Altered structural connectivity and functional brain dynamics in individuals with heavy alcohol use elucidated via network control theory

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Abstract

Heavy alcohol use (HAU) and its associated conditions, such as alcohol use disorder (AUD), impact millions of individuals worldwide. While our understanding of the neurobiological correlates of alcohol use has evolved substantially, we still lack models incorporating whole-brain neuroanatomical, functional, and pharmacological information under one framework. Here, we utilize diffusion and functional magnetic resonance imaging to investigate alterations to brain dynamics in $N = 130$ individuals with a high amount of current alcohol use. We compared these alcohol using individuals to $N = 308$ individuals with minimal use of any substances. We find that individuals with HAU had less dynamic and complex brain activity, and through leveraging network control theory, had increased control energy to complete transitions between activation states. Further, using separately acquired positron emission tomography (PET) data, we deploy an *in silico* evaluation demonstrating that decreased D2 receptor levels, as found previously in individuals with AUD, may relate to our observed findings. 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.

1 Introduction

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, there are limited effective treatment methods available, and relapse rates are around 60% [1]. Significantly, it's 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, 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 (VTA) and dorsal striatum, including the nucleus accumbens (NAc). 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 pathways (amygdala and hippocampus) that in certain individuals can lead to transition from goal directed to habitual control over drug-seeking behaviors [3]. Several positron emission tomography (PET) studies have revealed that people with 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, have less than usual dopamine-mediated pleasure from everyday life and therefore may 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 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 in others would be suppressed by top-down inhibition, but in susceptible individuals result in compulsive behavior [11]. Together, the current evidence points toward neurobiological mechanisms of SUDs, which likely involve differences in receptor concentration/function, brain activity patterns and anatomy (gray and white matter [12]). However, a unifying computational model integrating multi-modal observations into a single framework has not been proposed, no doubt hampering our ability to understand the neurobiological mechanisms of SUDs, which in turn is dampening our ability to develop effective therapies to reduce their burden.

Here, we turn our attention towards understanding heavy alcohol use (HAU), combining whole-brain structural, functional, and pharmacological information from diffusion MRI (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 D2 antagonist amulsipride compared to placebo [17]. They also showed that TE was negatively correlated with genetically predicted D2 receptor concentration, indicating those likely to have lower concentration of D2 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). We thus 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 utilize a network control framework to better 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 compare TE in individuals with current heavy use of alcohol to that of individuals with minimal use of substances. We further relate 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 investigate how white matter differences in HAU might alter signal propagation between subcortical structures and the frontoparietal network (FPN). Finally, we incorporate D2 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 observed findings.

2 Methods and Materials

2.1 Participants

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

2.2 Transition probability and state transitions

Using the partition of brain-states from k-means clustering (see Supplementary 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.

2.3 Transition energy (TE)

TE here is defined as the minimum energy input into a network—here, the structural connectome—required to move from one state to another [14, 28, 29] (see Supplementary 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 NxN structural connectivity 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 NxN 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 Supplementary Methods for further elaboration on TE, state definitions, and the dopamine dysfunction paradigm.

2.4 Meta-state complexity (MSC)

We calculated the meta-state 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 (VIS-/+ or DMN-/+) to construct the meta-state time-series (Figure 3a). We then used the Lempel-Ziv algorithm (LZ76) [31] to quantify the compressability of, or information contained in, each binary meta-state 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 precise sequence of brain-states.

2.5 Statistical Comparisons

All between-group comparisons involving fMRI data (Figure 2b,d,e,f; Figure 3b) were made using ANOVAs controlling for age, sex, age:sex interaction, and fMRI in-scanner motion (average frame-wise displacement (FD)). Between group-comparisons investigating SC differences alone (Figure 4c,d) were made using the same ANOVA design as above sans fMRI in-scanner motion. Full tables for ANOVA results are located in the Supplementary Information. Correlations between average TE and the number of state-transitions (Figure 2g) and MSC (Figure 3c) were calculated using Spearman's rank-correlation and p-values were obtained from permutation testing. The comparison between FPN to subcortex TE and subcortex to FPN TE (Figure 4b) was performed using both groups of participants and a paired t-test. Finally, the comparison of average TE obtained using the true D2 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 (pFDR).

3 Results

3.1 Commonly recurring patterns of brain activity

Data-driven clustering of all subjects' regional BOLD fMRI time-series revealed four commonly recurring patterns of brain activity (Figure 1) that we operationalize as brain-states herein. The identified brain-states consisted of two pairs of anticorrelated activity patterns (i.e. meta-states), 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-/+).

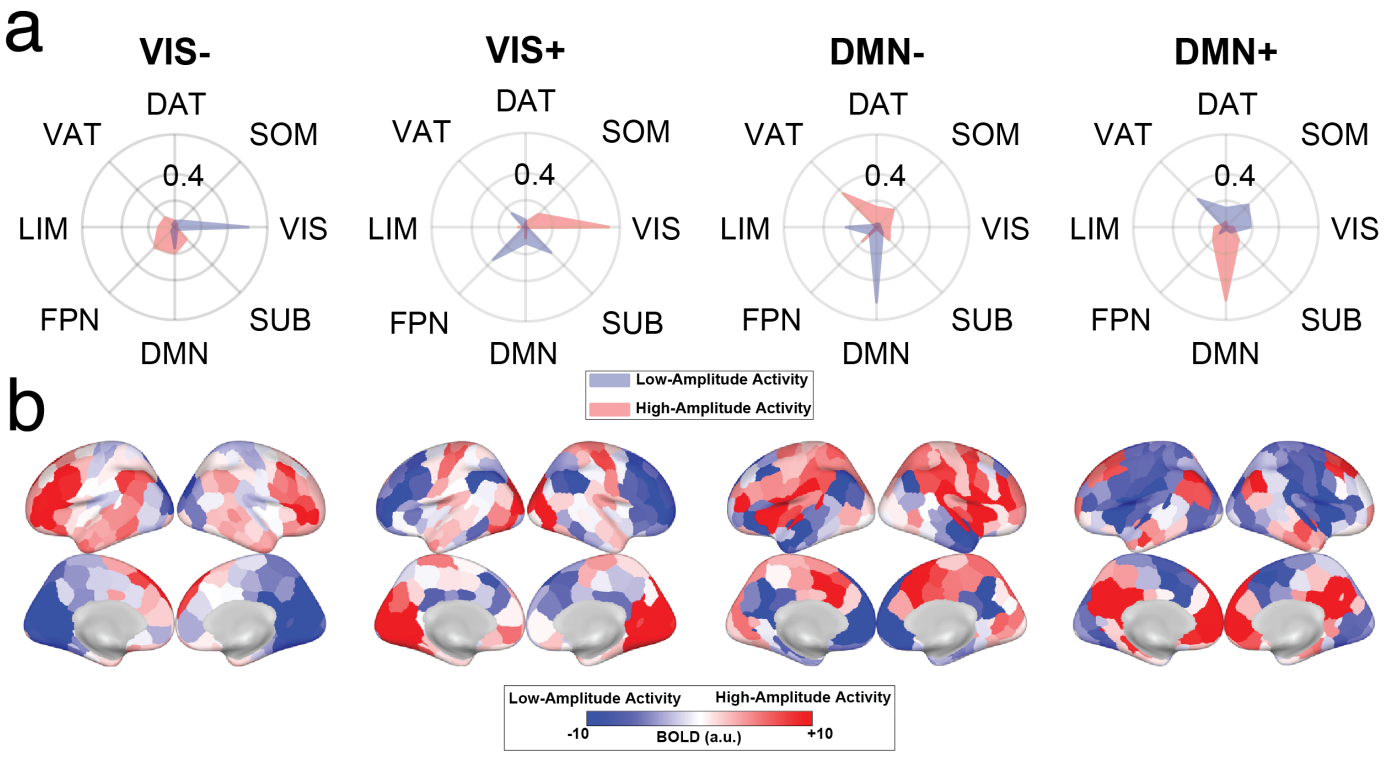

Figure 1: Four commonly recurring patterns of brain activity (brain-states) were identified using k-means clustering. Displayed are the group-average centroids. (a) Cosine similarity with canonical resting-state networks [32] was calculated for the positive (high-amplitude) and negative (low-amplitude)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

3.2 Less dynamic brain activity paired with larger TE in HAU

We calculated pairwise transition probabilities between each of the four brain-states (Figure 2a). In group-wise comparisons of these transition probabilities, only trends existed. Individuals with HAU showed a trend for lower likelihood of transitioning out of the DMN- state into the VIS- ($F = 4.92$, uncorrected p = 0.0389, pFDR = 0.210) and VIS+ ($F = 4.27$, uncorrected p = 0.0384, pFDR = 0.210) states, and a higher likelihood of staying in the DMN- state ($F = 7.3$, uncorrected p = 0.007, pFDR = 0.116) (Figure 2b), although none of these effects were significant after multiple comparisons correction. In general, individuals with HAU had fewer state transitions on average compared with non-SUD individuals ($F = 7.24$, pFDR = 0.0111) (Figure 2e). Applying network control theory to participants' structural connectomes, we also calculated the minimum control energy, or *transition energy (TE)*, between each of the four brain-states for each

individual (Figure 2c). Group-average transition probabilities and TE were inversely correlated (Figure S1; rho = -0.81, p = 0.0001), indicating that transitions which required more energy were less probable. Individuals with HAU showed higher TE for nearly every transition except for those into the DMN+ state (Figure 2d). Averaging across all pairwise transitions, HAU individuals also had larger average TE compared to non-SUD individuals (Figure 2f). Finally, across the entire group, individuals with larger average TE had fewer observed state transitions (rho = -0.77, pFDR $<$ 0.0001) (Figure 2g).

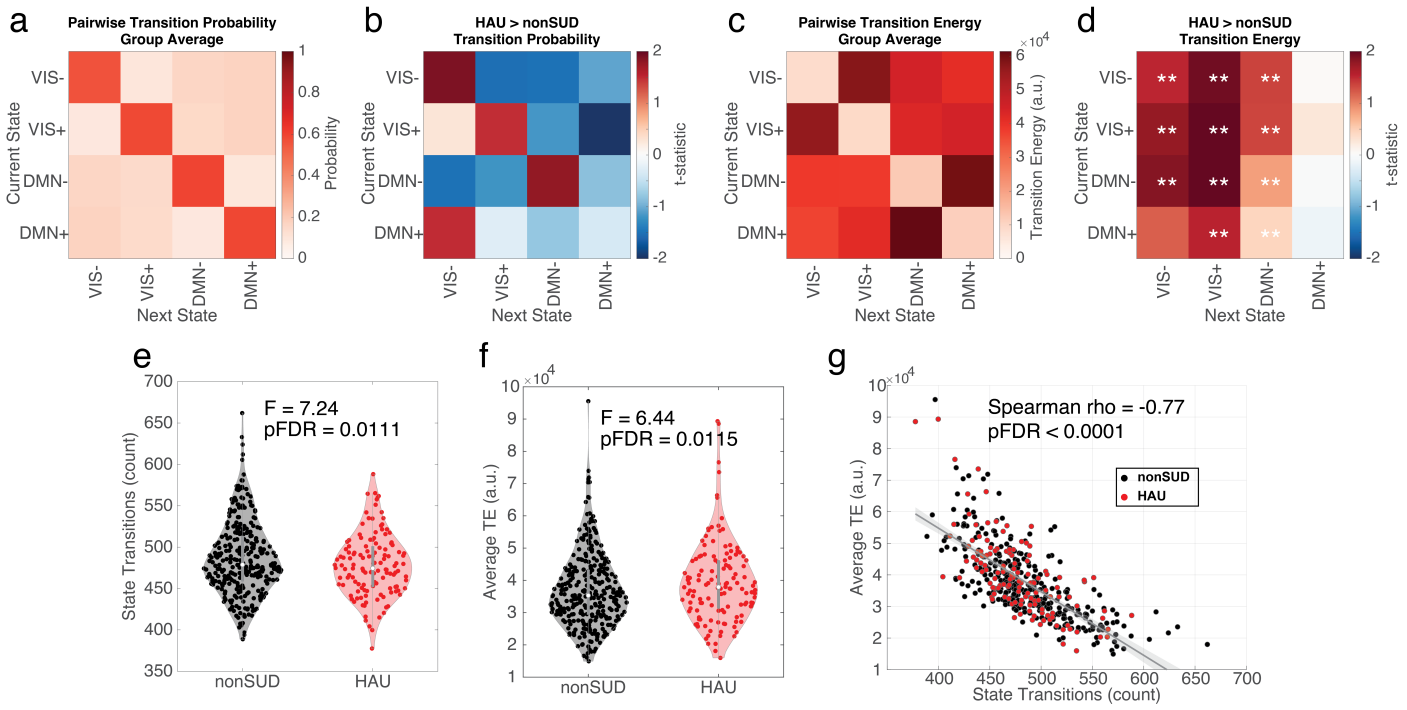

Figure 2: (a) Group-averaged pairwise transition probabilities observed between the four brain-states. (b) A trending group-effect for HAU on pairwise transition probabilities was observed for transitions out of DMN- and into VIS+/- and for maintaining the DMN- state. (c) Group-averaged pairwise TE. (d) Individuals with HAU had larger TE for the majority of potential state transitions. (e) There were overall 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 (b) and (d), t-statistics are visualized to illustrate the direction, however asterisks still represent p-values obtained from ANOVAs. * uncorrected p $<$ 0.05; ** pFDR $<$ 0.05. TE = transition energy. a.u. = arbitrary units.

While brain activity in HAU individuals 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 compared to individuals without SUD (F = 10.92, pFDR = 0.0031) (Figure 3b), and average TE was negatively correlated with MSC across individuals (rho = -0.63, pFDR $<$ 0.0001) (Figure 3c). MSC and state transitions, two related metrics, were also correlated (Figure S2; rho = 0.86, pFDR $<$ 0.0001).

3.3 Higher subcortex to FPN TE in HAU

We next turned our attention towards TE between canonical subcortical and FPN states (Figure 4a) in order to test for asymmetrical communication patterns between these two parts of the brain in individuals with and without HAU. Due to homogeneous state definition across individuals (see Supplementary Methods), this analysis is only revealing 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 = -112, pFDR ¡ 0.0001) (Figure 4b). There was no group difference in TE between individuals with HAU and non-SUD individuals for the transition for the transition from the FPN to the subcortex ($F = 1.63$, pFDR = 0.2027) (Figure 4c). However, individuals with HAU did have larger TE for the transition from subcortex to FPN ($F = 6.04$, pFDR = 0.0216) (Figure 4d). Considering the direction of both trends, we performed a post-hoc evaluation of HAU's effect on the TE asymmetry of these two transitions–that is–do individuals with HAU have a larger delta for transitioning one direction (FPN to subcortex) versus the other direction (subcortex to FPN)? Here, there was a slight trend suggesting that individuals with HAU have a larger TE asymmetry ($F = 2.83$, uncorrect p = 0.0934).

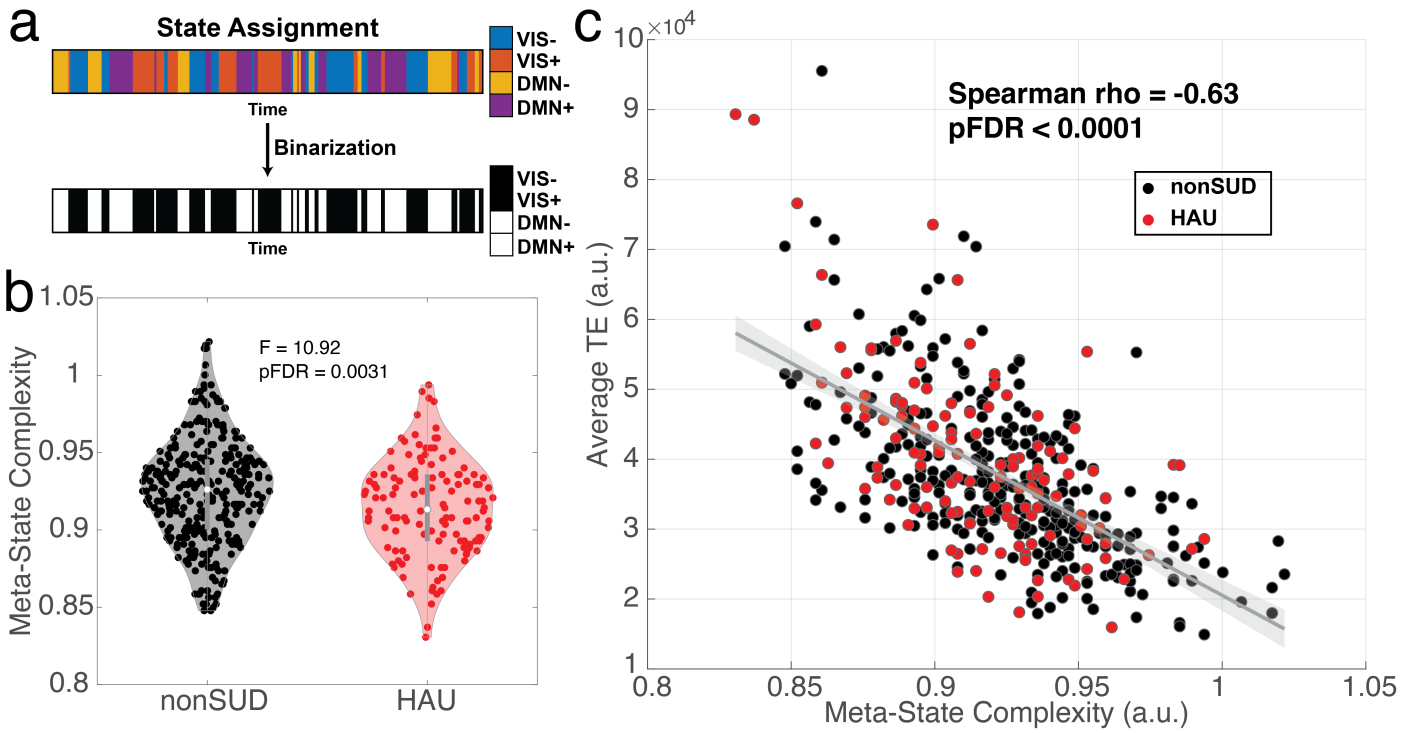

Figure 3: (a) Each participant's partition of brain-states obtained from k-means clustering was binarized based on assignment to either VIS-dominated or DMN-dominated states. (b) Lempel-Ziv compressibility was run on the binarized sequences to characterize the complexity of the brain-state sequences (meta-state complexity; MSC). Individuals with HAU had significantly lower MSC compared to non-SUD individuals. (c) On an individual level, MSC and average TE were negatively correlated.

3.4 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 D2 receptor density maps (derived from PET scans in a separate population). We then assessed the impacts of D2 receptor depletion by recalculating average TE with a series of perturbed receptor maps and comparing the average TE from the perturbed D2 receptor maps to that of the true D2 receptor map (Figure 5a). We found that depleting the regions with the highest density of D2 receptors (>95th percentile which are mostly regions in the dorsal striatum), by 20 (t = 10.4, pFDR < 0.0001), 30 (t = 20.4, pFDR < 0.0001), 40 (t = 21.5,

pFDR < 0.0001), and 50% ($t = 8.5$, pFDR < 0.0001) resulted in significant TE increases compared to the original, unperturbed map (Figure 5b).

3.5 Replications

We replicated our results in numerous ways. First, we repeated k-means clustering with k = 2-12 clusters and assessed HAU's impact on state transition count and average TE using each resulting partition. We found that HAU individuals had lower state transitions and higher average TE than non-SUD individuals for each value of k tested (Figure S4). We also successfully replicate 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). Lastly, we re-analyzed state transitions, average TE, MSC, FPN to subcortex TE, and subcortex to FPN TE in three 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 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 HAU only, we found that all results were replicated, except for the finding of increased transition energy 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, $F = 7.97$, pFDR $= 0.005$; subcortex to FPN, $F = 14.13$, pFDR $= 0.0003$).

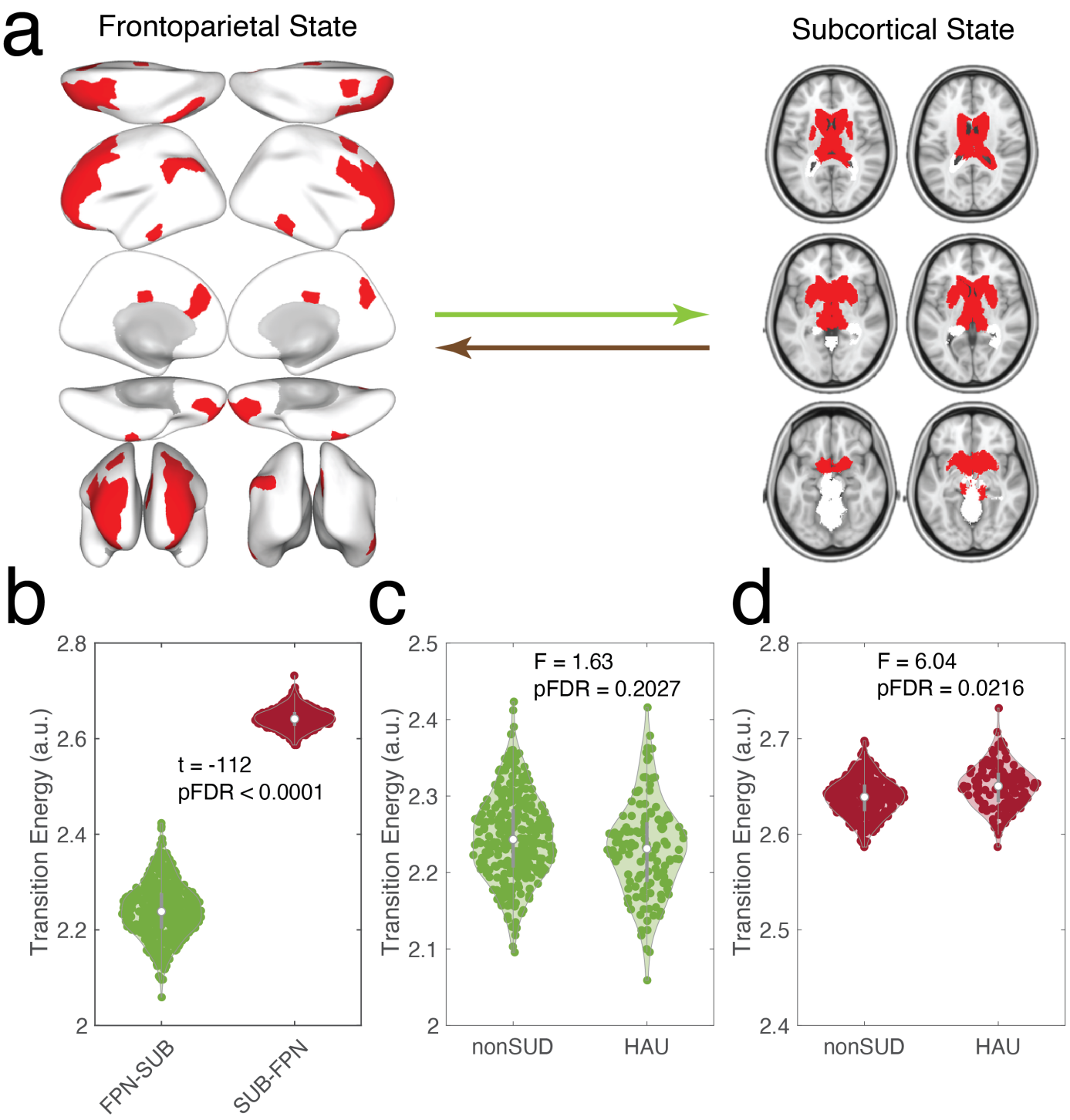

Figure 4: (a) TE between canonical states of the frontoparietal network (FPN) and subcortical regions. (b) Across all subjects, it was more difficult to transition from the subcortex to the FPN (up the hierarchy) than it was to transition in the reverse direction (down the hierarchy). (c) There was no group effect on transitioning from the FPN to the subcortical network. (d) Individuals with HAU required more energy to transition from the subcortex to the FPN than those without an SUD.

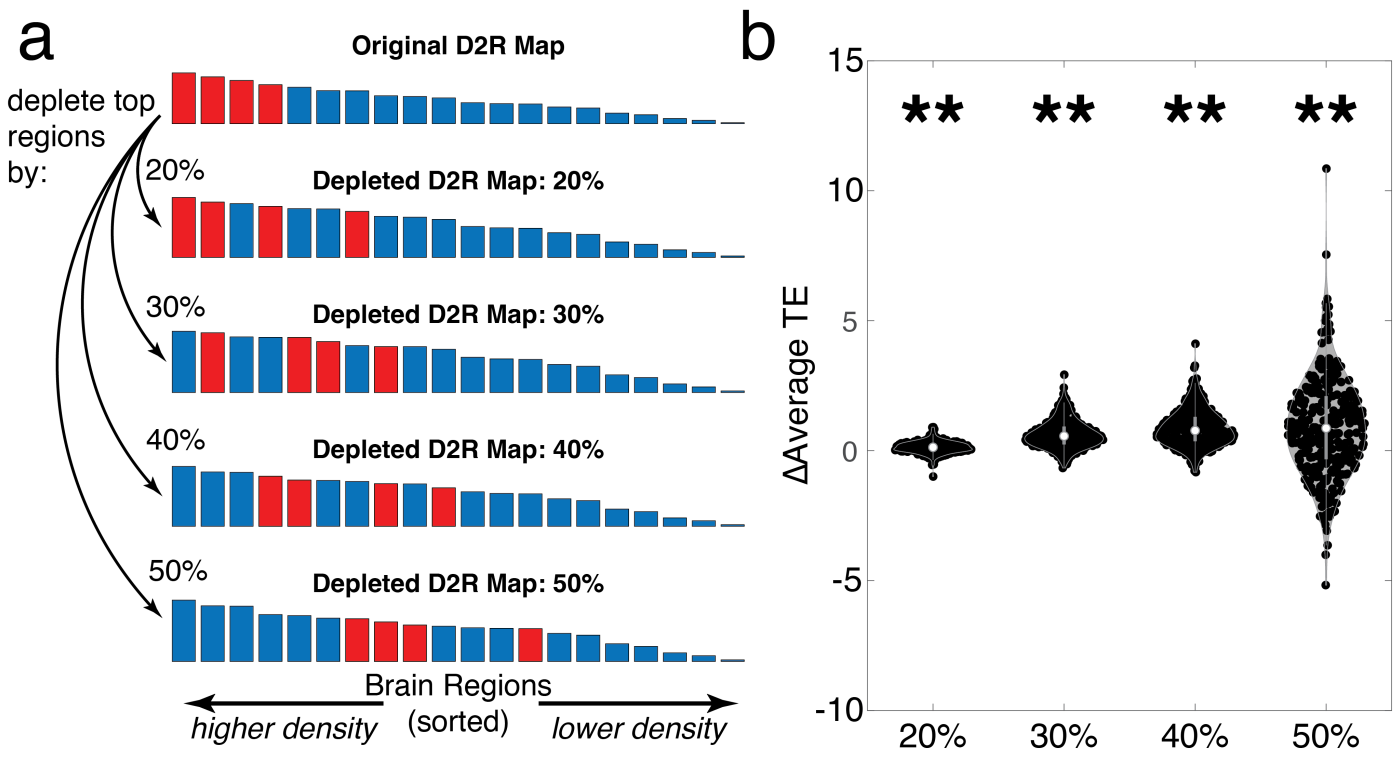

Figure 5: D2 receptor depletion simulation paradigm. (a) Top: the original PET-derived D2 receptor map ordered by the average density of D2 receptor availability per region (20 randomly selected regions shown for illustration purposes). To simulate dopamine receptor depletion or dysfunction, regions above the 95th percentile of D2 receptor density - mostly in the dorsal striatum, are depleted from their original values by 20, 30, 40, and 50%. Each of these maps were then used as control weights for calculating average TE for non-SUD individuals and the results of each depleted map was compared against those from the original map. (b) Each depleted map resulted in an increase in average TE compared to the original map. D2R = D2 receptor. ** pFDR < 0.0001

4 Discussion

We applied network control theory to understand how current HAU alters both structure and function of the human brain in 438 individuals. Using individuals' structural connectivity networks from dMRI and functional states from fMRI data, we found that TE in the brain was higher in individuals who have current HAU compared to 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 subjects (Figure 2g; Figure 3c). Using canonical states implicated in substance use, we found that HAU individuals 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 D2 receptor expression), increased TE (Figure 5), mirroring the empirical results observed in HAU.

Network control theory 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 comprise the *control energy*, which we refer to simply as *transition energy (TE)*. Here, we calculated the TE between four 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 compared to non-SUD individuals (Figure 2d,f). In addition, state-transitions and MSC were decreased in individuals with HAU compared to non-SUD. 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, here assessed via MSC, has been shown to index different states of consciousness as well as various brain disorders [24, 27, 30]. Brain entropy is impacted by the acute and/or chronic administration of various substances including alcohol [34], caffeine [35], nicotine [36], 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 decreases brain entropy, a result that matches the sub-acute effects observed here in chronic heavy users of alcohol. 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 is modulated by disease [20] and pharmacological intervention [24, 25].

Higher TE and lower dynamics that either precede or are a result of HAU likely indicates decreased neural flexibility [41–43] which may be reflective of 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 also 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 post-dosing in major depressive disorder (MDD) [51], and enhances top-down response to alcohol and emotional cues 2-days post-dosing in AUD [52]. Psilocybin has demonstrated promise in treating AUD, 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 suggests potential treatment targets.

Previous work suggests that network control theory 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 additionally, that individuals who required less energy to activate the FPN had higher executive functioning. Here, we studied the bi-directional transitions between the subcortex and the FPN (Figure 4) due to the known involvement of dopaminergic mesocorticaolimbic signaling pathways and fronto-subcortical circuits in addiction [10, 55–57]. We found that HAU individuals 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 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 decreased executive functioning found in HAU [60].

Individuals with HAU show reduced levels of D2 receptors in subcortical limbic and striatal areas, which is also where

D2 receptors are most dominantly expressed [4, 61, 62]. We developed an *in silico* D2 receptor depletion model in order 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 five different sets of control weights corresponding to increasing amounts of disruption to typical D2 receptor signaling. Importantly, by using rank-normalized control weights, our paradigm is sensitive to perturbations in spatial pattern alone, and not impacted by changes in distribution characteristics. We found that reducing the amount of control given to the regions most richly expressed in D2 receptors increased TE (Figure 5). This suggests a potential link between decreased D2 receptor functioning and larger TE in HAU. Indeed, prior work has demonstrated increased TE in individuals administered a D2 antagonist and negative correlations between genetically estimated D2 receptor densities and global TE [17].

To understand if our findings here were specific to HAU, or would be found in disordered use of other substances as well, we repeated our main analyses in two 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). Here we found that group-level impacts 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 impacted 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 controls. 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 three replications suggest that heavy alcohol use's association with our functionally-derived metrics may be unique compared with other substances while the structurally-derived metrics appear 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 multi-substance use on human brain structure and function.

While this analysis utilizes state-of-the-art single-site data acquired in 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:age interactions in our results, we did not seek to formally evaluate these relationships here; 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 HAU's impacts on human brain structure and function. We found functional landscapes in HAU were reflective of less dynamic and complex activity, with greater barriers to transition between brain-states compared to 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 multi-modal NCT framework for uncovering shifts

in brain dynamics and potentially for uncovering neurobiological mechanisms of these shifts. The latter understanding is key if we are to better diagnose, prevent, track and treat HAU so we can help reduce the individual and societal burden of this debilitating disorder.

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Disclosures

The authors have no competing interests to declare.

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