Dopamine Modulates Effective Connectivity in Frontal Cortex

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Abstract

■ There is increasing evidence that the left lateral frontal cortex is hierarchically organized such that higher-order regions have an asymmetric top–down influence over lower order regions. However, questions remain about the underlying neuroarchitecture of this hierarchical control organization. Within the frontal cortex, dopamine plays an important role in cognitive control functions, and we hypothesized that dopamine may preferentially influence top–down connections within the lateral frontal hierarchy. Using a randomized, double-blind, within-subject design, we analyzed resting-state fMRI data of 66 healthy young participants who were scanned once each after administration of bromocriptine (a dopamine agonist with preferential affinity for D2 receptor), tolcapone (an inhibitor of catechol-O-methyltransferase), and placebo, to determine whether dopaminergic stimulation modulated effective functional connectivity between hierarchically organized frontal regions in the left hemisphere. We found that dopaminergic drugs modulated connections from the caudal middle frontal gyrus and the inferior frontal sulcus to both rostral and caudal frontal areas. In dorsal frontal regions, effectivity connectivity strength was increased, whereas in ventral frontal regions, effective connectivity strength was decreased. These findings suggest that connections within frontal cortex are differentially modulated by dopamine, which may bias the influence that frontal regions exert over each other. ■

INTRODUCTION

Cognitive control is crucial in selecting and regulating internal representations in accordance with our goals. The left frontal cortex is critical for cognitive control and is thought to be organized in a hierarchical manner such that higher-order regions influence lower order regions more than vice versa (Badre & D'Esposito, 2009). It has recently been proposed that the mid-lateral frontal cortex may form the "top" of a control hierarchy, directing the convergence of rostral and caudal frontal influences to perform goal-directed behaviors (Badre & Nee, 2018; Vogelsang & D'Esposito, 2018; Nee & D'Esposito, 2016, 2017).

Cognitive control functions supported by the frontal cortex have also been associated with the neuromodulator dopamine (Robbins, 2000). The frontal cortex has top–down control over ascending brainstem neuromodulatory systems (Robbins & Arnsten, 2009; Robbins, 2005), and in turn, these ascending brainstem projections influence frontal cortex (Ott & Nieder, 2019; Williams & Goldman-Rakic, 1998). Furthermore, it has been shown that dopamine receptors are not uniformly distributed across the brain, but instead show regional specificity (Vogelsang & D'Esposito, 2018; Palomero-Gallagher, Amunts, & Zilles, 2015). We have proposed that the regional specificity of the dopamine receptor distribution in frontal cortex may contribute to the functional organization of this region, and in particular the asymmetric hierarchical influence that frontal regions exert over each other (Vogelsang & D'Esposito, 2018). However, this hypothesis has thus far not been empirically tested.

Previously, Goldman-Rakic and colleagues examined dopamine axon density in the macaque monkey lateral frontal cortex. They showed there was lower axon density within the most rostral frontal regions, and this density increased toward the more caudal pre-premotor cortex and then decreased again for the primary motor cortex (Williams & Goldman-Rakic, 1993). Thus, in the macaque data, the highest dopamine axon density was observed around the pre-premotor cortex. More recently, Palomero and colleagues reviewed several studies that reported the neurotransmitter densities of receptor binding sites in the human brain (Vogelsang & D'Esposito, 2018; Palomero-Gallagher et al., 2015). Relative to other frontal cortical regions, dopamine D1 receptor (DRD1) density was greater in the mid-lateral frontal cortex. In addition, dopamine D2 receptor (DRD2) binding is much lower compared with the DRD1 in frontal cortex (Lidow, Goldman-Rakic, Gallager, & Rakic, 1991). These prior observations of the dopamine receptor distributions across the frontal cortex in monkeys and humans pose

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an important question for how these dopaminergic distributions relate to hierarchical control in the frontal cortex. Given the convergence between the putative "top" of the frontal cortical hierarchy and the regional enrichment of DRD1, we hypothesized that dopamine may have a strong modulatory effect on the asymmetric influence that higher-order to lower-order regions have within the hierarchical control architecture of the frontal cortex.

To this end, we conducted an effective connectivity analysis of resting-state fMRI data across six left frontal regions that have previously been associated with various levels of hierarchical cognitive control across the frontal cortex (Nee & D'Esposito, 2016, 2017). Nee and D'Esposito used dynamic causal modeling (DCM) to quantify relative levels of hierarchical control in a task that involved three levels of cognitive control that varied in abstraction. The effective connectivity results suggested that the mid-lateral frontal cortex had the strongest asymmetries in hierarchical control (i.e., stronger outgoing vs. incoming connections), indicating this subregion of frontal cortex may be the top of the control hierarchy. Notably, this work focused on the left hemisphere because of left lateralization often observed in studies of hierarchical control (Bahlmann, Blumenfeld, & D'Esposito, 2015; Jeon, Anwander, & Friederici, 2014; Nee & Brown, 2013; Badre & D'Esposito, 2009; reviewed in Badre & Nee, 2018), potentially consistent with hypothesized frontal asymmetries in processes of task setting (left) and monitoring (right; Stuss, 2011). Here, we used the connectivity architecture from Nee and D'Esposito (2016) to compute the effect of dopaminergic modulation on the effective connectivity strengths between these left frontal regions using spectral dynamic causal modeling (spDCM).

We analyzed data from a sample of 66 healthy participants who underwent resting-state fMRI on three separate days, once after administration of the DRD2 agonist bromocriptine, once after administration of the catechol-O-methyltransferase (COMT) inhibitor tolcapone, and once after administration of a placebo, in a counterbalanced, double-blinded fashion. Currently, there are no United States Food and Drug Administration-approved DRD1 drugs available for human research. However, by inhibiting the degradation of dopamine by COMT, tolcapone is thought to selectively increase cortical dopamine tone (Tunbridge, Bannerman, Sharp, & Harrison, 2004). Because the cortex, unlike the striatum, relies upon COMT to remove approximately 50% of released dopamine (Käenmäki et al., 2010) and because cortical regions are enriched for D1 receptors relative to other dopamine receptor subtypes (Lidow et al., 1991), COMT inhibition is also thought to induce a relatively selective upregulation of cortical D1 activity (Schacht, 2016). We then used spDCM to directly investigate whether dopamine most strongly modulates frontal regions that have been shown to exert high hierarchical influence over other regions (Vogelsang & D'Esposito, 2018). Given that tolcapone and bromocriptine predominantly act on the DRD1 versus DRD2, respectively, we could also investigate potential differential effects of these two dopamine receptors on effective connectivity in frontal cortex.

METHODS

Participants

Eighty individuals with normal or corrected-to-normal vision participated in this experiment, which was part of a larger study (Furman, Naskolnakorn, Ye, Kayser, & D'Esposito, 2020) on dopaminergic mechanisms of cognitive control. All participants received financial compensation for their involvement. Participants were excluded if they had a history of cardiac or neurological disorders, currently used psychoactive medication or tobacco, had other contraindications to fMRI or the study medications (e.g., pregnancy), or were heterozygous for the COMT Val158Met genotype (genotyping was an important part of the larger study, hence this exclusion criterion). All participants provided written informed consent, and the experiment was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley. Fourteen participants demonstrated excessive motion during one of their resting-state sessions and were excluded from further analysis (see below for more details on motion parameter exclusion). Therefore, the final sample consisted of 66 participants (mean age = 21.3 years; range = 18–30 years; 18 men, 48 women). The sample size was based on our previous publications on this data set (see Furman, Pappas, White, Kayser, & D'Esposito, 2021; Furman et al., 2020), as well as the previous study on hierarchical control by Nee and D'Esposito (2016, 2017).

Pharmacological Manipulations

All pharmacological fMRI data were collected using a randomized, double-blind, placebo-controlled, within-subject design. Participants received either bromocriptine (1.25 mg), tolcapone (200 mg), or placebo during each of their three visits; thus, every participant received each type of drug during one of the three experimental days. Because tolcapone can discolor the urine, all tablets, including placebo, contained 25 mg of riboflavin to (a) mask this effect when tolcapone was administered and (b) ensure that participants could not distinguish such effects across sessions. Bromocriptine is a dopamine receptor agonist with ~100 fold more binding affinity for the DRD2 than the DRD1 (Gerlach et al., 2003), whereas tolcapone is an inhibitor of COMT, which plays a critical role in catabolizing frontal cortical dopamine (Tunbridge et al., 2004). In particular, COMT inhibition increases dopamine tone in the frontal cortex because of COMT's larger role in dopamine metabolism within the frontal cortex compared with basal ganglia (Tunbridge et al., 2004). To ensure that imaging data were acquired during the

window of maximal plasma concentration for both drugs, a 6-min eyes open, resting-state fMRI scan occurred approximately 75 min after ingestion of the pill, which was timed to be in the window of maximal plasma concentration for both drugs (Cameron, Wallace, Al-Zughoul, Kayser, & D'Esposito, 2018; Kvernmo, Härtter, & Burger, 2006; Nyholm, 2006; Jorga, Fotteler, Heizmann, & Zürcher, 1998). The average number of days between scanning sessions was 9 days (median = 7) between Sessions 1 and 2, and 10.9 days (median = 7) between Sessions 2 and 3, with 2 days as the minimum between sessions. With respect to subjective differences between sessions, participants were at chance performance when prompted to identify the drug condition (bromocriptine, placebo, or tolcapone; Furman et al., 2021).

fMRI Data Acquisition

MRI was performed at the Henry H. Wheeler, Jr. Brain Imaging Center at the University of California, Berkeley, on a Siemens TIM/Trio 3 T MRI using a 12-channel head coil. T1-weighted magnetization prepared rapid gradient echo images were collected for spatial normalization ($240 \times 256 \times 160$ matrix of 1 mm^3 isotropic voxels; repetition time = 2300 msec; echo time = 2.98 msec; field of view = 256; sagittal plane; flip angle = 9; voxel size $1 \times 1 \times 1$ mm; 160 slices). Functional images were acquired using an EPI sequence with 36 interleaved ascending slices and $3 \times 3 \times 3.5$ mm voxels (repetition time = 2000 msec; echo time = 24 msec; flip angle = 65; field of view = 192 mm, 180 volumes).

fMRI Data Analysis

MRI data were first converted to Brain Imaging Data Structure format and were verified using the Brain Imaging Data Structure validator: https://bids-standard.github.io/bids-validator/. Imaging data were preprocessed using FMRIPREP Version 1.1.4 (Esteban et al., 2019; https://fmriprep.readthedocs.io), which is based on Nipype (Gorgolewski et al., 2011). T1 images were corrected for intensity non-uniformity using N4BiasFieldCorrection (Tustison et al., 2010; ANTs 2.2.0). The T1 images were skull stripped using antsBrainExtraction.sh (ANTs 2.2.0) with OASIS as a target template. The T1 images were then segmented into cerebrospinal fluid, white matter, and gray matter using *fast* (FMRIB Software Library [FSL] 5.0.11; Zhang, Brady, & Smith, 2001).

Functional images were motion corrected using *mcflirt* (FSL 5.0.11; Jenkinson, Bannister, Brady, & Smith, 2002) and slice-time corrected using *3dTshift* in AFNI (Cox, 1996). The BOLD time series were corrected for head-motion and susceptibility distortions. The functional images were then co-registered to the T1-weighted images using flirt (FSL 5.0.11; Jenkinson & Smith, 2001) and boundary-based registration with 9 degrees of freedom (Greve & Fischl, 2009). Motion artifacts in the functional images were removed using ICA-AROMA (Pruim et al., 2015). Corresponding denoised runs were produced after this step, and the BOLD time series were resampled to MNI152NLin2009cAsym standard space. In addition, a set of nuisance regressors was extracted to allow for component-based noise removal (CompCor; Behzadi, Restom, Liau, & Liu, 2007), and principal components were estimated after high-pass filtering the BOLD time series using a discrete cosine filter with 128-sec cutoff for both tCompCor and aCompCor. The six aCompCor components, as well as the 24 motion parameters (six head motion parameters, their first temporal derivatives, and the 12 corresponding squared items) and the global signal were then regressed out of the functional images. Global signal regression has been a controversial topic: It does minimize the effects of motion artifacts, yet it can lead to anticorrelations and cause distance-dependent artifacts (Ciric et al., 2018). However, we were only interested in comparing the effects of each dopaminergic drug within each participant and therefore the potential drawbacks of global signal regression do not apply here. Furthermore, global signal regression not only corrects for motion-related artifacts but also diminishes the differences between sessions/groups, thus making it less likely that a bias will be introduced (Power et al., 2014). Finally, a high-pass filter of 0.008 Hz was applied and, as a final step, the data were smoothed with a 6-mm Gaussian kernel.

Quality Control of Motion-related Artifacts

It has been increasingly recognized that motion-related artifacts can have a significant impact on resting-state fMRI-data analysis, leading to biased outcomes (e.g., Ciric et al., 2018; Parkes, Fulcher, Yücel, & Fornito, 2018). Therefore, we verified that there were no motion-related differences between the drug sessions. With regard to controlling for motion effects in the data set, participants were excluded from the analysis if any of the following criteria were met in any of the sessions: (1) mean framewise displacement (mFD) was > 0.3 mm; (2) scanning data contained more than 30% motion spikes, with a spike being defined as a single FD of > 0.3 mm; or (3) any FD > 5 mm. On the basis of these criteria, 14 participants were excluded from the data set: Six participants exhibited excessive movement during the bromocriptine drug session; four participants exhibited excessive movement during the placebo drug session; and four participants exhibited excessive movement during the tolcapone drug session, resulting in a final sample of 66 participants. The mFD for each of the drug sessions was minimal for bromocriptine (mFD = 0.15 mm; *SEM* = 0.009), placebo (mFD = 0.14 mm; *SEM* = 0.007), and tolcapone (mFD = 0.15 mm; *SEM* = 0.007), and no statistical difference was observed between these drug sessions either before or after exclusion of the 14 participants (one-way ANOVA F values < 1).

Time-series Extraction

For each of the resting-state sessions, we extracted the time series for six ROIs that were previously used in a DCM model to examine frontal interactions during various levels of cognitive control (Nee & D'Esposito, 2016; Figure 1A). These regions were all along the left lateral surface of the frontal cortex and included the lateral frontopolar cortex (FPI), middle frontal gyrus (MFG), caudal middle frontal gyrus (cMFG), inferior frontal sulcus (IFS), inferior frontal junction (IFJ), and superior frontal sulcus (SFS). The coordinates, all reported in Montreal Neurological Institute (MNI) space, are presented in Table 1. Only data from left hemisphere ROIs were analyzed given that prior fMRI studies on hierarchical control found predominantly left lateralized activity (Badre & Nee, 2018). Moreover, past work focused on the left hemisphere wherein distinct effects of stimulus-domain (i.e., spatial vs. linguistic) were observed affording the ability to examine domain-general versus domain-specific directed influences underlying cognitive control (Nee & D'Esposito, 2016). The specific set of ROIs were chosen based upon consistent univariate activations across distinct cognitive control demands, high functional connectivity indicative of underlying structural connections, connections that have been posited based upon nonhuman primate work, all while providing sufficient spacing to distinguish ROIs from one another (Nee & D'Esposito, 2016). The time series were extracted using the principal eigenvariate of all voxels in a 6-mm radius sphere around each ROI. The time series extracted in this step were used for the subsequent spDCM analysis.

Table 1. Coordinates in MNI Space for the Six Frontal Regions Used in the spDCM Analysis

	MNI Coordinate		
ROI	*x*	*y*	*z*
Lateral frontal pole (FPI)	−44	48	4
MFG	−38	28	44
cMFG	−26	14	52
IFS	−52	20	28
IFJ	−40	10	20
SFS	−24	4	54

DCM

To examine interactions between the six frontal regions and their influence on each other, we used DCM. Specifically, we used spDCM for resting-state fMRI data (Friston, Kahan, Biswal, & Razi, 2014) as implemented in SPM12 (Welcome Trust Center for Neuroimaging UCL, http://www.fil.ion.ucl.ac.uk/spm). DCM is used to make inferences about the directional influence of regions and how these interactions change as a function of task (Stephan et al., 2010). DCM models define effective connectivity (expressed in Hz) as the rate of change of one region relative to another region (Almgren et al., 2018). Utilizing priors about the underlying BOLD data, DCM estimates parameters in Bayesian fashion that best fit the data (posteriors), the most important being the directed connection strength from one region to another. Here, priors were set at default levels leaving the model to specify the absence or presence of a connection. Present connections were indicated by a prior expectation of 1/128 Hz and prior covariance of 1/64 Hz in accordance with software defaults. spDCM has been developed to analyze directional influence of regions during resting state. As resting-state data do not have any input or task modulations, effective connectivity is estimated by fitting the cross spectra data rather than the BOLD time series (Friston et al., 2014). The cross spectra data represent generalized measures of functional connectivity that retain a temporal aspect, and hence, it is possible to make inferences about the directional influences (Friston et al., 2014). spDCM for resting-state data estimates the intrinsic connectivity (i.e.,

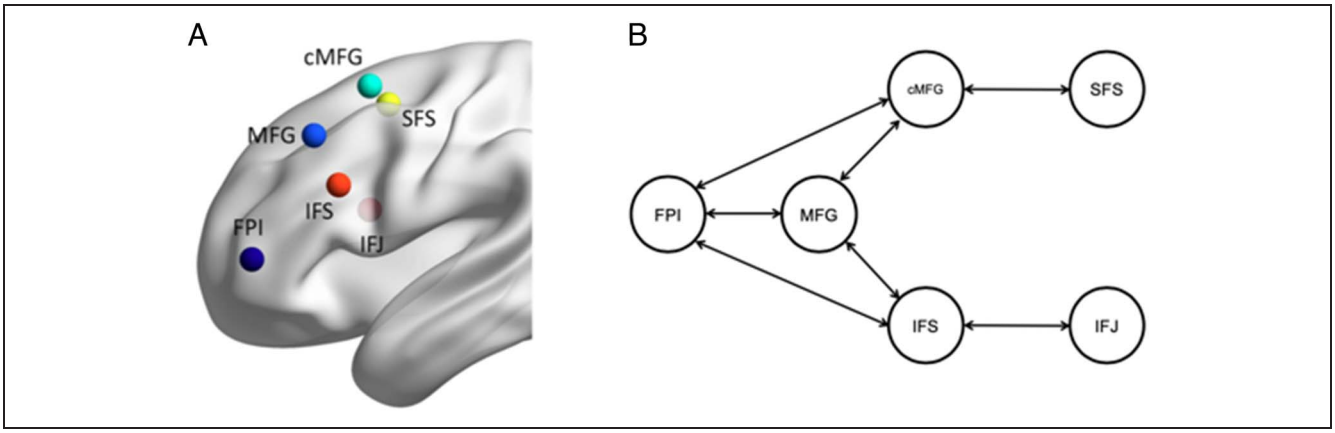

Figure 1. (A) ROIs derived from Nee and D'Esposito (2016) used for the DCM analysis. (B) DCM model used to identify connections that were present across the three resting-state fMRI sessions.

the "A" matrix) between brain regions from observed BOLD responses. It is computationally more efficient compared with DCM of the complete time series (Razi et al., 2017; Razi, Kahan, Rees, & Friston, 2015), has been shown to have strong construct validity (Razi et al., 2015; Friston et al., 2014), and has been shown to have excellent reliability at the group level (Nee, 2021).

First- and Second-level spDCM Analysis

A parent model was created that consisted of the six frontal ROIs with fixed bidirectional connections, based on Nee and D'Esposito (2016; Figure 1B). We used a three-step approach in our spDCM analysis. The first step involved estimation of the posterior probabilities of the parameters, which was conducted using spDCM (*spm_dcm_fit.m*) for each participant and session. In the second step, we defined the contrasts of interest per participant using Parametric Empirical Bayes (PEB). In the third step, we entered these contrasts into a group level using PEB to model the average connectivity across all participants for these specific contrasts based upon subject-level posteriors (Zeidman et al., 2019; Friston et al., 2016). PEB is a fully Bayesian and hierarchical second-level analysis framework implemented in SPM12. For each connection in the model that is being tested, the hierarchical model, as implemented in PEB, treats each connection as a random (between-subjects) effect. The advantage of the PEB framework is that it utilizes both the expected values and the covariance of the parameters from the single subject level—that is, the full posterior densities—to compute group-level results (Zeidman et al., 2019). This approach offers an advantage compared with classical parametric tests (e.g., ANOVA, *t* test) and may be particularly useful for pharmacology data sets, in which the effect of a drug may vary widely across participants (Cools & D'Esposito, 2011). We also included the self-connections in the spDCM model (i.e., the connection that each ROI has with itself, which in a DCM model can be interpreted as reflecting recurrent dynamics); however, we do not present those results here because we were only interested in the interregional connections.

We first took the full model as presented in Figure 1B and examined which connections were present across all three drug sessions (the Group effect); this step would subsequently allow us to characterize the connections that we wanted to examine for both dopamine drugs versus placebo. We opted for this approach because we argued that examining dopamine drugs versus placebo should only be conducted on those connections of the parent model that are affected by the drugs in the first place. To identify the Group effect, we first ran a PEB (*spm_dcm_peb.m*) with a covariance measure of the effect across all three drug sessions. This analysis resulted in a subject-specific PEB model, which was then entered into a group-level PEB model that included one regressor (comprising a column of ones) to model the average connectivity across all participants. This three-step PEB approach provided us the connections that were present across the three drug sessions (the Group effect). This initial spDCM contained 20 parameters (all bidirectional connections pictured in Figure 1B plus six "self" connections). Parameters were calculated using Bayesian Model Reduction, iteratively discarding parameters that made no contribution to the model evidence (Zeidman et al., 2019). The connections that were present across the three drug sessions were then used in a new model to examine the effect of dopamine drugs versus placebo on these connections.

We thus subsequently ran a new three-step PEB (*spm_dcm_peb.m*) on only those connections that were present in the Group contrast for each participant with a covariance measure to assess (1) effective connectivity on placebo, (2) bromocriptine versus placebo, (3) tolcapone versus placebo, and (4) bromocriptine versus tolcapone. This analysis again resulted in a subject-specific PEB, which was then entered into a group-level PEB model that included one regressor that comprised a column of ones to model the average connectivity across all participants. This approach gave us a profile of placebo alone, as well as the effects of bromocriptine and tolcapone versus

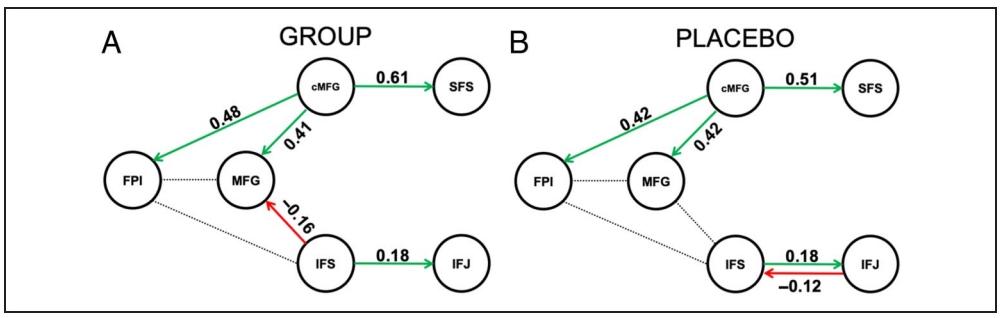

Figure 2. Interactions within the LPFC were modeled using DCM. Arrows indicate the direction of influence, numbers indicate the strength of influence, and colors indicate positive (green) and negative (red) influence. Dotted lines are connections that were part of the full model but that were not significant in the current contrasts. (A) Modulations of connectivity present across all three sessions (i.e., bromocriptine, tolcapone, and placebo). (B) Modulations of connectivity in the placebo session.

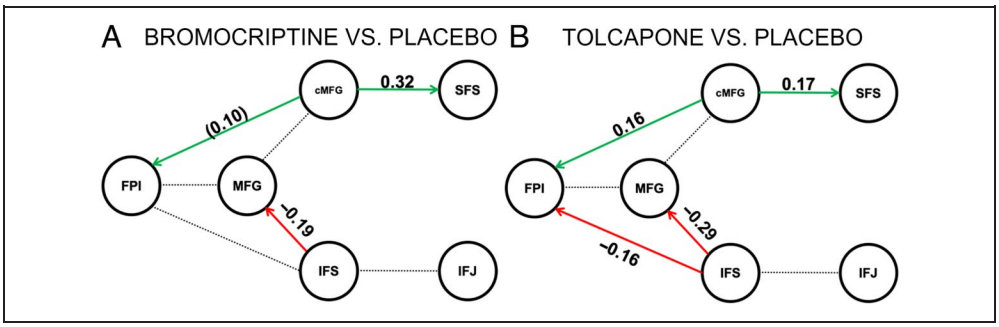

Figure 3. Interactions within the LPFC were modeled using DCM for both drug sessions (bromocriptine [A] and tolcapone [B]) versus placebo. Arrows indicate the direction of influence, numbers indicate the strength of influence, and colors indicate positive (green) and negative (red) influence. Dotted lines are connections that were part of the full model. Connection strengths in parentheses did not survive the posterior probability of $p > .95$.

placebo and both drugs versus each other, on those connections in the A matrix. For all spDCM analyses, including both the participant and the group-level PEB, default settings were used such that the prior covariance of the connections was the same at the session, subject, and group level, whereas the between-sessions and between-subjects covariance was 1/16th of the prior covariance of the connections at the session level. Inference on the effective connectivity measures was only made when the posterior probability criterion was 0.95 or higher for each connection.

RESULTS

Using a PEB approach with resting-state fMRI data (see Methods section for more details), we assessed effective connectivity between six ROIs that were previously used in a DCM model to examine frontal interactions during various levels of cognitive control (Nee & D'Esposito, 2016, 2017). We only report here effects that exceeded a posterior probability of 0.95 or higher, which represents very strong evidence that a certain connection or connection difference is observed in our data. We first identified the connections that were present across all three sessions (the group effect), which included positive effective connectivity strength in outgoing projections from the cMFG to the FPI, MFG, and SFS, and from the IFS to the IFJ, as well as a negative effective connectivity strength from the IFS to the MFG (see Figure 2A). Next, we examined patterns of effective connectivity in just the placebo session (Figure 2B), as well as in each drug session versus placebo (Figure 3). The placebo session pattern largely reflected the group effect except for the absence of a negative IFS to MFG modulation, and the presence of a negative IFJ to IFS modulation (Figure 2B).

The contrast of each drug session versus placebo revealed that bromocriptine compared with placebo increased the connectivity strength from the cMFG to the SFS and decreased the connectivity strength from the IFS to the MFG (Figure 3A). Tolcapone compared with placebo showed these same effects, as well as increased connectivity strength from the cMFG to the FPI and decreased effective connectivity strength from the IFS to the FPI (Figure 3B). For illustration purposes, in Figure 3, we also present, in parentheses, the strength of effective connectivity of the corresponding connections for each model that did not pass the statistical threshold of $p > .95$. This depiction highlights that both drugs have similar effects on effective connectivity strengths and avoids an erroneous interpretation that an effect observed in one model but not another reflects a significant difference between the models (see Nieuwenhuis, Forstmann, & Wagenmakers, 2011). We also directly compared the two dopaminergic drugs (bromocriptine vs. tolcapone and vice versa), which did not reveal any differences in the effective connectivity strengths across frontal regions. Finally, to verify that the dopaminergic drug effects we observed were not related to across-session variability, we performed a session order analysis comparing the three scanning sessions with each other, irrespective of the drug administered. This control analysis did not reveal any differences between the scanning sessions (all posterior probabilities below 0.95), indicating that across-session variability cannot explain our effective connectivity results. Overall, the data indicate that dopamine increases the strength of dorsal connections, whereas it decreases the strength of ventral connections.

DISCUSSION

In this experiment, we examined whether dopamine modulates the influence that hierarchically organized regions in left frontal cortex exert over each other. We conducted an effective connectivity analysis on resting-state fMRI data collected in a group of participants who were administered two types of dopamine drugs (the DRD2 agonist bromocriptine and the COMT inhibitor tolcapone) in a randomized, double-blind, placebo-controlled, within-subject design. Using a model consisting of six a priori left frontal cortex ROIs obtained from Nee and D'Esposito (2016, 2017), we found a general pattern of positive effective connectivity arising from cMFG to rostral and caudal frontal areas, common to all experimental conditions (Figure 2A). Both dopaminergic drugs increased cMFG influences to the caudal frontal cortex (SFS), whereas tolcapone additionally increased cMFG

influences to rostral frontal cortex (FPI). Concomitantly, dopaminergic drugs reduced influences from the more ventral IFS, with bromocriptine reducing IFS to MFG influences and tolcapone reducing IFS influences on both MFG and FPI. There were no significant differences between the two dopaminergic drugs. In summary, these results together indicate that exogenous dopaminergic stimulation modulates effective connectivity from mid lateral frontal to more anterior and posterior frontal regions.

There is extensive evidence that the left frontal cortex is hierarchically organized (Nee & D'Esposito, 2016, 2017; Nee & Brown, 2012; Badre & D'Esposito, 2009; Koechlin & Summerfield, 2007), and it is proposed that some frontal regions have "dominant" influence over other frontal regions (Nee & D'Esposito, 2016), which we refer to as a "control hierarchy" (e.g., Vogelsang & D'Esposito, 2018; Nee & D'Esposito, 2016, 2017). A potentially important contributor to this control hierarchy might be brainstem dopaminergic modulation of frontal cortex, yet this potential modulatory role of dopamine on frontal interactions has not been fully specified. We previously hypothesized that dopaminergic projections from the midbrain may have strong contributions to the functional organization of the frontal cortex (Vogelsang & D'Esposito, 2018). Specifically, both the ventral tegmental area and the substantia nigra project to frontal cortex, with nonhuman primate studies showing that the ventral tegmental area projects to medial frontal and substantia nigra predominantly projects to mid-lateral frontal cortex (Ott & Nieder, 2019; Williams & Goldman-Rakic, 1998). Furthermore, DRD1 receptors, which are more prominent in frontal cortex than DRD2 receptors (Palomero-Gallagher et al., 2015), are not uniformly distributed across frontal cortex. For instance, the mid-lateral frontal cortex appears to have higher DRD1 receptor density compared with other frontal regions (Vogelsang & D'Esposito, 2018; Palomero-Gallagher et al., 2015).

Given that previous studies have demonstrated that pharmacological manipulations induce the largest changes in blood flow in those regions with higher receptor neurotransmitter densities (Dukart et al., 2018), we hypothesized that the frontal cortex may exhibit a pattern of dopamine receptor distribution that allows for regions higher in the control hierarchy, such as the MFG, to be the most strongly modulated by dopaminergic input. In support of this hypothesis, we found significant dopaminergic modulation of effective connectivity from cMFG and IFS consistent with a mid-lateral frontal preponderance of dopamine receptors. Correspondingly, results from task-based fMRI and TMS studies have led to the proposal that mid-lateral PFC regions, and cMFG and IFS in particular, are sites where top–down and bottom–up information converges to influence action (Nee, 2021; Nee & D'Esposito, 2016, 2017). Our data suggest that dopaminergic drugs may have an impact on cognitive control processes that require such convergence.

The additional finding that dopaminergic drugs have opposing influences on more dorsal and ventral frontal areas was unexpected. Given that some models of cognitive control postulate that dorsal and ventral areas support different functions (e.g., maintenance vs. manipulation of information, verbal vs. spatial information; Romanski, 2004; Goldman-Rakic, 1987), it is possible that these connectivity differences reflect this underlying functional organization. Future work using task-based studies will be necessary for determining its significance for hierarchical cognitive control.

Our prior studies of effective connectivity of frontal cortex found that MFG, rather than the more caudal cMFG, is the top of the frontal control hierarchy (Badre & Nee, 2018; Nee & D'Esposito, 2016, 2017). There are several possible explanations for this discrepancy between the present study and previous studies. In prior studies, we examined effective connectivity during a demanding cognitive control task, rather than during the resting-state. In addition, prior ROIs were functionally defined on the individual level to minimize influences on between-individuals topological variability, whereas, in the present study, the ROIs were fixed for all individuals and based upon the group coordinates derived from our prior work. Thus, differences between these studies may be because of the effect of task demands, spatial localization of ROIs, or both. Future work comparing effective connectivity among frontal areas in both task and rest using individually tailored ROIs versus group ROIs may help to resolve this discrepancy.

Previous studies in animals have found that modulation of different dopamine receptor types has opposite effects on cognitive control processes; D1 receptor modulation in frontal cortex mediates cognitive stability whereas D2 receptor modulation in the striatum mediates cognitive flexibility (Cools & D'Esposito, 2011; Crofts et al., 2001). Unfortunately, there are no United States Food and Drug Administration-approved D1 receptor agonist drugs currently available for use in healthy humans to directly test for specific effects of D1 versus D2 receptor stimulation. However, administration of bromocriptine and tolcapone has been used in humans to indirectly investigate the function of these dopamine receptors. Bromocriptine is a dopamine agonist with preferential affinity for D2 receptors whereas tolcapone increases the accumulation of extracellular dopamine without exclusively affecting the binding at a particular class of dopamine receptor. However, tolcapone has a greater influence on cortical D1 receptors (Bilder, Volavka, Lachman, & Grace, 2004), given that D1 receptors are more abundant in the frontal cortex than are DRD2 (Vogelsang & D'Esposito, 2018; Lidow et al., 1991), and thus inhibition of dopamine degradation will preferentially enhance cortical DRD1 signaling (Furman et al., 2020). In this study, we did not find evidence that stimulation of different dopamine receptors differentially influences cortical connectivity given that the pattern of modulation of frontal connectivity was similar for both dopaminergic drugs.

Understanding why stimulation of D1 and D2 receptors produced similar effects on effective connectivity will likely require further work to understand their effects on local and subcortical circuitry. Given the dependence of frontal cortex on COMT for dopamine clearance, tolcapone likely has a greater effect in cortical regions than in striatum, where dopamine is recycled via the dopamine transporter (Yavich, Forsberg, Karayiorgou, Gogos, & Männistö, 2007; Matsumoto et al., 2003). Thus, it is likely that the effects of tolcapone on frontal connectivity we observed in this study were because of direct dopamine receptor stimulation in frontal cortex. In contrast, bromocriptine acts on D2 receptors, which are more prominent in subcortical regions (Hall et al., 1994; Camps, Cortés, Gueye, Probst, & Palacios, 1989). However, bromocriptine may influence frontal cortical dynamics indirectly via striatal pathways. For example, D2 autoreceptor activation or postsynaptic D2 receptor binding could enhance striatal indirect pathway activity by reducing phasic dopamine release. In either case, these effects would lead to thalamic excitation of frontal cortical regions. As a result, activation of cortical D1 receptors and activation of striatal D2 receptors within the indirect pathway might both enhance information flow within cortico-striatal-thalamic loops, resulting in similar secondary effects on intracortical connectivity.

Other studies have investigated the effect of dopaminergic modulation on the functional connectivity of large-scale cortical and subcortical networks. For example, Honey and colleagues (2003) found that sulpiride, a DRD2 antagonist, enhanced functional connectivity between the striatum and thalamus, and Kelly and colleagues (2009) found that L-dopa modulated connectivity within distinct cortico-striatal pathways. It has also been found that bromocriptine modulated the functional connectivity between the caudate and posterior frontal cortex (specifically, the IFJ), and connectivity between striatal subregions, during the performance of a rule-switching task (Stelzel, Fiebach, Cools, Tafazoli, & D'Esposito, 2013). Furthermore, Wallace and colleagues found that bromocriptine differentially impacts fronto-striatal functional connectivity depending on whether an individual exhibited a high versus low working memory capacity (Wallace, Vytlacil, Nomura, Gibbs, & D'Esposito, 2011). Piray and colleagues found that bromocriptine and sulpiride modulate effective connectivity between striatal subregions (Piray et al., 2017). In addition, genetic studies have found that a functional polymorphism within the gene encoding COMT influences functional connectivity within a network of regions including the caudate, anterior cingulate, and parts of the middle and inferior frontal gyri (Tunbridge, Farrell, Harrison, & Mackay, 2013) and that individual differences in baseline dopamine synthesis affect coupling between putative frontoparietal and default mode networks, as well as between frontoparietal and dorsal attention networks (Dang, O'Neil, & Jagust, 2012). It is clear from these studies that dopamine modulates functional connectivity of large-scale cortical and subcortical networks. However, this is the first study that has investigated the effects of dopamine on effectivity connectivity between frontal regions.

One major limitation of the current study is that no hierarchical control task data were collected and thus the conclusions drawn regarding the functional meaning of dopamine and hierarchical control remain speculative. However, recent work has demonstrated that brain connectivity architectures are largely stable across "states" as several studies have highlighted that brain architecture and network organization remain similar between numerous tasks and rest (e.g., Kraus et al., 2021; Gratton et al., 2018). This work suggests that choice of "task" may be immaterial for examining connectivity architectures. Collecting data in the "resting" state was here therefore used as a matter of convenience and simplicity. Given the evidence cited, we expect that the results we observed in the "resting" data to generalize data collected during "tasks," providing a baseline for understanding how dopaminergic drugs modify brain connectivity. However, we know that these intrinsic networks that we have demonstrated are modulated by dopaminergic drugs will likely interact with cognition in a task-dependent manner. Detailing such interactions, the specific circumstances under which they occur, and their impacts on behavior would be fruitful follow-ups to pursue.

A second limitation of the present study is the accuracy with which effective connectivity can be modeled from BOLD data. Relative to nondirectional estimates (e.g., functional connectivity), directional estimates of regional interactions offer the potential for increased mechanistic insight into brain function. However, inferring such directionality from the BOLD signal is challenging. This challenge is not unique to applying techniques such as DCM to BOLD data to infer underlying effective connectivity, but is a challenge for any modeling technique that attempts to bridge scales. Indeed, any computational modeling approach that aims to bridge neuronal to macroscale measurements is necessarily impoverished, and parameters estimated thereof must be treated with caution. Nevertheless, modeling is driven by the merit of demonstrating sufficiency of a model to produce observed data, which serves to constrain an otherwise limitless model space, thereby fostering future research. Here, although we cannot say that the estimated parameters map onto the underlying physiology with certainty, we can say that the modeled parameters are sufficient to generate the observed cross-spectral densities of the BOLD signals. Moreover, the DCM approach to examining effectivity connectivity has been validated using combined electrophysiological and fMRI recordings (David et al., 2008), biophysical modeling (Lee, Friston, & Horwitz, 2006), and optogenetic fMRI (Bernal-Casas, Lee, Weitz, & Lee, 2017). Spectral DCM is a more recent technique, but has been demonstrated to have construct validity (Razi et al., 2015; Friston et al., 2014), and excellent group-level reliability (Nee, 2021). Nevertheless, following up the present

work with causal methods would be fruitful for validating the model and demonstrating necessity.

In summary, our findings suggest that dopamine may play an important role in modulating the effective connectivity between lateral frontal regions, by acting on the outgoing projections from the cMFG and IFS to more rostral and caudal frontal regions. In this way, dopamine may bias the influence that these regions have on more rostral and caudal frontal regions. However, several questions remain unanswered. Can the strength of the effective connectivity in these lateral frontal regions be directly related to dopamine receptor density? What are the behavioral consequences (e.g., in terms of cognitive flexibility vs. cognitive stability) of these dopaminergic connectivity effects in the lateral frontal cortex? Answers to these questions will allow for further development of neural models of cognitive control.

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Data Availability Statement

The data that support the findings of this study are available from the senior author (M. D.), upon reasonable request. The code used for the spDCM analyses is publicly available via: https://github.com/davidamadeusvogelsang/spDCM_DA_Hierarchy.

Author Contributions

David A. Vogelsang: Conceptualization; Data analysis; Writing—Original + final draft. Daniella J. Furman: Conceptualization; Data acquisition; Writing—Final draft. Derek E. Nee: Data analysis; Writing—Final draft. Ioannis Pappas: Data analysis; Writing—Final draft. Robert L. White III: Conceptualization; Data acquisition; Writing—Final draft. Andrew S. Kayser: Conceptualization; Writing—Final draft. Mark D'Esposito: Conceptualization; Funding acquisition; Writing—Final draft.

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Diversity in Citation Practices

A retrospective analysis of the citations in every article published in this journal from 2010 to 2020 has revealed a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience (JoCN)* during this period were M(an)/M = .408, W(oman)/M = .335, M/W = .108, and W/W = .149, the comparable proportions for the articles that these authorship teams cited were M/M = .579, W/M = .243, M/W = .102, and W/W = .076 (Fulvio et al., *JoCN*, 33:1, pp. 3–7). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

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