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Altered Structural Connectivity and Functional Brain Dynamics in Individuals With Heavy Alcohol Use Elucidated via Network Control Theory

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ABSTRACT

BACKGROUND: Heavy alcohol use and its associated conditions, such as alcohol use disorder, impact millions of individuals worldwide. While our understanding of the neurobiological correlates of alcohol use has evolved substantially, we still lack models that incorporate whole-brain neuroanatomical, functional, and pharmacological information under one framework.

METHODS: Here, we utilized diffusion and functional magnetic resonance imaging to investigate alterations to brain dynamics in 130 individuals with a high amount of current alcohol use. We compared these alcohol-using individuals to 308 individuals with minimal use of any substances.

RESULTS: We found that individuals with heavy alcohol use had less dynamic and complex brain activity, and through leveraging network control theory, had increased control energy to complete transitions between activation states. Furthermore, using separately acquired positron emission tomography data, we deployed an in silico evaluation demonstrating that decreased D_2 receptor levels, as found previously in individuals with alcohol use disorder, may relate to our observed findings.

CONCLUSIONS: This work demonstrates that whole-brain, multimodal imaging information can be combined under a network control framework to identify and evaluate neurobiological correlates and mechanisms of heavy alcohol use.

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Alcohol use disorder (AUD) is a long-term and recurring neurological condition that can continue unabated despite significant adverse effects on the person, their family, and the broader community. However, the root neurobiological causes of AUD remain undefined, effective treatment methods are limited, and relapse rates are approximately 60% (1). Significantly, it has been observed that only a fraction of individuals who regularly consume addictive substances eventually develop a substance use disorder (SUD). This emphasizes the urgent need to uncover biological elements that predispose a person to develop SUDs and to improve prevention and treatment paradigms.

Individuals with an SUD may be vulnerable because of genetics, developmental differences, hormones, life experiences, or environmental and/or adverse social exposures (2). The brain's reward circuitry, stimulated by most addictive drugs, depends greatly on dopamine signaling, particularly in the ventral tegmental area and dorsal striatum, including the nucleus accumbens. Chronic exposure to dopamine-stimulating drugs, such as alcohol, can trigger glutamatergic-mediated changes in the striato-thalamo-cortical (specifically orbitofrontal and anterior cingulate cortex [ACC]) and limbic (amygdala and hippocampus) pathways that can lead to a transition from goal-directed to habitual control over drug-seeking behaviors in certain individuals (3). Several positron emission tomography (PET) studies have revealed that people with an SUD of alcohol (4), cocaine (5), heroin (6), and methamphetamine (7) have reduced concentrations of dopamine receptors. One hypothesis is that individuals with lower dopamine receptor levels, due to genetics and/or because of their environment or life experiences, obtain less-than-usual dopamine-mediated pleasure from everyday life and may therefore be susceptible to habitual seeking of drug-induced increases in dopamine.

Neuroimaging studies have begun to reveal differences in brain structure and function in individuals with SUDs. A recent meta-analysis revealed brain structures involved across levels of use (SUD vs. occasional vs. long-term) and substance type, including the thalamus, insula, inferior frontal gyrus, and superior temporal gyrus (8). Further neuroimaging evidence points to a possible reduction in top-down inhibitory control of bottom-up signaling (9), which may support the proposed hypothesis of SUD as a disease of control dynamics (10). In susceptible individuals, certain stimuli (bottom-up signals) may activate strong urges that would be suppressed in others by top-down inhibition but result in compulsive behavior in susceptible individuals (11). Together, the current evidence points toward neurobiological mechanisms of SUDs, which likely

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involve differences in receptor concentration/function, brain activity patterns, and anatomy [gray and white matter (12)]. However, a unifying computational model integrating multimodal observations into a single framework has not been proposed, which has undoubtedly hampered our ability to understand the neurobiological mechanisms of SUDs, thereby dampening our ability to develop effective therapies to reduce their burden.

Here, we turned our attention toward understanding heavy alcohol use (HAU), combining whole-brain structural, functional, and pharmacological information from diffusion magnetic resonance imaging (dMRI), functional MRI (fMRI), and PET to investigate brain dynamics in individuals from the Human Connectome Project's young adult dataset (13). Using the brain's structural (white matter) network as a guide, network control theory (NCT) (14) enables mapping of the brain's dynamic state space by quantifying the energy required to transition between functional states. This type of energy can be referred to as control or transition energy (TE). Recent work has utilized these tools to demonstrate that although the resting human brain has a spontaneous tendency to prefer certain brain state transitions over others, cognitive demands can overcome this tendency in a way that is associated with age and cognitive performance (15–17). NCT has proven useful in describing brain dynamics in various cognitive states (15,18), neuropsychiatric/degenerative conditions (16,17,19–21), and development (22,23). Importantly, NCT has also captured changes in brain dynamics due to neuromodulation (17,24–26). One such fMRI study showed increased TE under the D_2 antagonist amulsipride compared with placebo (17). This study also showed that TE was negatively correlated with genetically predicted D_2 receptor concentration, indicating that those likely to have lower concentration of D_2 receptors also had higher TE. This evidence supports the use of NCT to reveal shifts in the brain's energetic landscape in response to receptor modulation/concentration and, importantly, the hypothesis that decreased dopamine receptor function/concentration, as is known to occur in HAU, results in increased energetic demand to travel through the brain's state space (i.e., increased TE). Thus, we propose using NCT as a unifying computational modeling approach that incorporates the effect of white matter and/or dopamine receptor differences in individuals with HAU on their brain activity dynamics with the goal of understanding neurobiological mechanisms of HAU at the whole-brain level.

We utilized a network control framework to improve our understanding of how brain structure and function is altered in HAU. Using functional brain states from resting-state fMRI and the brain's structural connectivity (SC) from dMRI, we compared TE in individuals with current HAU to that of individuals with minimal use of substances. We further related these shifts in energetic demands to the complexity of brain activity, a well-known biomarker of information processing and brain health (27). Then, to investigate changes in top-down and bottom-up signaling, we investigated how white matter differences in HAU may alter signal propagation between subcortical structures and the frontoparietal network (FPN). Finally, we incorporated D_2 receptor densities from PET to build a modeling framework that simulates dysfunction of the dopamine system and provides evidence for a mechanistic explanation for our findings.

METHODS AND MATERIALS

Participants

We used data from participants of the Human Connectome Project—Young Adult S1200 (13) release. See the Supplemental Methods for full details on participants and selection criteria for each group. Individuals with current HAU were assigned to the HAU group (n = 130; 30 female; mean age = 28 years, SD = 3.7). Non-SUD individuals (n = 308; 213 female; mean age = 29 years, SD = 3.8) were individuals who did not have a diagnosis of any SUD, were not binge drinkers, and reported having $<$2 drinks per day on average for the past year.

Transition Probability and State Transitions

Using the partition of brain states from k-means clustering (see the Supplemental Methods for details), we calculated transition probabilities for each individual as the probability that any given state i was followed by state j. The number of state transitions for each individual was calculated as the number of times that any given state i was followed in the next volume by any state j where $j \neq i$. These metrics were calculated separately for each fMRI scan and then averaged across scans prior to comparison.

Transition Energy

TE is defined here as the minimum energy input into a network—here, the structural connectome—that is required to move from one state to another (14,28,29) (see the Supplemental Methods for dMRI acquisition and processing and structural network estimation). To model neural dynamics, we used a linear time-invariant model: $\dot{x}(t) = Ax(t) + Bu(t)$, where A is an individual's N $\times$ N SC matrix (normalized by its maximum eigenvalue plus 1 and subtracted by the identity matrix to create a continuous system) (29), $x(t)$ is the regional activation at time t, B is the N $\times$ N matrix of control points, and u(t) is the external input into the system. Here, N is the number of regions in our parcellation. We selected $T = 1$ for the time horizon, as in previous studies (15,20,22,24,25,28). See the Supplemental Methods for further elaboration on TE, state definitions, and the dopamine dysfunction paradigm.

Metastate Complexity

We calculated the metastate complexity (MSC) of each individual's k-means partition as previously described (24,30).

In short, each individual's partition was binarized based on assignment to either of the pairs of anticorrelated states (visual network [VIS]−/+ or default mode network [DMN]−/+) to construct the metastate time series. We then used the Lempel-Ziv algorithm (LZ76) (31) to quantify the compressability of, or information contained in, each binary metastate time series. This metric was calculated individually for each fMRI scan and then averaged across scans prior to comparison. MSC captures information above and beyond the absolute number of state transitions and is sensitive to the precise sequence of brain states.

Statistical Comparisons

All between-group comparisons involving fMRI data were made using analyses of variance (ANOVAs) controlling for age, sex, age-by-sex interaction, and fMRI in-scanner motion (average framewise displacement). Between-group comparisons investigating SC differences alone were made using the same ANOVA design as above sans fMRI in-scanner motion. Full tables for ANOVA results are provided in the Supplement. Correlations between average TE and the number of state transitions and MSC were calculated using Spearman's rank-correlation, and p values were obtained from permutation testing. The comparison between FPN and subcortex TE and subcortex and FPN TE was performed using both groups of participants and a paired t test. Finally, the comparisons of average TE obtained using the true D_2 receptor map as a control strategy versus deplete maps were made using paired t tests. All p values were corrected for multiple comparisons using the Benjamini-Hochberg method where indicated (false discovery rate–corrected p [p_{FDR}]).

RESULTS

Commonly Recurring Patterns of Brain Activity

Data-driven clustering of all subjects' regional blood oxygen level–dependent fMRI time series revealed 4 commonly recurring patterns of brain activity (Figure 1) that we operationalize as brain states herein. The identified brain states consisted of 2 pairs of anticorrelated activity patterns (i.e., metastates), the first dominated by low- and high-amplitude activity in the visual network (VIS−/+), and the second by low- and high-amplitude activity in the default mode network (DMN−/+).

Less Dynamic Brain Activity Paired With Larger TE in HAU

We calculated pairwise transition probabilities between each of the 4 brain states (Figure 2A). In groupwise comparisons of these transition probabilities, only trends existed. Individuals with HAU showed a trend for a lower likelihood of transitioning out of the DMN− state into the VIS− (F_{432} = 4.92, uncorrected p = .0389, p_{FDR} = .210) and VIS+ (F_{432} = 4.27, uncorrected p = .0384, p_{FDR} = .210) states and a higher likelihood of staying in the DMN− state (F_{432} = 7.3, uncorrected p = .007, p_{FDR} = .116) (Figure 2B), although none of these effects were significant after correction for multiple comparisons. In general, individuals with HAU had fewer state transitions on average than non-SUD individuals (F_{432} = 7.24, p_{FDR} = .0111) (Figure 2E). Applying NCT to participants' structural connectomes, we also calculated the minimum control energy, or TE, between each of the 4 brain states for each individual (Figure 2C). Group-average transition probabilities and TE were inversely correlated (ρ = −0.81, p = .0001) (Figure S1), indicating that transitions that required more energy were less probable. Individuals with HAU showed higher TE for nearly every transition except for transitions into the DMN+ state (Figure 2D). Averaging across all pairwise transitions, individuals with HAU

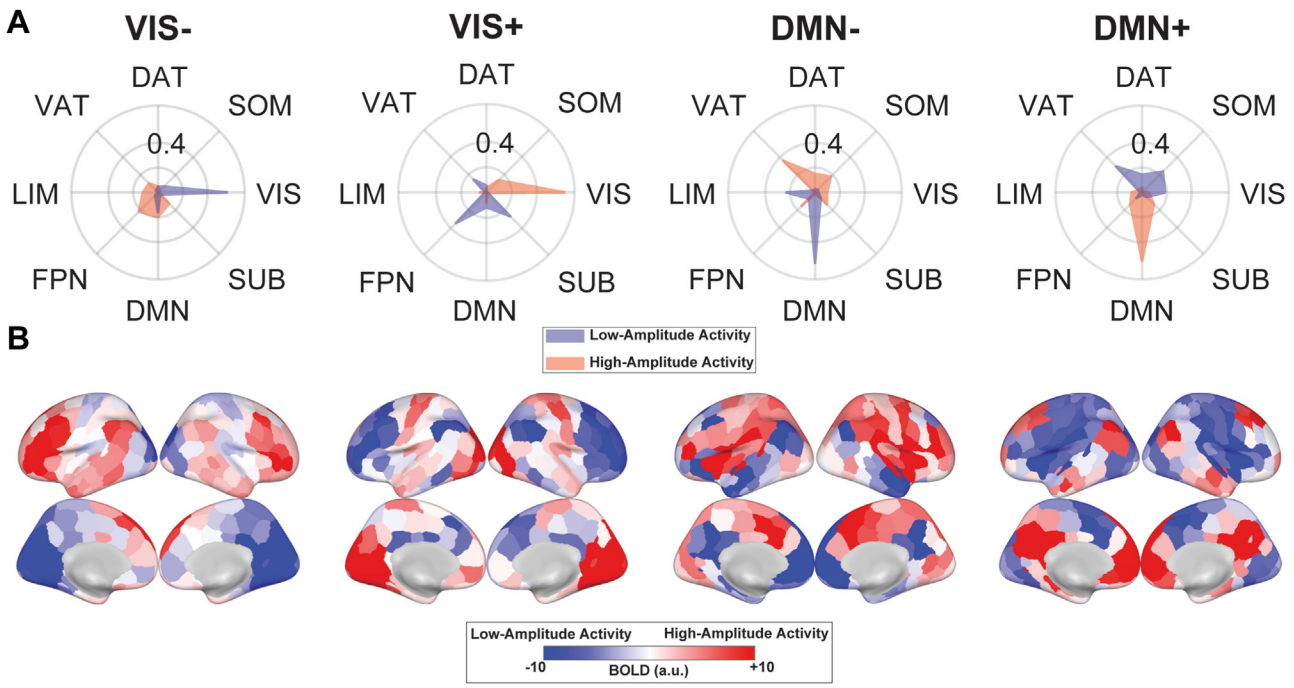

Figure 1. Four commonly recurring patterns of brain activity (brain states) were identified using k-means clustering. Group average centroids are displayed. **(A)** Cosine similarity with canonical resting-state networks (32) was calculated for the positive (high-amplitude) and negative (low-amplitude) components separately for each brain state. Each brain state is labeled by its maximal cosine similarity value. **(B)** Mean blood oxygen level–dependent (BOLD) activation of each brain state plotted on the cortical surface. a.u., arbitrary units; DAT, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; LIM, limbic network; SOM, somatomotor network; SUB, subcortical structures; VAT, ventral attention network; VIS, visual network.

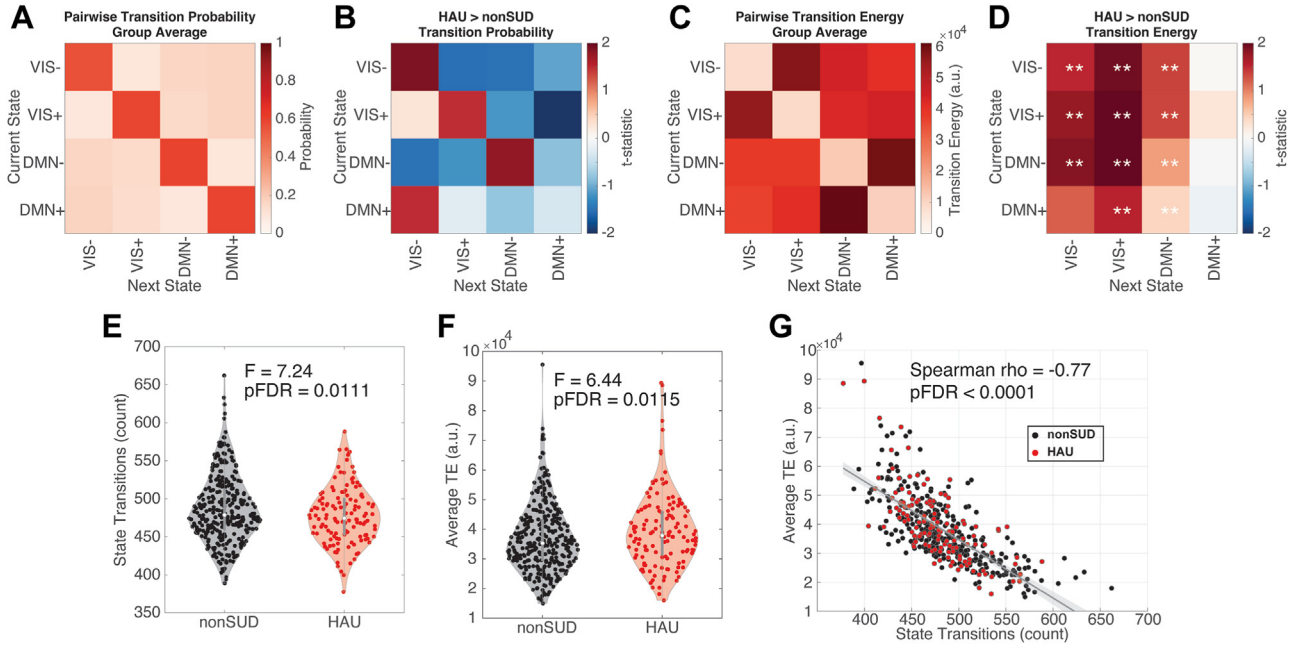

Figure 2. **(A)** Group-averaged pairwise transition probabilities observed between the 4 brain states. **(B)** A trending group effect for heavy alcohol use (HAU) on pairwise transition probabilities was observed for transitions out of the default mode network (DMN−) and into the visual network (VIS−/+) and for maintaining the DMN state. **(C)** Group-averaged pairwise transition energy (TE). **(D)** Individuals with HAU had larger TE for the majority of potential state transitions. **(E)** Overall, there were fewer state transition observed in individuals with HAU. **(F)** The average TE across all transitions was larger in individuals with HAU. **(G)** Average TE was negatively correlated with the number of empirically observed state transitions on an individual level. In panels **(B)** and **(D)**, *t* statistics are visualized to illustrate the direction; however, asterisks still represent *p* values obtained from analyses of variance. *uncorrected $p < .05$, **$p_{FDR} < .05$. a.u., arbitrary units; p_{FDR}, false discovery rate–corrected; SUD, substance use disorder.

also had larger average TE than non-SUD individuals (Figure 2F). Finally, across the entire group, individuals with larger average TE had fewer observed state transitions ($\rho = -0.77$, $p_{FDR} < .0001$) (Figure 2G).

While brain activity in individuals with HAU was less dynamic in terms of having fewer observed state transitions, this is not a measure of brain activity complexity or information content. To this end, we next computed the MSC of individuals' brain state time series (Figure 3A). Individuals with HAU showed lower MSC than individuals without SUD ($F_{432} = 10.92$, $p_{FDR} = .0031$) (Figure 3B), and average TE was negatively correlated with MSC across the 2 groups ($\rho = -0.63$, $p_{FDR} < .0001$) (Figure 3C). MSC and state transitions, 2 related metrics, were also correlated ($\rho = 0.86$, $p_{FDR} < .0001$) (Figure S2).

Higher Subcortex-to-FPN TE in HAU

Next, we turned our attention toward TE between canonical subcortical and FPN states (Figure 4A) to test for asymmetrical communication patterns between these 2 parts of the brain in individuals with and without HAU. Due to homogeneous state definition across individuals (see the Supplemental Methods), this analysis only revealed differences driven by changes in the white matter SC network. For all individuals, it required less energy to transition from the FPN to the subcortex than it did to transition in the reverse direction ($t_{437} = -112$, $p_{FDR} = .0001$) (Figure 4B). There was no group difference in TE between individuals with HAU and non-SUD individuals for the transition from the FPN to the subcortex ($F_{432} = 1.63$, $p_{FDR} = .2027$) (Figure 4C). However, individuals with HAU had larger TE for the transition from subcortex to FPN ($F_{432} = 6.04$, $p_{FDR} = .0216$) (Figure 4D). Considering the direction of both trends, we performed a post hoc evaluation of HAU's effect on the TE asymmetry of these 2 transitions to examine whether individuals with HAU had a larger delta for transitioning in one direction (FPN to subcortex) versus the other direction (subcortex to FPN). There was a slight trend suggesting that individuals with HAU had a larger TE asymmetry ($F_{432} = 2.83$, uncorrected $p = .0934$).

Simulated Dopamine Dysfunction Results in Increased Average TE

We deployed an in silico paradigm for studying the impacts of depleted dopamine receptor availability on TE (Figure 5). We simulated energies associated with typical dopaminergic functioning by calculating the average TE for non-SUD individuals using control weights derived from regional D_2 receptor density maps (derived from PET scans in a separate population). Then we assessed the impacts of D_2 receptor depletion by recalculating average TE with a series of perturbed receptor maps and comparing the average TE from the perturbed D_2 receptor maps to that of the true D_2 receptor map (Figure 5A). We found that depleting the regions with the highest density of D_2 receptors (>95th percentile, which are mostly regions in the dorsal striatum) by 20% ($t_{307} = 10.4$, $p_{FDR} < .0001$), 30% ($t_{307} = 20.4$, $p_{FDR} < .0001$), 40% ($t_{307} =$

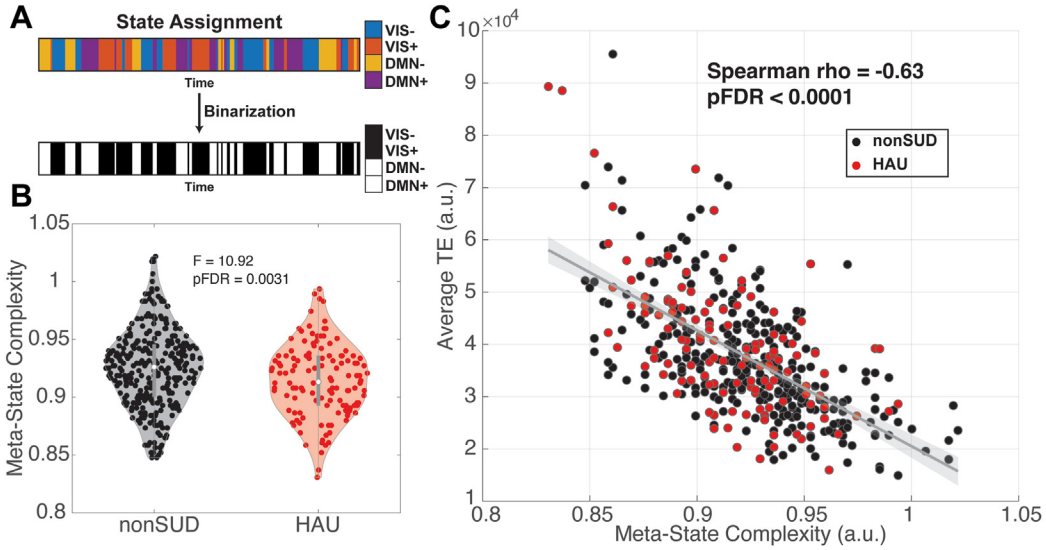

Figure 3. **(A)** Each participant's partition of brain states obtained from *k*-means clustering was binarized based on assignment to either visual network (VIS)–dominated or default mode network (DMN)–dominated states. **(B)** Lempel-Ziv compressibility was run on the binarized sequences to characterize the complexity of the brain state sequences (metastate complexity). Individuals with heavy alcohol use (HAU) had significantly lower metastate complexity compared with individuals without substance use disorder (non-SUD). **(C)** On an individual level, metastate complexity and average transition energy (TE) were negatively correlated. a.u., arbitrary units; p_{FDR}, false discovery rate–corrected.

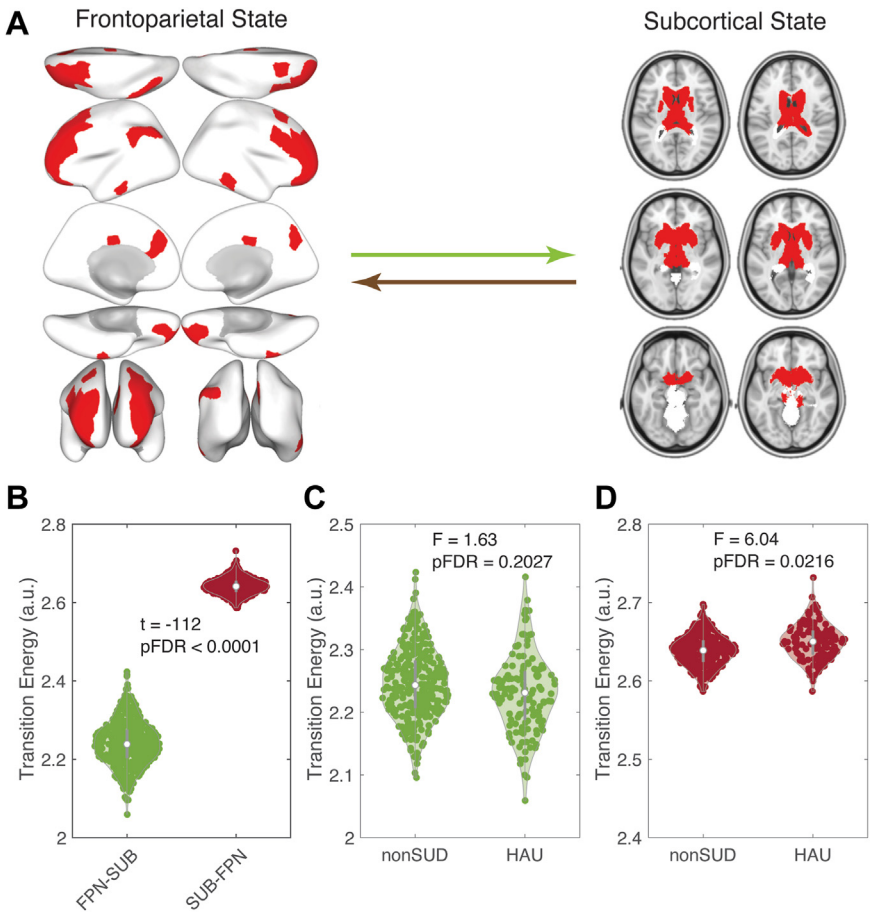

Figure 4. **(A)** Transition energy between canonical states of the frontoparietal network (FPN) and subcortical regions. **(B)** Across all participants, it was more difficult to transition from the subcortex to the FPN (up the hierarchy) than it was to transition in the reverse direction (down the hierarchy). **(C)** There was no group effect on transitioning from the FPN to the subcortical network. **(D)** Individuals with heavy alcohol use (HAU) required more energy to transition from the subcortex to the FPN than those without a substance use disorder (non-SUD). a.u., arbitrary units; p_{FDR}, false discovery rate–corrected; SUB, subcortical structures.

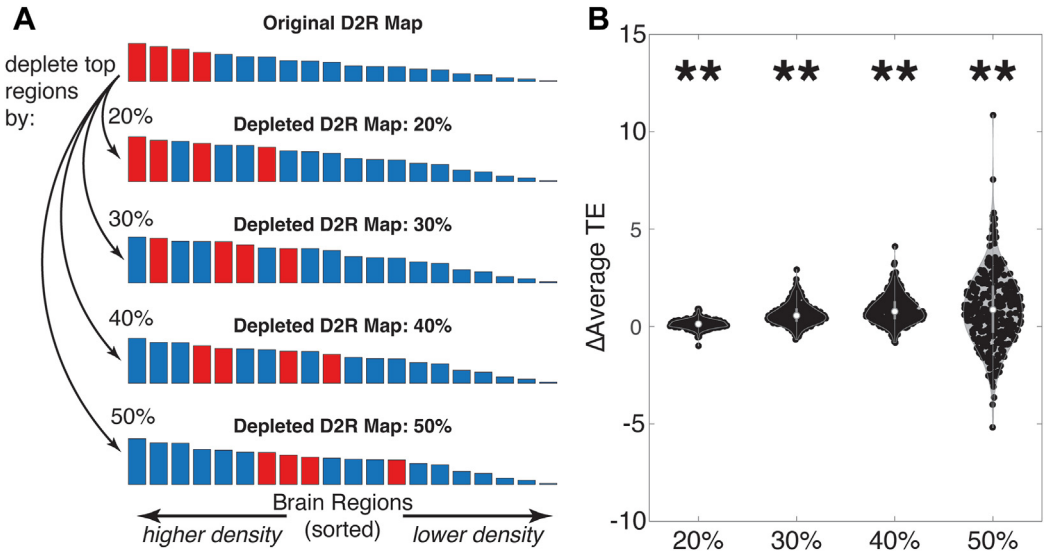

Figure 5. D_2 receptor (D2R) depletion simulation paradigm. **(A)** The original positron emission tomography–derived D2R map (top) ordered by the average density of D2R availability per region (20 randomly selected regions shown for illustration purposes). To simulate dopamine receptor depletion or dysfunction, regions above the 95th percentile of D2R density, mostly in the dorsal striatum, are depleted from their original values by 20%, 30%, 40%, and 50%. Each of these maps was then used as control weights for calculating average transition energy (TE) for individuals without substance use disorder, and the results of each depleted map were compared against those from the original map. **(B)** Each depleted map resulted in an increase in average TE compared with the original map. $^{**}p_{FDR} < .0001$.

21.5, $p_{FDR} < .0001$), and 50% ($t_{307} = 8.5$, $p_{FDR} < .0001$) resulted in significant TE increases compared with the original, unperturbed map (Figure 5B).

Replications

We replicated our results in numerous ways. First, we repeated *k*-means clustering with $k = 2$ to 12 clusters and assessed HAU's impact on state transition count and average TE using each resulting partition. We found that individuals with HAU had lower state transitions and higher average TE than non-SUD individuals for each value of *k* tested (Figure S4). We also successfully replicated our dopamine dysfunction model using the partitions from $k = 3$ and $k = 5$ (Figure S5). We replicated our findings of increased subcortex-to-FPN TE in HAU using continuous time-averaged states derived from fMRI (33) in place of the binary states studied in the main analysis (Figure S6). Finally, we reanalyzed state transitions, average TE, MSC, FPN-to-subcortex TE, and subcortex-to-FPN TE in 3 additional groups of individuals: 1) 100 individuals with HAU who did not show disordered use of any other substances (HAU-only) (Figure S7), 2) 53 individuals who had marijuana (MJ) abuse/dependence and did not show disordered use of any other substances (MJ-only) (Figure S8), and 3) 26 individuals who had both HAU and marijuana abuse/dependence and did not show disordered use of any other substance (HAU+MJ) (Figure S9). For the HAU-only group, we found that all results were replicated, except for the finding of increased TE from the subcortex to the FPN, which only showed a trend. We found that none of the functionally derived results (state transitions, average TE, and MSC) were replicated in the MJ-only group. There was a trend for changes in the structure only–derived results (FPN-to-subcortex TE and subcortex-to-FPN TE) in the same direction as was observed in the main text. For the final group, HAU+MJ, we found that the functionally derived results did not replicate, but structure-based differences were evident by large effect sizes (FPN-to-subcortex, $F_{339} = 7.97$, $p_{FDR} = .005$; subcortex-to-FPN, $F_{339} = 14.13$, $p_{FDR} = .0003$).

DISCUSSION

We applied NCT to understand how current HAU altered both the structure and function of the human brain in 438 individuals. Using individuals' SC networks from dMRI and functional states from fMRI data, we found that TE in the brain was higher in individuals who had current HAU than those with minimal use of substances (non-SUD) (Figure 2D, F). Higher TE in HAU occurred alongside a concomitant decrease in the number of state transitions (Figure 2E) and MSC measured with resting-state fMRI (Figure 3B). Additionally, both the number of state transitions and MSC were strongly anti-correlated with average TE across all participants (Figures 2G and 3C). Using canonical states implicated in substance use, we found that individuals with HAU required more energy to transition from the subcortex to the FPN (Figure 4D). Finally, we found that increasing the amount of dopamine dysfunction (by shifting control away from dorsal striatum regions with high D_2 receptor expression) increased TE (Figure 5), mirroring the empirical results observed in HAU.

NCT is a computational framework that enables the quantification of state TE in the brain (14). Transitions are modeled as a diffusion of initial states through the brain's structural connectome, with energy being injected at each node (brain region) to control the trajectory toward the desired final state. The integration of these inputs over the length of the trajectory

comprises the control energy, which we refer to simply as TE. Here, we calculated the TE between 4 commonly recurring patterns of brain activity in the resting-state fMRI time series of each individual (Figure 1). Consistent with our hypothesis, individuals in the HAU group had larger TE than non-SUD individuals (Figure 2D, F). In addition, state transitions and MSC were decreased in individuals with HAU compared with non-SUD individuals. These findings suggest that brain dynamics under substance use, specifically alcohol, reflect a system entrenched in a state of low complexity and decreased information processing (27).

Brain entropy, which was assessed here via MSC, has been shown to index different states of consciousness as well as various brain disorders (24,27,30). Brain entropy is affected by the acute and/or chronic administration of various substances including alcohol (34), caffeine (35), nicotine (36), and cocaine (37), as well as the psychedelics LSD, psilocybin, and DMT (30,38–40). Sevel *et al.* (34) found that the acute administration of alcohol in healthy drinkers decreased brain entropy, a result that matches the subacute effects observed in chronic heavy users of alcohol in the current study. Given that our energy and entropy results mirrored one another, we formally tested their association by correlating average TE and MSC across individuals (Figure 3C) and found a significant negative correlation. This relationship is consistent with previous studies showing an inverse relationship between TE and entropy that was modulated by disease (20) and pharmacological intervention (24,25).

Higher TE and lower dynamics that either precede or are a result of HAU likely indicate decreased neural flexibility (41–43) that may reflect decreased cognitive flexibility in disordered alcohol use (44–47), as previous studies have found. In addition, decreased cognitive and cortical arousal in HAU (48) may lead to increased fMRI signal amplitude (49) that influences average TE. The acute administration of psychedelic compounds increases cognitive and cortical arousal (50) and decreases TE (24,25). The classic psychedelic psilocybin, in addition to acutely decreasing TE in healthy volunteers (24), also increases neural and cognitive flexibility 4 weeks postdosing in individuals with major depressive disorder (51) and enhances top-down response to alcohol and emotional cues 2 days postdosing in AUD (52). Psilocybin has demonstrated promise in treating AUD, with the most robust evidence demonstrated by a significant reduction in alcohol consumption over a 32-week period in a randomized clinical trial of 95 participants with AUD and an active placebo control (53). Taken together, these findings shed light on processes linking decreased cognitive and neural arousal and flexibility in HAU with our current findings of increased TE and suggest potential treatment targets.

Previous work suggests that NCT can capture structural differences relevant for executive functioning and development (22,54). Cui *et al.* (54) demonstrated that the amount of energy required to activate the FPN decreases throughout development and also that individuals who required less energy to activate the FPN had higher executive functioning. Here, we studied the bidirectional transitions between the subcortex and the FPN (Figure 4) due to the known involvement of dopaminergic mesocorticolimbic signaling pathways and frontosubcortical circuits in addiction (10,55–57). We found that individuals with HAU required more energy to transition from the subcortex to the FPN than non-SUD individuals (Figure 4D). This finding suggests that the coarse-grained structural connectome topology of individuals with HAU is organized in a way that limits the natural diffusion of information from subcortical structures to the FPN. This possibly relates to the atrophy of regions belonging to corticostriatal-limbic circuits observed in HAU (58,59) or increased difficulty in activating the FPN, which could be associated with the decreased executive functioning found in HAU (60).

Individuals with HAU show reduced levels of D_2 receptors in subcortical limbic and striatal areas, which is also where D_2 receptors are most dominantly expressed (4,61,62). We developed an in silico D_2 receptor depletion model to test the correspondence between spatial patterns of aberrant dopaminergic signaling and our observation of increased TE in the HAU group. We recalculated average TE in non-SUD individuals using 5 different sets of control weights corresponding to increasing amounts of disruption to typical D_2 receptor signaling. Importantly, by using rank-normalized control weights, our paradigm is sensitive to perturbations in spatial pattern alone and not affected by changes in distribution characteristics. We found that reducing the amount of control given to the regions most richly expressed in D_2 receptors increased TE (Figure 5). This suggests a potential link between decreased D_2 receptor functioning and larger TE in HAU. Indeed, prior work has demonstrated increased TE in individuals administered a D_2 antagonist and negative correlations between genetically estimated D_2 receptor densities and global TE (17).

To understand whether the current findings were specific to HAU or would be found in disordered use of other substances as well, we repeated our main analyses in 2 separate groups of participants: those with only HAU (HAU-only) and those with only marijuana abuse/dependence (MJ-only, the next largest disordered substance-using group behind HAU). In the current study, we found that group-level impact on the fMRI-derived metrics (state transitions, average TE, and MSC) was consistent in the HAU-only group (Figure S7) but not in the MJ-only group (Figure S8). Metrics affected exclusively by the structural connectome topology (subcortex-to-FPN TE) only showed trends consistent with the main text for each group. Given that the structure-based results did not replicate in the HAU-only group or the MJ-only group, we were curious about the subset of individuals in the main analysis who were both heavy drinkers and marijuana users (HAU+MJ). In this case, we found no differences in the functionally derived measures between this group and non-SUD control group. However, the structure-based measures were significantly different in this group at a level above what is observed in any of the other groups (Figure S9). Taken together, these 3 replications suggest that the association of HAU with our functionally derived metrics may be unique compared with other substances while the structurally derived metrics seem to be moderately associated with both heavy alcohol and marijuana use and are especially associated with heavy use of more than one substance (alcohol and marijuana). Further work is warranted to elucidate the differential impacts of substance use and multisubstance use on human brain structure and function.

While this analysis utilizes state-of-the-art single-site data acquired from a large number of participants, these findings

still warrant validation in external datasets of similar scope and quality. While we controlled for sex, age, and sex-by-age interactions, we did not seek to formally evaluate these relationships; we will do so in future work. Due to the limitations of the available data, we were not able to take into account important factors for substance use such as the amount of time since the most recent drink or the duration of alcohol use.

We combined dMRI, fMRI, and PET to perform a whole-brain evaluation of the impacts of HAU on human brain structure and function. We found that functional landscapes in HAU were reflective of less dynamic and complex activity, with greater barriers to transition between brain states compared with individuals without an SUD. We also found higher energetic demands to propagate signals through the structural connectome from the subcortex to the FPN in HAU and, finally, evidence that dopamine receptor dysfunction could be a contributing mechanism to this increased energetic demand for state transitions in HAU. This study demonstrates the ability of this multimodal NCT framework to uncover shifts in brain dynamics and potentially uncover neurobiological mechanisms of these shifts. Understanding the latter is key if we are to better diagnose, prevent, track, and treat HAU so that we can help reduce the individual and societal burden of this debilitating disorder.

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