Dopaminergic modulation of hemodynamic signal variability and the functional connectome during cognitive performance

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Abstract

Dopamine underlies important aspects of cognition, and has been suggested to boost cognitive performance. However, how dopamine modulates the large-scale cortical dynamics during cognitive performance has remained elusive. Using functional MRI during a working memory task in healthy young human listeners, we investigated the effect of levodopa (L-dopa) on two aspects of cortical dynamics, blood oxygen-level-dependent (BOLD) signal variability and the functional connectome of large-scale cortical networks. We here show that enhanced dopaminergic signaling modulates the two potentially interrelated aspects of large-scale cortical dynamics during cognitive performance, and the degree of these modulations is able to explain inter-individual differences in L-dopa-induced behavioral benefits. Relative to placebo, L-dopa increased BOLD signal variability in task-relevant temporal, inferior frontal, parietal and cingulate regions. On the connectome level, however, L-dopa diminished functional integration across temporal and cingulo-opercular regions. This hypo-integration was expressed as a reduction in network efficiency and modularity, and co-occurred with a relative hyper-connectivity in paracentral lobule and precuneus. Both, L-dopa-induced BOLD signal variability modulation and functional connectome modulations proved predictive of an individual's L-dopa-induced gain in behavioral performance, namely response speed and perceptual sensitivity. Lastly, L-dopa-induced modulations of BOLD signal variability were correlated with L-dopa-induced modulation of nodal connectivity and network efficiency. Our findings underline the role of dopamine in maintaining the dynamic range of, and communication between, cortical systems, and how these relate to inter-individually differing benefits from dopamine during cognitive performance.

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Introduction

Dopaminergic neurotransmission supports cognitive functions, such as flexible updating and stable maintenance of working memory (Goldman-Rakic, 1995; Wang et al., 2004; Vijayraghavan et al., 2007; Cools and D'Esposito, 2011; Kobayashi et al., 2017). Dopamine (DA) plays an important role in modulating synaptic strengths of cortico-striatal pathways that subserve a wide range of cognitive functions (Reynolds and Wickens, 2002). Interestingly, a mere increase of DA level is not beneficial in every individual, and can even be detrimental to task performance depending on individuals' baseline DA and cognitive performance (Cools and Robbins, 2004; for a review, see Cools and D'Esposito, 2011).

How changing the amounts of DA impacts the cortical dynamics at large scale, and importantly, its relation to individuals' cognitive performance, has remained unclear. Here, using a double-blind L-dopa vs. placebo intervention during functional MRI, we investigate how DA increase modulates large-scale cortical dynamics during cognitive performance, and whether this modulation can explain intermittent, inter-individually differing behavioral benefits from enhanced levels of DA in healthy young adults.

DA neurotransmission helps maintain the dynamic range of neural circuits by regulating low-frequency tonic firing and phasic activity of DA neurons (Grace, 1995; Venton et al., 2003; Grace, 2016; Kobayashi et al., 2017). This in turn can have important consequences for cortical dynamics at larger scale, and ultimately cognitive performance. Specifically, DA helps maintain moment-to-moment cortical dynamics as measured by signal variability (Garrett et al., 2015; Guitart-Masip et al., 2016), which has been proposed to underlie optimal cognitive performance (McIntosh et al., 2008; Garrett et al., 2015; Guitart-Masip et al., 2016; Armbruster-Genç et al., 2016; see Grady and Garrett, 2014 for a review). Thus, it is plausible to relate the impact of DA on cognitive performance with the modulation of cortical signal variability as a result of changes in neuronal firing patterns (Paladini et al., 2003). Indeed, age-related loss of DA neurons has been shown to reduce variability of hemodynamic cortical responses, which has been predictive of lower cognitive performance in older compared to younger adults (Garrett et al., 2015; Guitart-Masip et al., 2016).

Furthermore, the midbrain dopaminergic system innervates widespread areas of cortex ranging from sensory to motor and prefrontal regions (e.g., see Jaber et al., 1996; Seger and Miller, 2010; Frank, 2011, for reviews). Thus, changing DA availability may also modulate brain dynamics on the network level (Kahnt and Tobler, 2017) by altering functional associations among distributed cortical regions, which shape the "functional connectome" in the human brain (Giessing and Thiel, 2012; Carbonell et al., 2014; Finn et al., 2015; Bell and Shine, 2016; Cassidy et al., 2016; Mill et al., 2017). Functional connectivity by definition depends on the statistical associations between BOLD signals over time. Thus, as higher DA availability can increase moment-to-moment BOLD signal variability by enhancing neural phasic activity (Paladini et al., 2003), DA availability could also impact the functional connectivity between widespread cortical regions. Indeed, brain signal variability has been previously suggested as a proxy for information-processing capacity within the brain networks (Stam et al., 2002; McIntosh et al., 2008; Lippe et al., 2009; Mišić et al., 2011; Vakorin et al., 2011; McIntosh et al., 2014). Specifically, higher signal variability has been associated with higher nodal centrality (an indication of an important node which has many connections) and network efficiency (an indication of having a higher capacity for parallel information processing; Mišić et al., 2011). Besides, the difference in signal variability between two cortical nodes has been shown to correlate with the amount of information transferred between them (Vakorin et al., 2011). Accordingly, networks showing higher signal variability have been proposed to have a greater potential for diverse functional configurations (McIntosh et al., 2014). Further, theories of brain metastability suggest that large-scale brain dynamics fluctuate between integrated and segregated network states, where signal variability would facilitate coordinated, flexible shifts between different network configurations (Deco et al., 2011; Tognoli and Kelso, 2014; Deco and Kringelbach, 2017).

Lastly, few studies have looked at the impact of DA on the functional connectome. DA (and noradrenaline) appear to increase local functional connectivity within fronto-parietal areas during working memory performance (Hernaus et al., 2017), while DA antagonists decrease resting-state network efficiency (Achard and Bullmore, 2007). Nevertheless, it remains unknown how DA

modulates large-scale brain network organization during cognitive performance, and how this modulation links to modulations in BOLD signal variability and behavior.

The current study will address three questions: First, we investigate how changing DA availability modulates large-scale cortical signal and network dynamics during cognitive performance. Second, we ask whether the extent of these modulations can explain the wide range of inter-individual differences in behavioral benefits from DA during cognitive performance (Cools and Robbins, 2004; for a review, see Cools and D'Esposito, 2011). Finally, we examine whether L-dopa-induced modulations in cortical signal variability correlate with L-dopa-induced modulation of the functional connectome. To answer these questions, we conducted an fMRI study in which young healthy listeners performed a previously established auditory working memory task (Lim et al., 2015) with and without a single dose (150 mg) of the DA precursor L-dopa. We used graph-theoretical network analysis to explore the impact of L-dopa on the functional connectivity and integration of large-scale cortical networks engaged during the auditory working memory task.

We predicted that L-dopa would increase brain hemodynamic signal variability in cortical regions important for auditory working memory performance. On the network level, our tentative hypothesis was that L-dopa would alter the integration of distributed cortical regions involved in the auditory working memory task, as previous studies suggest higher global integration of brain networks as the system-level mechanism for working memory performance (Cohen and D'Esposito 2016; Finc et al. 2017). Guided by previous work (Cools and Robbins, 2004; Cools and D'Esposito, 2011), we anticipated that the inter-individual differences in behavioral benefits from DA would relate to the degrees of DA modulations in BOLD signal variability and functional networks across participants. Lastly, based on the previous accounts on the role of higher brain signal variability in cortical information processing and flexible network dynamics, we expected a direct relation between DA modulations in BOLD signal variability and the functional connectome.

Materials and Methods

Participants

Twenty-two healthy young participants (mean age 27.9 years, age range 25–35 years; 12 females) took part in the study. Two additional participants completed the experiment, but were removed from data analysis due to excessive head movements inside the scanner (i.e., total movement > 3.5 mm of translation or degrees of rotation; scan-to-scan movement > 1.5 mm or degrees). Participants reported no histories of neurological or psychiatric disorders, and none were under any chronic medication. Participants were recruited from the Max Planck Institute for Human Cognitive and Brain Sciences database. Prior to participation all volunteers received a separate debriefing session regarding L-dopa by in-house physicians (B.S. and L.D.). All participants gave written informed consent, and were financially compensated (60€ total). All procedures were in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University of Leipzig (EudraCT number 2015-002761-33).

Procedure

All participants underwent two double-blind, counterbalanced fMRI sessions, separated by at least one week. Procedures in both sessions were identical. Each session was completed after administering orally either 150-mg L-dopa (Madopar LT; 150-mg Levodopa/37.5-mg benserazide) or placebo. On each scanning (i.e., medication) session, blood pressure and heart rate were measured four times throughout the experiment: before and after in-take of the pills, and before and after the fMRI scanning. Exclusion criteria were based on physiological changes after medication (i.e., greater than ±20 mm Hg in blood pressure and/or ±10 beats per minute in heart rate); none of the participants were excluded based on these criteria. Before and after pill ingestion, participants completed a questionnaire regarding subjective feelings and physical symptoms (Bond and Lader, 1974). None of the participants were excluded due to side effects of drugs. One participant felt nauseated after the completion of the whole experiment (i.e., including the second fMRI experiment); thus N = 22 data were included in the subsequent analyses.

Approximately 35 minutes after in-take of medication, the fMRI scan started. During this interim period (i.e., prior to scanning), participants completed a short practice session in a separate behavioral testing room to ensure that they understood the main experimental (auditory working memory) task. After the practice session, participants were placed in the scanner and went through a short hearing test of the auditory syllables used in the task with the on-going scanner noise in the background. Time from medication administration to scan onset in minutes was later used as a nuisance regressor in all models reported (see *Statistical analysis*).

We acquired eight functional blocks on each medication session (approximately 50 minutes). During each block, participants completed a total of 16 trials. Behavioral responses were collected via MR-compatible response keys. Participants used both index fingers, each assigned to one of two response keys, to give their response. The mapping between hands and response keys were counterbalanced across participants. All auditory stimulation was presented through MR-Confon headphones (Magdeburg, Germany), with Music safe pro earplugs (Alpine Hearing Protection) providing additional attenuation.

Auditory working memory task

During fMRI acquisition, participants performed a previously established auditory working memory task—a syllable pitch-discrimination task implemented with retroactive cues (see Lim et al., 2015 for full details on the task and materials). Syllable tokens were recorded by a native German female speaker. There were 12 different tokens (with varying pitch) for each syllable category, and one token for each category was randomly selected and presented during the encoding phase. The pitch of syllable tokens was manipulated using Praat (version 5.3). All sound tokens were digitized at 44.1 kHz, had a duration of 200-ms, and normalized to equivalent amplitude (root-mean-squared dB full scale; RMS dBFS).

In brief, on each trial participants encoded two distinct auditory syllables (i.e., /da/ and /ge/ presented in a random order), and detected a change in the pitch of one of the syllables after a delay period (jittered between 9–13 s). During the maintenance of the encoded syllables, one of the two

types of retro-cue was presented for 1 s on the screen; on equal probability for each task block, a valid cue (written syllable, "da" or "ge") or a neutral cue ("xx") was presented. The valid cue was used to direct participants' attention to one of the to-be-probed auditory syllable. The neutral cue, however, did not provide any information about upcoming auditory probe. After 5–7 s following the visual retro-cue, an auditory probe syllable was presented.

Within a 4-s time window upon hearing the probe, participants compared the pitch of the probe syllable to that of the same category syllable heard during encoding, and responded "high" or "low" accordingly. Syllable pitch change that occurred at probe was parametrically varied in four steps (±0.125 and ±0.75 semitones) relative to its original pitch heard during encoding. On each trial, participants received a visual feedback (written as "correct" or "incorrect" in German) for 500 ms.

Note that the current study is focused on investigating the overall effect of L-dopa on on-going BOLD signal dynamics during the auditory working memory performance. Thus, we here will not elaborate on the (potentially more complex) phasic effects and interactions involving the cue manipulation.

MRI data acquisition and preprocessing

Whole-brain functional MRI data were collected using a Siemens MAGNETOM Prisma 3T. Functional data were acquired with a 20-channel head/neck coil using an echo-planar image (EPI) sequence [repetition time (TR) = 2000 ms; echo time (TE) = 26 ms; flip angle (FA) = 90°; acquisition matrix = 64 × 64; field of view (FOV) = 192 mm × 192 mm; voxel size = 3 × 3 × 3 mm; inter-slice gap = 0.3 mm]. Each image volume had forty oblique ascending axial slices parallel to the anterior commissure–posterior commissure (AC–PC) line.

Structural images of fifteen participants were available from the database of the Max Planck Institute (Leipzig, Germany), where a magnetization prepared rapid gradient echo (MP-RAGE) sequence had been used to acquire the structural images [TR = 2300 ms; TE = 2.01–2.98 ms; FA = 9°; 1-mm isotropic voxel; 176 sagittal slices]. For participants without pre-existing structural images in the database, a high-resolution T1-weighted structural image was acquired using an MP-RAGE

sequence [TR = 2300 ms; TE = 2.98 ms; FA = 9°; 1-mm isotropic voxel; 176 sagittal slices] at the end of the second fMRI session.

Preprocessing. During each functional block 181 volumes were acquired. To allow signal equilibration the first two volumes of each block were removed, and the remaining 179 volumes per block were used for the subsequent analyses. Preprocessing steps were undertaken in SPM12 (Frackowiak et al., 2004). First, the functional images were spatially realigned to correct for head motion using a least square approach and the six rigid body affine transformations. Then, the functional volumes were corrected for slice timing to adjust differences in image acquisition times between slices. This is accomplished by a shift of the phase of the sinusoids that make up the signals. Subsequently, functional images were coregistered to each individual's structural image. This is achieved by first segmentation of the structural image using tissue probability maps, and then registering the image segments using the rigid body transformations and based on normalized mutual information as an objective function (unified segmentation; Ashburner and Friston, 2005). The resulting functional volumes were then spatially normalized to the standard stereotactic MNI space. No spatial smoothing was applied on the volumes to avoid potential artificial distant-dependent correlations between voxels' BOLD signals (Fornito et al., 2013; Stanley et al., 2013), which subsequently constitute the input data for functional connectivity analysis (Figure 1C).

Cortical parcellation. Brain nodes were defined using a parcellated AAL template (Tzourio-Mazoyer et al., 2002) encompassing 485 uniform and compact grey-matter cortical regions (Fornito et al., 2010; Zalesky et al., 2010; Figure 1C). This template was used to estimate the mean BOLD signals across voxels within each cortical region per participant. To minimize the effects of spurious temporal correlations induced by physiological and movement artifacts, a general linear model (GLM) was constructed to regress out white matter and cerebrospinal fluid (CSF) mean time series together with the six rigid-body movement parameters (Hallquist et al., 2013; Jo et al., 2013). Subsequently, the residual time series obtained from this procedure were concatenated across the eight blocks per medication session for each participant. The time series were further processed through two analysis streams (Figure 1C): one analysis focused on BOLD signal variability (univariate approach) and the

other on functional connectivity and network topology (multivariate approach; McIntosh and Misic, 2013; Misic and Sporns, 2016). Since one of the questions that the present study aims to answer is the direct relation between dopaminergic modulation of brain signal variability and networks, we used the same cortical nodes across the two analysis streams.

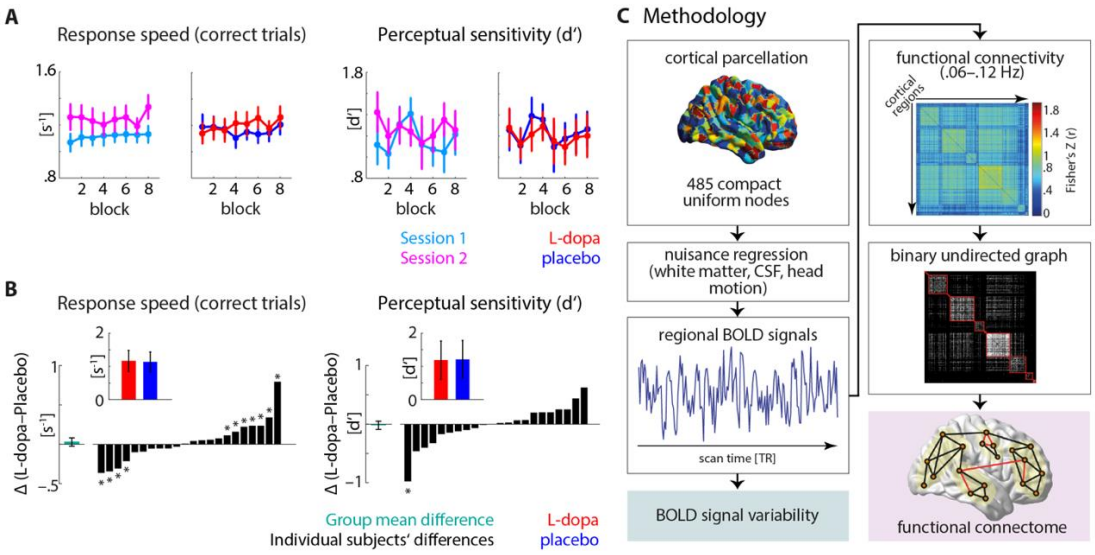

Figure 1. Overview of the behavioral performances and the methodology used in the study. **(A)** Behavioral performances measured by response speed (left) and perceptual sensitivity d' (right) across eight blocks of the auditory working memory task (adapted from Lim et al., 2015). Block-wise performances are shown based on the order of the scanning sessions and based on the medication sessions. Error bar: ±1 standard error of the mean (SEM). **(B)** Individuals' and group average behavioral performances in response speed (left) and perceptual sensitivity d' (right). The left most bar (cyan) in each plot represents the group mean difference (Δ: L-dopa–placebo). Error bar: ±1 SEM difference. Asterisk (*): individual subjects (black bars) exhibiting significant behavioral modulations under L-dopa. Inset bars: mean performances (±1 SEM) of the corresponding measures. **(C)** Two analysis streams were used to investigate two aspects of brain dynamics: signal variability and large-scale network topology. Both analyses used mean BOLD signals across voxels within each of 485 parcellated cortical regions. BOLD signal variability was computed as the variance of BOLD signal through each fMRI session. The topology of the functional connectome was analyzed using graph-theoretical metrics, which captured network interactions across cortex on local, intermediate and global scales of topology (Betzel and Bassett, 2016). These include local network efficiency (a metric related to the clustering of a network; red triangle), network modularity (a measure of decomposability of a network into communities; light ovals) and global network efficiency (a metric inversely related to the shortest path between nodes; red path).

BOLD signal variability

Prior to quantifying signal variability, we equated the mean BOLD signal throughout the experiment blocks for each medication session to remove block-wise drifts (e.g., Garrett et al., 2010, 2011, 2013). To this end, we demeaned the residual BOLD time series such that the signal for each cortical region of each block was at zero. For each region, BOLD signal variability was expressed as the variance of the resulting normalized signal concatenated for each medication session (i.e., across 8 blocks). The main focus of the current study is on the amount of behavioral and neural modulations from L-dopa relative to placebo. Thus, instead of computing a difference between two standard deviations of BOLD signal (cf. Garrett et al., 2010, 2011, 2013), the difference measure of the variances was used to

compute actual differences in signal variability while avoiding scaling changes due to the non-linear transformation from variance to standard deviation.

Signal variability for each cortical region represents region-level signal dynamics. Signal variability on the whole-brain level was computed as the mean variance across all cortical regions (i.e., 485 regions). Signal variability was separately quantified for the L-dopa and placebo sessions. L-dopa-induced modulation of signal variability was then quantified as the difference of BOLD signal variability between L-dopa versus placebo (i.e., L-dopa–placebo). As such, we treated the placebo session as baseline for both brain and behavior during the auditory working memory task.

Functional connectivity

First, mean residual time series were band-pass filtered by means of maximum overlap discrete wavelet transform (Daubechies wavelet of length 8; Percival and Walden 2000), and the results of the filtering within the range of 0.06–0.12 Hz (wavelet scale 2) were used for further analyses. It has been previously documented that the behavioral correlates of the functional connectome are best observed by analyzing low-frequency large-scale brain networks (Salvador et al., 2005; Achard et al., 2006; Achard et al., 2008; Giessing et al., 2013; Alavash et al., 2015a). The use of wavelet scale 2 was motivated by previous work showing that performance during cognitive tasks predominately correlated with changes in functional connectivity in the same frequency range (Bassett et al., 2010; Alavash et al., 2015b; Alavash et al., 2016). To obtain a measure of association between each pair of cortical regions, Pearson correlations between wavelet coefficients were computed, which resulted in one 485 × 485 correlation matrix for each participant and medication session (Figure 1C).

Connectome analysis

Brain graphs were constructed from the functional connectivity matrices by including the top 10% of the connections in the graph according to the rank of their correlation strengths (Ginestet et al., 2011; Fornito et al., 2013). This resulted in sparse binary undirected brain graphs at a fixed network density of 10%, and assured that the brain graphs were matched in terms of density across participants and

medication sessions (van Wijk et al., 2010; van den Heuvel et al., 2017). To investigate whether choosing a different (range of) graph density threshold(s) affects functional connectivity and network topology differences between placebo and L-dopa (Garrison et al., 2015), we examined the effect of graph thresholding using cost-integration approach (Ginestet et al., 2014; Figure S2).

Mean functional connectivity was calculated as the average of the upper-diagonal elements of the sparse connectivity matrix for each participant per medication session. In addition, three key topological metrics were estimated: mean local efficiency, network modularity, and global network efficiency. These graph-theoretical metrics were used to quantify functional integration of large-scale brain networks on the local, intermediate, and global scales of topology, respectively (Figure 1C; Alavash et al., 2017; Betzel and Bassett, 2016).

For each topological property, we computed a whole-brain metric, which collapses the measure of network integration into one single value, and a regional metric characterizing the same network property but for each cortical region (Rubinov and Sporns, 2010). The regional network metrics were therefore used to localize cortical regions contributing to the L-dopa-induced modulations observed on the whole-brain level. We used nodal connectivity (also known as 'nodal strength') as the regional measure of mean functional connectivity. Local efficiency was computed within each cortical region's neighborhood graph as the regional measure of mean local efficiency. Finally, nodal efficiency was measured to capture the integration of a given region to the entire network, hence representing the regional measure of global network efficiency (see Figure 1C for an illustration). Below we provide the formalization of the above-mentioned graph-theoretical network metrics.

Nodal connectivity and degree. Nodal connectivity was measured as the average weights of the connections linking a cortical node to the other nodes. Nodal degree (a simple measure of degree centrality) was quantified as the number of connections per node. Disintegrated nodes were identified as nodes with a degree of zero, accordingly.

Global network efficiency. In a graph-theoretical sense, global network efficiency is a measure of information processing capacity of a network. For a given graph G comprised of N nodes, global efficiency E_{global} summarizes the capacity of the network for parallel processing across

distributed nodes. This metric is estimated by the inverse of the harmonic mean of the shortest path lengths (i.e. the smallest number of intervening connections) between each pair of nodes $L_{i,j}$:

$$E_{global} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{i,j}} \qquad \text{(Eq.1)}$$

An efficient network is characterized by having a short average minimum path length between all pairs of nodes. Such a network is considered to have high efficiency in parallel (or global) information processing (Bullmore and Sporns, 2009). Likewise, nodal efficiency at node i, $E_{nodal(i)}$, (as the regional measure of global network efficiency) is inversely related to the path length of connections between a specific node and the rest of the nodes (Latora and Marchiori, 2001):

$$E_{nodal(i)} = \frac{1}{(N-1)} \sum_{j \in G} \frac{1}{L_{i,j}} \qquad \text{(Eq.2)}$$

Local network efficiency. By slightly zooming out from a given node within a graph, the nearest neighbors of the node that are directly connected to each other form a cluster. This local integration can be quantified based on the local efficiency of node i, $E_{local(i)}$, which is mathematically equivalent to global efficiency (Eq.1) but is computed on the immediate neighborhood of node i. On the whole-brain level, mean local efficiency can be quantified by averaging local efficiency across all nodes:

$$E_{local} = \frac{1}{N} \sum_{i \in G} E_{local(i)} \qquad \text{(Eq.3)}$$

Network modularity. Modularity describes the decomposability of a network into non-overlapping sub-networks, characterized by having relatively dense intra-connections and relatively sparse inter-connections. Rather than an exact computation, modularity of a given network is estimated using optimization algorithms (Lancichinetti and Fortunato, 2009; Steinhaeuser and Chawla, 2010). The extent to which a network partition exhibits a modular organization is measured by a quality function, the so-called *modularity index* (Q). We used a common modularity index originally proposed by Newman (2006), and employed its implementation in the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) which is based on the modularity maximization algorithm known as Louvain (Blondel et al., 2008). The modularity index is defined as:

$$Q = \frac{1}{2W}\sum_{i,j}\left[A_{i,j} - \gamma\frac{k_i k_j}{2W}\right]\delta(c_i, c_j) \qquad \text{(Eq.4)}$$

Q ranges between –1 and 1. In Eq. 4, $A_{i,j}$ represents the weight (zero or one if binary) of the links between node i and j, k_i=$\sum_j A_{i,j}$ is the sum of the weights of the links connected to node i, and c_i is the community or module to which node i belongs. The δ-function $\delta(u,v)$ is 1 if $u = v$ and 0 otherwise, and $W = \frac{1}{2}\sum_{i,j} A_{i,j}$. Similar to previous work (Bassett et al., 2010; Alavash et al., 2016), the structural resolution parameter γ (see Fortunato and Barthelemy, 2007; Lohse et al., 2014) was set to unity for simplicity. The maximization of the modularity index Q gives a partition of the network into modules such that the total connection weight within modules is as large as possible, relative to a commonly used null model whose total within-module connection weights follows $\frac{k_i k_j}{2W}$. Thus, a "good" partition with Q closer to unity gives network modules with many connections within and only few connections between them; in contrast, a "bad" partition with Q closer to zero gives network modules with no more intra-module connections than expected at random (Good et al, 2010). Thus, higher Q reflects higher functional segregation on the intermediate level of network topology (Rubinov and Sporns, 2010; Betzel and Bassett, 2016). Due to stochastic initialization of the greedy optimization, the module detection algorithm was applied 100 times for each brain graph, and the partition that delivered the highest Q value was kept (see Lancichinetti and Fortunato, 2012; Bassett et al., 2013, for other approaches to construct representative high-modularity partitions).

Statistical analysis

Control of medication-session order and other confounding factors. In the present study, all participants went through the same procedure twice on separate days. We did not expect to observe learning during the auditory working memory task, but we examined the potential learning effect within and between the two sessions in order to control for potential confounds in interpreting the L-dopa effect. First, we examined a potential learning over task blocks within each scan session, and whether the degree of learning differs between the two sessions (see Figure S6). Neither behavioral measures showed any significant learning effect across blocks (Table S1). Also, we did not find any

significant differences in the degree of potential learning between the first versus second session or between L-dopa versus placebo (Figure 1A; Figure S6; Table S1). Using a similar approach, we investigated changes in measures of brain dynamics within each session over task blocks. We only found significant linear increases in signal variability and functional connectivity over task blocks (see Figure S6 and Table S1 for details). However, important for the current study, there was no significant difference between placebo and L-dopa sessions.

Next, we examined if there is any difference in mean performances between two sessions. We observed significant effects of session order (first vs. second scan session), regardless of medication conditions, on both behavioral and brain measures. Participants' responses were significantly faster in the second session ($F_{1,21} = 8.66$; $p = 0.008$). Also, global network efficiency and network modularity (Q) were significantly higher in their second session (E_{global}: Cohen's d = 0.4, p = 0.008; Q: Cohen's d = 0.43, p = 0.02). This could be arguably due to differences in arousal and/or having an easier time in performing the auditory working memory task, as participants are likely to be more relaxed and adapted to drug administration, scan procedure, and task during the second session (Fan et al., 2012; Kitzbichler et al., 2011; Stevens et al., 2012).

Importantly, to control for potential confounding factors in the interpretation of L-dopa effects, all ensuing comparisons of L-dopa versus placebo were performed on residualized measures, that is, after regressing out covariates of no interest. These covariates included medication-session order (L-dopa first vs. placebo first), body mass index (BMI), and time from medication administration to scan onset.

In recent years, the potential confounding impact of head motion or non-neural physiological trends on the temporal correlations between BOLD signals has been raised by multiple studies (see Murphy et al., 2013; Power et al, 2015 for reviews). In the current study, we conducted additional analyses using measures of head motion to ensure that movement was not different between L-dopa and placebo sessions (see Figure S3). Furthermore, we ensured that the participants heart rate before, during, and after scanning were not significantly different between the first and second session or between L-dopa and placebo session (see Table S2).

Behavioral data. For each medication session, we calculated average response speed on correct trials (i.e., an inverse of response time) and a bias-free measure of perceptual sensitivity, d′ (MacMillan and Creelman, 2004). In order to assess the overall effect of L-dopa on behavioral performance across participants, we performed a separate repeated-measures analysis of variance (ANOVA) on response speed and perceptual sensitivity d′. To control for potential confounding factors in the interpretation of L-dopa effects, covariates of no interest (as listed above) were regressed out from the behavioral measures prior to conducting an ANOVA.

To visualize the robustness of L-dopa-induced change in individual participant's performance (Figure 1B), single-subject 95% confidence intervals (CIs) were constructed based on bootstrapped performance differences between L-dopa and placebo. For each participant, we created 1,000 replications of the data by resampling the participant's single-trial data of each session (i.e., resampling of 128 trials); based on these data we estimated the corresponding behavioral measure for each session. For a given behavioral measure, a significant change under L-dopa (versus placebo) per participant was inferred if the bootstrapped 95% CI did not cover zero.

Medication effects on brain measures. On the whole-brain level, statistical comparisons of signal variability and network metrics between L-dopa and placebo sessions were based on exact permutation tests for paired samples. We used Cohen's d for paired samples as the corresponding effect size (Gibbons et al., 1993; Hentschke and Stuttgen, 2011; Lakens, 2013).

On the regional level, and for the analysis of both BOLD signal variability and network metrics, a bootstrap procedure with 10,000 replications was employed to test the medication effect. The bootstrap procedure allowed us to use a CI-based correction method to account for multiple comparisons across cortical regions (see below). For every cortical region per participant, we first computed the difference between the regional metrics (i.e., L-dopa–placebo). Then, the bootstrap distribution of the mean difference across all participants was estimated and used for statistical inference. Finally, Cohen's d for paired samples was calculated as an effect size (Gibbons et al., 1993; Hentschke and Stuttgen, 2011; Lakens, 2013).

Correlational analyses. We further performed correlation analyses to examine whether the individual magnitude of L-dopa-induced modulations of BOLD signal variability and networks would relate to the individual magnitude of behavioral modulations. To this end, we computed the L-dopa-induced modulations by taking a difference (i.e., L-dopa–placebo) in both brain and behavioral measures. As such, we treated the placebo session as baseline for both brain and behavior during the auditory working memory task. Consistent with the analysis of behavioral data described above, we accounted for the potential confounding factors prior to the correlation analyses by regressing out the covariates of no interest (i.e., medication-session order, BMI, time from medication administration to scan onset).

Correlations between L-dopa-induced modulations in brain dynamics (i.e., BOLD signal variability or brain network metrics) and modulations in task performance were tested using rank-based Spearman correlation (rho). On the whole-brain level, the significance of the correlations was tested using a permutation test with 10,000 randomizations (Pesarin and Salmaso, 2010). On the regional level, a bootstrap procedure with 10,000 replications of the correlation coefficients was used for statistical inference. Using the same bootstrap procedures, we further examined the relationship between dopamine-related modulation of BOLD signal variability and modulations of the functional connectome.

Significance thresholds. For all statistical tests, we used α = 0.05 (two-sided) as uncorrected threshold of significance. For the regional analysis, and to correct for multiple comparisons entailed by the number of brain regions, we implemented the false coverage-statement rate (FCR) correction method (Benjamini and Yekutieli, 2005; applied e.g. in Obleser et al., 2010; Alavash et al., 2017). This method first selects the regions where the bootstrap distribution of the mean difference or correlation coefficients do not cover zero at the confidence level of 95%. In a second correction pass, FCR-corrected CIs for these selected regions are (re-)constructed at a level of $q_{FCR} = 1 - F_s \times \frac{q}{F_t}$, where F_s is the number of selected regions at the first pass, and F_t is the total number of brain regions. The

tolerated rate for false coverage statements is *q*, here 0.05, at which the enlarged FCR-corrected intervals thus control the false-positive rate at the desired level.

Results

Effect of L-dopa on behavioral performances

Figure 1B illustrates the effect of medication (i.e., L-dopa vs. placebo) on overall behavioral performances in the auditory working memory task. Neither behavioral performance measures showed a consistent medication effect overall across participants (repeated-measures ANOVA with nuisance variables controlled; main effect of medication on response speed: $F_{1,21} = 0.22$, $p = 0.65$, $\eta^2_p = 0.01$; main effect on perceptual sensitivity d': $F_{1,21} = 0.13$, $p = 0.73$, $\eta^2_p = 0.006$).

However, there was sizable inter-individual variation in the degree to which behavior benefitted (or suffered) from the L-dopa manipulation (see Cools and D'Esposito, 2011 for review). According to single-subject bootstrapped distributions of the L-dopa versus placebo difference, most participants did not exhibit significant detriments or benefits in perceptual sensitivity d' under L-dopa. Response speed showed a similar, if more clear-cut, inter-individual variation, with 7 out of 22 participants exhibiting a significant response speed-up under L-dopa, and 4 out of 22 participants showing significant slowdown (Figure1B). Hence, in the next sections, we further investigated whether such inter-individual differences of benefit from DA (see also Sharot et al., 2012) can be explained by L-dopa-induced modulations in brain dynamics.

Modulation of signal variability under L-dopa vs. placebo

We started by investigating whether L-dopa modulates BOLD signal variability. We tested BOLD signal variability changes (L-dopa vs. placebo) on the whole-brain (i.e., average signal variability across all regions) as well as regional level. On the whole-brain level, a slight increase in BOLD signal variability with L-dopa relative to placebo was observed, but this increase was not statistically significant ($M_{L\text{-}dopa-Placebo} = 1.33$; Cohen's d = 0.24; $p = 0.30$).

Next, we continued by analyzing signal variability on the regional level. L-dopa-induced modulations of signal variability were evident and statistically significant across a distributed set of sensory as well as heteromodal cortical regions. As illustrated in Figure 2A, we observed increased BOLD signal variability under L-dopa in bilateral superior temporal cortices extending from anterior to posterior portions, in bilateral inferior frontal gyri (IFG), and in right supramarginal gyrus (SMG). Also, L-dopa increased signal variability in visual cortical regions including bilateral fusiform gyri. In addition, an L-dopa-induced BOLD signal variability increase was observed in the cingulate cortex, bilateral motor cortices in the pre- and post-central regions, and the right temporo-parietal junction. Except for one region in the left middle frontal gyrus exhibiting a decrease in variability under L-dopa (Cohen's d = 0.31), our results demonstrate that a distributed set of cortical regions relevant for the task increases its signal variability under L-dopa. On the contrary, applying the same contrast (i.e., L-dopa versus placebo) to mean BOLD activation during task performance (see Figure S7 for details) did not yield any region showing a significant medication effect.

Subsequently, we investigated whether the extent of L-dopa-driven modulations in BOLD signal variability correlated with individuals' behavioral benefits from L-dopa. For each region, we evaluated the relationship based on 10,000 bootstrapped iterations of correlation (i.e., Spearman's rho) between modulations of BOLD signal variability and modulations of behavioral performance under L-dopa (i.e., L-dopa–placebo).

With respect to response speed, individuals' BOLD signal variability modulations under L-dopa correlated with their gain in response speed under L-dopa. Specifically, greater signal variability in right IFG, bilateral precentral regions, bilateral angular gyri/SMG, and left parietal regions, correlated with faster responses under L-dopa (Figure 2B, left). The opposite pattern (i.e., lower variability correlating with higher response speed gain under L-dopa) was only observed in the subgenual anterior cingulate cortex.

With respect to perceptual sensitivity, the degree of BOLD signal variability modulation also correlated positively with L-dopa-induced change in d'—especially so in the left insula, bilateral superior temporal pole, and left parahippocampus (Figure 2B, right). Conversely, signal variability

modulations in left postcentral/motor cortical regions exhibited significant negative correlations with d′ change.

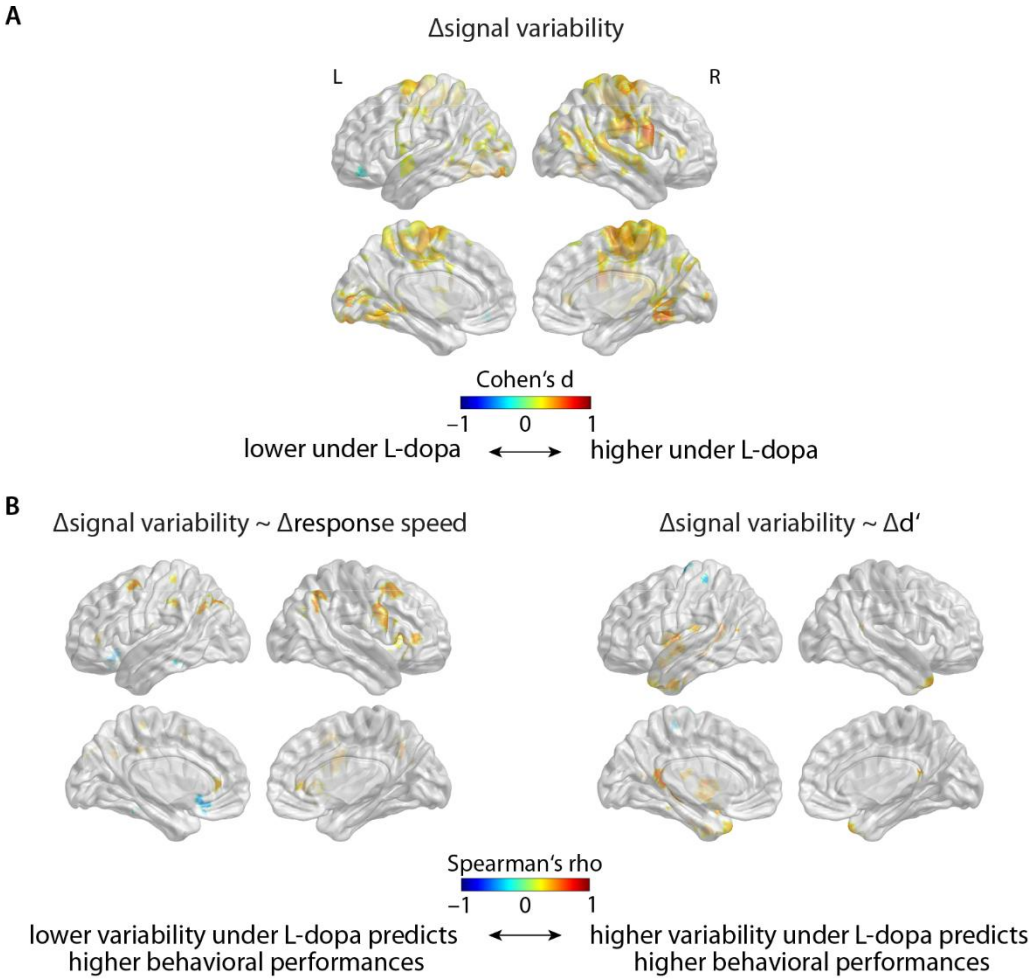

Figure 2. L-dopa-related modulation of BOLD signal variability and its relation to modulations of behavioral performance. **(A)** Cortical regions exhibiting significant change in signal variability under L-dopa versus placebo. The difference in signal variability (i.e., Δ: L-dopa–placebo) was expressed as Cohen's d effect size. **(B)** Cortical regions exhibiting significant correlations between L-dopa-induced modulations of signal variability and behavioral performance. Response speed (left) and perceptual sensitivity d′ (right). Statistical significance (corrected for multiple comparisons) was ensured based on non-zero coverage of FCR-corrected 95% CIs of the 10,000 replications of bootstrapped distribution of the respective measures in (A) and (B) for each region (see Materials and Methods). Visualizations on the cortical surface were rendered using BrainNetViewer (Xia et al., 2013). L: left; R: right.

Whole-brain modulation of the functional connectome under L-dopa vs. placebo

One of the aims of the present study is to answer how dopaminergic modulation impacts the brain network dynamics engaged in a cognitive task. We approached this question by measuring functional connectivity and integration of large-scale cortical networks. This was accomplished by graph-theoretical analysis of fMRI data obtained from the participants who performed the auditory working memory task separately under L-dopa and placebo. We compared the brain network metrics between L-dopa and placebo across participants. This comparison revealed significant modulations in the connectivity and topology of brain networks under L-dopa versus placebo (Figure 3).

First, functional connectivity showed a significant increase—that is, a relative 'hyper-connectivity'—under L-dopa as compared to placebo (Cohen's d = 0.4, p = 0.03; Figure 3A, top left). This relative hyper-connectivity was also observed when we compared the mean of raw functional connectivity strengths (i.e., without graph-thresholding; Cohen's d = 0.35, p = 0.04). In addition, we found a significant alteration in the functional connectivity distribution—in particular its median and variance—under L-dopa relative to placebo (Figure S4).

Second, functional integration of brain networks showed a significant decrease under L-dopa versus placebo. This relative 'hypo-integration' of brain networks was consistently observed on the local, intermediate and global scales of topology. More specifically, local efficiency of brain networks—a measure inversely related to the topological distance between network nodes within local cliques or clusters—was significantly lower under L-dopa than placebo (Cohen's d = 0.43, p = 0.003; Figure 3A, top right). In addition, modularity of brain networks—grouping of partner nodes within sub-networks—significantly decreased under L-dopa in contrast to placebo (Cohen's d = 0.53, p = 0.002; Figure 3A, bottom left). Moreover, global network efficiency—a metric known to measure the capacity of brain networks for parallel processing—was significantly lowered under L-dopa compared to placebo (Cohen's d = 0.4, p = 0.012; Figure 3A, bottom right). This relative hypo-integration under L-dopa turned out to be—at least partly—due to higher fractions of disintegrated nodes in brain networks under L-dopa compared to placebo (Figure S1). Thus, L-dopa consistently diminished network integration within the functional connectome on different scales of topology.

Similar results were found when brain networks were constructed on different wavelet scales (Figure S5).

Next, we investigated whether the reorganization of the functional connectome under L-dopa explains the degree of the participants' behavioral gain from L-dopa during the working memory task. We tested the correlation between the modulation (i.e., L-dopa–placebo) in the functional connectome on the one hand, and the modulation in task performance on the other hand. The change in task performance correlated significantly with both, the modulation in functional connectivity and global efficiency of brain networks (Figure 3B). Specifically, participants who showed higher degrees of hyper-connectivity under L-dopa also displayed higher gains in response speed under L-dopa than placebo (Figure 3B, left). Besides, participants with lower degrees of global network efficiency (equivalently more pronounced hypo-integration) under L-dopa showed higher perceptual sensitivity (d'; Figure 3B, right). However, the correlation between modulations in mean local efficiency or network modularity (Q) of the functional connectome and either of the performance measures were not significant (E_{local}~response speed: rho = 0.01, p = 0.9; E_{local}~d': rho = –0.23, p = 0.3; Q~response speed: rho = –0.26, p = 0.23; Q~d': rho = 0.19, p = 0.4).

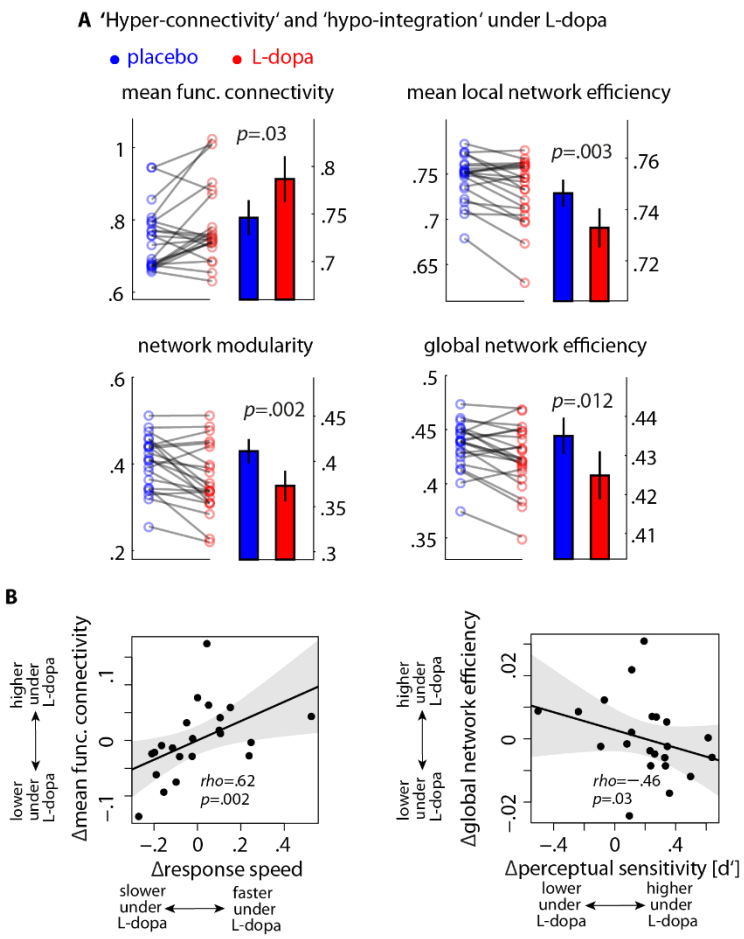

Figure 3. Modulation of the functional connectome under L-dopa and its relation to modulations of behavioral performance. **(A)** Whole-brain network metrics under L-dopa and placebo were compared using permutation tests. Circles connected by lines indicate individuals' brain network metrics under placebo and L-dopa. Bar plots show group average brain network metrics (error bars: ±1 SEM). There was a significant increase in functional connectivity—a relative 'hyper-connectivity'—under L-dopa versus placebo. Moreover, functional integration of brain networks showed a significant decrease—a relative 'hypo-integration'—under L-dopa. This pattern was consistently observed for local network efficiency, network modularity and global network efficiency. **(B)** Correlations between modulations of the functional connectome and modulations in behavioral performance (Δ: L-dopa–placebo). Participants who showed higher degrees of hyper-connectivity under L-dopa responded faster. Besides, participants with more pronounced hypo-integration under L-dopa (i.e., lower global network efficiency) showed higher perceptual sensitivity d'. The significance of the Spearman's correlations (rho) was tested using permutation tests with 10,000 randomizations. Shaded area shows two-sided parametric 95% CI. Note that, prior to correlation analysis, all measures were residualized w.r.t. medication session order (L-dopa first versus placebo first), BMI, and time from medication administration to scan onset.

Regional modulation of the functional connectome under L-dopa vs. placebo

To localize cortical regions contributing to the L-dopa-induced modulations observed on the whole-brain level (Figure 3), we analyzed the functional connectome on the regional level. To this end, we used nodal network metrics representing a given network property at each cortical region (see Materials and Methods: *Connectome analysis*). Consistent with the whole-brain level analysis, we compared the regional network properties of the functional connectome between L-dopa versus placebo. We found distributed cortical regions showing significant modulations in their functional connectivity and integration under L-dopa compared to placebo (Figure 4A).

These modulations were found in both directions, i.e. L-dopa > placebo and L-dopa < placebo. More precisely, under L-dopa relative to placebo, regions overlapping mainly with paracentral lobule and precuneus underwent a relative hyper-connectivity (Figure 4A first panel, warm regions; Figure 4B, red connections). The most consistent pattern pointed to both hypo-connectivity and hypo-integration under L-dopa within temporal and cingulo-opercular regions (Figure 4A, cold regions; Figure4B, red nodes). In particular, nodal connectivity and nodal degree of cortical regions mostly in the inferior division of temporal cortex as well as frontal operculum were decreased under L-dopa relative to placebo (Figure 4A, first row). In addition, nodal network efficiency of regions within the inferior portion of temporal cortex, anterior cingulate and frontal operculum was significantly lower under L-dopa than placebo. These findings were further supported by the existence of higher number of disintegrated nodes under L-dopa versus placebo (Figure 4B, red nodes).

Next, we tested the correlation between regional modulation (i.e., L-dopa–placebo) of the functional connectome and modulations in behavioral performances. We found significant correlations between modulations of behavioral performances and modulations of nodal connectivity and nodal efficiency (Figure 5). Consistent with the correlations observed on the whole-brain level (Figure 3B), participants who showed increased nodal connectivity (i.e., hyper-connectivity) in bilateral superior temporal/angular gyri and anterior cingulate under L-dopa, also responded faster under L-dopa (Figure 5, left, red circles). Moreover, decreased nodal network efficiency (i.e., hypo-

integration) of a brain node within the right frontal operculum/insula under L-dopa correlated with higher behavioral gains in perceptual sensitivity (Figure 5, right, blue circle).

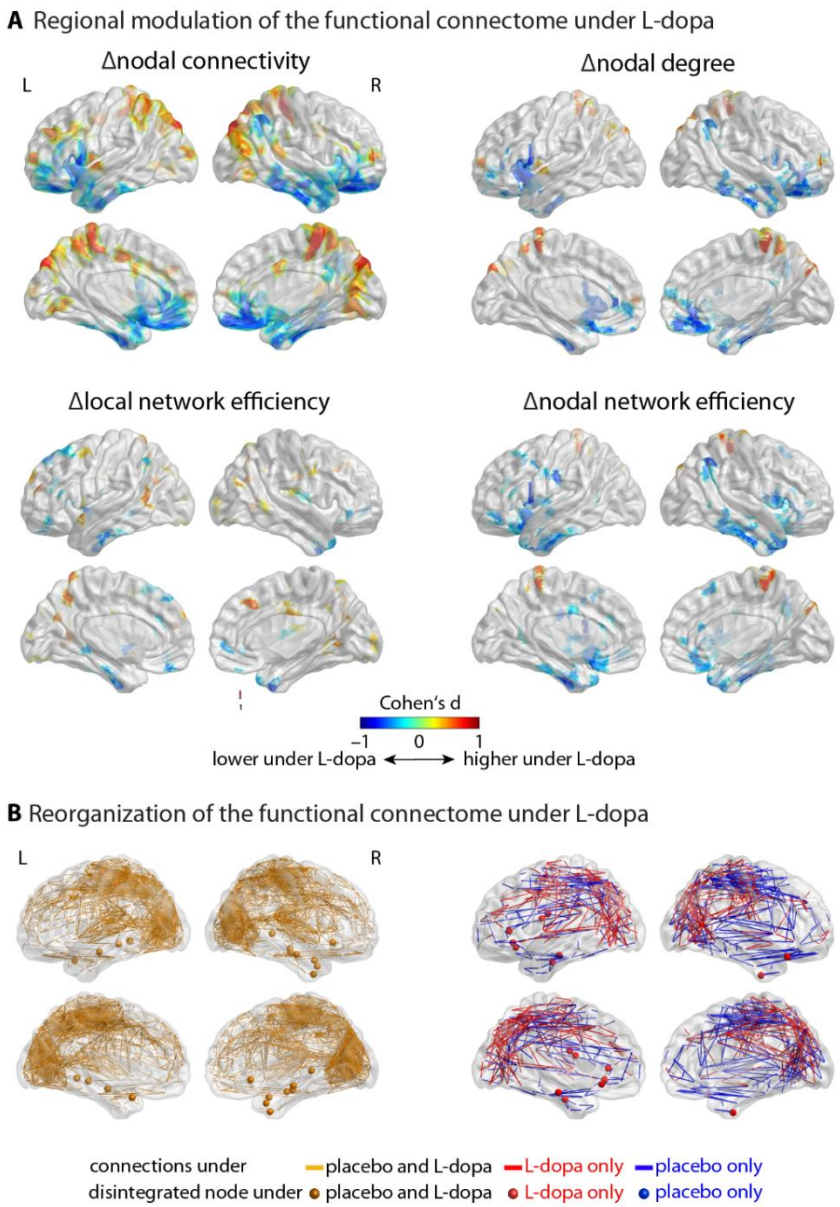

Figure 4. Cortical regions exhibiting functional connectome modulations under L-dopa. **(A)** Nodal network metrics of cortical regions were compared between L-dopa and placebo using bootstrap procedures with 10,000 replications of group average differences (Δ: L-dopa–placebo). The significance of the differences was inferred based on the FCR-correction method accounting for multiple comparisons ($p < 0.05$). Functional connectivity and network integration were significantly increased (warm regions) or decreased (cold regions) under L-dopa in contrast to placebo, with predominant hypo-integration of temporal and cingulo-opercular regions (cold regions). **(B)** Visualization of the topological reorganization of the functional connectome under L-dopa versus placebo. Orange links in the left panel represent putative functional connections engaged during the auditory working memory task under both placebo and L-dopa. A number of disintegrated nodes were consistently present under both placebo and L-dopa, mainly within the left and right temporal cortices (orange nodes). Blue links in the right panel represent functional connections which exist under placebo only. Red links represent functional connections which exist under L-dopa only. Compared to the core network (left panel), the functional connectome displayed an additional set of disintegrated nodes under L-dopa in temporal and cingulo-opercular regions (red nodes) but not under placebo (no blue node). Functionally disintegrated nodes were identified as nodes having a degree of zero. Group-average networks were constructed by thresholding the mean functional connectivity maps (network density set to 5% for better visualization). See Figure S2 for a thorough investigation of graph thresholding.

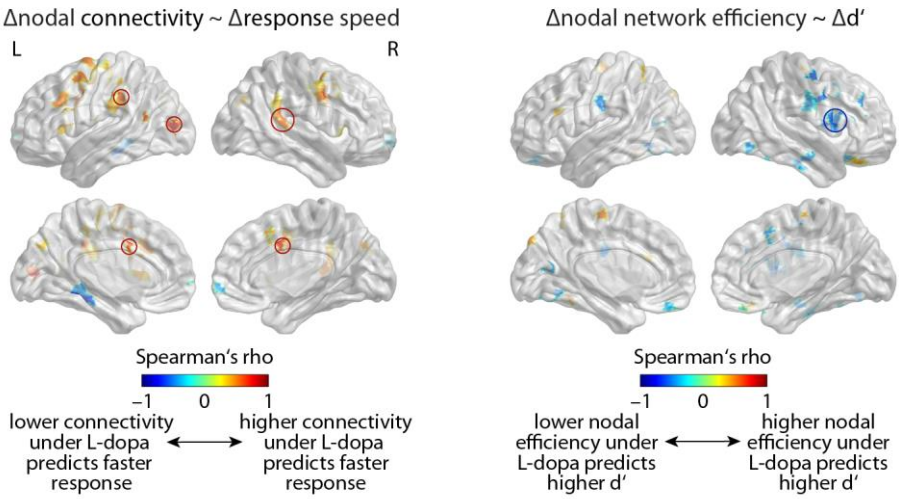

Figure 5. Cortical regions where modulation of the functional connectome correlated with modulations in task performance. Modulation of nodal connectivity in bilateral superior temporal/angular gyri and anterior cingulate (left panel, red circles) under L-dopa positively correlated with the change in response speed during the auditory working memory task (Δ: L-dopa–placebo). Additionally, lower nodal network efficiency of a brain node within the right frontal operculum/insula (right panel, blue circle) under L-dopa correlated with higher perceptual sensitivity d'. The correlation at each region was tested using a bootstrap procedure for Spearman's rho (10,000 replications). Circles highlight the regions that survived FCR correction ($p < 0.05$). Colored regions without circles are visualized at the uncorrected level.

Relationship of modulations in signal variability and modulations in the functional connectome

Given that L-dopa significantly modulated BOLD signal variability and network organization of the functional connectome, we further investigated whether these modulations in cortical dynamics directly relate to each other across participants. Specifically, we examined which cortical regions exhibit a relationship between the modulation of their signal variability under L-dopa (versus placebo) and the modulation in their network configuration within the functional connectome under L-dopa (versus placebo). We thus separately analyzed the correlations between the modulations of three regional network metrics (i.e., nodal connectivity, local network efficiency, and nodal network efficiency) and modulation in signal variability across cortical regions.

Figure 6 illustrates cortical regions exhibiting robust correlations between modulations in BOLD signal variability and regional network metrics under L-dopa (versus placebo). Across participants, we found that the extent of L-dopa-induced changes in BOLD signal variability positively correlated with the extent of nodal connectivity changes in broadly distributed cortical regions, spanning temporal, cingulate, frontal, and parietal cortices (Figure 6, top).

Interestingly, L-dopa-related modulation of BOLD signal variability correlated with the extent of modulation in individuals' brain network efficiency, both on local and global scales of topology. Specifically, network efficiency within each node's neighborhood graph (i.e., local efficiency) as well as its functional integration to the whole-brain graph (i.e., nodal efficiency) significantly correlated with BOLD signal variability in distributed cortical regions. Increased signal variability specifically in temporal, left inferior frontal, cingulate, as well as insula cortices correlated with higher network efficiency in similar regions (Figure 6, bottom). Notable exceptions were visual areas (within the occipital and inferior temporal cortices), which showed negative correlations between modulations in BOLD signal variability and network efficiency.

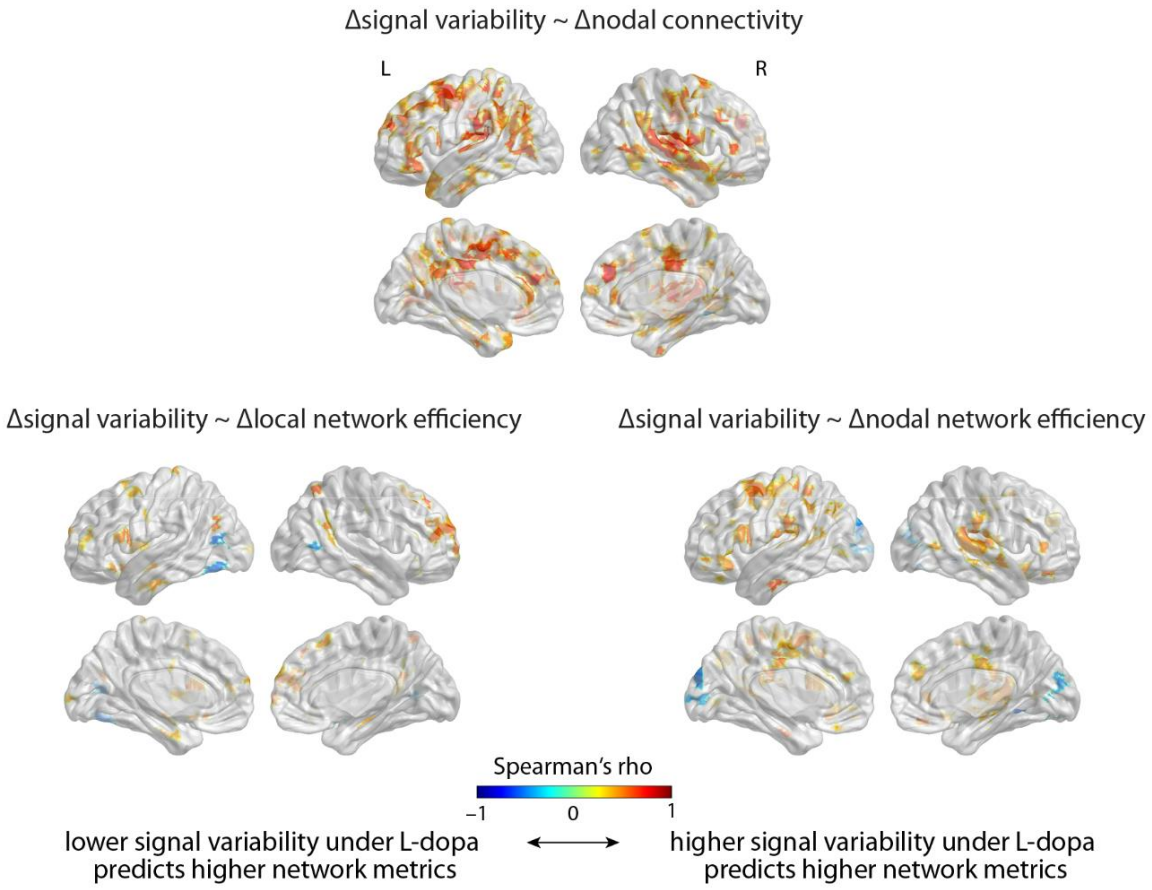

Figure 6. Cortical regions exhibiting significant correlations between the respective modulations of BOLD signal variability and the functional connectome under L-dopa. The extent of L-dopa-induced modulation (Δ: L-dopa–placebo) of signal variability showed predominantly positive correlations to that of nodal connectivity (top), local network efficiency (bottom, left) and nodal network efficiency (bottom, right) across participants. The significance of the correlations were inferred based on the FCR correction accounting for multiple comparisons ($p < 0.05$).

Discussion

How does dopamine modulate large-scale cortical dynamics, and how does this in turn affect cognitive performance? We addressed this question by investigating the effect of L-dopa on BOLD signal variability and the functional connectome while young adults performed an auditory working memory task. We examined L-dopa-induced modulations of brain dynamics and behavior relative to placebo, and the relationships between these modulations.

L-dopa increases BOLD signal variability

In our sample, L-dopa generally increased BOLD signal variability. Notably, the individual extent of this increase correlated with the behavioral benefit from L-dopa. Our findings are consistent with recent studies emphasizing the importance of signal variability in predicting well-functioning cognitive operations (Garrett et al., 2010; Grady and Garrett, 2014), and the role of DA in boosting BOLD signal variability (Garrett et al., 2015).

Specifically, we found that L-dopa increased signal variability in distributed cortical regions deemed relevant for the auditory working memory task. These regions include bilateral superior temporal cortices, often associated with auditory and speech perception (Liebenthal et al., 2005; Obleser and Eisner, 2009). A similar effect was also observed in the bilateral IFG and right SMG, regions implicated in pitch and verbal working memory (Gaab et al., 2003; Obleser and Eisner, 2009). Additionally, L-dopa increased signal variability in domain-general networks overlapping with fronto-parietal and cingulo-opercular regions putatively associated with task control (Dosenbach et al., 2007). A further analysis of mean BOLD activation revealed that the similar cortical regions, in which L-dopa increased signal variability (i.e., auditory, visual, and insular cortices), were indeed engaged during task performance in both sessions (see Figure S7). However, no region exhibited a significant difference between mean BOLD activations under L-dopa relative to placebo on the corrected level. These results indicate that BOLD signal variability reflects a different aspect of neural computation as compared to event-related mean BOLD activation. In line with Garrett et al. (2015), our data suggest

that this variability might also be the more sensitive measure in capturing dopaminergic modulation than mean BOLD activation.

Interestingly, distinct cortical regions appeared relevant in explaining individuals' behavioral benefits from L-dopa. Our results show that loci of signal variability modulations that correlated with response speed versus d' gains are indeed different. Signal variability in motor and parietal regions seems to underlie response speed gain, whereas L-dopa-induced sensitivity benefits were associated with signal variability changes in parahippocampal area, where activity is related to episodic memory/encoding (Amaral and Insausti, 1990; Davachi et al., 2003; Chowdhury et al., 2012). As we have not observed speed–accuracy trade-offs with the benefits from L-dopa ($p = 0.90$), it is a tenable hypothesis that signal variability in distinct cortical regions contributes complementarily to behavioral performance.

Dopaminergic neurotransmission is essential in maintaining neural signal dynamics by balancing phasic and tonic neural activities (Grace, 1995; Venton et al., 2003). Given that highly variable signals convey more information (McIntosh et al., 2008), our findings underline the role of DA in maintaining the dynamic range of neural systems involved in cortical processing of task-relevant information.

L-dopa substantially modulates the functional connectome

During the auditory working memory task, L-dopa reduced the functional integration across cortical regions. This hypo-integration manifested at different topological scales, and was concurrent with nodal disintegration of temporal and cingulo-opercular regions. Since the brain graphs were matched in network density across participants and sessions, this hypo-integration cannot be due to network density differences (cf. van den Heuvel et al., 2017). Further, the L-dopa-induced hyper-connectivity and hypo-integration were consistent across a wide range of network densities at different graph thresholds (Figure S2). Disintegration of certain nodes, mostly in temporal and cingulo-opercular regions, may be interpreted as diminished statistical dependency (co-activation or functional cross-talk; not to be mistaken by anatomical disconnection) between these and other cortical regions during auditory working memory processing. Given that hypo-integration was dominantly observed in nodal

degree and network efficiency of temporal and cingulo-opercular regions, this reorganization most likely stems from a functional disintegration of these nodes from regions less relevant for the task (arguably the default mode network; see Guitart-Masip et al., 2016; Nagano-Saito et al., 2017).

Note that we use the terms 'integration' and 'disintegration' within the framework of graph theory. In a functional connectome and on the global scale of network topology, for a brain graph to display greater network integration (increased capacity for parallel processing), long distance correlations are required. In sparsely connected functional networks (as in our case), short distance connections predominate, and are typically associated with greater strength of connectivity (Vértes et al., 2012). Thus, increase in connectivity most likely would indicate formation of local neural processing (equivalently, lower functional integration, Rubinov and Sporns, 2010). As such, a network shifts from having a globally-integrated topology to a more clustered and segregated topology. In our data, however, we observed a significant decrease in global efficiency, but also in local efficiency and modularity. Accordingly, the network reorganization was not a functional shift toward higher segregation. We thus investigated an alternative functional reorganization, namely nodal disintegration, which could potentially attenuate all three topological measures. Our analysis revealed significantly stronger nodal disintegration under L-dopa compared to placebo (Figure S1).

Interestingly, the above hypo-integration correlated with L-dopa-induced sensitivity benefits: participants with more pronounced hypo-integration on both whole-brain and regional levels (right frontal operculum/insula) showed higher d'. These correlations were specific to network efficiency—a measure inversely related to topological distances, which further supports the functional disintegration of task-relevant regions.

Accordingly, L-dopa-induced hypo-integration might indicate a functional shift of the temporal and cingulo-opercular regions from a globally integrated state to a more autonomous engagement in task processing. Previous work suggests that the cingulo-opercular network is crucial for sustained attention (Dosenbach et al., 2006, 2007; Vaden et al., 2013), hemostatic salience processing (Seeley et al., 2007), tonic alertness (Sadaghiani and D'Esposito, 2015; Coste and Kleinschmidt, 2016) and dynamic coordination between the default mode network and the central executive network (Menon

and Uddin, 2010; Uddin, 2015). Thus, the more autonomous state of this network can increase the signal-to-noise ratio in cortical information processing, and help maintain to-be-attended (here, syllable pitch) information.

To further investigate whether the effects arise from task-related neural dynamics or modulation of spontaneous activity (Ponce-Alvarez et al., 2015; Bolt et al., 2017), we used a general linear model (GLM) with finite impulse response (FIR) basis functions (0–22 s relative to trial onset) to estimate task-related BOLD activity. Subsequently, the residual data obtained from the GLM was used for analyzing signal variability and connectivity of spontaneous activity (Zhang and Li, 2010; Cole et al., 2014; Alavash et al., 2015b; Finc et al., 2017; Bolt et al., 2017). This analysis did not reveal any significant difference in signal variability or network dynamics of spontaneous brain activity between placebo and L-dopa. This result supports that, in our sample, L-dopa modulated task-related cortical dynamics, thereby altering the signal variability and the functional connectome of cortical regions engaged during the auditory working memory task. Note that, as mentioned above, we did not find a significant difference between task-related mean BOLD activations (Figure S7) under L-dopa relative to placebo on the corrected level. Overall, based on our main findings, task-related BOLD signal and network dynamics of distributed cortical regions may be more sensitive measures in capturing dopaminergic modulation than mean BOLD activation.

To date, only few studies have investigated the effect of DA on brain networks, mostly focusing on resting-state or fronto-striatal functional connectivity (Nagano-Saito et al., 2008; Kelly et al., 2009; Cole et al., 2013; Bell et al., 2015). Our study, in contrast, focuses on large-scale cortical interactions during a listening task with attention and memory components. On the whole-brain level, we found an overall hyper-connectivity under L-dopa. On the regional level, however, we found that L-dopa decreased nodal connectivity of temporal and cingulo-opercular regions (Figure 4, cold regions and red nodes), whereas it increased nodal connectivity of paracentral lobule and precuneus (Figure 4, red connections). This apparent inconsistency between the direction of the global and regional results can be explained by network disintegration. We found that temporal and cingulo-opercular regions were functionally disintegrated (Figure 4B; red nodes) from the remaining of the whole-brain network

(Figure 4B; red connections). The connected component includes the paracentral/precuneus nodes, whose significant increase in nodal connectivity contribute to the hyper-connectivity observed on the whole-brain level. The disintegrated nodes, on the other hand, do not contribute to whole-brain functional connectivity simply due to the absence of connections (hypo-connectivity/-integration). Thus, functional connectivity on the whole-brain level remained significantly higher under L-dopa relative to placebo, the extent of which correlated with individuals' response speed gains from L-dopa.

Modulation of signal variability correlates with modulations of the functional connectome

DA-driven modulation of signal variability showed significant positive correlations with modulations of nodal connectivity and network efficiency mainly in temporal and anterior cingulate cortices known to be crucial for listening behavior (Langers and Melcher, 2011; Erb et al., 2013). One might associate these findings with the fact that connectivity between two signals, expressed as their correlation, requires a certain amount of variability. However, the present findings more likely reflect a systematic relationship between two measures of cortical dynamics. First, our findings point to the correlation between modulations (L-dopa versus placebo) in two measures of brain dynamics rather than within-session correlations. Second, regional network metrics are multivariate measures: nodal connectivity is estimated as mean correlation between a region's signal and its node-pairs' signals, and nodal network efficiency is estimated based on topological distances between a given node and every other node in the network. Notably, for two regional signals to show coherent fluctuations over time, not only variability (information) but also covariance (coordination) is necessary (Carbonell et al., 2014; Cole et al., 2016). Thus, correlation between the modulation in variability of a regional signal and the modulation in the network wiring of the same region is most likely a systematic relation between two measures of cortical dynamics.

Furthermore, such systematic relationship in our data was supported by a conjunction analysis of L-dopa effects on signal variability and functional connectivity. Overlapping cortical regions exhibited overall L-dopa-related *increase* both in signal variability and functional connectivity (Figure S8). However, no common region was found to show L-dopa-related *decrease* in both measures. This lack

of overlap suggests that network disintegration under L-dopa in temporal and cingulo-opercular regions (Figure 4B) arises from modulation in co-activation of (communication between) these regions and other regions, rather than mere modulation of their signal variability. Likewise, the direct linear relationship between functional connectivity and variability were only found to be positive (Figure 6A). Taken together, our study motivates the importance of investigating both aspects of cortical dynamics—that is, signal variability and connectivity—as two complementary measures.

These findings can be understood in terms of information-processing capacity (McIntosh et al., 2008; McIntosh et al., 2014), and integration of information across the functional connectome (Tononi et al., 1994; Tononi et al., 1998; Sporns, 2003; Stam and van Straaten, 2012). Our findings are consistent with previous studies reporting positive correlations between entropy of resting-state EEG signals and nodal centrality and network efficiency (Mišić et al., 2010, 2011). Nodes conveying more information are characterized by many connections and short/direct paths to the rest of the network, thereby optimally 'relaying' local information across the connectome (see Timme et al., 2016 for a recent evidence based on networks of neural spikes). Thus, our findings suggest that L-dopa maintains cortical signal variability as well as dynamic communication involved in processing of task-relevant information.

Limitations and future directions

The present study examined how L-dopa modulates cortical dynamics during working memory performance. Previous studies have emphasized the importance of striatal dopamine in working memory (Frank et al., 2001; Cools et al., 2008; Landau et al., 2009; Guitart-Masip et al., 2016), and even observed an opposite effect of signal variability change with aging in cortical versus subcortical structures (e.g., Garrett et al., 2010). Future investigations would be necessary to examine the influence of DA on neocortical versus subcortical signal variability and networks (Bell and Shine, 2016), and their differential contributions to behavior.

Here, we did not observe a main effect of L-dopa on behavioral performance, but a notably high inter-individual variability in benefits from L-dopa. The absence of an overall effect may be due to the

well-known inverted U-shaped effect of DA: Individuals' baseline levels of cognitive performance, endogenous DA, and/or genetic variations in dopamine metabolism determine the direction of L-dopa-related benefits/detriments (Goldman-Rakic et al., 2000; Vijayraghavan et al., 2007; Cools and D'Esposito, 2011; Pearson-Fuhrhop et al., 2013).

Lastly, our sample only involved young participants. Garrett et al. (2015) found that, compared to young adults, stronger DA-related signal variability effects were observed in older age group, whose dopaminergic system may be relatively more degenerated. Additionally, intrinsic hemodynamic signal variability in visual, sensorimotor, executive and default mode networks has been shown to decrease across lifespan (Nomi et al., 2017). Thus, in the current study the room for improvement with L-dopa might be smaller in contrast to dopaminergic effects reported in aged participants (Landau et al., 2009; Chowdhury et al., 2012; Garrett et al., 2015; Guitart-Masip et al., 2016). Also, more long-term training might be necessary to observe overall benefits with L-dopa in healthy, young individuals (Knecht et al., 2004).

Conclusion

We showed that an increase of dopamine level while performing an auditory working memory task modulated BOLD signal variability and the functional connectome predominantly in temporal and cingulo-opercular regions. Notably, the degree of these modulations predicted inter-individual differences in behavioral benefits from L-dopa. The findings thus provide insights on understanding the source of prominent inter-individual differences of L-dopa effects on cognitive performance. Our study fills a critical gap in knowledge regarding dopaminergic modulation of univariate and multivariate aspects of cortical dynamics. The data provide first evidence for a direct link between dopaminergic modulation of BOLD signal variability and the functional connectome. Dopamine thus appears to maintain the dynamic range of, and communication between, cortical systems involved in processing task-relevant information during cognitive performance.

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