426$ , beta = 0.680,  $p = 0.003$ ), the color naming condition (adj.  $R^2 = 0.542$ , beta = 0.755,  $p < 0.001$ ), and the interference condition (adj.  $R^2 = 0.242$ , beta = 0.538,  $p = 0.026$ ). These results indicate that the state-dependent contrast between FPN–DMN vdFC captures general aspects of Stroop performance related to cognitive flexibility.

### Flexibility parameters

To control for the possibility that results were due to the chosen window and shift parameters, we replicated all significant findings with varied window lengths (45 s, 60 s, 75 s, 90 s, 105 s). Furthermore, the intraclass correlation coefficient (ICC; (McGraw and Wong, 1996)) of FPN–DMN vdFC across these window lengths was very high (ICC = 0.983, 95% confidence interval 0.982–0.983,  $p < 0.001$ ). Furthermore, using different shifts between the windows (5 s, 10 s, 15 s, 20 s, 25 s, 30 s) also yielded significantly similar results (ICC = 0.993, 95% CI 0.9928–0.9934,  $p < 0.001$ ). In order to optimize sensitivity to short temporal dynamics, all analyses in all cohorts were performed with ~60-s windows and ~10-s shift or ~50-s overlap between each window, similar to previous work and computational modeling of optimal windowing parameters (Leonardi and Van De Ville, 2014; Leonardi et al., 2014).

### Influence of frame-to-frame displacement

We also processed data in a more stringent way, by scrubbing time points showing high frame-to-frame displacements. We found these large displacements in seven of the 17 subjects, with four subjects showing a single large displacement, three subjects having two large movements, and one subject having three large movements. All these (and preceding and following) time points were removed from these subjects' time series, after which flexibility was recalculated. Results



**Fig. 3.** The association between state-dependent FPN–DMN variability of dynamic functional connectivity and cognitive flexibility. Note: (A) Depicts the association between cognitive flexibility and task-state variability of dynamic functional connectivity (vdFC) between the frontoparietal network (FPN) and default mode network (DMN). In (B), the association between resting-state FPN–DMN vdFC and cognitive flexibility is shown. Finally, (C) shows the relationship between the ratio of task versus resting-state FPN–DMN vdFC and cognitive flexibility. All values are depicted in z-scores.

show the same statistically significant associations of cognitive flexibility with resting-state FPN–DMN flexibility (adj.  $R^2 = 0.333$ , beta =  $-0.612$ ,  $p = 0.009$ ), task-state

**Table 2.** Non-significant predictors of cognitive flexibility

Predictor	Beta In	t-value	p-value
<i>Task-state</i>			
Within FPN vdFC	0.123	0.548	0.592
Within DMN vdFC	0.365	1.633	0.125
FPN–DMN stationary connectivity	0.052	0.246	0.809
Within FPN stationary connectivity	0.209	1.025	0.323
Within DMN stationary connectivity	0.057	0.270	0.791
Motion	−0.241	−1.206	0.248
Age	0.005	0.025	0.980
Gender	−0.028	−0.134	0.896
Education	−0.258	−1.278	0.222
<i>Resting-state</i>			
Within FPN vdFC	0.034	0.121	0.906
Within DMN vdFC	0.495	2.167	0.048
FPN–DMN stationary connectivity	−0.171	−0.806	0.433
Within FPN stationary connectivity	0.145	0.562	0.583
Within DMN stationary connectivity	0.126	0.550	0.591
Motion	−0.076	−0.371	0.716
Age	−0.052	−0.251	0.805
Gender	−0.128	−0.599	0.559
Education	−0.109	−0.534	0.602

Note: FPN = frontoparietal network, DMN = default mode network, vdFC = variability of dynamic functional connectivity. Dependent variable was cognitive flexibility in both regression analyses. *p*-Values are uncorrected for multiple comparisons and are all non-significant after FDR; therefore none of these covariates were entered into the analysis.

FPN–DMN flexibility (adj.  $R^2 = 0.342$ , beta = 0.619,  $p = 0.008$ ), and the ratio between the two (adj.  $R^2 = 0.523$ , beta = 0.743,  $p = 0.001$ ). These results indicate that our findings are not influenced by frame-to-frame displacements over 0.2 mm.

## DISCUSSION

We found that state-dependent vdFC between the FPN and DMN is related to cognitive flexibility, and more so

than stationary connectivity between these networks. During the performance of a task for cognitive flexibility, more dynamic connectivity between the FPN and DMN is associated with better cognitive performance, while the opposite is true for resting-state FPN–DMN vdFC. Furthermore, the state-dependent contrast in FPN–DMN vdFC is more strongly related to cognitive flexibility than either state by itself.

We confirmed that higher task-state dynamics of connectivity between the FPN and DMN is predictive of increased cognitive flexibility, corroborating and extending previous results regarding the association between these dynamics and in-scanner cognitive performance on working memory, attentional, and cognitive flexibility tasks (Fornito et al., 2012; Spreng and Schacter, 2012; Cole et al., 2013; Monti et al., 2014; Beaty et al., 2015). Underlying this relationship could be a mechanism in which the task necessitates a higher level of FPN–DMN dynamics in order to focus selective attention on and allocate resources to the cognitive demands at hand, and inhibit irrelevant stimuli and responses. Our results further indicate that this relationship not only applies to the level of dynamics measured during cognitive performance, but also generalizes to cognitive flexibility measured outside the scanner.

On the other hand, increased FPN–DMN vdFC during the resting-state was associated with poorer cognitive flexibility. This finding seems to generally contradict some imaging studies, which show positive correlations between resting-state dynamics and a range of different cognitive tasks (Hellyer et al., 2014; Jia et al., 2014), as well as increased daydreaming frequency (Kucyi and Davis, 2014). However, these studies did not specifically investigate the FPN and DMN, the interactions between them, or the domain of cognitive flexibility. More in line with our results, Lin and colleagues do report that increased variance of connectivity of the PCC to other DMN regions during the resting-state is associated with slower reaction times on a subsequent attention task

**Table 3.** Associations between cognitive flexibility and other network dynamics.

Network	DA	VA	VIS	MOT	LIM
<i>Task-state</i>					
FPN	0.932	0.358	0.366	0.378	0.265
DMN	0.407	0.894	0.760	0.358	0.338
DA	NA	0.299	0.189	0.994	0.792
VA	NA	NA	0.174	0.587	0.276
VIS	NA	NA	NA	0.517	0.873
MOT	NA	NA	NA	NA	0.066
<i>Resting-state</i>					
FPN	0.553	0.252	0.074	0.710	0.805
DMN	0.877	0.974	0.620	0.154	0.721
DA	NA	0.912	0.074	0.634	0.394
VA	NA	NA	0.142	0.128	0.819
VIS	NA	NA	NA	0.692	0.491
MOT	NA	NA	NA	NA	0.202

Note: FPN = frontoparietal network, DA = dorsal attention, VA = ventral attention, VIS = visual, MOT = motor, LIM = limbic. Values indicate predictor *p*-values of variability of dynamic functional connectivity between each network pair (taking motion, age, gender, educational level into account as potential covariates; uncorrected for multiple comparisons), using cognitive flexibility as the dependent variable.

(Lin et al., 2015). Similarly, Sadaghiani and colleagues also report increased DMN dynamics to precede misses more often than hits in a perceptual attention task (Sadaghiani et al., 2015). Taking these and our current results together, the view that resting-state dynamic connectivity always serves to facilitate mind wandering and ameliorates adaptive reconfiguration of network states once cognitive performance is demanded may not hold for FPN–DMN interactions and/or the domain of cognitive flexibility.

Most variance in cognitive flexibility was explained by the ratio between FPN–DMN dynamics during task versus rest: the more flexible functional connectivity was during Stroop task performance compared to the resting-state, the better a subject performed outside the scanner. In other words, a large state-dependent FPN–DMN vFC contrast is beneficial when it comes to cognitive flexibility. Previous studies focusing on static connectivity alone have already pointed out that the interactions between the FPN and DMN are highly complex and may even change during a single task (Hellyer et al., 2014; Hearne et al., 2015; Piccoli et al., 2015), rendering FPN–DMN vFC (as opposed to dynamics of one network by itself, for instance) of great importance for the direction of correlation. The FPN is generally considered a ‘task-positive’ network, while the DMN is down-regulated more strongly as cognitive load increases (Rosazza and Minati, 2011; Anticevic et al., 2012; Hugdahl et al., 2015; Spielberg et al., 2015). This state-dependent functionality has been hypothesized to be due to the balance between activation and inhibition. A strongly active DMN at rest relates to greater task-related down-regulation, and vice versa for the FPN (Anticevic et al., 2012; Leech and Sharp, 2014), although the correlation of this state-dependent functionality with cognitive functioning has been ambiguous (Spreng et al., 2013; Hellyer et al., 2014; Hearne et al., 2015; Piccoli et al., 2015).

We show, for the first time, that even though resting-state and task-state FPN–DMN vFC may not be statistically correlated nor different, their values and particularly the contrast between the two states, explain a large proportion (~53%) of variance in cognitive flexibility. It may be speculated that the contrast of FPN–DMN vFC during the resting-state versus the task quantifies a measure of cognitive control of the subject. Moreover, this novel measure of cognitive flexibility correlated with performance in an independent session. The relationship seems quite specific to the interaction between the FPN and DMN, since vFC within and/or between any of the other subnetworks was unrelated to cognitive performance. Furthermore, the absence of an (anti)correlation between resting-state and task-state FPN–DMN vFC suggests that this finding is specifically important for cognitive flexibility in the individual subject, instead of the two states merely mirroring each other within-subject. The state-dependent contrast in vFC between the FPN and DMN has not been investigated in relation with cognitive functioning before, although both resting-state and task-state investigations of vFC itself do indicate that these

networks are highly dynamic across states (Cole et al., 2013; Allen et al., 2014; Betzel et al., 2016).

Some limitations must be taken into account when interpreting these results. We used a relatively small sample size, although the cohort was quite homogeneous. Furthermore, the resting-state is difficult to investigate in the setting of dynamical connectivity, among others because of low signal-to-noise ratio (SNR) and non-neural contributions to temporal fluctuations in connectivity (Hutchison et al., 2013). However, the simple measure of vFC (i.e. the standard deviation of connectivity across sliding windows of rs-fMRI) used here was consistent and robust across many different parameters. It also did not correlate with motion or any of the other possible confounders and neither did its association between cognitive flexibility. Another possible limitation of our methods is the use of literature-based definition of the DMN and FPN, instead of determining their spatial layout individually. However, using individual definitions also brings about some problems, while the currently used definition has been extensively studied with respect to reproducibility (Yeo et al., 2011). Furthermore, it would be interesting to further investigate task-state dynamics according to the type of trial (i.e. congruent versus incongruent) and the different subdomains of cognitive functioning related to these, although the limited number of time points collected precludes such an analysis in this cohort. Future studies could for instance investigate the dynamics of connectivity between cortical and striatal regions, as these connections have been shown particularly relevant in the incongruent condition (Vatanssever et al., 2016).

## CONCLUSION

We show state-dependent vFC between the FPN and DMN to be related to cognitive flexibility. This study sheds new light on the cognitive relevance of dynamic reconfiguration between these networks across states. It also points out the importance of taking the entire state landscape of dynamic connectivity into account when trying to explain cognitive flexibility.

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