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 in more than two thirds of the participants and to different degrees. Hypo-integration co-occurred with relative hyper-connectivity in paracentral lobule and precuneus, as well as posterior putamen. Both, L-dopa-induced BOLD signal variability modulation and functional connectome modulations proved predictive of an individual’s L-dopa-induced benefits 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 their explanatory power for inter-individual differences in benefits from dopamine during cognitive performance.

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. To date, studies undertaking dopaminergic intervention have focused on only certain aspects of brain networks, i.e. long-range connection between prefrontal and visual cortices (Noudoost and Moore, 2011a, 2011b) and fronto-striatal or resting-state functional connectivity (Nagano-Saito et al., 2008; Kelly et al., 2009; Cole et al., 2013; Bell et al., 2015). In addition, the direct relationship between dopaminergic modulation of signals and networks associated with on-task cortical processing has not been studied yet. Recent advances in whole-brain modelling of large-scale cortical networks aid addressing these questions (Bell and Shine, 2016; Mill et al., 2013).
2017). 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 elevated 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, 2016; Venton et al., 2003; 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) or changes on neurovascular coupling and dynamics, which can affect the signal-to-noise ratio of the BOLD signal (e.g., Handwerker et al., 2007; Zaldivar et al., 2014). For instance, compared to younger adults, older adults often exhibited a greater effect of DA challenge on the variability of hemodynamic cortical responses (Garrett et al., 2015; Guitart-Masip et al., 2016), which has been linked to cognitive performance differences between older and younger adults.

Furthermore, the midbrain dopaminergic system innervates widespread areas of cortex ranging from sensory to motor and prefrontal regions (for review see e.g., Jaber et al., 1996; Seger and Miller, 2010; Frank, 2011). 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 (Giesing 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 brain signals over time. Thus, as higher DA availability may increase moment-to-moment brain signal variability, potentially by enhancing neural phasic activity (Paladini et al., 2003), DA availability could also impact the functional connectivity between widespread cortical regions. Previous accounts based on neural spike measurements suggest that, in the primary visual cortex, much of the variability is shared among large groups of neurons (Lin et al., 2015), and reflects global fluctuations affecting all neurons, which substantially increase correlations among pairs of neurons (Goris et al., 2014; Scholvinck et al., 2015). Thus, a direct relation between higher signal variability and stronger functional connectivity is predictable. Indeed, brain signal variability has been previously suggested as a proxy for information-processing capacity within 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, in brain networks derived from neuromagnetic signals, it has been shown that the net information transferred between nodes depends on their signal variability—as measured by sample entropy—and time scale (Vakorin et al., 2011). Accordingly, it has been proposed that brain networks showing higher nodal centrality over time have a greater potential for diverse functional configurations (McIntosh et al., 2014). Further, theories of brain meta-stability 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 Krügelbach, 2017).

Lastly, only a 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 (Herniau et al., 2017), whereas DA antagonists increase resting-state network efficiency (Ahard 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 brain 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 address these questions, we conducted an fMRI experiment in which young healthy listeners performed a previously established auditory working memory task (Lin 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.
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