Salience Network Reorientation and Rigidity in Veterans with Mild Traumatic Brain Injury and Alcohol-Use Disorder

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BACKGROUND

Alcohol use disorder (AUD) co-occurs in **35% of Veterans with mild traumatic brain injury (mTBI)**, worsening clinical outcomes beyond either condition alone. Yet this **treatment-refractory comorbidity** remains **understudied**.

The triple network model proposes that the **salience network (SN)** regulates behavior by shifting between:

- **Control (CN)** → external, goal-directed processing
- **Default mode (DMN)** → internal, self-referential processing

How this **balance** is altered in **mTBI+AUD — across circuits and timescales —** is **unknown.**

HYPOTHESIS

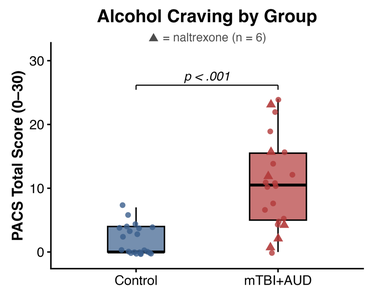
In mTBI+AUD, SN coupling shifts toward DMN and away from CN, trapping the brain in internally driven states that fuel craving and undermine cognitive control.

PARTICIPANTS

44 U.S. Veterans

- 22 Veterans with **mTBI+AUD**
- 22 age-, sex-, ethnicity-matched Veteran **controls**

Inclusion: *DSM-5 AUD (SCID-5) + ≥1 documented mTBI (VA/DoD criteria); Psychiatric comorbidities (PTSD, depression, anxiety) permitted in both groups.*



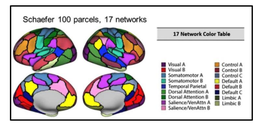
	mTBI+AUD	Control	p
DEMOGRAPHICS			
Age, yrs, M (SD)	44.4 (8.3)	42.9 (10.4)	
Male, n (%)	21 (95.5)	21 (95.5)	
White, n (%)	13 (59.1)	18 (81.8)	
Black/African American, n (%)	3 (13.6)	3 (13.6)	
Hispanic/Latino, n (%)	10 (45.5)	10 (45.5)	
mTBI CHARACTERISTICS			
Lifetime mTBIs, median (range)	3 (1–3+)	—	
> 10 yrs since mTBI, n (%)	18 (81.8)	—	
MEDICATIONS, n (%)			
Any psychotropic medication	17 (77.3)	7 (31.8)	
Naltrexone	6 (27.3)	0	
CLINICAL MEASURES, M (SD)			
PTSD Checklist for DSM-5 (PCL-5)	24.5 (14.2)	7.9 (11.8)	**< .001**
Beck Depression Inventory-II (BDI-II)	14.0 (9.6)	4.5 (6.1)	**< .001**
Beck Anxiety Inventory (BAI)	8.6 (6.0)	4.1 (6.4)	**.022**
Penn Alcohol Craving Scale (PACS) *	**10.7 (7.1)**	**1.9 (2.3)**	**< .001**
Timeline Followback (TLFB), 30-day	49.4 (68.7)	3.8 (5.8)	**.006**

APPROACH

Cross-sectional design: Resting-state functional MRI (rsfMRI) + behavioral assessments

Acquisition: rsfMRI · 2 × 10 min · TR = 555 ms · 1080 frames per run, 3060 frames total
Preprocessing: CONN v22.a · aCompCor · 12 motion parameters + bandpass 0.008-0.09Hz
Parcellation: Schaefer-100 → Yeo 17 network → **5 subnetworks (a priori)**

- **Cont-A** (Control) — *dlPFC, IPS*
- **VAN-A** (Core Salience) — *aINS, dACC, parietal op.*
- **VAN-B** (Salience) — *vlPFC, IPL, mp-PFC*
- **DMN-A** (Core Default Mode) — *mPFC, PCC, precuneus*
- **DMN-B** (Default Mode) — *vmPFC, lat. temp., IPL*



1 COMPUTE EDGES · Fisher-z correlations, parcel pairs
- **Within** 5 subnetworks *(specificity)*
- **Between** pairs × hemisphere → **12 a priori edges**

2A STATIC
- Full 20-min scan
- **Linear mixed effects**, within hemisphere
- Parallel models: **Group** & **Craving** (PACS)
- FDR · sensitivity covariates

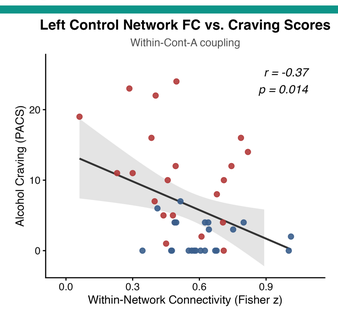
2B DYNAMIC
- 45-s sliding windows (81 TRs, 1-frame step, ~1000/run)
- **FD-adjusted linear regression**, within hemisphere
- Parallel models: **Group** & **Craving** (PACS)
- Replicated Run 1 & Run 2

RESULTS

① Static Connectivity

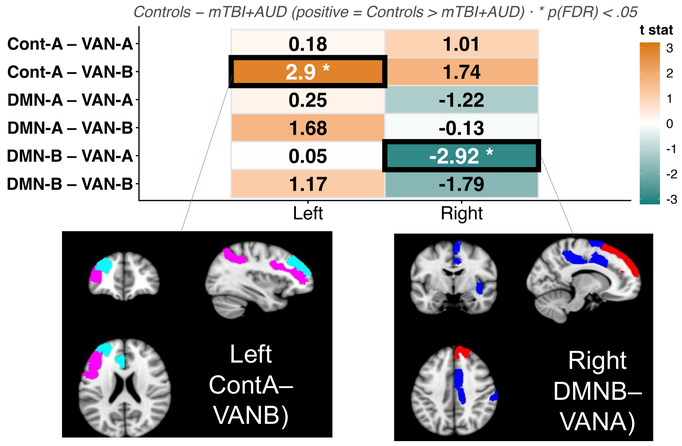
WITHIN-NETWORK COUPLING

Within-network connectivity was similar across groups; **notably, left control network (Cont-A) connectivity tracked craving, driven by left dlPFC parcels.**



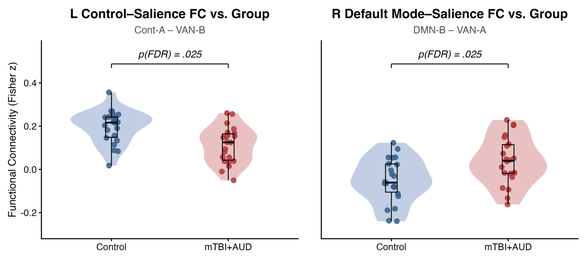
BETWEEN-NETWORK COUPLING

Two of 12 between-network edges show significant group differences:



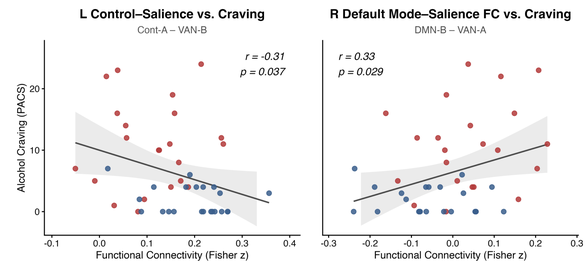
TWO KEY EDGES: GROUP DIFFERENCES

mTBI+AUD : ↓ L CN–SN (Cont-A–VAN-B) and ↑ R DMN–SN (DMN-B–VAN-A) FC



RELATIONSHIP TO CRAVING

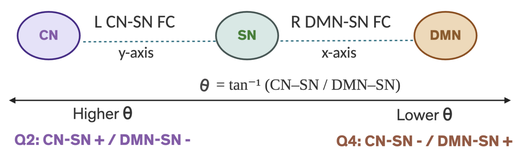
These same edges are associated with alcohol craving across participants.



② State-Space

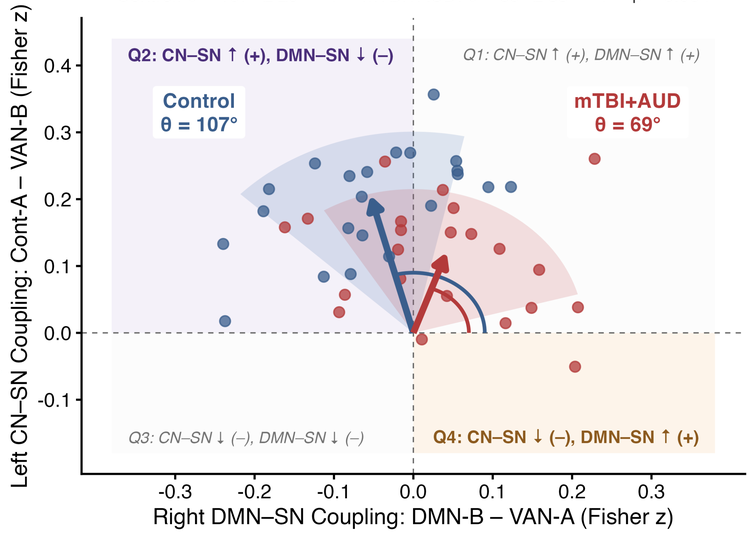
STATE-SPACE FRAMEWORK

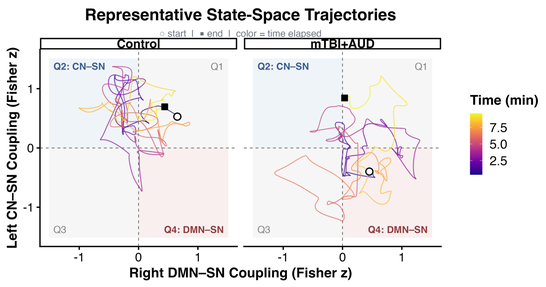
CN–SN and DMN–SN coupling are projected into a shared 2D space where each participant is positioned by their **R DMN–SN coupling (x)** and **L CN–SN coupling (y)**. .



GROUP DIFFERENCE IN ORIENTATION

mTBI+AUD shows a shift toward DMN–SN–oriented states

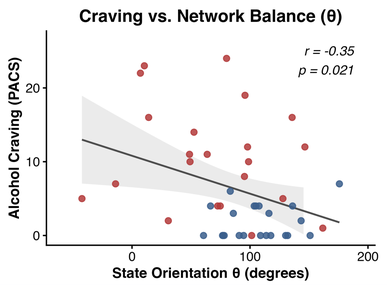




Example state-space trajectories over time from two participants.

RELATIONSHIP TO CRAVING

Greater DMN–SN orientation is associated with higher craving



Control • mTBI+AUD

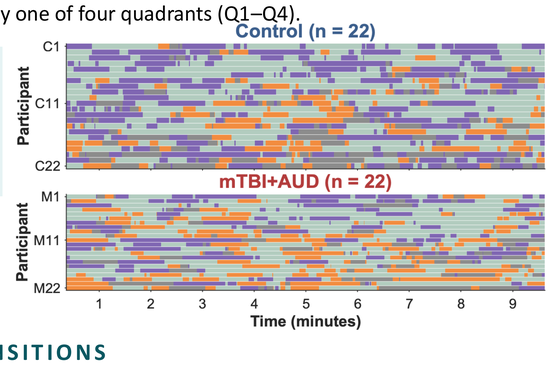
③ Dynamic Connectivity

CAPTURING STATE-SPACE DYNAMICS

At each 45-s window, participants occupy one of four quadrants (Q1–Q4).

TWO DYNAMIC METRICS

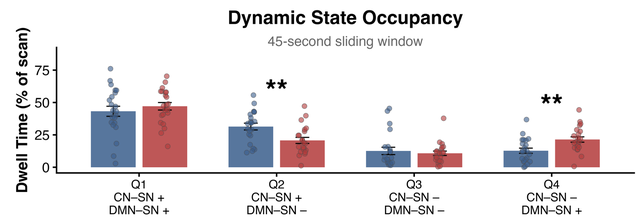
- **Dwell time** (% of scan in each quadrant)
- **State-switching rate** (% windows with a quadrant change)

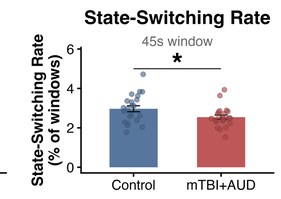


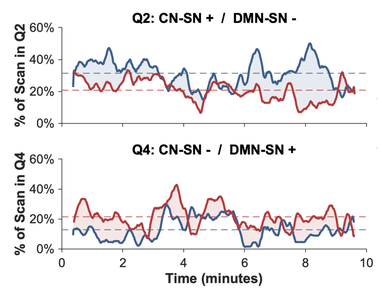
Q1: Both + | Q1: Both - | **Q2: CN-SN + / DMN-SN -** | **Q2: DMN-SN - / DMN-SN +**

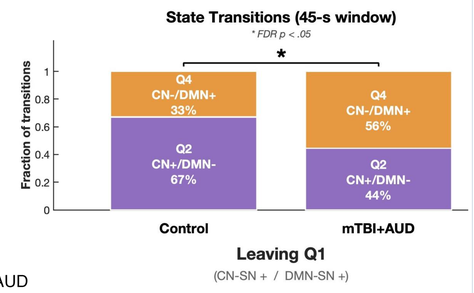
STATE OCCUPANCY AND TRANSITIONS

Controls occupy CN–SN–oriented states and switch more frequently, whereas mTBI+AUD occupy DMN–SN–oriented states with reduced switching and transitions biased toward DMN–SN states.



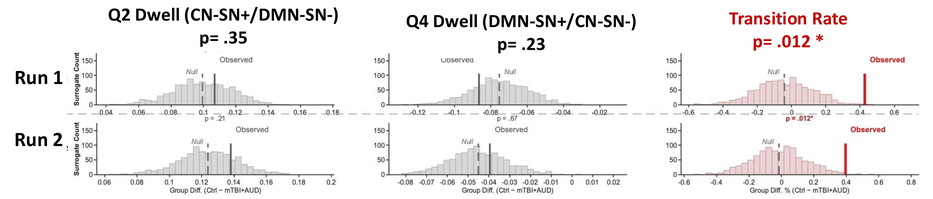






PHASE RANDOMIZATION

Phase-randomized surrogates preserve static connectivity while removing temporal ordering.



Reduced state-switching in mTBI+AUD exceeds this null, indicating a uniquely dynamic effect

Key Takeaways

- Veterans mTBI+AUD show **reoriented** SN subnetwork coupling (CN–SN ↓, DMN–SN ↑) that tracks alcohol craving, and **reduced moment-to-moment state-switching** between network configurations.
- This network reorientation and rigidity may inform **neuromodulation targets** for treatment-refractory mTBI+AUD.