Dopaminergic medication normalizes aberrant cognitive control circuit signalling in Parkinson's disease

Weidong Cai,[1,2] Christina B. Young,[3] Rui Yuan,[1] Byeongwook Lee,[1] Sephira Ryman,[3] Jeehyun Kim,[3] Laurice Yang,[3] Victor W. Henderson,[2,3,4] Kathleen L. Poston[2,3,5] and Vinod Menon[1,2,3]

1 Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

2 Wu Tsai Neurosciences Institute, Stanford University School of Medicine, Stanford, CA 94305, USA

3Department of Neurology & Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

4 Department of Epidemiology & Population Health, Stanford University School of Medicine, Stanford, CA 94305, USA

5 Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA 94305, USA

Correspondence to: Weidong Cai, PhD

1070 Arastradero Rd., Palo Alto, CA 94304, USA

E-mail: wdcai@stanford.edu

Correspondence may also be addressed to: Vinod Menon, PhD

E-mail: menon@stanford.edu

Running title: Dopamine and brain circuits in PD

Abstract

Dopaminergic medication is widely used to alleviate motor symptoms of Parkinson's disease (PD), but these medications also impact cognition with significant variability across patients. It is hypothesized that dopaminergic medication impacts cognition and working memory in PD by modulating frontoparietal-basal ganglia cognitive control circuits, but little is known about the underlying causal signalling mechanisms and their relation to individual differences in response to dopaminergic medication. Here we use a novel state-space computational model with ultra-fast (490 msec resolution) fMRI to investigate dynamic causal signalling in frontoparietal-basal ganglia circuits associated with working memory in 44 PD patients ON and OFF dopaminergic medication, as well as matched 36 healthy controls. Our analysis revealed aberrant causal signaling in frontoparietal-basal ganglia circuits in PD patients OFF medication. Importantly, aberrant signaling was normalized by dopaminergic medication and a novel quantitative distance measure predicted individual differences in cognitive change associated with medication in PD patients. These findings were specific to causal signaling measures, as no such effects were detected with conventional non-causal connectivity measures. Our analysis also identified a specific frontoparietal causal signaling pathway from right middle frontal gyrus to right posterior parietal cortex that is impaired in PD. Unlike in healthy controls, the strength of causal interactions in this pathway did not increase with working memory load and the strength of load-dependent causal weights was not related to individual differences in working memory task performance in PD patients OFF medication. However, dopaminergic medication in PD patients reinstated the relation with working memory performance. Our findings provide new insights

into aberrant causal brain circuit dynamics during working memory and identify mechanisms by which dopaminergic medication normalizes cognitive control circuits.

Keywords: cognitive control; dopamine; controllability; dynamical; state-space models

Abbreviations: PD = Parkinson's disease; HC = Healthy controls; MDSI = Multivariate dynamic state-space systems identification; LL = Low load; HL = High load; DL = Distractor load; SDMT: Symbol digit modalities test; MDS-UPDS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; LEDD = levodopa equivalent daily dosage; RT = reaction time; GLM = general linear model; HRF = hemodynamic response function; SVR = support vector regression; AI = anterior insula; PMC = premotor cortex, MFG = middle frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex, PUT/GP = putamen/globus pallidus; DMPFC = dorsomedial prefrontal cortex; STN = subthalamic nuclei

Introduction

Cognitive impairment is a pervasive non-motor symptom of Parkinson's disease (PD) with over 40% of all non-demented PD patients meeting criteria for mild cognitive impairment [1]. There are no effective treatments for cognitive deficits in PD [2], which stands in stark contrast to an armamentarium of dopaminergic medications that provide effective relief for PD motor symptoms [3]. Almost all PD patients take dopaminergic medications to improve motor symptoms associated with the disorder [4], and these pharmacological treatments have also been shown to impact working memory and executive functions [5-7], which are reliant on distributed frontoparietal-basal ganglia regions influenced by dopaminergic signalling [8-10]. However, little is known about underlying causal signalling mechanisms and their relation to individual cognitive differences in dopaminergic medication. Here, we use novel computational methods and a system neuroscience approach to investigate aberrant dynamic causal circuits in PD and to examine the effect of dopamine on brain circuit dynamics in individual patients ON and OFF dopaminergic medication.

Lewy body neuronal inclusion is the pathological hallmark of PD, with subsequent degeneration of midbrain dopaminergic neurons and dopamine depletion in the basal ganglia [11]. Optimal dopamine signalling is critical for normal functioning of frontoparietal-basal ganglia circuits involved in working memory [12-15]. While some studies have suggested that dopaminergic mediation used to treat the motor symptoms of PD has no beneficial or even have detrimental effect on cognitive functions [16-20], others point to improved treatment response in both motoric and cognitive domains [21-25]. Such inconsistent medication effects have been also observed within the working memory domain [5-7, 24]. Notably studies have revealed dissociable effects of dopaminergic medication on different cognitive tasks in the same cohorts of PD patients [26, 27], suggesting that the cognitive effects of dopaminergic medication may depend on several factors

including individual differences in functioning of cortical-subcortical circuits taxed by specific cognitive demands [13]. We address this possibility here by using computational modelling of dynamic causal signalling in frontoparietal-basal ganglia systems important for working memory and examining how dopaminergic medication in PD affects frontoparietal-basal ganglia dynamics and its relation to working memory performance and cognitive profiles.

Working memory, a component of executive function that refers to the ability to maintain and manipulate information in the absence of sensory input [28-30], is one of most prominent cognitive domains of impairment in PD patients [31]. Neuroimaging studies in PD patients have reported contradictory findings regarding activation profiles associated with working memory with evidence for reduced activation in PD [32, 33] or compensatory activation in frontal and parietal cortices as well as basal ganglia [34-36]. Although dopaminergic medication in PD has been shown to modulate activation in prefrontal cortex and striatum during working memory [37, 38], a recent meta-analysis of 22 studies investigating working memory in PD failed to pinpoint a specific neural correlate associated with executive or working memory dysfunction in PD [39]. The authors argued that the lack of findings might arise from methodical inconsistencies and a lack of quantitatively rigorous analysis of functional brain circuits. Crucially, as most neuroimaging studies of PD to date have focused on identifying abnormal responses in regional brain activation, little is known about how aberrant context-dependent causal interactions in cognitive control circuits underlying working memory and executive function lead to cognitive dysfunction [40]. We address this gap by examining how dopaminergic medication influences causal signalling in cognitive control circuits and determining whether global dopaminergic-induced changes in these circuits improves cognition.

Here, we investigate causal dynamic circuit mechanisms, involving frontoparietal-basal ganglia systems that are consistently implicated in working memory, in two groups of individuals: (i) PD patients ON (PD-ON) and OFF (PD-OFF) dopaminergic medication and (ii) age-, sex-, education- and head motion-matched healthy controls (HC). We probed dynamic causal interactions between brain regions using multivariate dynamic state-space systems identification (MDSI) [41-43]. MDSI uses a state-space model for estimating context-dependent dynamic causal interactions in latent neuronal signals after taking into account inter-regional variations in hemodynamic response. A particular advantage of MDSI is that it does not require testing a large number of pre-specified models, which is especially problematic as the number of the models to be tested increases exponentially with the number of nodes [43]. This approach not only enabled us to probe large-scale causal circuits associated with working memory, but also allowed us to determine how PD and dopaminergic medication asymmetrically affects causal circuits.

Eighty PD and HC participants completed a Sternberg working memory task during fMRI scanning. Each PD participant completed cognitive testing and MRI scanning in both ON and OFF medication sessions in a within-subject design so that each acts as his/her own control (**Figure 1A**). Participants viewed a set of stimuli for 2 seconds (**Figure 1B**), and following a jittered delay period varying between 4 and 8 seconds, were presented with a probe to which they indicated whether the probe was part of the stimulus set they had viewed earlier. Working memory load was modulated across three levels: low load (LL), high load (HL), and distractor load (DL). In the LL condition, stimuli consisted of a set of five identical digits; in the HL condition, stimuli consisted of five different digits; and in the DL condition, stimuli included different digits and task-irrelevant letters. Each PD participant also completed the Symbol Digit Modalities Test (SDMT), a brief test of working memory, attention switching, and processing

speed that has been widely used to probe general cognitive functioning in PD [44-46], in both the ON and OFF medication states. This design allowed us to probe dopaminergic effects of medication on causal brain circuit dynamics and their relation to both task performance and standardized measures of cognition.

Figure 1E provides an overview of our data analysis pipeline. We first identified frontoparietal-basal ganglia regions involved in the Sternberg working memory task (**Figure 1C, D**) and used MDSI to compute directed causal interactions between these regions of interest. Second, we evaluated network-level causal signalling mechanisms, their modulation by dopaminergic medication in PD participants, and relation to standardized measures of cognitive functioning. We computed a distance metric (**Figure 2A**) to quantify the degree of similarity between HC and each PD participant ON and OFF dopaminergic medication, and tested the hypothesis that dopaminergic medication reduces dissimilarity in dynamic causal interactions within frontoparietal-basal ganglia circuits in PD. We further hypothesized that changes in similarity of dynamic causal interactions would predict dopamine-related changes in general cognitive function. Finally, we identified specific causal links that showed load-dependent deficits in PD compared to HC participants, and investigated their relation to dopaminergic medication and behavioural performance on the in-scanner Sternberg task. We hypothesized that frontoparietal and prefrontal-basal ganglia links would show impairments in PD and that the degree of impairment would predict task deficits. Our findings described below demonstrate that dynamic causal interactions involving distributed brain regions important for working memory are aberrant in PD and that dopaminergic medication restores the function of frontoparietal-basal ganglia circuitry in these patients.

Materials and Methods

Participants

All participants were enrolled in the Stanford Alzheimer's Disease Research Center. Inclusion criteria for HC included age ≥ 60 years; no neurological, psychiatric or medical conditions causing cognitive impairment determined through history and neurological examination; and cognitively normal as determined by clinical consensus after formal testing that included the National Alzheimer's Coordinating Center Uniform Data Set (version 3) neuropsychological battery. PD was determined by UK Brain Bank criteria [47] after a comprehensive neurological screening exam and the Movement Disorders Society-Unified Parkinson's disease Rating Scale motor assessment (MDS-UPDRS part III) [48] both OFF and ON dopaminergic medications. PD participants completed formal neuropsychological testing with the Uniform Data Set version 3 battery which occurred within 6 months of the fMRI session. A total of 48 HCs completed the Sternberg task in one fMRI session and 39 PD participants completed the Sternberg task in two separate ON and OFF fMRI sessions in random order. Two participants (2 HC) were excluded for excessive motion (i.e., mean motion >1.5 standard deviations above the interquartile range), three participants (2 HC, 1 PD) were excluded for poor task performance (i.e., <65% accuracy), and two participants (2 PD) were excluded because MDSI parameter estimation did not converge. Thus, a total of 44 HCs (71±6 years old; 25F/19M; **Table 1**) and 36 PD participants (69±7 years old; 21F/15M; 29 PD with no cognitive impairment, 7 PD with mild cognitive impairment) were included in the final analyses. The sample size was determined by power analysis (see **Supplementary Methods**).

All participants provided written consent and the Stanford University Institutional Review Board approved all study protocols.

Symbol Digit Modality Test (SDMT)

The SDMT is a sensitive neuropsychological test that assesses working memory, attention switching, and processing speed, and has been shown to be sensitive to cognitive changes in PD [44-46]. Each participant in the PD group completed the written SDMT during the ON and OFF medication states.

Sternberg task

Participants performed a modified Sternberg working memory task during fMRI **(Figure 1B**). Each trial consisted of either low-load (LL), high-load (HL), or distractor-load (DL) working memory conditions. Accuracy and mean reaction time (RT) were recorded for each trial. Each scan included four runs, with each consisting of 6 LL, 6 HL, and 6 DL working memory trials randomly intermixed. The stimulus presentations were implemented using E-Prime (v2.0; Psychology Software Tools, Pittsburgh, PA; 2002) and projected at the center of the screen. Prior to each fMRI session, participants completed a practice session of the task.

Data acquisition

The fMRI images were collected using a 3T scanner. A total of 790 functional images were acquired using multiband echo-planar imaging with the following parameters: 42 slices aligned with the anterior-posterior commissure line, with interleaved order, repetition time (TR) = 490 ms, echo time = 30 ms, multi-band factor = 6, flip angle 45°, field of view = 222 x 222 mm, matrix = 74 x 74, 3 mm slice thickness, and voxel size = 3 x 3 x 3 mm. The first 12 time points were removed to allow for signal equilibration, leaving 778 time points for each participant. Each participant's T1-weighted anatomical scan had been acquired using a magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (256 slices with a 176*256 matrix; voxel size 1.00x0.977x0.977mm^3).

fMRI preprocessing

A standard preprocessing pipeline was implemented using SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), as well as in-house programs in MATLAB (MathWorks), details described in **Supplementary Methods**.

GLM analysis

For each task and subject, a general linear model (GLM) was used, which included regressors of interest for LL, HL and DL conditions and 6 nuisance regressors for head motion. Both canonical hemodynamic response function (HRF) and its time-derivative were used to convolve the stimulus function to form the regressors. The significant activation patterns were determined using a voxel-wise height threshold of $p < 0.01$ and an extent threshold of $p < 0.01$ with family-wise error correction using a nonstationary suprathreshold cluster-size approach based on Monte-Carlo simulations [49]. Brain activation maps associated with specific task conditions and PD-related differences are shown in **Supplementary Figure S3**.

Working memory network

We built a network model involving frontoparietal and basal ganglia regions most consistently implicated in working memory, including middle frontal gyrus (MFG)/dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), premotor cortex (PMC), dorsomedial prefrontal cortex (DMPFC), bilateral anterior insula (AI), and putamen/globus pallidus (PUT/GP) [40, 50-52]. The precise location of network nodes was based on task-activation peaks that overlapped with these brain regions, as demarcated by the Brainnetome atlas [53]. Peaks were determined using combined task-fMRI data from both HC and PD groups, and a one-way ANOVA with a factor of task condition (LL, HL, DL) (**Figure 1C**, **1D**). Bilateral subthalamus nuclei (STN), whose coordinates were determined by a high resolution structural MRI study [54], were also included in

the network given its critical role in cognitive impairment [55-58] and stimulation-based treatment in PD patients [59, 60 61, 62], as well as its role in dopaminergic modulation of brain circuits [63]. Both factors are particularly relevant in the context of our investigation of the effects of dopamine modulation on causal signaling among brain areas involved in working memory. Moreover, our Sternberg working memory task included a DL condition that requires greater inhibitory control processes which are known to engage the STN as demonstrated in animal [64-67] and human studies [68-71]. Finally, the STN is specifically involved in high-conflict decision-making, which is necessary for accurate performance on the Sternberg task, through its role in the hyperdirect pathway involving the prefrontal cortex [55-58].

Mean time series were extracted from each of the resulting thirteen working memory network nodes. A multiple linear regression approach with 6 realignment parameters (3 translations and 3 rotations) was applied to reduce head motion-related artifacts, and the resulting time series were further linearly detrended, normalized, and high-pass filtered (>0.008Hz).

MDSI model for estimating causal interactions from fMRI data

MDSI estimates context-dependent causal interactions between multiple brain regions in latent quasi-neuronal state while accounting for variations in hemodynamic responses in these regions [43]. Analysis of MDSI, its modulation by task, group and medication, and relation to behavior are described in the **Supplementary Methods**.

MDSI-distance analysis

To evaluate the effect of dopamine treatment on global causal mechanisms in PD, we developed a distance metric to quantify the dissimilarity in dynamic causal interactions between PD ON and OFF medication condition in comparison to HCs. The distance (d) is defined by the sum of square of causal weight difference between each PD participant and mean of HC group. The

absolute geometric distance allows us to quantify overall divergence of each PD participant from healthy controls across all the network connections. The algorithm used to compute the MDSI-distance for each PD participant is illustrated in **Figure 2A**. Paired *t*-tests were used to examine whether the distance of between PD-OFF and HC is significantly different from the distance between PD-ON and HC.

MDSI-distance predicts cognitive function

To examine whether MDSI-distance could account for individual differences in the effect of dopaminergic medication on cognition in PD, we conducted multivariate regression analysis using linear support vector regression (SVR). The MDSI-distance in each task condition, LL, HL and DL, were used as features to predict the difference in SDMT scores assessed during ON and OFF states. One PD participant did not complete SDMT test and two outliers were identified using a 2.5 standard deviation of the group mean cutoff, leaving 33 data PD participants for this analysis. The model was evaluated using the Leave-one-out cross validation. Each time, one data point was selected as a test set and the rest of the data were used as a training set. The training set was then used to train a SVR model, which was then applied to the test set for classification. This procedure was repeated N times with each data point used exactly once as a test set. *Pearson*'s correlations were used to evaluate prediction performance.

PPI analysis

We used general psychophysiological interaction (gPPI) [72] to estimate non-causal task modulated connectivity, and details described in **Supplementary Methods**.

Data availability

All data used in this study will be shared upon request from qualified investigators.

Results

Cognitive impairments in PD participants

PD participants evaluated OFF dopaminergic medication had significantly worse SDMT scores than HCs ($t_{(71)}$ = 2.04, p = 0.04, *Cohen's d* = 0.46, **Table 1**). No significant difference was found between HC and PD-ON groups (p = 0.11). We then examined the effect of dopaminergic medication on cognition (**Table 1**). There was no significant difference between PD-OFF and PD-ON in SDMT (p > 0.4).

Working memory performance in PD off dopaminergic medication (PD-OFF) vs. HC participants

Both HC and PD participants showed high performance on the Sternberg task, with average accuracies over 90% in all conditions (i.e., LL, HL, DL) (**Table 1**). A two-way analysis of variance (ANOVA) with factors group (HC, PD-OFF) and condition (LL, HL and DL) revealed a significant main effect of condition ($F_{(2,156)}$ = 10.39, p = 5.78e-05, *Cohen's f* = 0.12) such that accuracies were significantly higher in LL compared to HL ($t_{(79)}$ = 4.97, p = 3.80e-06, *Cohen's d* = 0.56) and DL ($t_{(79)}$ = 3.45, p = 0.0008, *Cohen's d* = 0.39) conditions (**Table 1**); accuracies in HL and DL conditions were equivalent ($t_{(79)}$ = 0.32, p = 0.75, *Cohen's d* = 0.04). There was no significant interaction between group and condition ($F_{(2,156)}$ = 1.74, p = 0.18, *Cohen's f* = 0.02) and no significant main effect of group ($F_{(1,78)}$ = 1.38, p = 0.24, *Cohen's f* = 0.02).

A similar ANOVA on reaction time (RT) on correct trials revealed a significant main effect of condition ($F_{(2,156)}$ = 179.85, p = 2e-16, *Cohen's f* = 1.52) such that responses were significantly faster in the LL in comparison to HL ($t_{(79)}$ = 14.66, p = 2.2e-16, *Cohen's d* = 1.64) and DL ($t_{(79)}$ = 14.53, p = 2.2e-16, *Cohen's d* = 1.62) conditions (**Table 1**), but there was no difference in RT between HL and DL conditions ($t_{(79)}$ = 1.73, p = 0.09, *Cohen's d* = 0.19). There was no

significant interaction between group and condition ($F_{(2,156)}$ = 0.28, p = 0.76, *Cohen's f* = 0.06) and no significant main effect of group ($F_{(1,78)}$ = 0.16, p = 0.69, *Cohen's f* = 0.05).

Working memory performance in PD participants off (PD-OFF) vs. PD participants on (PD-ON) dopaminergic medication

A two-way repeated measures ANOVA with factors PD medication state (PD-OFF, PD-ON) and task condition (LL, HL and DL) revealed a significant main effect of task condition ($F_{(2,70)}$ = 11.09, p = 6.6e-05, *Cohen's f* = 0.56) such that accuracies were significantly higher in the LL compared to HL ($t_{(71)}$ = 4.61, p = 1.76e-05, *Cohen's d* = 0.54) and DL ($t_{(71)}$ = 3.75, p = 0.0004, *Cohen's d* = 0.44) conditions; there was no significant difference in accuracy between HL and DL conditions ($t_{(71)}$ = 0.38, p = 0.70, *Cohen's d* = 0.05). There was no significant interaction between PD medication state and task condition ($F_{(2,70)}$ = 2.60, p = 0.08, *Cohen's f* = 0.17) and no significant main effect of medication state ($F_{(1,35)}$ = 1.48, p = 0.23, *Cohen's f* = 0.16).

A similar repeated measures ANOVA was performed with RT on correct trials. This analysis revealed a significant main effect of task condition ($F_{(2,70)}$ = 79.4, p = 2e-16, *Cohen's f* = 1.51) such that responses were faster for LL compared to HL ($t_{(71)}$ = 11.82, p = 2.2e-16, *Cohen's d* = 1.39) and DL ($t_{(71)}$ = 12.37, p = 2.2e-16, *Cohen's d* = 1.46) conditions, as well as for HL compared to the DL condition ($t_{(71)}$ = 2.07, p = 0.04, *Cohen's d* = 0.24). There was no significant interaction between PD medication state and task condition ($F_{(2,70)}$ = 0.24, p = 0.79, *Cohen's f* = 0.08) and no significant main effect of medication state ($F_{(1,35)}$ = 1.67, p = 0.21, *Cohen's f* = 0.22).

Dynamic causal interactions in the Sternberg working memory task

We first identified frontoparietal-basal ganglia ROIs that showed task-load effects in a combined group of HC and PD-OFF participants (**Figure 1C**) , all of which have been widely implicated in

a range of working memory tasks (**Figure 1D, Table 2**). To investigate condition-specific causal interactions between all nodes of the frontoparietal-basal ganglia circuit in each participant, we applied MDSI and the strength of causal interactions was estimated in the latent neuronal space across all nodes without having to test multiple models, allowing us to determine a directed asymmetric 13x13 connectivity matrix. Our analysis revealed multiple significant directed causal interactions between frontoparietal-basal ganglia network during LL, HL, DL conditions (p = 0.05, FDR corrected) in HC, PD-OFF, and PD-ON groups (**Supplementary Figure S1**).

Dopaminergic medication improves network-level causal interactions in PD

To examine whether dopaminergic medication improves causal signaling mechanisms in PD at the network-level, we computed a distance measure to quantify the extent of dissimilarity in dynamic causal interactions among all the nodes in the frontoparietal-basal ganglia network in each PD medication state (OFF or ON) relative to HCs. Briefly, distance metric was defined as the sum of square of differences in causal weights across all ROI pairs between each PD participant and the HC group (**Figure 2A**). We conducted a two-way ANOVA with factors medication (OFF, ON) and task condition (LL, HL and DL). Although there was no significant interaction between medication state and task condition ($F_{(2,70)}$ = 0.33, p = 0.72, *Cohen's f* = 0.10) and no significant main effect of task condition ($F_{(2,70)}$ = 0.09, p = 0.92, *Cohen's f* = 0.05), there was a significant main effect of medication state ($F_{(1,70)}$ = 7.45, p < 0.01, *Cohen's f* = 0.46). Post-hoc analysis revealed that distance between PD-OFF and HC was significantly greater than that between PD-ON and HC in LL ($t_{(35)}$ = 2.04, p = 0.04, *Cohen's d* = 0.34), HL ($t_{(35)}$ = 2.44, p = 0.02, *Cohen's d* = 0.41) and DL ($t_{(35)}$ = 2.26, p = 0.03, *Cohen's d* = 0.38, **Figure 2B**) conditions. These results demonstrate that dopaminergic medication improves network-level causal interactions in the PD group.

To further test whether the dopaminergic medication effect on network-level signaling in the PD group is specific to causal interactions, we conducted the same analysis in non-causal task-modulated connectivity estimated using gPPI. We used the same distance metric to estimate dissimilarity in network-level gPPI weights between PD and HC in ON and OFF sessions. There was no significant difference in distance metric in any task condition between the ON and OFF sessions (*ps*>0.3), indicating that dopaminergic medication specifically improves casual interactions rather than connectivity in general.

Relation between changes in network-level causal interactions and cognition with dopaminergic medication

Next, we examined whether changes in network-level causal signaling is related to individual differences in cognitive function with dopaminergic medication. We trained a support vector regression model based on network distance between the PD-ON and PD-OFF states, to predict changes in SDMT scores between ON and OFF dopaminergic medication and evaluated performance of the model using leave-one-out cross validation. Network distance changes accurately predicted SDMT changes between ON and OFF states (r=0.36, p=0.04, **Figure 3**). These results demonstrate that changes in causal signaling patterns within cognitive control circuitry contributes to cognitive changes in PD.

Working memory load-dependent modulation of dynamic causal interactions and relation to behavior in HC

Next, we identified causal signaling pathways that showed consistent working memory load-dependent modulation in HCs and determined whether these pathways are associated with individual differences in HC working memory task performance. Paired *t*-tests revealed that in HCs, load-dependent modulation of the causal interaction from the rMFG to rPPC

(rMFG→rPPC) was significant in the HL versus LL conditions ($p < 0.05$, FDR corrected, **Figure 4A**) and in the DL versus LL conditions ($p = 0.006$), suggesting a consistent load effect in causal interaction of rMFG→rPPC across high load conditions (**Supplementary Figure S2**). There was no significant difference between the DL versus HL conditions ($p> 0.3$). Notably, load-dependent modulation of this frontoparietal causal link was highly right lateralized ($p<0.01$, see **Supplementary Results**).

Next, we sought to determine whether this causal link rMFG→rPPC was behaviorally relevant. Our analysis focused on working memory load effects in the relation to RT since accuracy was uniformly high. We found that the strength of dynamic casual interaction was not significantly related to Sternberg performance when the HL vs. LL contrast was used (p>0.45). However, the strength of the causal link rMFG→ rPPC contrasting DL vs. LL conditions was correlated with RT differences between these condition (r=-0.33, p=0.02, **Figure 4B**).

Dopaminergic modulation of the relation between rMFG→ rPPC *and behavioral performance in PD*

Having identified rMFG→ rPPC as a causal signaling pathway that showed consistent working memory load-dependent modulation in HCs and a direct relation to working memory task performance, we then determined whether this link is impaired in PD-OFF. First, we conducted a two-way ANOVA with factors group (HC, PD-OFF) and condition (LL, HL and DL) revealed a significant interaction between group and condition ($F_{(2,156)} = 8.56$, $p = 0.0003$, *Cohen's f* = 0.33) but no significant main effect of group ($F_{(1,78)} = 0.10$, $p = 0.75$, *Cohen's f* = 0.04) and condition ($F_{(2,156)} = 1.95$, $p = 0.15$, *Cohen's f* = 0.16). Post-hoc analysis found that the load-dependent strength of the causal link rMFG → rPPC was significantly weaker in PD-OFF compared to HC in both the DL and HL relative to LL task conditions (ps<0.005, **Supplementary Figure S2**).

We then examined whether dopaminergic medication improves load-dependent modulation of the causal link rMFG→rPPC in PD and did not find significant effect in either DL or HL relative to LL task conditions (*ps*>0.05).

Next, we examined whether dopaminergic medication restores the load-dependent relation between rMFG→ rPPC causal interactions and behavioral performance assessed using RT, as was discovered in HCs above. We found that the strength of the causal link rMFG→ rPPC was not significant in the PD-OFF group (r=0.13, p=0.45, **Figure 4C**) but was significant in the PD-ON group (r=-0.44, p=0.007, **Figure 4D**). Comparison of the correlations confirmed that the correlation coefficient was significantly weaker in PD-OFF than HC (p=0.02, *Fisher*'s z test) and significantly weaker in PD-OFF than PD-ON (p=0.005, *Dunn* and *Clark*'s z test). These results suggest that stronger load-dependent causal interaction in rMFG→ rPPC is associated with better behavioral performance, and this relationship is impaired in PD but restored by dopaminergic medication.

To further examine whether the relationship between the strength of the causal link rMFG→ rPPC and behavioral performance was confounded by age, sex and head motion, we conducted multiple linear regression analyses. Our analyses confirmed that the causal strength of rMFG→ rPPC was the only significant predictor of RT differences between DL and LL task conditions in both HC and PD-ON groups after controlling age, sex and frame-wise displacement (ps<0.05, **Table 3**). These results demonstrate that the robustness of the relationship between dynamic causal interaction of rMFG→ rPPC and behavioral performance.

Finally, we determined whether the relation between the strength of the causal link rMFG→ rPPC and behavioral performance could be uncovered by gPPI; no significant brain-behavior

relations were found with gPPI (p>0.3). These results demonstrate the specificity of brain-behavior relations estimated by MDSI (see **Supplementary Materials** for additional details).

Robustness of the main findings

We conducted additional analyses to determine the robustness of our findings. Specifically, we examined whether medication effect on network-level causal signaling and its relation to cognition are stable without inclusion of STN-related connections, as well as the impact of other medication factors. Results from these analyses, described in the **Supplementary Materials**, were equivalent to our main findings, highlighting the robustness of our findings.

Discussion

We used novel computational tools and state-space causal modeling to investigate dynamic causal circuits underlying working memory in PD patients ON and OFF dopaminergic medication. Our study incorporated several innovations at the computational, methodological and design levels. First, rather than examining regional activation or static functional connectivity, we used high temporal fMRI sampling of 490 msec to probe dynamic causal mechanisms in PD patients ON and OFF dopaminergic medication. This allowed us to uncover dynamic processes that are not observable with conventional approaches, as demonstrated by our lack of findings using acausal functional connectivity techniques. Second, we used a novel state-space approach that allows testing of modulatory effects of working memory on all links. Our approach overcomes the limitation of having to test a limited set of models in a combinatorically large space of models that precludes testing of all possible models. Finally, we examined task-related casual circuits involved in cognitive control using a larger sample (PD=36, HC=44) than previous studies [39] and incorporated a within-subject design to examine dopaminergic effects in

PD participants. Thus, we are able to examine how within-subject level changes due to dopaminergic medication relate to dynamic brain circuits and cognition.

Our analysis revealed aberrant causal signaling in frontoparietal-basal ganglia circuits in PD patients OFF medication, which were normalized by dopaminergic medication. Quantitative distance measures predicted individual differences in cognitive change associated with medication in PD. We also identified a specific frontoparietal causal signaling pathway that is impaired in PD patients. More specifically, unlike in HCs, the causal interaction from rMFG to rPPC (rMFG→ rPPC) was not modulated by working memory load and the strength of load-dependent causal weights was not related to individual differences in working memory performance in PD participants OFF medication. However, dopaminergic medication reinstated the relation between load-dependent casual interactions from rMFG to rPPC and working memory task performance. Our findings provide novel insights into aberrant causal brain circuit dynamics during working memory and demonstrate that dopaminergic medication normalizes cognitive control circuits.

L-DOPA normalizes aberrant network-level causal signaling in frontoparietal-basal ganglia cognitive control circuits

Most investigations examining the neural correlates of working memory in PD have focused on regional task activation [9, 32, 73-77]. A recent meta-analysis of 13 studies examining working memory in PD failed to identify consistent abnormal activation during working memory performance in PD patients compared to HCs [39]. Similarly, the few studies that have examined task-modulated connectivity have also yielded inconsistent findings [78-80]. For example, one study showed a lack of attention-modulated connectivity between prefrontal regions and premotor cortex in PD patients [80]. Another study reported both increased and decreased cognitive control-

modulated cortical-basal ganglia connectivity in PD [79]. Other studies have reported reduced corticocortical and cortical-subcortical connectivity in PD patients following working memory training [81]. Resting-state connectivity has been examined more extensively and a recent meta-analysis showed reduced default mode network connectivity in PD patients with cognitive impairment [82]. However, resting-state does not provide insight into brain activity during cognitive activity and indeed, one study showed that despite resting-state compromise in PD, task-related connectivity can be adequately engaged to enable near normal task performance [79]. We took a quantitatively rigorous circuit analysis approach to probe dynamic causal mechanisms in the human brain. MDSI simultaneously estimates the causality between regions under each task condition within the same modeling framework while accounting for variations in hemodynamic responses in these regions. Importantly, we used a multivariate circuit distance measure to determine the effect of dopaminergic medication on causal circuit dissimilarity between PD and HCs. Our analysis revealed that dopaminergic medication reduced dissimilarity of causal circuit signaling between PD and HC in each of the three working memory load conditions. We suggest that multivariate circuit measures involving distributed cortico-cortico and cortico-basal ganglia circuits engaged in working memory and cognitive control [40, 69, 83-85] may allow us to better capture the effects of dopaminergic medication. Such measures may also allow us to overcome limitations of previous approaches which have focused on individual brain regions or specific inter-regional links which have resulted in inconsistent findings [39]. Crucially, the present study is the first to demonstrate normalization of network-level causal signaling through dopaminergic medications in PD.

Network-level causal signaling predicts individual differences in dopaminergic treatment response

Levodopa and dopaminergic agonists are highly effective in alleviating motor symptoms associated with dopamine deficiency in PD patients [4]. However, their effects on cognition in PD varies considerably across individuals and is likely influenced by factors such as differences in medication history, dosage, type of medication used, metabolism and dopamine regulation [86, 87]. Given the wide range of factors that can influence dopaminergic medication-related cognitive changes, examination of individual differences has the potential to provide better insight into mechanisms of treatment response. We therefore assessed the relation between medication-related changes in network similarity and changes in cognitive functioning using the SDMT, a brief cognitive test of working memory, attention switching, and processing speed [44-46]. We found that dopaminergic modulation of network-level causal signalling predicted medication-related changes in cognitive functioning in PD patients. Importantly, we tested this relationship using a cross-validation procedure such that a trained model is used to predict the medication effect on cognition based on the medication effect on global network-level signalling of unseen data. Results suggest that alterations in network-level dynamic causal interactions in the frontoparietal-basal ganglia cognitive control system are a mechanism by which dopaminergic medication affects cognitive functioning in PD patients. Our results further suggest that medication-related changes in network-level signalling may be an objective biomarker of treatment response.

Dopamine reinstates relation between frontoparietal causal signaling and working memory performance in PD

The MFG and PPC are key nodes of the frontoparietal working memory network [88-91]. Their neuronal activity profiles are tightly linked to the ability to maintain and manipulate the content of working memory [30, 92-96]. Human neuroimaging studies have consistently reported activation of the MFG and PPC during working memory task performance [83, 97-101] and have furthermore highlighted consistent co-activation of the two regions across a wide range of working memory tasks [50-52, 102]. Consistent with these reports, we found robust coactivation of the rMFG and rPPC in HC as well as PD participants. Crucially, we observed significant load-dependent modulation in causal signalling from the rMFG to rPPC (rMFG → rPPC) in HCs. Notably, this brain-behaviour relationship was only observed in the more demanding DL condition which required participants to suppress attention to distractors while encoding task-relevant stimuli. This result is consistent with the hypothesis that the MFG plays a key role in top-down control of working memory, including selection of task-relevant information and suppression of task-irrelevant information [83, 103], whereas the PPC plays an important role in temporal storage of information [104, 105]. Consistent with this hypothesis, a recent study has shown dissociable effects from stimulation of the two regions in a working memory task using transcranial magnetic stimulation (TMS) [106]. Specifically, theta-TMS (excitatory to neural activity) on MFG improves performance on trials with task-relevant cues whereas alpha-TMS (inhibitory to neural activity) on PPC has positive effect on trials with task-irrelevant cues.

The higher load-dependent modulation of dynamic causal interactions in the right frontoparietal circuit, compared to the left, may reflect right hemispheric dominance across a broad range of cognitive control tasks [107, 108]. Interestingly, a previous n-back working memory study in healthy

controls, using visually-displayed letters, has also found the right lateralized increase in dynamic causal interactions with cognitive load in connection between DLPFC and parietal cortex [109]. More importantly, our analysis identified aberrancies in top-down causal signaling from the rMFG to the rPPC in PD patients. In HCs, the strength of rMFG → rPPC load-dependent causal interactions predicted individual differences in reaction time, demonstrating the relevance of this causal pathway for efficient task performance during the presence of a distractor. In PD patients OFF dopaminergic medication, the rMFG → rPPC link was significantly less modulated during the presence of a distractor, and there was no relation between the strength of interaction and working memory performance. Notably, like in HCs, the strength of causal rMFG → rPPC signaling was correlated with working memory performance in the PD ON group. Thus, dopaminergic medication restores behaviorally relevant causal signaling from the rMFG to rPPC in PD patients, likely allowing for more efficient manipulation of relevant versus irrelevant information, reduced interference, and ultimately improved working memory performance. Our findings are consistent with reports that dopamine specifically reduces interference [110] and that the ability to suppress distractions which is impaired in PD-OFF participants improves with dopaminergic medication [21]. This aligns well with our finding that it was during the DL task, which specifically requires suppression of distractors, that dopaminergic medication reinstated the relationship between causal signaling from rMFG to rPPC and working memory performance. Our findings thus suggest that causal signaling from rMFG to rPPC may be an underlying mechanism of impaired gating of relevant versus irrelevant items and thereby increased interference in PD [111].

Limitations

We found that dopaminergic modulation of network-level causal signalling in PD patients predicted medication-related changes in cognitive functioning as assessed using the SDMT, a standardized test of working memory, attention switching, and processing speed that has been widely used to probe general cognitive functioning in PD [44-46]. However, dopaminergic modulation on network-level causal signalling did not directly predict medication-related changes in performance on the Sternberg working memory fMRI task, likely due to the high levels of task performance in PD patients (> 90% accuracy in all task conditions). While our findings highlight the role of causal interaction between MFG and PPC in the DL task, associated with selection of task-relevant information and suppression of task-irrelevant information, a limitation here is that our study could not dissociate specific working memory and cognitive control processes. Finally, due to computational limitations, we were not able to examine dynamic causal interactions across all task-related regions covering the entire brain. This does not mean that other left out brain regions, such as caudate and cerebellum, are not important for working memory, PD, or dopaminergic modulation. Future work is needed using computational algorithms that can handle large network size, along with fast-sampling rate as used here, to probe the role of other brain areas implicated in working memory.

Conclusion

We used state-space modeling to uncover causal signaling mechanisms within a core frontoparietal-basal ganglia circuit implicated in working memory in PD patients and further examined the effects of dopaminergic medication. Our analysis revealed that dopaminergic medication can normalize abnormality in network-level causal signaling in PD and the extent of dopaminergic modulation on causal mechanism in frontoparietal-basal ganglia network can predict the effect of medication on cognition. More specifically, in comparison to HCs, PD

patients have weakened load-dependent modulation of frontal-parietal causal interaction. Dopaminergic medication can restore the association between causal strength of rMFG→ rPPC and working memory performance in PD patients, similar to what is observed in HCs, but this was diminished in PD patients when they were OFF medication. Our findings highlight aberrant causal signaling between key working memory regions as an important neurobiological feature of PD and provide novel evidence for supporting positive effects of dopaminergic medication in high-order cognitive system in PD patients. The approach and methods developed here are useful for probing broad medication effects on cognitive systems in neurological and psychiatric disorders.

FUNDING

This research was supported by grants from the National Institute of Health (P50 AG047366, P30 AG066515, P50 NS062684, NS08608505, MH121069).

AUTHOR CONTRIBUTIONS

Conceptualization: W.C., K.L.P., V.M.; Methodology: W.C., R.Y., B.L., V.M.; Data acquisition: K.L.P, J.K., L.Y., V.W.H.; Investigation: W.C., R.Y., B.L., V.M.; Writing: W.C., C.B.Y., K.L.P., V.M.

COMPETING INTERESTS

The authors declare no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1. Task design and data analysis pipeline. (**A**) Within-subject study design: Each Parkinson's disease (PD) participant has two visits, one while ON medication (PD-ON; green) and the other while OFF medication (PD-OFF; red). During each visit, PD participants underwent clinical (MDS-UPDRS and SDMT) testing and MRI scanning with performance on an event-related Sternberg working memory fMRI task. (**B**) Illustration of the low-load (LL), high-load (HL) and distractor-load (DL) Sternberg working memory task conditions. (**C**) ANOVA analysis amongst healthy controls (HC) and PD-OFF was used to uncover load effects (LL vs. HL vs. DL) and identify regions of interest (ROIs). Statistical map was thresholded at $p<0.001$ FWE corrected. (**D**) ROIs used in the MDSI analysis: (1) lAI, (2) rAI, (3) DMPFC, (4) lPM, (5) rPM, (6) lMFG, (7) rMFG, (8) lPPC, (9) rPPC, (10) lPUT/GP and (11) rPUT/GP. (12) lSTN and (13) rSTN coordinates were determined from a previous study [54]. (**E**) Overview of data analysis pipeline. We first extracted timeseries from each ROI and applied MDSI to determine dynamic causal interactions from each participant in the LL, HL and DL task conditions. MDSI-derived causal influences were then used to investigate: (1) dissimilarity in network-level causal signaling between PD and HC, and whether this dissimilarity was reduced by dopaminergic medication, (2) whether dopaminergic medication-related changes in network dissimilarity is related to individual differences in cognition, (3) links that showed load-dependent effects on causal signaling, and (4) the relationship between causal signaling and working memory task performance. AI: anterior insula; DMPFC: dorsomedial prefrontal cortex; PM: premotor cortex; MFG: middle frontal gyrus; PPC: posterior parietal cortex; PUT/GP = putamen/globus pallidus ; STN: subthalamic nuclei.

Figure 2. Dopaminergic medication reduces MDSI distance in PDs. (**A**) Schematic illustration of the algorithm used to compute MDSI-based dissimilarity measure (distance) in each PD participant. The distance (d) is defined by the sum of the square of MDSI weight difference between each PD participant and the mean of the HC group. Note that d^k is the distance metric for k^{th} PD participants; N is the total number of non-diagonal edge (i,j) in MDSI weight matrix per condition; $W_{i,j}^k$ is the MDSI weight on edge (i,j) for k^{th} PD participant; $\overline{W_{i,j}^{HC}}$ is the mean MDSI weight on edge (i,j) for all HCs. (**B**) Dopaminergic medication reduces MDSI-based distance, which quantifies the dissimilarity in network-level causal signaling between each PD participant and the HC group, in each task condition (i.e., LL, HL, DL) (all *ps* < 0.05). *, $p<0.05$.

Figure 3. Medication effect on MDSI distance in relation to cognitive function. MDSI-based distance in causal signaling patterns predicted changes in symbol digit modalities test (SDMT) scores between ON and OFF medication states in PD participants (r=0.36, p=0.04). A support vector regression model based on network distance between the PD-ON and PD-OFF states was used to predict changes in SDMT scores between ON and OFF dopaminergic medication.

Figure 4. Causal signaling in frontoparietal network in relation to load effect. (**A**) MDSI analysis revealed a significant load-dependent casual influence from rMFG to rPPC in healthy controls (HC). **(B-D)** Relation between the strength of causal signaling from the rMFG to rPPC (rMFG → rPPC) and working memory performance is rescued by dopaminergic medication: (**B**) Healthy controls, HC; (**C**) PD participants off dopaminergic medication, PD-OFF; and (**D**) PD participants ON medication, PD-ON.

Table 1 Demographic information and behavioral performance

	CTL	PD		CTL vs. PD-OFF		PD-OFF vs. PD-ON	
		PD-OFF	PD-ON	t-/chi-stats	p-value	t-/chi-stats	p-value
sample size	44	36					
age (years old)	71 ± 6	69 ± 7		1.81	0.07		
sex (f/m)	25/19	21/15		0	1		
education (years)	17 ± 2	17 ± 2		0.66	0.51		
MDS-UPDRS III		35 ± 11	22 ± 8			9.31	5.34×10^{-11}
SDMT	51 ± 11	45 ± 11	46 ± 13	2.04	0.04	0.71	0.49
max Disp (mm)	2.29 ± 1.29	2.39 ± 1.88	2.15 ± 0.90	0.27	0.79	0.82	0.42
max FD (mm)	1.06 ± 1.06	1.06 ± 0.95	0.86 ± 0.42	0.002	0.99	1.41	0.17
Stern LL ACC (%)	97 ± 4	97 ± 4	97 ± 6	0.39	0.7	0.4	0.69
Stern HL ACC (%)	92 ± 5	94 ± 7	91 ± 9	2.21	0.03	2.08	0.04
Stern DL ACC (%)	93 ± 9	93 ± 8	93 ± 9	0.03	0.98	0.2	0.85
Stern LL RT (ms)	998 ± 229	1017 ± 219	1054 ± 272	0.38	0.71	1.21	0.23
Stern HL RT (ms)	1282 ± 243	1292 ± 280	1344 ± 327	0.17	0.87	1.41	0.17
Stern DL RT (ms)	1290 ± 253	1326 ± 312	1363 ± 352	0.55	0.58	0.93	0.36

Table 2 Working memory regions of Interest (ROIs) used in the multivariate dynamical systems identification (MDSI) analysis

index	ROIs	x	y	z
1	right PM	50	−2	48
2	left PM	−50	−2	48
3	right PPC	26	−64	44
4	left PPC	−26	−64	44
5	midline DMPFC	−1	16	50
6	right MFG	38	47	17
7	left MFG	−38	47	17
8	right AI	−32	22	2
9	left AI	32	22	2
10	right PUT	27	−11	4
11	left PUT	−27	−11	4
12	right STN	11	−12.5	−7
13	left STN	−8	−13.5	−7

Table 3 Relation between load-dependent modulation of the strength of causal signalling between the right middle frontal gyrus and posterior parietal cortex (rMFG→rPPC) and reaction time differences between distractor (DL) and low-load (LL) task conditions

	beta	t-value	p-value
HC			
rMFG→rPPC	−0.26	−2.24	0.03 *
Age	0.003	0.66	0.51
Sex	−0.001	−0.04	0.97
mean FD	−0.33	−0.54	0.59
PD-OFF			
rMFG→rPPC	0.18	0.76	0.45
Age	0.002	0.38	0.71
Sex	0.002	0.05	0.96
mean FD	0.34	0.31	0.76
PD-ON			
rMFG→rPPC	−0.54	−2.55	0.02 *
Age	0.001	0.17	0.86
Sex	0.006	0.17	0.86
mean FD	−0.19	−0.25	0.81

The strength of the causal link rMFG→ rPPC contrasting DL vs. LL conditions was correlated with RT differences between these conditions in healthy controls (HC) and PD-ON, but not in the PD-OFF, groups. Results of multiple linear regression analyses controlling for age, gender, and head motion. mean FD: mean framewise displacement

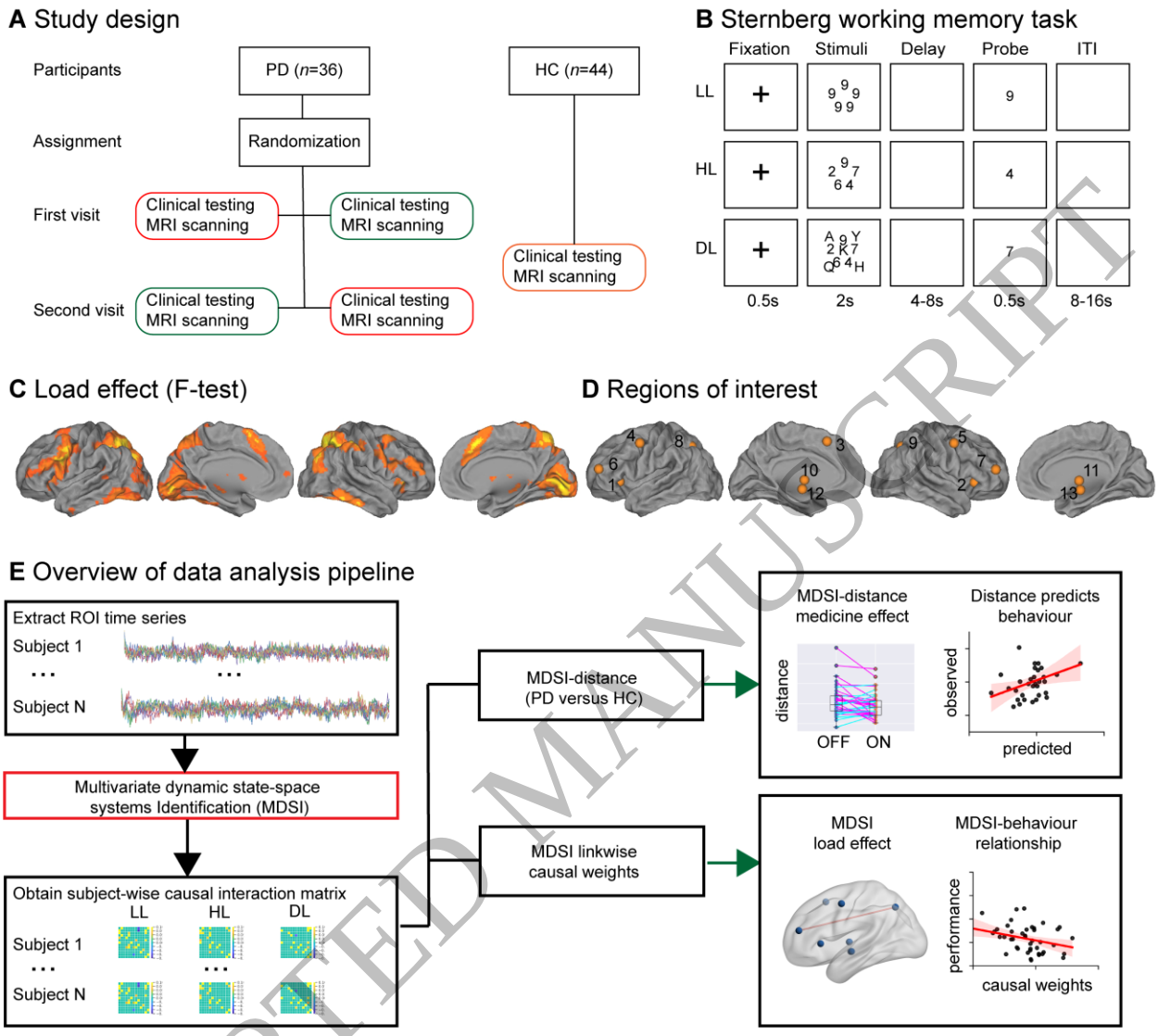

Figure 1
165x146 mm (1.2 x DPI)

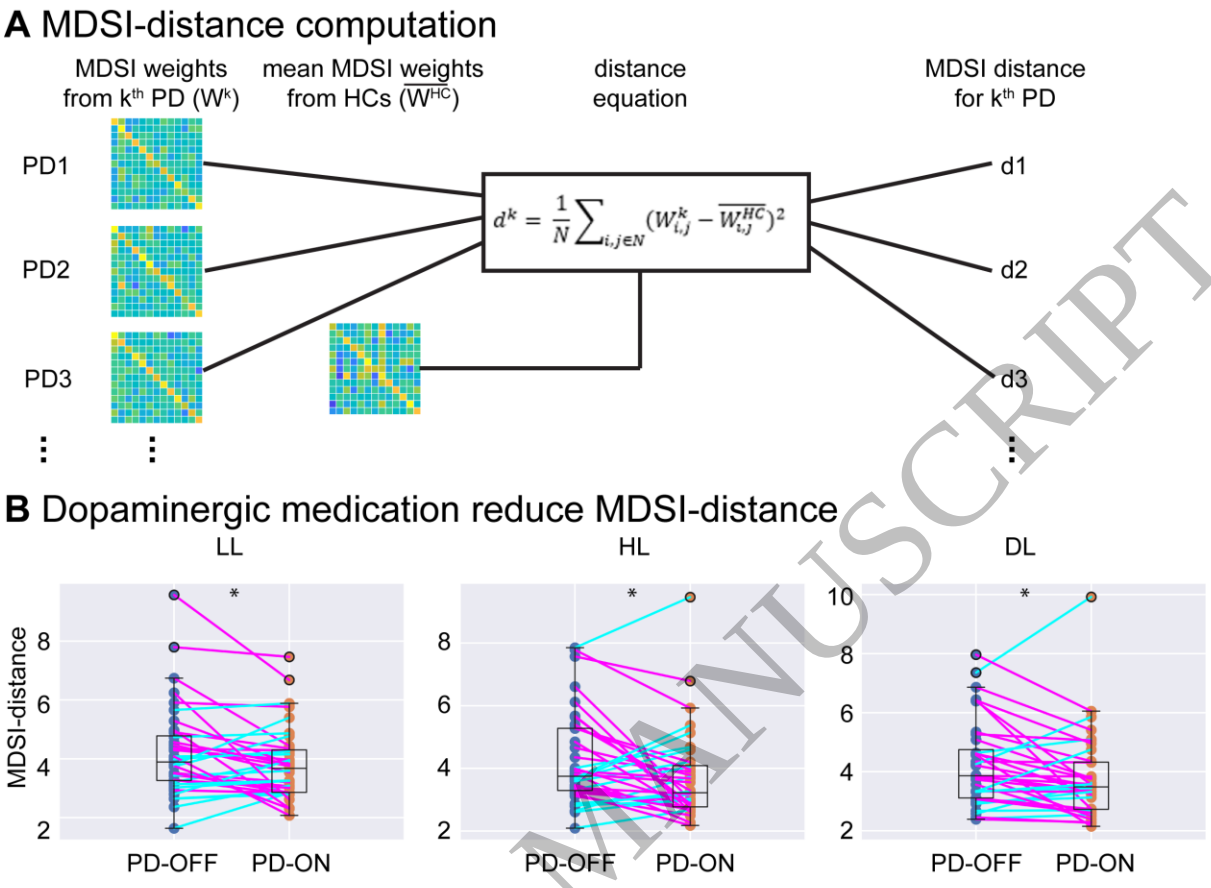

Figure 2
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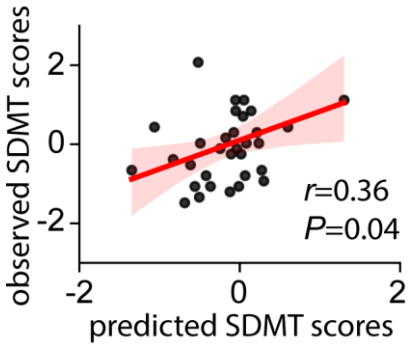

Figure 3
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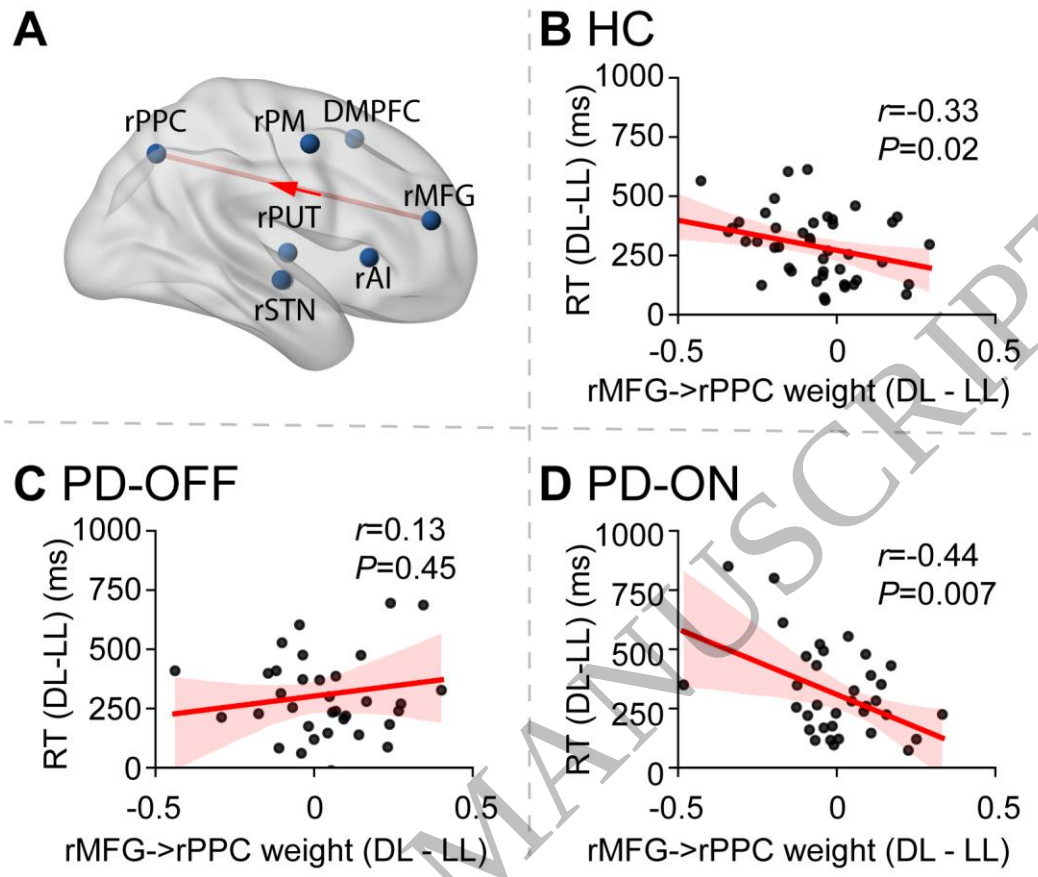

Figure 4
136x116 mm (1.2 x DPI)