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Catecholaminergic Modulation of Large-Scale Network Dynamics Is Tied to the Reconfiguration of Corticostriatal Connectivity

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ABSTRACT

Large-scale brain network function is critical for healthy cognition, yet links between such network function, neurochemistry, and smaller-scale neurocircuitry are unclear. Here, we evaluated 59 healthy individuals using resting-state fMRI to determine how network-level temporal dynamics were impacted by two well-characterized pharmacotherapies targeting catecholamines: methylphenidate (20 mg) and haloperidol (2 mg)—administered via randomized, double-blind, placebo-controlled design. Network temporal dynamic changes were tested for links with drug-induced alterations in complex corticostriatal connections as this circuit is a primary site of action for both drugs. Methylphenidate increased time in the default mode network state (DMN $p < 0.001$) and dorsal attention network state (DAN $p < 0.001$) and reduced time in the frontoparietal network state ($p < 0.01$). Haloperidol increased time in a sensory motor-DMN state ($p < 0.01$). The magnitude of change in network dynamics induced by methylphenidate vs. placebo correlated with the magnitude of methylphenidate-induced rearrangement of complex corticostriatal connectivity ($R = 0.32$, $p = 0.014$). Haloperidol did not alter complex corticostriatal connectivity. Methylphenidate enhanced time in network states involved in internal and external attention (DMN and DAN, respectively), aligning with methylphenidate's established role in attention. Methylphenidate also significantly changed complex corticostriatal connectivity by altering the relative strength between multiple corticostriatal connections, indicating that methylphenidate may shift which corticostriatal connections are prioritized relative to others. Findings show that these corticostriatal circuit changes are linked with large-scale network temporal dynamics. Collectively, these findings provide a deeper understanding of large-scale network function, set a stage for mechanistic understanding of network engagement, and provide useful information to guide medication use based on network-level effects.

Trial Registration: Registry name: ClinicalTrials.gov; URL: Brain Networks and Addiction Susceptibility—Full Text View—ClinicalTrials.gov; URL Plain text: https://classic.clinicaltrials.gov/ct2/show/NCT01924468; Identifier: NCT01924468

1 | Introduction

Resting-state brain networks have provided critical insight into the macro-scale functional organization of the brain, which is implicated in healthy cognition and psychopathology (Menon and D'Esposito 2022; Menon 2011; Zhang and Volkow 2019). A key next step is to understand how the function of these distributed brain networks correspond with changes in neurochemistry

Summary

- Whether and how catecholaminergic pharmacological agents impact large-scale functional network temporal dynamics remains unclear.
- Methylphenidate increased the amount of time spent in, and transitions to, network states involved in both external and internal attention—specifically the dorsal attention network state and default mode network state—suggesting that even at rest, methylphenidate may prime the brain to engage in both external or internal attentional states.
- Methylphenidate-induced enhancement of time spent in the default mode network state was coupled to methylphenidate's rearrangement of striatal connectivity profiles with cortex.

and more focal functional circuits. While catecholamines, such as dopamine, have been implicated in large-scale network function (Zhang and Volkow 2019; Braun et al. 2021; de la Cruz et al. 2020; Shafiei et al. 2019), more work using emerging methods is needed to gain a deeper understanding of how catecholaminergic agents impact large-scale network function. Collectively, this line of research promises to enhance the field's basic neurobiological understanding of brain network function and will shed light on how well-characterized therapeutics impact the brain on a new scale.

A novel approach to assess how catecholamines modulate large-scale network function is resting-state network temporal dynamics, which is measured using resting-state functional magnetic resonance imaging (fMRI) data. In contrast to static resting state fMRI analyses which calculates the functional connectivity (rs-fc) between brain regions across time (thus leading to one value for the entire resting-state scan), temporal dynamics capture how brain network engagement changes across time. One technique to measure network temporal dynamics is the sliding window approach. Sliding window cuts fMRI data into often overlapping bins or "windows" across time and rs-fc is then calculated at each window, allowing for the assessment of rs-fc across time. More recently, co-activation pattern (CAP) analysis, which does not use functional connectivity approaches, has been used to measure temporal dynamics by identifying transient states the brain is in at any given timepoint of the scan. Specifically, CAP analysis identifies CAPs based on the synchronicity of the magnitude of activation of spatially discrete brain regions, and these transient states spatially align with known networks generated from standard rs-fc methods (Damoiseaux et al. 2006; Smith et al. 2009). We thus refer to these transient states as "transient network states". Using CAP analysis, we can identify how often one transitions into a transient network state, how long they persist in the state once it has formed, and the overall time they spend in that transient network state across a given scan.

Resting-state temporal dynamics of large-scale brain networks have been shown to be central to adaptive functioning, as aberrance in resting-state network temporal dynamics is implicated in numerous forms of psychopathology including ADHD (Cai et al. 2018; Mizuno et al. 2022), nicotine dependence (Quam et al. 2024; Wang et al. 2020; Wang et al. 2021), cocaine use disorder (Zhai et al. 2023), and schizophrenia (Kottaram et al. 2018; Kottaram et al. 2019). Dopaminergic transmission has been directly implicated in one *task-based* analysis of network temporal dynamics, which demonstrated that dopamine modulates the dynamics of brain state transitions relevant to working memory (Braun et al. 2021). However, the evidence linking catecholaminergic transmission to resting-state network temporal dynamics is less clear. One study in children with ADHD indicated that the dopamine and norepinephrine reuptake inhibitor methylphenidate normalized disrupted network temporal dynamics at rest (Mizuno et al. 2022). The remaining evidence linking catecholamines and resting-state network temporal dynamics is indirect, where aberrant catecholaminergic transmission—particularly dopaminergic transmission—is thought to be a principal disruption in many psychopathologies which reliably exhibit altered network temporal dynamics (Cai et al. 2018; Mizuno et al. 2022; Quam et al. 2024; Wang et al. 2020; Wang et al. 2021; Zhai et al. 2023; Kottaram et al. 2018; Kottaram et al. 2019). Taken together, the direct influence of catecholaminergic transmission on the intrinsic temporal function of the brain's large-scale networks (e.g., temporal function at rest) seems likely but remains largely unknown, creating a gap in our understanding of how neuromodulators govern this central component of macro-scale brain function.

Our previous work in healthy young adults from the Human Connectome Project (HCP) used CAP analysis to define eight transient network states, which overlap with well-defined core neurocognitive networks (e.g., the default mode network [DMN], frontoparietal network [FPN], and dorsal attention network [DAN]) (Janes et al. 2020). Here, we apply these network state definitions to investigate how acute administration of catecholaminergic agents affect the temporal properties of large-scale brain networks, with functional relevance, during resting-state fMRI scans in healthy adults. Specifically, in one scan condition, we administered methylphenidate (MPH), a dopamine and norepinephrine transporter (DAT/NET) reuptake inhibitor which acts globally to increase extracellular dopamine and norepinephrine and has been shown to enhance cognition due to MPH's impact on striatal function (Kodama et al. 2017; van den Bosch et al. 2022; Westbrook et al. 2020; Wilens 2008). In a second scan condition, we administered haloperidol (HAL), a selective antagonist of D2/D3 receptors located primarily in the striatum. In a third scan condition, we administered placebo. These drugs were administered randomly across participants and allowed us to probe the impact of catecholaminergic agonism (MPH) and D2 antagonism (HAL) on temporal dynamics of large-scale brain networks.

We then move further to investigate ties between catecholaminergic modulation of macro-scale brain network temporal dynamics and more focal circuitry. On the circuit level, catecholamines, most notably dopamine, are known to act directly on the striatum and alter connectivity between the striatum and the cortex (Moyer, Wolf, and Finkel 2007). Though most fMRI analysis models simplify corticostriatal circuitry as a collection of independent connections between individual striatal nodes and individual cortical nodes, corticostriatal circuitry is much more complex. Individual striatal nodes receive projections

from multiple cortical regions, (Carter, Soler-Llavina, and Sabatini 2007; Choi, Ding, and Haber 2017), and preclinical data indicates that striatal function is shaped more by the collective properties of these multifaceted cortical input profiles than by any one cortical input alone (Carter, Soler-Llavina, and Sabatini 2007; Korponay, Choi, and Haber 2020). Moreover, striatal dopamine (modulated by both MPH and HAL) may play a key role in modulating how these *multiple cortical inputs* are *integrated* at striatal cells (Moyer, Wolf, and Finkel 2007). Finally, striatal activity is known to impact cortical function via the direct and indirect pathways through the basal ganglia (Haber 2016), providing a potential mechanism by which striatal dopamine-driven effects of MPH and HAL might impact large-scale cortical network dynamics.

As such, here we apply the recently developed connectivity profile analysis (Korponay, Stein, and Ross 2022) modeling framework to characterize how MPH and HAL alter multifaceted striatal connectivity profiles with cortex. Connectivity profile analysis computes a "profile" of connectivity between each striatal voxel and multiple cortical regions of interest. This enables the investigation of drug-induced connectivity changes that consider the combinatorial nature of multiple cortex connections with the striatum, which may have distinct cortical connectivity patterns at varying locations within the striatum. For instance, one metric of connectivity profile analysis measures the magnitude of change in the *relative* connectivity strength between multiple cortical regions and the striatum. We ultimately aim to determine whether the magnitude of catecholamine-driven change in striatal connectivity profiles with cortex is tied to the magnitude of catecholaminergic modulation of network temporal dynamics. Altogether, our design allows us to establish how dopamine/norepinephrine enhancement and D2 antagonism directly impact the temporal properties of macro-level brain networks and how this is tied to modulation of specific corticostriatal circuitry.

2 | Methods and Materials

2.1 | Participants

Participants included 59 healthy right-handed individuals between the ages 18 and 55 (Table 1). Participants were excluded for contraindications with fMRI scanning. Individuals with mental and physical health diagnoses and/or medications that interfere with the bold signal or alter metabolism of catecholaminergic agents were also excluded (see Supporting Information for details). Participants were recruited from Baltimore, MD and surrounding areas. The current study was reviewed and approved by the institutional review board of the National Institutes of Health. All participants provided written informed consent.

TABLE 1 | Demographics of sample.

Demographics	
	Healthy controls ($N = 59$)
Age (years)	39.32 ($SD = 11.25$)
Sex (male/female)	17/42
Race (*n*)	
Asian	5
Black/African American	11
More Than One Race	6
White/Caucasian	37
Ethnicity (*n*)	
Hispanic	9
Non-Hispanic	49
Unknown or not reported	1
Education (*n*)	
Less than High School	2
High School Complete/GED	8
Some/Partial Post-High School	22
College Graduate/Bachelor's Degree	18
Master's Degree	5
Professional Degree (MD, JD, PhD)	4

Note: Demographic characterization of sample.

2.2 | Study Design

All participants underwent resting-state fMRI scanning sessions with 3 drug conditions administered on separate days, in a double-blind placebo-controlled manner: placebo/placebo, HAL/placebo, and placebo/MPH. Doses were 2 mg oral HAL and 20 mg oral MPH; which are clinically relevant doses and have shown to alter activity/connectivity of brain regions of interest (Dipasquale et al. 2020; Luijten et al. 2013; Tomasi et al. 2011). Each scanning visit was identical and took place at drug peak: 4-h post HAL/placebo and 1-h post MPH/placebo; timed in accordance with absorption rates to ensure high and stable plasma levels of medication during the scan. To ensure each scan was identical, participants were administered drug or placebo twice on a given scan day, once at the HAL timepoint and once at the MPH timepoint. Participants only received one active drug on each study day and placebo at the other timepoint. On the placebo day, they were administered placebo at both timepoints. Prior to any medication administration, participants completed a nursing assessment, and following the scan session, participants met again with nursing staff to assess side effects.

2.3 | Neuroimaging Data

At each scan, data were collected using a Siemens Trio 3 T scanner with a 12 channel RF coil. For high-resolution anatomical scan, multi-planar rapidly acquired gradient echo-structural images were obtained with the following parameters (TR = 1.9 s, TE = 3.51 ms, slices = 208, matrix = 192 × 256, flip angle 9°, resolution 1.0 × 1.0 × 1.0 mm). For the 8-min resting state scan, gradient-echo, echo planar images were collected using oblique

axial scans 30° from AC-PC with AP phase encoding and the following parameters (TR = 2 s, TE = 27 ms, flip = 78°, vox resolution = 3.4375 × 3.4375 × 4 mm). Total frames were 240 and the first 5 were discarded.

Images were processed using FMRIB software library (FSL 6.0.0). Images underwent brain extraction, registration, spatial smoothing (6 mm), high-pass temporal filtering (100 s), and motion correction via MCFLIRT. Data were further cleaned to reduce artifacts using Independent Component Analysis via FIX (Salimi-Khorshidi et al. 2014; Griffanti et al. 2014) using a training set derived from the current data. The output of FIX was visually inspected to ensure proper noise removal.

2.4 | Pharmacological Impact on Network Temporal Dynamics

Previously, Janes et al. (2020) performed CAP analysis on resting state data from 462 individuals in the HCP (Essen et al. 2013) using 129 ROIs (cortical and striatal ROIs based on functional parcellation (Choi, Yeo, and Buckner 2012; Yeo et al. 2011); amygdala ROIs based on anatomical parcellation (Tzourio-Mazoyer et al. 2002)) and determined eight transient networks of CAPs (brain states) using k-means clustering. These eight brain states align with previously established resting state networks such as: the DMN, FPN, DAN, salience network (SN), and sensorimotor network (SMO) and thus we refer to the transient brain states as "transient network states." These transient network states had strong test–retest reliability in the HCP sample (Janes et al. 2020; Figure S1). To investigate how these eight transient network states behave dynamically at rest under different catecholaminergic drugs, first we extracted ROI time courses from the 129 ROIs. We then conducted CAP analysis with our CAPs defined as the eight transient network states, using the Capcalc package (https://github.com/bbfrederick/capcalc). From here, we derive (1) *total time* spent in each state across the entire resting-state scan, (2) number of *transitions* (i.e., entries) into each state during the entire resting-state scan, and (3) average *persistence* within the state once a transition into the state had occurred. These metrics are related—the total time one spends in a transient network state is made up of the total number of times one transitions into that state and the amount of time one spends persisting within the state. For instance, if a participant transitions into a state four times during the scan and spend 5 s on average persisting there each time, their total time in that state is 20 s.

To determine an effect of drug on temporal dynamics of transient network state activity at rest, we ran a repeated measures ANOVA that tested the drug (MPH, HAL, and PBO) × transient network state (state 1, state 2, state 3, state 4, state 5, state 6, state 7, and state 8) interaction on total time in transient network state. Following a significant drug × transient network state interaction, we ran eight subsequent repeated measures ANOVAs, testing effect of drug on total time in each state. In states where there was a significant drug effect on total time spent in transient network state after correcting for multiple comparisons (Bonferroni corrected: 0.05/8 = 0.00625), two post hoc paired *t*-tests compared MPH and HAL to placebo (Bonferroni corrected: 0.05/2 = 0.025). All ANOVAs and post hoc *t*-tests were conducted in R using the following packages: lme4 (1.1–32), lmertest (3.1–3), effectsize (0.8.3), and multcomp (1.4–23). All analyses controlled for age and sex.

In transient network states that exhibit significant change in total time in state under drug, we investigated whether changes to total time in state were driven by changes in (1) number of transitions to the state or (2) persistence within state. We ran separate post hoc paired *t*-tests comparing (1) transitions and (2) persistence between drug of interest to placebo. Post hoc analyses were Bonferroni corrected to account for all states tested. See Supporting Information methods for detailed description of transition analysis.

2.5 | Ties Between Network Temporal Dynamics and Static Network Function

Previous work has theorized that spending more time in the DMN and DAN at opposing times drives enhanced static DMN-DAN anti-correlation (Weber, Aleman, and Hugdahl 2022)—a known marker of healthy cognition (Hampson et al. 2010; Sala-Llonch et al. 2012). Separate literature consistently shows that MPH enhances static DMN-DAN anti-correlation (Sripada et al. 2013; Querne et al. 2017). We aimed to confirm that MPH enhances static DMN-DAN anti-correlation in our sample and tested the conjecture that static DMN-DAN anti-correlation is driven by DMN and DAN temporal dynamics. To do so, we obtained the DMN and DAN time courses by regressing the resting-state fMRI data on the spatial distribution of the DMN and DAN states, respectively. DMN-DAN anticorrelation values were then determined by correlating the time courses between these two networks and Fisher's R-to-Z transforming the correlation values. We then tested the effect of drug on DMN-DAN anticorrelation with a repeated measures ANOVA and post hoc *t*-tests (Bonferroni corrected). Next, we tested the relationship between static DMN-DAN anti-correlation and combined time spent in DMN and DAN, hypothesizing that increased time in DMN and DAN would be associated with greater magnitude of DMN-DAN anticorrelation (based on previous proposal; Weber, Aleman, and Hugdahl 2022). We fit a linear mixed model in R to estimate DMN-DAN anticorrelation score from time in DMN and DAN state combined (summed), when controlling for age, sex, drug, and drug × time in state interaction.

2.6 | Pharmacological Impact on Corticostriatal Configuration

To detect complex changes in corticostriatal connectivity, we conducted connectivity profile analysis (Korponay, Stein, and Ross 2022). Striatal function is shaped by the convergence of multiple cortical inputs more so than by any one cortical node alone (Carter, Soler-Llavina, and Sabatini 2007; Korponay, Choi, and Haber 2020). Here, connectivity profile analysis allowed us to model the multifaceted input received by striatal nodes from diverse areas of cortex and study drug-related changes in the properties of these "corticostriatal configuration profiles" (CSCPs) (Korponay, Stein, and Ross 2022).

To derive CSCPs, first, time courses were extracted from each voxel within the striatum mask and time courses were extracted from 53 cortical ROIs. The striatum mask was created by averaging the union of the caudate, putamen, and nucleus accumbens FreeSurfer parcellations of low head-motion subjects in a large normative sample (Figure S2; Korponay, Stein, and Ross 2021). For the 53 cortical regions of interest, we used the Yeo functional network atlas (Table S1; Yeo et al. 2011; http://www.freesurfer.net/fswiki/CorticalParcellation_Yeo2011), which was also used to define our CAPs (8 transient network states) in our prior work (Janes et al. 2020). These cortical regions of interest are chosen because of their location and membership to known functional networks that align with our transient network states, including the DMN, DAN, FPN, SN, as well as the limbic, sensorimotor, and visual network. We combined the cortical regions bilaterally; 8 cortical regions did not have a contralateral counterpart and thus are unilateral in the analysis. Correlation values between time courses of each striatal voxel and average time courses of each cortical ROI were calculated using ordinary least squares regression (with 3dDeconvulve in AFNI), then r values were Z-transformed using Fisher's R-to-Z. Next, CSCP metrics were calculated in MATLAB (2022b) (for details, see Korponay et al. 2022, and Supporting Information). Briefly, CSCP metrics include (1) *aggregate divergence* (AD): absolute sum of the change in connectivity for each ROI at each striatal voxel (drug—placebo), acting as a measure of absolute change in magnitude of connectivity under drug; (2) *rank order rearrangement* (ROR): cortical regions are ranked by their strength of connectivity with each striatal voxel under placebo and, separately, under drug. ROR is the absolute sum of change in order of strength of connectivity for each cortical ROI at each striatal voxel (drug—placebo), acting as a measure of absolute change in relative connectivity under drug; and (3) *entropy shift* (ES): change in distribution of the strength of corticostriatal connectivity values under drug compared to placebo. Here, CSCPs were conducted entirely within subject. Because CSCP metrics inherently compare drug to placebo, we also conducted within-session placebo CSCP metrics for statistical analysis ($PBO_{firsthalf}$-$PBO_{secondhalf}$). This score compared the first and second half of placebo data. In total, scores were derived across three conditions: MPH-PBO, HAL-PBO, and $PBO_{firsthalf}$-$PBO_{secondhalf}$.

To determine statistical significance, we calculated subject-wise average scores of each CSCP metric for each condition. We then ran three repeated measures ANOVAs—one for each metric (AD, ROR, and ES)—comparing the drug conditions (Bonferroni corrected). If significant, post hoc *t*-tests compared MPH-PBO, HAL-PBO, and $PBO_{firsthalf}$-$PBO_{secondhalf}$ (Bonferroni corrected). Where post hoc *t*-test revealed a significant drug effect, we then aimed to identify specific areas of the striatum that were significantly altered by drug. We computed subject-level striatal maps of significant CSCP metrics. We then performed a voxel-wise paired *t*-test between significant drug-placebo and within-session placebo condition using SPM12.

2.7 | Ties Between Modulation of Network Temporal Dynamics and Corticostriatal Reconfiguration

We tested whether, under the same drug, significant change in network temporal dynamics was related to significant alterations in CSCP metrics. To do so, first we calculated one subject-wise score of absolute change in time spent in states under drug. Absolute change in time spent in states was derived by summing the absolute value of change in time in each of the eight states ($time_{stateN}$ under drug—$time_{stateN}$ under placebo). We then tested the relationship between subject-wise score of significant CSCP metric and absolute change in time spent in states. Where there was a significant relationship, we aimed to confirm that this relationship, involving change in time spent in *all* states, was specifically driven by change in time spent in states whose temporal dynamics were determined to be significantly modulated by drug. The goal of this confirmation was to parse out which networks are involved in the relationship between temporal dynamic network properties and functional corticostriatal circuitry. This was assessed by comparing correlations (Diedenhofen and Musch 2015), where x remained CSCP score while y varied as absolute change in: total time spent in all eight states, total time spent in states significantly altered by drug, and total time spent in states not significantly altered by drug. See exact equations in Supporting Information methods.

We conducted further exploratory post hoc analysis to localize which striatal nodes and individual networks are involved in significant relationships. In contrast to a CSCP score defined as the mean CSCP score at *all* striatal voxels per subject, node-specific CSCP scores were derived from the mean of voxels in each significant striatal node identified in the voxel-wise *t*-test. Correlations were calculated between node-specific CSCP scores and change in time spent in each state significantly modulated by drug.

3 | Results

3.1 | Network Temporal Dynamics

We first tested for effect of drug on total time spent in transient network state. There was a significant effect of transient network state ($F(16,928)=19.53$, $p<0.001$) and a drug × transient network state interaction ($F(16,928)=5.78$, $p<0.001$) on total time spent in transient network states. A significant effect of drug was noted for the DMN ($F(2,116)=15.29$, $p_{corr}<0.001$, $\eta^2=0.21$), DAN ($F(2,116)=12.42$, $p_{corr}<0.001$, $\eta^2=0.18$), FPN ($F(2,116)=5.95$, $p_{corr}<0.05$, $\eta^2=0.09$), and sensorimotor-occipital DMN (SM-DMN) state ($F(2,116)=9.97$, $p_{corr}<0.001$, $\eta^2=0.15$).

Post hoc analysis revealed that relative to placebo, MPH increased time spent in the DMN ($p_{corr}<0.001$, $d=0.74$) and DAN states ($p_{corr}<0.001$, $d=0.665$). Increased time was explained by MPH increasing the number of transitions into the DMN ($p_{corr}<0.001$, $d=0.72$) and DAN states ($p_{corr}<0.001$, $d=0.78$). In contrast, MPH had no impact on persistence in either state ($p_{corr}>0.05$). MPH also reduced the time spent in the FPN state relative to placebo ($p_{corr}<0.01$, $d=-0.445$) and reduced transitions into this state at a significance level that did not withstand Bonferroni correction ($p_{corr}=0.17$) without influencing persistence ($p_{corr}>0.05$) (Figure 1A–C).

Relative to placebo, HAL increased the time spent in the SM-DMN, which represents the co-activation of sensory motor regions and the DMN ($p_{corr}<0.01$, $d=0.49$). HAL increased the number of transitions into this state ($p_{corr}=0.013$, $d=0.48$) and increased the persistence within the SM-DMN at a level that did not withstand Bonferroni correction ($p_{corr}=0.054$) (Figure 1A–C).

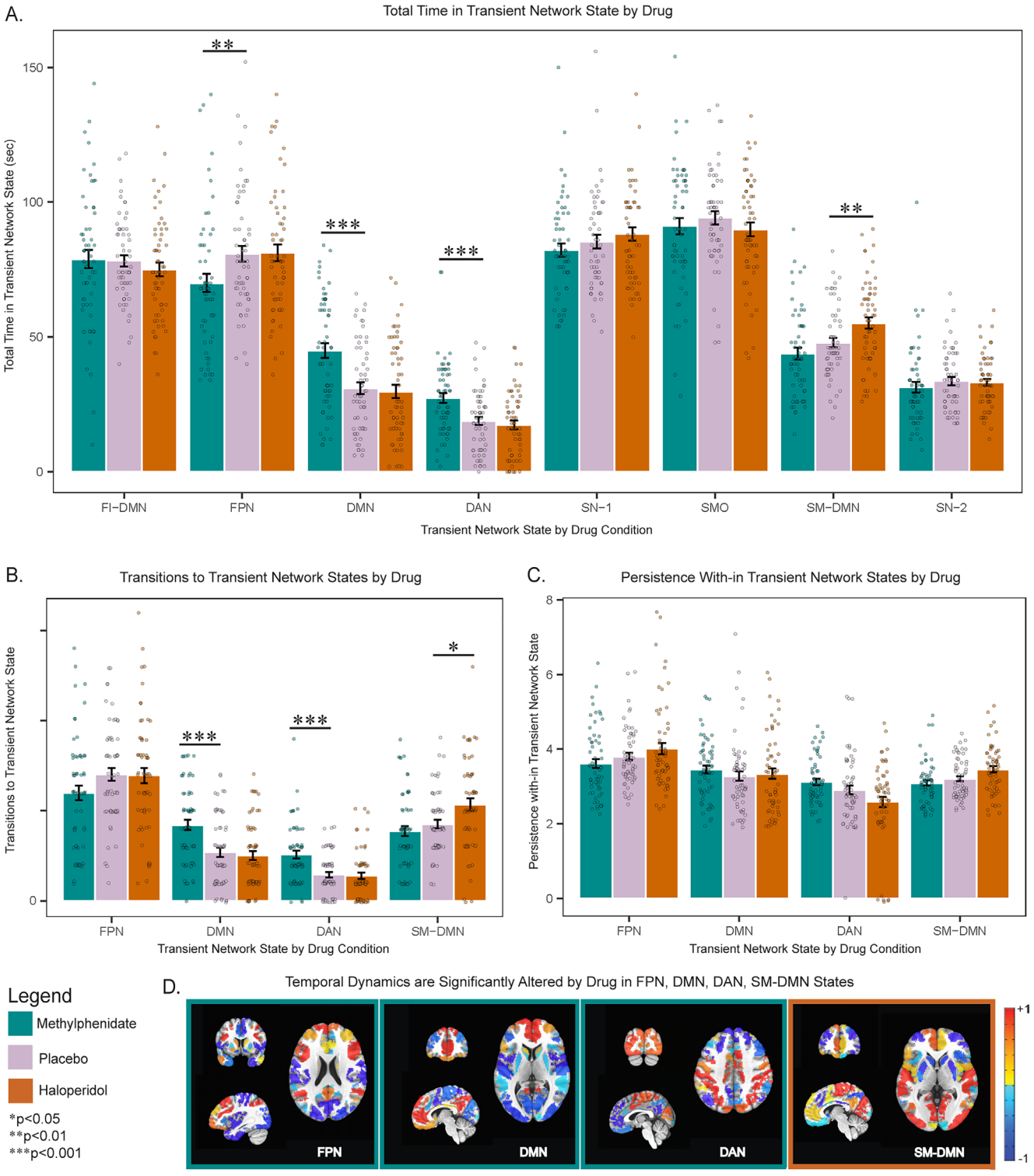

FIGURE 1 | Catecholaminergic agents significantly alter large-scale brain network temporal dynamics. (A) MPH increased time spent in DMN and DAN states and decreased time spent in FPN state. HAL increased time spent in SM-DMN state. (B) MPH increased transitions to DMN and DAN states while HAL increased transitions to SM-DMN state. (C) Neither MPH nor HAL altered time spent persisting within DMN, DAN, FPN, or SM-DMN state. (D) A visualization of FPN, DMN, DAN, and SM-DMN states of which dynamics are significantly altered by MPH (outlined in green) or HAL (outlined in orange). −1 is most negative relative activation; +1 is most positive relative activation. MPH: Methylphenidate; HAL: Haloperidol; FI-DMN: Fronto-insular default mode network state; FPN: Frontoparietal network state; DMN: Default mode network state; DAN: Dorsal attention network state; SN-1: Salience network state 1; SMO: Sensory motor occipital state; SM-DMN: Sensory motor default mode network state; SN-2 salience network state 2. *$p_{corr} < 0.05$, **$p_{corr} < 0.01$, ***$p_{corr} < 0.001$.

3.2 | DMN-DAN Anticorrelation

There was a significant effect of drug on the DMN-DAN anti-correlation ($F(2,116)=11.6$, $p<0.001$, $\eta^2=0.17$). Post hoc comparisons confirmed that MPH had a significantly greater magnitude of static DMN-DAN anti-correlation versus placebo (Figure 2A, $p_{corr}=0.0014$, $d=0.57$) which aligns with previous literature (Sripada et al. 2013; Querne et al. 2017), whereas HAL did not significantly differ from placebo ($p_{corr}>0.05$). We then tested the hypothesis that greater magnitude of static DMN-DAN anti-correlation could be driven by increased time spent in both the DMN and DAN. Time in DMN and DAN combined negatively estimated DMN-DAN correlation independently of drug conditions (Figure 2B, $p<0.001$, conditional $R^2=0.72$, marginal $R^2=0.59$). This lends significant evidence toward the conjecture (Weber, Aleman, and Hugdahl 2022) that enhanced anti-correlation of the DMN and DAN is driven by spending more time both states, at opposing times.

3.3 | Corticostriatal Configurations

We measured catecholaminergic manipulation of corticostriatal circuitry by measuring effect of drug on CSCP metrics: AD, ROR, and ES. There was a significant effect of drug on ROR, the measure of absolute change in *relative* corticostriatal connectivity, following repeated measures ANOVA ($F(2,116)=15.36$, $p_{corr}<0.001$, $\eta^2=0.21$). There was no effect of drug on AD or ES ($p_{corr}>0.05$), which measure the absolute magnitude of change in corticostriatal connectivity values and change in distribution of the strength of corticostriatal connectivity values, respectively. Post hoc comparisons revealed that the MPH-PBO condition exhibited significantly higher ROR compared to within-session placebo ($p_{corr}<0.001$, $d=0.86$) and HAL-PBO ($p_{corr}<0.001$, $d=0.73$; Figure 3A). There was no difference between HAL-PBO and within-session placebo ($p_{corr}>0.05$). This result shows that corticostriatal connectivities which were relatively weaker under placebo became relatively stronger under methylphenidate and vice versa, at a statistically significant level when measuring total amount of change in relative strength.

To localize striatal nodes where MPH significantly induced higher magnitude of ROR compared to placebo, we conducted a voxel-wise paired *t*-test of striatal ROR value maps comparing MPH-PBO to within-session placebo. This revealed five clusters where MPH significantly induced higher magnitude of ROR compared to placebo: right dorsal caudate; left dorsal caudate; right nucleus accumbens and ventral caudate; left nucleus accumbens; left ventral caudate (Table S2). See Supporting Information results for details on how cortical regions significantly changed in rank order at the five striatal clusters.

3.4 | Network Temporal Dynamics × Corticostriatal Configurations

To determine links between smaller-scale circuitry and the time-varying engagement of large-scale networks, we tested associations between significant corticostriatal reconfiguration and change in network temporal dynamics under the same drug. MPH both significantly increased ROR—the absolute change in relative corticostriatal connectivity—and altered network temporal dynamics (Figures 1 and 3). We thus tested the association between magnitude of ROR and change in time spent in transient network states under MPH. There was a significant positive relationship between magnitude of ROR (averaged across the entire striatum) and absolute change in time spent in all transient network states under MPH ($R=0.29$, $p=0.025$).

We examined whether this relationship was driven by change in time spent in the FPN, DMN and DAN states, as we determined that MPH significantly altered the time spent in these three states (Figure 1A). There was a significant relationship between magnitude of ROR and absolute change in time spent in FPN, DMN and DAN states under MPH ($R=0.32$, $p=0.014$) while there was no significant relationship between magnitude of ROR and absolute change in time spent in all states excluding FPN, DMN and DAN ($R=0.12$, $p>0.05$) (Figure 4). The relationship between magnitude of ROR and absolute change in time spent in all states was significantly stronger than the relationship involving change in time spent in states *excluding* FPN, DMN, DAN states ($z=1.87$, $p=0.031$) and not significantly different from the relationship involving only absolute change in time spent in FPN, DMN and DAN states ($z=0.37$, $p>0.05$) (Figure 4). We thus concluded that MPH-induced change in time spent in FPN, DMN and DAN combined is principally responsible for the association between MPH-induced change in time spent in all states and magnitude of corticostriatal ROR.

In an exploratory analysis, we aimed to localize specific striatal nodes where magnitude of ROR may be associated with change in time spent in the FPN, DMN or DAN. We averaged ROR values for each subject at each of the five striatal nodes previously identified (Table S2). We then tested associations between node-wise ROR and change in time spent in FPN, DMN and DAN independently—ultimately yielding 15 correlation tests (5 nodes × 3 transient network states). Change in time spent in the DMN alone was significantly positively related to ROR at the left dorsal striatum (Figure 5B, $R=0.4$, $p_{uncorr}=0.0015$; $p_{corr}=0.0225$). The positive relationship with the right dorsal striatum (Figure 5D, $R=0.35$, $p_{uncorr}=0.006$, $p_{corr}>0.05$) did not survive multiple comparisons correction. However, these relationships did not significantly differ from each other ($z=-0.87$, $p>0.05$). No other relationships were significant following multiple comparisons correction. These exploratory findings demonstrate that the magnitude at which MPH reshuffles the relative connectivity strength between different cortical regions and the dorsal caudate is associated with the amount that MPH enhances time spent in the DMN at rest.

4 | Discussion

Methylphenidate increased the amount of time spent in the DMN and DAN states by increasing the frequency of transitions into both states. This finding is compelling given MPH's known role in attention and the fact that both states play a role in different types of attention. While the DMN plays a critical role in processes requiring internally focused attention such as episodic

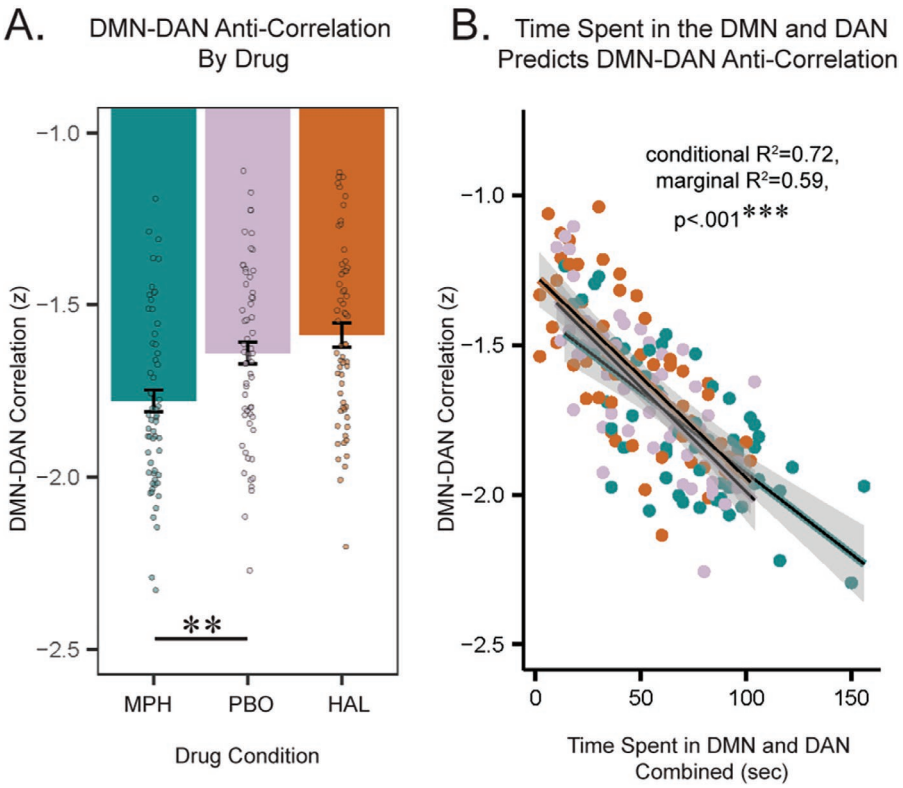

FIGURE 2 | DMN-DAN static anticorrelation is tied to DMN and DAN temporal function. (A) MPH significantly strengthens DMN-DAN anti-correlation. (B) The combination of time spent in DMN and DAN states negatively predicts DMN-DAN correlation values independently of drug. MPH: Methylphenidate; HAL: Haloperidol; DMN: Default mode network; DAN: Dorsal attention network. $^{**}p_{corr} < 0.01$.

memory (Spreng et al. 2010; Andrews-Hanna et al. 2010; Buckner, Andrews-Hanna, and Schacter 2008; Turnbull et al. 2019), the DAN is involved in the regulation of external attention, which is required to meet external task demands (Spreng et al. 2010; Newman et al. 2003). Thus, even at rest, MPH facilitates dynamic transitions into attentional states, suggesting that MPH primes the brain to engage in both internal and external attentional demands. This finding builds on previous literature of MPH's known role in attentional enhancement and provides novel insight whereby MPH inherently increases transitions into both externally and internally focused attention-related networks. MPH also suppressed the amount of time spent in the FPN. Previous work has shown that the FPN facilitates goal-directed behavior via flexible switching between the DMN and the DAN to accomplish an internally or externally oriented task, respectively (Spreng et al. 2010). Consistent with theories which posit MPH enhances cognitive efficiency (Volkow et al. 2008), the suppression of time spent in the FPN coupled with enhanced entries into DMN and DAN may indicate that under MPH, less FPN-related effort is needed to facilitate goal-directed attention.

In a follow-up analysis, we confirmed that in addition to enhancing time spent in DMN and DAN, MPH strengthens static DMN-DAN anti-correlation. Stronger anti-correlation between the DMN and the DAN at rest is a known marker of healthy cognition (Devaney et al. 2021), and it has been hypothesized that increased anti-correlation of these networks is driven by increased time spent in both brain networks, at opposing times (Weber, Aleman, and Hugdahl 2022). Here, we prove this conjecture that a stronger DMN-DAN anti-correlation is related to increased time in both DMN and DAN states. Our findings thus show that MPH drives changes in network temporal dynamics which explain known markers of cognitive enhancement identified by static functional connectivity measures.

Pharmacological challenge by HAL, in contrast, increased the amount of time in the SM-DMN state. Though it may appear counterintuitive that both MPH and HAL enhanced time in DMN-related states, the DMN and SM-DMN states are neurobiologically distinct co-activated patterns (Janes et al. 2020). The enhancement of an SM-related network fits with known effects of antipsychotics on sensorimotor systems, including extrapyramidal motor side effects of first generation antipsychotics (e.g., HAL), as well as HAL-induced alteration of brain activity during motor tasks (Goozee et al. 2016). Moreover, HAL is used as a first-line medication to treat schizophrenia, a disorder which exhibits altered temporal function of SM and DMN (Kottaram et al. 2019; Cattarinussi et al. 2023). The current finding in healthy controls that acute HAL enhances temporal function of two networks temporally disrupted in those with schizophrenia underscores the necessity of considering pharmacological impact of medication when analyzing temporal network function in clinical populations. This consideration may clarify mixed findings in the field (Cattarinussi et al. 2023). Taken together, the distinct effects of MPH and HAL demonstrate that MPH and HAL impact the inherent temporal function of different large-scale networks.

Given that MPH and HAL have heightened locus of action at the striatum and act to modulate large-scale brain networks, we assessed how MPH and HAL impact corticostriatal

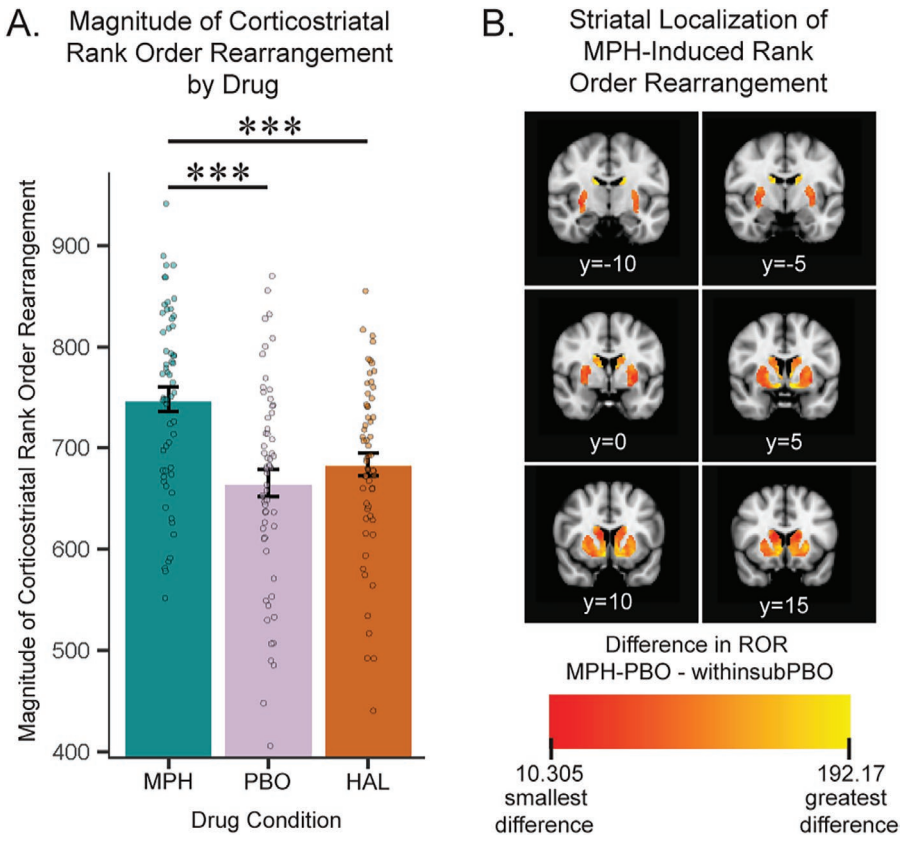

FIGURE 3 | Methylphenidate significantly heightens the magnitude of rank order rearrangement in corticostriatal connectivity profile. (A) Under MPH, there is significantly higher magnitude of ROR—measure of absolute change in relative corticostriatal connectivity—compared to placebo (within-session placebo rearrangement) and HAL (HAL-PBO rearrangement). (B) Heatmap comparing magnitude of ROR at striatal voxels in MPH-PBO condition compared to within-session placebo condition. Across PBO and MPH conditions, relative connectivity strength between multiple cortical regions and the more **red** striatal voxels is more stable. In contrast, more yellow striatal voxels exhibiter greater change in relative connectivity strength with cortical regions under MPH compared to PBO. ROR: Rank order rearrangement; MPH: Methylphenidate; HAL: Haloperidol; PBO: Placebo. ***$p_{corr} < 0.001$.

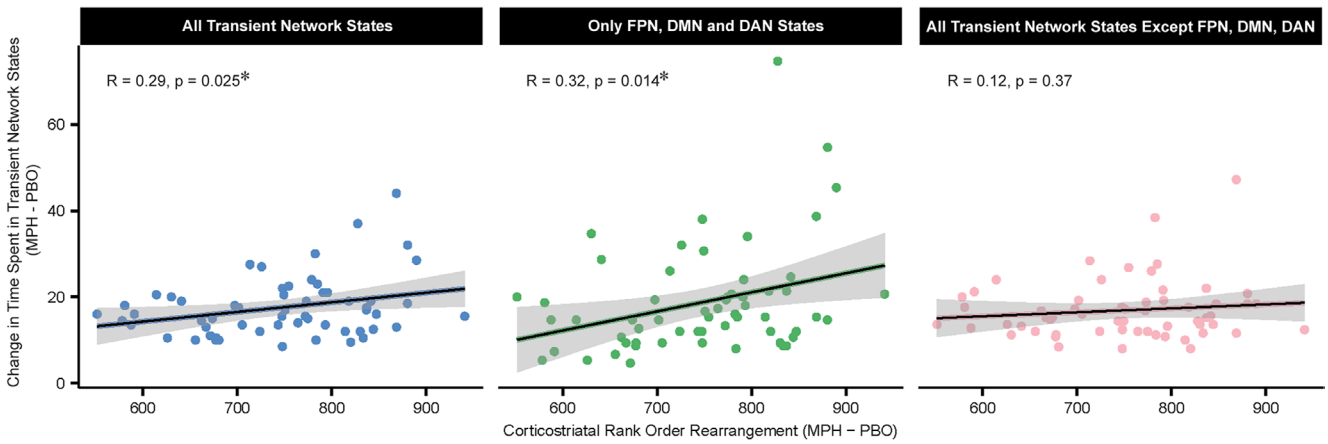

FIGURE 4 | Change in network temporal dynamics is related to modulation of functional corticostriatal circuitry under methylphenidate. Change in network temporal dynamics is associated with altered corticostriatal rank order rearrangement under MPH. Change in network temporal dynamics is operationalized as the sum, for each state tested, of the absolute value of the difference in total time spent in the state (MPH-PBO). Three panels vary by *y*-axis where left panel *y* = change in time spent in all states, middle panel *y* = change in time spent in only FPN, DMN, and DAN states, right panel *y* = change in time spent in all states except FPN, DMN, and DAN states. All *Y*-axis measures were divided by the number of states summed. MPH: Methylphenidate, PBO: Placebo; DMN: Default mode network; DAN: Dorsal attention network; FPN: Frontoparietal network.

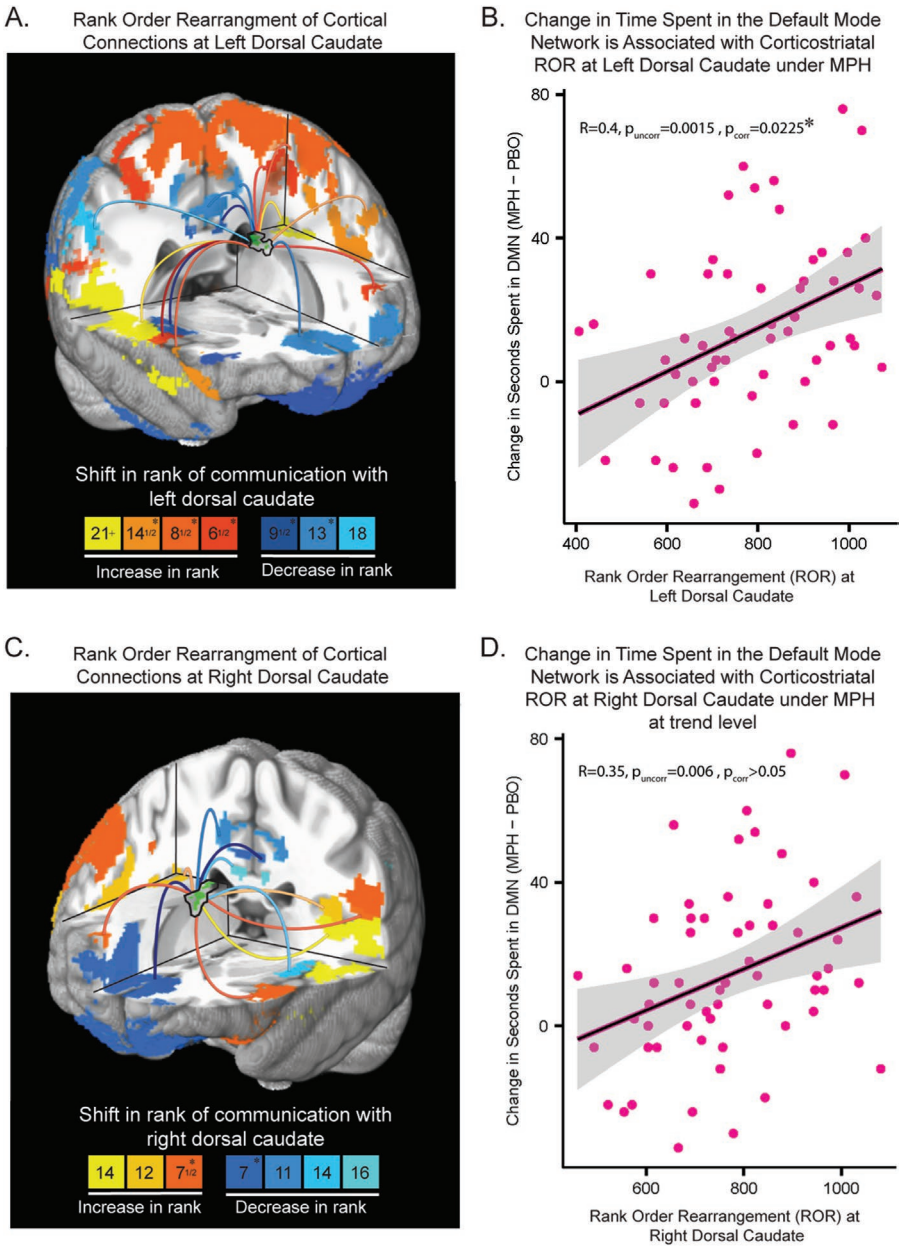

FIGURE 5 | Methylphenidate-induced changes in the *relative* strength of connectivity between cortical regions and the dorsal caudate is associated with more time spent in the default mode network under methylphenidate. (A) and (C) ROR at left dorsal caudate (A) and right dorsal caudate (C), depicting absolute change in relative connectivity between multiple cortical regions and the dorsal caudate node under MPH compared to PBO: Green regions are the data-driven striatal nodes of significant MPH-induced ROR previously identified by a voxel-wise paired *t*-test. Cortical regions are color coded to depict how their relative connectivity strength with the specified caudate node, or "rank of communication," shifts under MPH compared to under PBO. Regions shown shift at least 5 ranks. Color key at bottom indicates magnitude of change in rank where * indicates a mean magnitude of change for that color—this value only varies by ±2 values at maximum. Exact amount of change per significant cortical region is depicted in Figure S5. (B) and (D). Correlations between ROR at left dorsal caudate (B) and at right dorsal caudate (D) and change in time spent (seconds) in the DMN state under MPH compared to PBO. MPH: Methylphenidate; PBO: Placebo; DMN: Default mode network; $^{*}p_{\text{corr}} < 0.05$.

function and whether this relates to drug-induced changes in network temporal dynamics. We obtained CSCPs, which aim to capture complex functional corticostriatal interactions by quantifying connectivity patterns between multiple cortical regions and individual striatal nodes, as AD, ROR, and ES, where AD captures magnitude of change in absolute connectivity strength between multiple cortical regions and the striatum, ROR captures magnitude of change in relative connectivity strength between multiple cortical regions and the striatum, and ES captures the change in distribution strength of corticostriatal connections (i.e., few strong connectivities vs. many strong connectivities which may collectively impact brain function). Challenge by HAL had no effect on CSCP measures. Challenge by MPH, in contrast, altered ROR but did

not alter AD or ES. Previous work also has shown that each configuration property (AD, ROR, ES) is modulated independently and likely represents distinct neurobiological properties which may differentially shape striatal node function (Korponay, Stein, and Ross 2022). We build on this to show that different pharmacological agents have distinct action on configuration profiles.

In altering ROR alone, MPH specifically made relatively weaker corticostriatal connections relatively stronger (and vice-versa)—effectively *reshuffling* the "rank" of which cortical connections are the strongest, at distinct striatal nodes. In doing so, MPH appears to rearrange the influence that different corticostriatal communications have (Friston 2011) to ultimately contribute to altered brain function. Thus, we provide evidence that elevated extracellular dopamine and norepinephrine alter which specific corticostriatal connections are the strongest or weakest, and this *reshuffling* of the relative connectivity strength of cortical regions with the striatum potentially reflects a shift in the priority of corticostriatal communications. It may be, at least in part, that MPH acting at the striatum significantly alters how cortical input is integrated in striatal cells (Moyer, Wolf, and Finkel 2007)—though given MPH's global action and effects on catecholamines broadly, future work is needed to disentangle this assertion. MPH-induced ROR occurs significantly at bilateral counterparts in the dorsal caudate and at the right and left nucleus accumbens and ventral caudate. Anatomically, these striatal nodes are engaged in corticostriatal loops (Haber 2003), and functionally, the dorsal caudate is tied to FPN while the ventral nodes identified here are linked to the DMN and limbic network (Choi, Yeo, and Buckner 2012).

Importantly, we provide novel evidence that MPH-induced corticostriatal ROR is tied to MPH-induced change in network temporal dynamics. The magnitude of ROR at the left and right dorsal caudate nodes are independently positively associated with network dynamic change; particularly related to enhancement of time spent in the DMN state. Translational research has established that the dopamine system and corticostriatal circuits, involving the dorsal caudate specifically, are implicated in addiction, ADHD, and the pharmacological action of MPH in the treatment of ADHD (King et al. 2019; Crawford et al. 1998; Volkow et al. 2007; Schulz et al. 2017). More recent evidence has built on this historical understanding to illustrate that activity of neurocognitive networks, particularly DMN, is aberrant in these disorders (Zhang and Volkow 2019; Cai et al. 2018; Quam et al. 2024; Broulidakis et al. 2022; Picon et al. 2020). However, a gap remains in linking the largely pre-clinical body of circuit-based evidence to large-scale brain network function. Our findings reveal a link between MPH-induced changes in functional corticostriatal circuitry and temporal dynamic function of the DMN. These results may suggest that dopaminergic agonism alters how cortical connections with the dorsal caudate are prioritized, leading to changes in temporal dynamic function of brain networks, particularly the DMN. If this is true, it would expand on theory that *static* DMN functional connectivity is modulated by D2/D3 receptors (which are located in the striatum) (Zhang and Volkow 2019) and suggest a specific locus and mechanism of regulation at the dorsal caudate, a striatal region functionally defined by its role in cognitive control (Choi, Yeo, and Buckner 2012; Gordon et al. 2021).

4.1 | Limitations

A limitation of this work is that our scan length was only 8 min, and we are unable to assess test–retest reliability of our findings. However, our prior work using data from the HCP showed high test–retest reliability of the transient network states defined in that sample (Janes et al. 2020). These HCP-defined states were applied in the current analysis, thus allowing for a focus on reproducible states. Another limitation of the present work is that baseline dopaminergic function was not assessed using PET. This may be relevant as others have shown that individual variance in dopaminergic function may impact the action of MPH (Volkow et al. 2002; Sayalı et al. 2023). However, the current participants were healthy with no clinical appearance of dopaminergic disruptions. We also used a within-subjects design, which reduces the impact of individual variance. While we defined a relationship between temporal dynamics and corticostriatal configuration, we relied on correlational analyses and are unable to determine a causal relationship between these changes. As articulated in the discussion, we speculated that changes in corticostriatal interactions may drive the influence of MPH on temporal dynamic function; this hypothesis needs to be confirmed in future work. However, even in the absence of a causal link, we provide comprehensive evidence of MPH's impact on temporal dynamics and related static resting state features that differ significantly from HAL. Finally, while the scope of this work focused on drug-induced changes in temporal properties of known transient network states, we did not assess how pharmacology may have impacted the spatial distribution of brain states. While it was necessary to hold the spatial definition of states constant to evaluate changes in their temporal properties, future work evaluating spatial changes in coactivation patterns will be of value.

4.2 | Conclusion

We find that pharmacological agents—MPH and HAL—have distinct impacts on network temporal dynamics and on corticostriatal configuration. Temporal dynamic findings suggest that MPH may prime the brain to engage in both external- and internal-oriented attention, revealing a novel understanding of MPH action which aligns with known effects of MPH-induced enhancement of external attention and expands our knowledge of MPH-induced enhancement of internal attention. Further, we show that while HAL does not alter corticostriatal configurations, MPH specifically alters ROR, acting to reshuffle the relative connectivity strength of multiple cortical regions with the striatum. The magnitude of this "reshuffling," across the striatum and specifically at dorsal caudate is tied to MPH-induced change in brain network temporal dynamics, particularly the DMN. Thus, this work suggests that MPH-induced changes in dorsal caudate communication with the cortex may play a role in driving time-varying engagement of the DMN and other large-scale brain networks, though future work is required to determine the causality of this association. Our findings ultimately uncover catecholamine-driven links between nuanced corticostriatal circuitry and large-scale brain network temporal dynamics, paving the way for a mechanistic understanding of the neurochemistry and neurocircuitry governing macro-scale brain network engagement.

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Ethics Statement

The current study was reviewed and approved by the institutional review board of the National Institutes of Health.

Consent

All participants provided written informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.