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Using deep learning to identify brain networks mediating cognitive and motor impairments in alcohol use disorder

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Alcohol Use Disorder (AUD), with a lifetime prevalence of 29.1% in the U.S., is associated with functional impairment affecting visuospatial working memory, executive functions, and motor control. The objective of this study was to distinguish people with AUD from controls on the basis of functional brain and neuropsychological measures that would contribute to identifying mechanisms of AUD-related dysfunction. A data-driven, deep-learning framework jointly analyzed 6105 region-to-region connections from resting-state functional MRI and 16 cognitive and motor performance scores. The deep learning method first derived 16 brain networks aligned with neuropsychological functions and then combined them into 14 functional units. After determining the most important functional unit for diagnostic classification, mediation analysis identified the neural pathways of that unit through which AUD affects neuropsychological performance. The Temporal Attention Network (TAN) fully mediated the effect of AUD diagnosis on spatial working memory (Visual Span). TAN also fully mediated the effects of AUD on visually guided attention, set-shifting, and motor performance (Trail Making Test), which, in parallel was mediated by a second network, the Sensorimotor Network (SMN). In conclusion, selective and dissociable brain functional and neuropsychological relationships differentiated individuals with AUD from controls. These relations, which were identified with deep learning technology and replicated on an independent dataset of people with HIV (with or without AUD comorbidity), provide support for brain functional substrates of commonly observed, AUD-related neuropsychological deficits.

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INTRODUCTION

Alcohol Use Disorder (AUD) [1, 2], a leading preventable cause of morbidity and mortality in the US with a yearly prevalence of 10% [3–5], is associated with cognitive and motor impairment, [6, 7] particularly affecting processes of attention, executive control, learning and memory, [8, 9] visuospatial working memory, [8–10] and speeded motor function [11, 12]. Given the complexity of each function affected, a search for their neural substrates requires examination of multiple brain systems to identify disruption and their contribution to impairing the multifaceted neuropsychological skills. This search is especially challenging in AUD because of its widespread untoward effects on brain structural [13–16] and functional integrity [17–20] that could exert independent or integrated influences on affected neuropsychological (NP) functions.

Compromise of selective NP functions in AUD has been successfully linked to disturbances in brain functional networks captured by resting-state functional magnetic resonance imaging (rs-fMRI) [17–22]. Compared to controls, people with AUD exhibited disruptions of functional connections between the posterior cingulate and multiple cerebellar subregions [17] that correlated with measures of postural imbalance [23]. Similarly, AUD adversely affected verbal fluency, working memory subsystems, and executive functions [21], known to be supported by frontal lobe systems. Finally, poor cortical connectivity in heavy drinkers correlated with low performance on cognitive tasks involving executive functions such as the Stroop Test, Symbol Digit Modalities Test, and Word Association tasks [22]. These individual findings typically relied on a priori defined brain networks for investigating functional compromise in AUD to the exclusion of networks and connectivity patterns underpinning NP functions untested with hypothesis-driven methods.

To date, identifying functional connectivity linked to a specific NP function has relied on univariate analyses conducted over a few a priori selected functional measures [24–30]. While successful in singular investigations, traditional univariate fMRI approaches assess voxel-wise activation independently and, therefore, are limited in their ability to characterize distributed interactions among multiple brain networks that support complex cognitive abilities [31–33]. Complex functions, like top-down cognitive and motor functions, require coordinated activity across large-scale neural networks rather than isolated regional activation [34, 35], some of which are often disrupted in alcohol use disorder [36, 37]. We hypothesized that unravelling this complexity would be possible through a data-driven approach that jointly modeled NP performance and brain connectivity measured with rs-fMRI. We

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Table 1. Comparison of demographics between AUD and Control groups and the number of female (F) and male (M) participants at baseline visit.

Demographic variables	AUD (N = 67)	Controls (N = 48)	t or χ^2	p	Cohen's d
Sex (F/M)	21/46	18/30	0.238	0.626	−0.130
Age at Baseline Visit (years)	51.55 ± 10.07	56.88 ± 11.58	−2.545	0.0126	0.493
Average Years between Visits	2.33 ± 0.98	2.19 ± 0.71	0.493	0.627	−0.173
SES at Baseline Visit [41] (lower Score=higher status)	39.16 ± 17.33	22.98 ± 9.35	6.393	<0.001	−1.103
Lifetime Alcohol Consumption (kg)	1158.77 ± 841.62	47.09 ± 69.66	10.761	<0.001	−1.724
AUD Age of Onset (years)	25.49 ± 9.58	–	–	–	–
Alcohol Sobriety (months)	9.00 ± 28.08	–	–	–	–
AUD Remission (months)	17.94 ± 38.67	–	–	–	–
SUD Remission (months)	114.60 ± 125.65	–	–	–	–

Substance Use Disorder (SUD) includes Cocaine, Amphetamines, Opioids, Sedatives, Hallucinogens, and Cannabis.

tested this hypothesis by applying a novel deep-learning method to the rs-fMRI and NP scores of 48 controls and 67 recruits diagnosed with AUD. We then replicated our finding on an independent dataset of 26 people with HIV and AUD comorbidity and 45 people with HIV without AUD comorbidity. Finally, to identify neural mechanisms underlying common functional impairments of AUD, a post-hoc analysis investigated the brain-NP pairings that were predictive of AUD.

MATERIALS AND METHODS

Participants

The dataset comprised neuroimaging and neuropsychological assessment collected from 82 visits of 67 participants diagnosed with AUD and 74 visits from 48 control participants (Table 1 and Supplementary Sample Size and Inclusion Criteria) by the Stanford-SRI International Neuroscience Program [38]. All participants gave written informed consent for partaking in the study, which was approved by the Stanford and SRI institutional review boards. The consenting process abided by The Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants in the AUD group met lifetime criteria for alcohol dependence or abuse as defined by the DSM-IV-TR [39], and/or criteria for AUD as outlined in the DSM-5 [40] determined from the SCID interview. Two-sample t-tests or chi-square tests (for dichotomous variables) compared differences between the two diagnostic groups (Table 1). The two groups did not differ in their sex ratio ($p = 0.626$), although the AUD group was younger ($p = 0.0126$) and had a lower socioeconomic status [41] (Table 1). The mean remission time from the most recent other Substance Use Disorders (SUD) was 114.60 ± 125.65 months (versus 17.94 ± 38.67 months for AUD), and the effect of other SUD on this analysis was considered negligible (see Supplementary Effect of Other Substance Use Disorder and Drinking Sobriety). Finally, the independent replication data set consisted of 26 people with HIV and AUD comorbidity (HIV + AUD), and 45 people with HIV without AUD comorbidity (HIV) (see Supplementary Replication Study and Table S9), all of whom completed the same protocol as the main study.

MRI acquisition and processing

Data from rs-fMRI were acquired on a 3 T GE Discovery MR750 scanner (Waukesha, MI) with 8-channel head coil (echo time=30 ms, dwell-time=0.388 ms, TR = 2200 ms, 2.5 mm isotropic after upsampling). During the rs-fMRI acquisition, participants were instructed to remain still with their eyes open and to think of nothing in particular. Acquisition durations ranged from approximately 5–10 min, corresponding to 135–274 frames per participant. The number of frames per participant did not significantly differ between the AUD and control groups (two-sample two-sided t-test, $t = -0.82$, $p = 0.4134$).

All scans were processed through the SIBIS pipeline [38, 42], which first non-rigidly registered the mean blood oxygenation level-dependent (BOLD) image to the SRI24 atlas (1.5 mm isotropic resolution) [43] and then applied the Nipype-based resting-state workflow [44]. Scans were excluded from the analysis if their frame-to-frame motion was above 0.75 mm. Motion outliers were then identified and removed using Nipype rapidart (framewise displacement threshold = 0.3 mm; intensity Z-threshold = 5) and modeled together with detrending terms in a general linear model (GLM) implemented in FSL [45], which was also used for frame interpolation. Physiological noise was estimated and regressed using Nipype CompCor [46] and FSL GLM. A discrete Fourier transform bandpass filter (0.01–0.1 Hz) was applied using Numpy v1.16.2 (http://www.numpy.org/) for temporal smoothing, and spatial smoothing was performed with a Gaussian filter of 5.0 mm full width at half maximum (FWHM [47]) kernel using FSL fslmaths [45]. At this point, scans were excluded if the duration of usable time points after removing outlier fMRI frames was below 180 s [38, 43]. A random split-half procedure was conducted to ensure the within-scan stability of our rs-fMRI acquisition (see Supplementary MRI Data Quality Check and Supplementary Fig. S1). Differences in rs-fMRI quality between controls and AUD are summarized in Supplementary Table S5.

For scans passing quantitative and visual quality control, the average regional time series was computed for each of 111 cortical and deep gray matter regions as defined by the SRI24 atlas [43]. For each regional time series, the global average BOLD signal was regressed out and then normalized to a mean of 0 and a standard deviation of 1. The resulting regional time series were correlated with Pearson correlations, which defined the 111 × 111 functional (region-to-region) connectivity matrix containing 6105 connections.

Neuropsychological assessment

Each participant had completed 16 neuropsychological (NP) tests at each visit. Tests assessing memory and learning included the California Verbal Learning Test (CVLT) [48], Rey-Osterrieth Complex Figure Test (ROCF) [49], and Wechsler Memory Scale-Revised [50] for Logical Memory (WMSR-LM). Attention and executive functions were measured with the Digit Symbol Test (DST) [51], Controlled Oral Word Association Test (FAS) [52], Semantic Fluency (SF) [53], Digit Span (WMSR-DS), Visual Span (WMSR-VS), Stroop Color and Word Test (SCWT) [54], and Trail Making Test (TMT) [55]. Motor coordination skills were evaluated with Alternate Finger Tapping (AFT) [56], Fine Finger Movement (FFM), and the Grooved Pegboard Test (GPT) [57]. Ruff Figural Fluency Test (RFFT) [58] assessed visuospatial and production abilities. Postural stability was evaluated with Ataxia Testing [59]. The Ishihara Test screened for red-green color blindness [60].

Each NP test was treated as a unified measure within its functional domain, reflecting the hierarchical integration of multiple neurological processes rather than individual dissociable functions. Sub-scale measurements of each of the 16 tests were then reduced to a single measure associated with the first component of a PCA analysis [61]. For bilateral measurements (such as the Ataxia tests performed while standing on the left or right leg), the PCA analysis was performed on the average across the values acquired on the left and right sides. Thus, each visit of a participant was encoded by 16 neuropsychological measurements (see Supplementary Neuropsychological Measurements and Table S1 for detailed descriptions of NP tests and Supplementary Table S2 for the statistical comparison of NP Assessments between AUD and Control Groups).

Deep learning analysis

A deep learning analysis (Fig. 1) first created a compact joint encoding of rs-fMRI networks and NP test scores for distinguishing AUD from controls (**Step 1** in Fig. 1). Specifically, **Step 1(a)** reduced the 111 × 111 connectivity

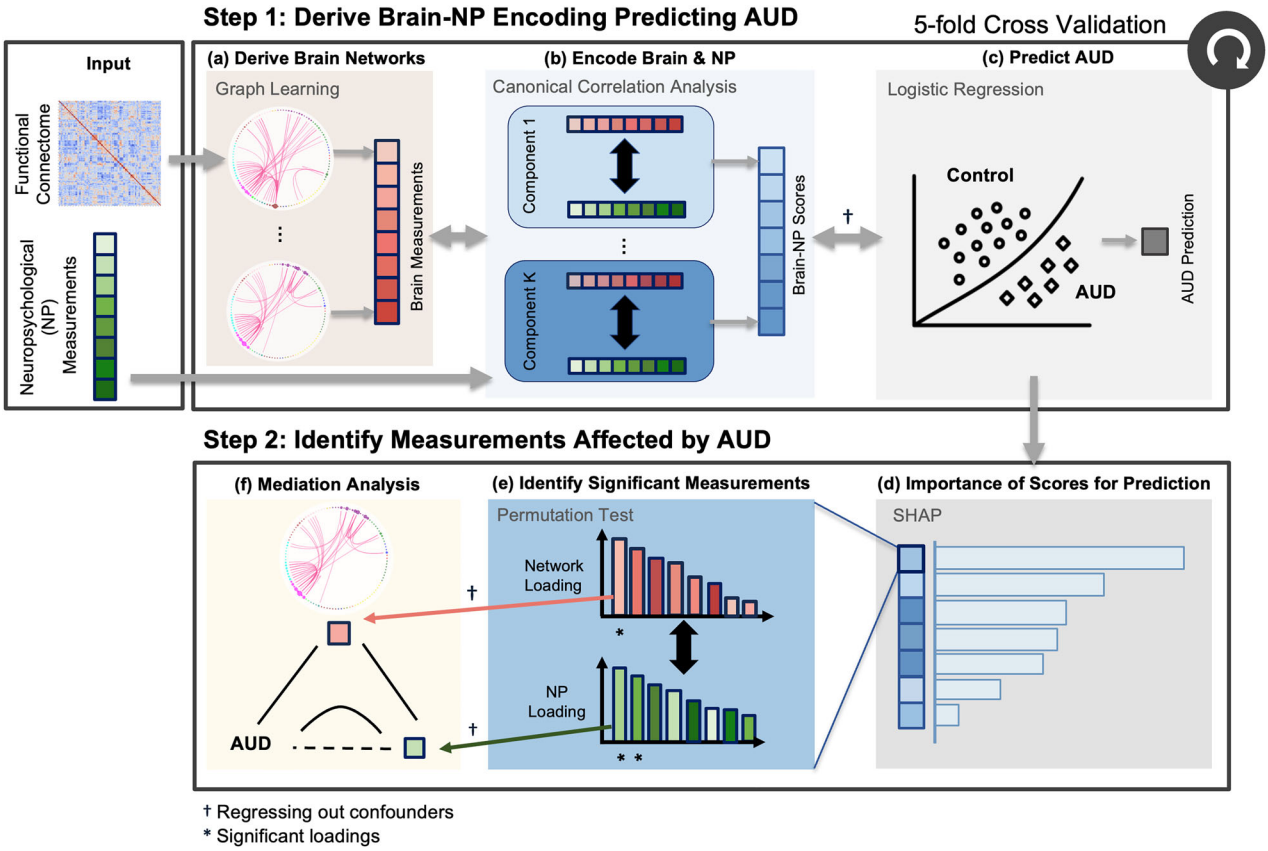


Fig. 1 Overview of the fully data-driven discovery of neuropsychology (NP) and brain functions affected by AUD. This discovery first derived a compact joint encoding of brain function and neuropsychology for distinguishing AUD from controls (**Step 1**). Specifically, (**a**) the functional connectivity matrix (Dimension: 111×111) was reduced to 16 brain networks and corresponding measurements using a deep learning approach that modeled brain networks as a graph. **b** This learning process was guided by the neuropsychological measures by coupling the graph learning approach with deep generalized canonical correlation analysis (GCCA). GCCA further reduced the measures across both the neuropsychological and brain functional domains into a compact joint encoding. **c** After regressing out confounders from the resulting brain-NP scores, the resulting residuals were the input to a logistic regressor model [68] trained in predicting AUD. Critically, the dimension of the joint encoding was determined with respect to optimizing the training accuracy of the regressor in a cross-validation setup. **Step 2** then identified the neuropsychological and brain functional measures affected by AUD. Specifically, (**d**) the most important brain-NP score for the classification process was determined by SHapley Additive exPlanations (SHAP) values [76]. **e** Of that component, the significant brain network and neuropsychological measures were identified by applying permutation testing to the corresponding loadings of GCCA. (**f**) Finally, statistical testing identified significant networks fully mediating the effect of AUD diagnosis on significant neuropsychological domains.

matrix into 16 brain network measurements by a graph learning framework, which represented matrices as graphs (derived by Graph Attention Network (GAT) [62]) and brain networks as subsets of that graph (derived via sub-graph learning [63]). The number of networks was selected a priori to align with the 16 NP assessments. These network measurements were derived by generalized canonical correlation analysis (GCCA) [64–66] (**Step 1(b)**) so that they maximally covary with the 16 NP measurements. To ease interpretability of our findings, we named the 16 brain functional networks derived by this deep learning analysis using a systematic expert review process. Specifically, two experienced neuropsychologists (author EMMO and author EVS, each with over 20 years of neuroimaging expertise) first independently named the networks based on their salient anatomical connections and functional relevance. Afterwards, they reviewed their naming convention together in order to reach consensus (described in Supplementary NP-informed Brain Networks).

GCCA reduced the 16 network measures and 16 NP measures to 14 GCCA components. It did so by defining each component through 16 network loadings and 16 NP loadings, which captured the importance of each measurement in defining that component. Based on those loadings, the magnitude of a component recorded at a visit (of a participant) then defined the brain-NP score. Based on the 14 brain-NP scores computed for a visit, **Step 1(c)** then predicted AUD in individuals by first regressing out potential confounders (i.e., sex, age, and socioeconomic status (SES)) using a generalized linear model (GLM) [67] and then applying a logistic regression classifier [68] to the residuals.

To determine the optimal settings (such as choosing 14 for the number of components in **Step 1(b))** of the three tasks in **Step 1** (i.e., training) and record the testing accuracy of the classification, we performed nested, stratified, grouped five-fold cross-validation. [69] To ensure that findings were generalizable, we repeated the cross-validation 10 times, where for each run the deep learning approach was initialized with a different seed point in **Step 1** (See Supplementary Table S8). For each of the 10 runs, we computed the testing accuracy by first recording the average balanced accuracy (BAcc) [70] and F1-score [71] across all visits of a subject (to account for intra-subject variation) and then computing the average across all subjects. To support the design choices of this analysis, we repeated the experiments by computing the accuracy of the approach by training the classifier of **Step 1(c)** using the following 3 different types of inputs: (1) directly on the raw NP scores; (2) only functional network scores derived from Independent component analysis (ICA) [72], Vanilla GCN [73], BrainGNN [74], or GAT-LI [75] being applied to functional connectivity matrices; and (3) by the output of multimodal analysis consisting of CCA (instead of GCCA) being applied to the 16 NP scores and the fMRI network scores derived by Principal Component Analysis (PCA) or ICA (See Supplementary Implementation and Evaluation).

After ensuring that the classification accuracy of **Step 1** was significantly ($p < 0.001$) above chance according to **a** Chi-Square Test, the post-hoc analysis **(Step 2)** then investigated which brain network and NP measures were most important for identifying AUD. Specifically, the model of **Step 1** was retrained on all 156 visits (without cross-validation). **Step 2(d)** then

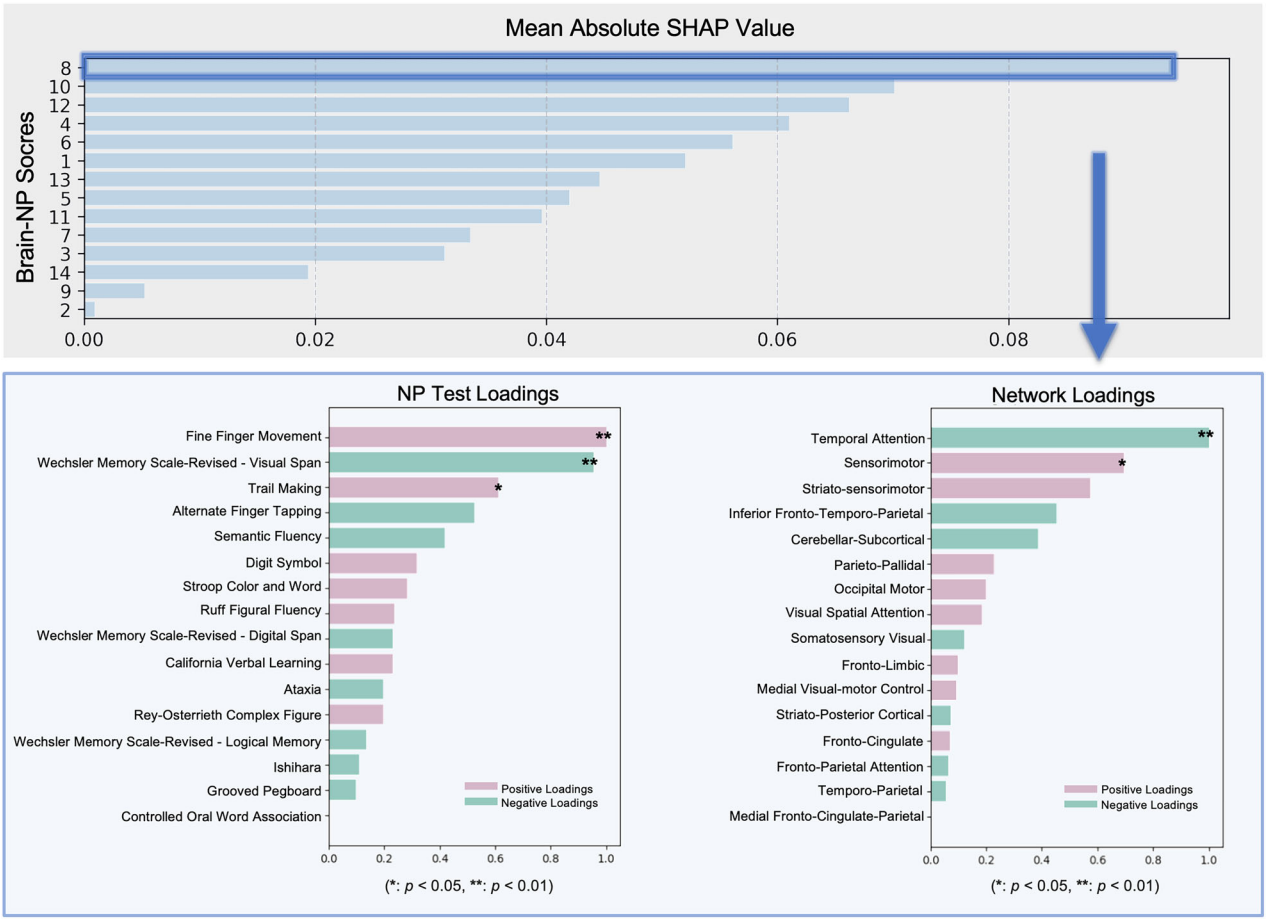


Fig. 2 Identification of neuropsychological and brain functional measures affected by AUD. Top row: **Step 2(d)** of the data driven analysis identified component 8 of the brain & NP encoding as having the highest Mean Absolute SHAP value with respect to AUD prediction (Step 1); Bottom row for component 8: **Step 2(e)** ranked the 16 Neuropsychology tests and 16 networks according to their canonical loadings. The loadings of three neuropsychological measures (Fine Finger Movement, Digit Span, Trail Making Test) and two network measurements (Temporal Attention Network and Sensorimotor Network) were significant after correcting for multiple comparisons with False Discovery Rate (FDR).

ranked the 14 brain-NP scores according to the SHapley Additive exPlanations (SHAP) value [76]. For the top-ranked score, the significance of the 16 networks and 16 NP measurements in defining the corresponding component were determined in **Step 2(e)** by applying permutation testing to their GCCA loadings. Further analysis was then confined to measurements with significant loadings ($p < 0.05$; False Discovery Rate (FDR) correction [77]).

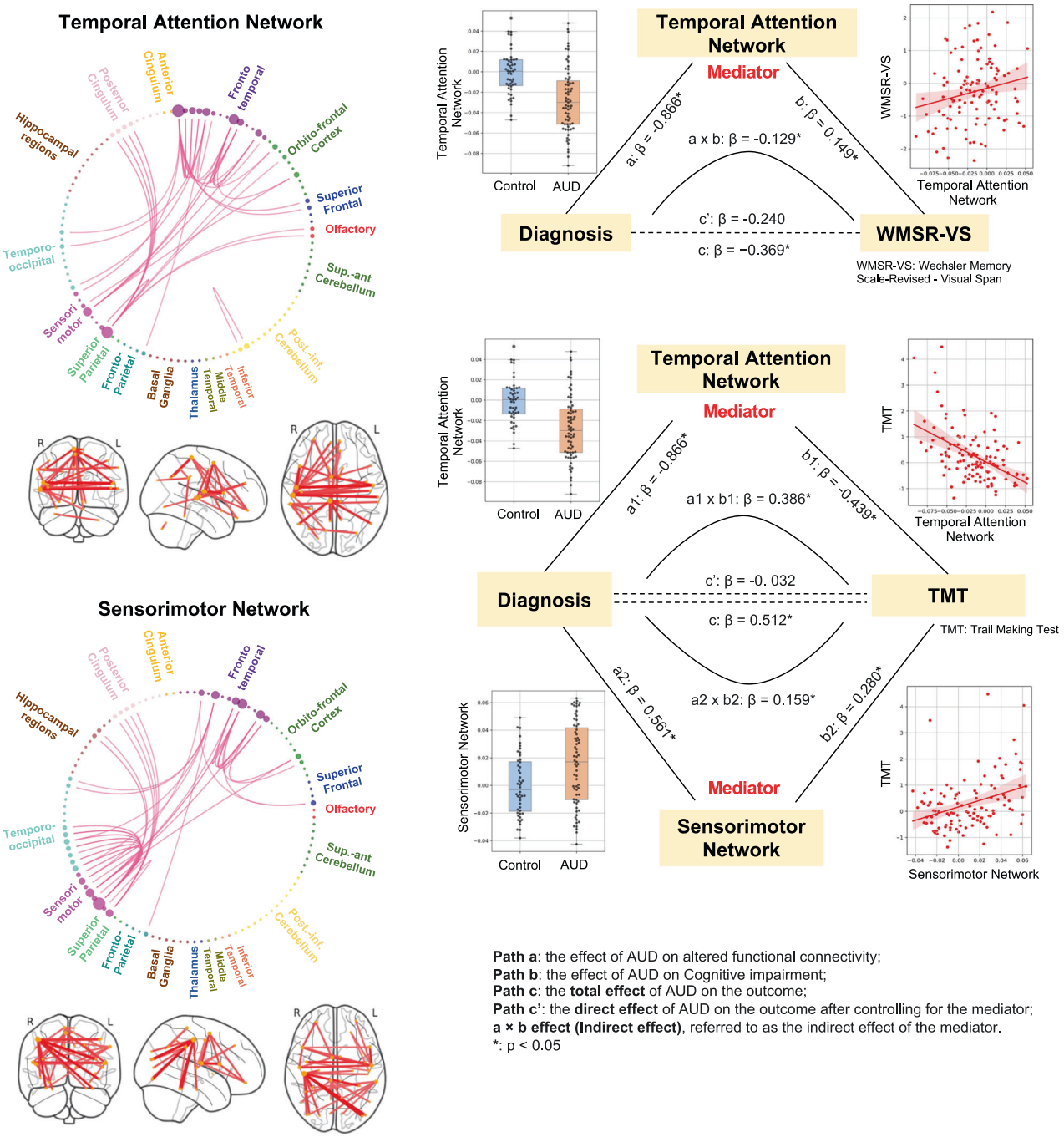
To examine the role of brain networks with respect to the impact of AUD on neuropsychological function, **Step 2 (f)** regressed out the potential confounders of age, sex, and SES via a GLM. Next, all measurements were normalized to z-scores and, for each subject, averaged across visits. For each significant brain network, the analysis then tested if the corresponding measurement fully mediated [78] the relationship between AUD diagnosis (independent variable) and the neuropsychological measures (outcome). Networks mediating the same diagnosis-measurement relationships were tested for parallel mediation by computing the indirect (mediation) effect via the product mediation method [79]. Any effect was considered significant if the 95% of bias-corrected confidence intervals returned by bootstrapping did not contain zero [80]. Additional details about the deep learning analysis are in the Supplementary Implementation and Evaluation.

To ensure that the findings based on the brain-NP encoding [**Step 1(a) &(b)**] generalized to other data set, we tested the model on an independently collected HIV replication data set (with or without AUD comorbidity). We did so by applying the model of **Step 1** (without any retraining) to the HIV replication data set and then recomputed the classification accuracy on this dataset. Next, we used this data set to repeat the mediation analysis of **Step 2** with respect to the significant brain networks and NP measures of the main analysis (See Supplement Replication Study).

RESULTS

Among the seven tested approaches, our multimodal deep learning method recorded the highest mean accuracy (71.58% ± 1.78 Balanced Accuracy and 74.08% ± 1.97 F1-score, Supplementary AUD Prediction and Table S8). To ensure that the predictions of this model were not confounded by differences in quality of rs-fMRI between AUD and controls (see Supplementary Table S5), analyses confirmed that neither head motion nor scan duration significantly correlated ($p < 0.05$) with the derived brain network scores (Supplementary Table S3) and brain-NP scores (Supplementary Table S4), i.e. the input to the classifier. Classification accuracy remained comparable when evaluating models only on participants without SUD history (Balanced Accuracy = 70.12% ± 2.35; F1-score = 72.33% ± 2.98). Furthermore, none of the brain-NP scores or brain network scores correlated with non-alcohol SUD remission time ($p > 0.1$, see Supplementary Tables S6 and S7).

The SHAP analysis of **Step 2(d)** identified the 8th brain-NP score (i.e., GCCA component) as the most influential for differentiating the AUD from the control group according to Fig. 2. For the 8th component, Fig. 2 also plots for the corresponding GCCA loadings (i.e., relative importance) of the 16 NP scores and the 16 network measures. NP tests with significant loadings (according to **Step 2(e)**) were Fine Finger Movement, Visual Span, and Trail Making. Additionally, 2 of the 16 network measures had significant loadings: the Temporal Attention Network (Fig. 3) and the Sensorimotor Network (Fig. 3). Specifically, the Temporal Attention



Path a: the effect of AUD on altered functional connectivity;
Path b: the effect of AUD on Cognitive impairment;
Path c: the **total effect** of AUD on the outcome;
Path c': the **direct effect** of AUD on the outcome after controlling for the mediator;
a × b effect (Indirect effect), referred to as the indirect effect of the mediator.
*: p < 0.05

Fig. 3 Outcome of the mediation analysis of Step 2 (f) across the significant neuropsychological and brain functional measurements listed in Fig. 2. Left: Brain connections of the two significant networks. Right: Significant mediations (95% bootstrap CI not including 0) of those networks between diagnosis and neuropsychological measurements. The Temporal Attention Network (TAN) fully mediated the effects of diagnosis on Wechsler Memory Scaled-Revised – Visual Span (WMSR-VS) and functioned together with Sensorimotor Network (SMN) as parallel mediators, jointly mediating the effect of AUD diagnosis on the Trail Making Test (TMT).

Network consisted of dense connections between fronto-temporal regions and also connections to sensorimotor and temporo-occipital areas. The Sensorimotor Network included dense connections between the postcentral gyrus, precentral gyrus, and supplementary motor areas, and extended posteriorly to the visual cortex and anteriorly to frontal regions.

According to Fig. 3 (all reported *p*-values are False Discovery Rate (FDR) corrected), significant correlations between Temporal Attention Network and Visual Span ($p = 0.032$) or Trail Making ($p < 0.0001$) were in the same direction, i.e., lower network activity correlated with worse performance (high values for Trail Making Test and low values for Visual Span). By contrast, the Sensorimotor Network functioned in the opposite direction, where higher network activity correlated with worse performance in the Trail Making Test ($p < 0.0001$). Neither network significantly correlated with Fine Finger Movement scores.

Next, the mediation model (Fig. 3 **Step 2(f)**) tested the significance of the two networks mediating the relationships among diagnosis and significant NP measures. Specifically, the Temporal Attention Network was significantly associated with AUD

Fig. 4 Absolute values of significant correlations ($p < 0.05$, FDR corrected, Pearson correlation) between each network and neuropsychological measures. Both the circle size and color represent the correlation coefficient (r). The top/right histogram illustrates the number of significant correlations for each neuropsychological measure/network. Neuropsychological measures and functional brain networks predictive of AUD were bolded. (RFFT: Ruff Figural Fluency Test; SF: Semantic Fluency Test; Ataxia: Ataxia Testing; CVLT: California Verbal Learning Test; ROCF: Rey-Osterrieth Complex Figure Test; WMSR-LM: Wechsler Memory Scale-Revised - Logical Memory; WMSR-VS: Wechsler Memory Scale-Revised - Visual Span; AFT: Alternated Finger Tapping; FAS: Controlled Oral Word Association Test; FFM: Fine Finger Movement; GPT: Grooved Pegboard Test; SCWT: Stroop Color and Word Test; DST: Digit Symbol Testing; TMT: Trail Making Test; WMSR-DS: Wechsler Memory Scale-Revised - Digital Span; Ishihara: Ishihara Test). Each of the networks identified in our data-driven analysis is significantly correlated with at least two neuropsychological measurements. Striato-sensorimotor Network has the most (9) significant correlation with neuropsychological measurements and RFFT significantly correlated with most (10 of the 16) networks.

diagnosis ($\beta = -0.866$, $p < 0.0001$) and Visual Span ($\beta = 0.149$, $p = 0.032$) and fully mediated their relationship (total effect $\beta = -0.369$, $p = 0.047$; indirect effect $\beta = -0.240$, $p = 0.039$). The parallel mediation analysis revealed that the total effect of AUD diagnosis on the Trail Making Test was significant (total effect $\beta = 0.512$, $p = 0.006$) and was mediated by both Temporal Attention Network (indirect effect $\beta = 0.386$, $p < 0.0001$) and Sensorimotor Network (indirect effect $\beta = 0.159$, $p < 0.0001$). The direct effect c′ between AUD diagnosis and any of the significant cognitive or motor measures after controlling for the mediators was not significant so that the two brain networks fully mediated the effect of AUD diagnosis on the Trail Making Test.

The replication study on the independent HIV cohort confirmed our prior findings as the accuracy of the logistic regression classifier (**Step 1(c)**) was significantly above chance (Balanced Accuracy = 61.90% ± 3.11, F1-score = 63.93% ± 2.20, $p = 0.0024$, Chi-Square Test) in distinguishing people with HIV and AUD comorbidity (HIV + AUD) from those without AUD comorbidity (HIV). When retraining just the logistic regression classifier on the HIV cohort and measuring the accuracy via 5-fold accuracy, the balanced accuracy increased to 69.45% ± 2.11 (72.02% ± 1.90 F1-score, Supplementary Table S10). Moreover, all previously reported mediation findings (investigated in **Step 2)** were again replicated on this data set (Supplementary Fig. S2), i.e., the Temporal Attention Network fully mediated the effect of AUD diagnosis (i.e., HIV vs HIV + AUD) on Visual Span test, and this network and the Sensorimotor Network fully mediated the effect of the AUD diagnosis on the Trail Making Test.

DISCUSSION

The primary aim of this study was to use a data-driven, deep learning search to distinguish individuals with a history of AUD from those without AUD based on jointly analyzing NP test scores and functional connectivity measures derived from rs-fMRI to reveal underlying brain substrates of commonly observed AUD-related deficits. Compared to prior studies examining AUD effects only on functional connectivity [17, 18] or only on NP functions [8, 21], novel to our analysis was a signature of selective functional brain-NP relations distinguishing AUD from controls. The classification was driven primarily by interactions between two functional brain networks (the Temporal Attention Network and the Sensorimotor Network) and three neuropsychological tests (Fine Finger Movement, Visual Span, and Trail Making). Further analysis revealed that the two networks fully mediated the effect of AUD diagnosis on Visual Span and Trail Making Test. The mediation analysis was replicated on an independently collected data set consisting of people with HIV (with or without AUD comorbidity) suggesting that our data-driven discovery identified functional brain substrates of AUD-related deficits even when confounded with another disorder.

This discovery required a data-driven analysis as the study would not have been powered for direct investigation of all (~100 K) pairs across the 16 neuropsychological and 6105 region-to-region connections. Instead, our deep learning analysis derived 16 brain networks tightly coupled with 16 NP tests (according to Fig. 4). For example, two tests that strongly coupled with the Bilateral Occipital Motor Network were, as expected, the Grooved Pegboard Test and the Trail Making Test as they both tested visual input processed by the occipital lobe and motor execution processed by the motor cortex [81, 82]. Another example is the Striato-sensorimotor Network, which has dense connections between the striatum (particularly putamen) and multiple regions including sensorimotor areas, occipital regions, and the frontal lobe (Supplementary Fig. S3). These connections play a critical role in motor control [83], sensory processing [84],

and higher-order cognitive functions (such as attention, decision-making, and working memory [85]) so that, as expected, the network was coupled with most of the NP tests. Also expected was that none of the 16 networks involved the default mode network, which is hypothesized to be disconnected from specific cognitive tasks and mostly activated during self-reflection [86]. Instead, our data-driven networks (Supplementary Fig. S3) closely relate to neural underpinnings of cognitive and motor function. In summary, the brain functional networks identified by the data-driven analysis corresponded to meaningful behavior and thus might explain why the corresponding brain-NP encoding was the only one involving brain function that resulted in a higher prediction accuracy of AUD than relying on NP measurements alone (Supplementary Table S8).

Notably, NP measurements alone showed strong predictive power in identifying AUD in individuals while this was not the case for relying solely on network scores derived from resting-state fMRI or using a simple brain-NP encoding that relied on functional networks being independently being derived from the NP scores (See Supplementary Table S8). Producing higher accuracy scores required extracting NP informed networks not only for this data set but also for the one consisting of people with HIV + AUD comorbidity. Note the encoding was not informative in identifying HIV by itself (Supplementary Replication Study and Table S11), which further demonstrated the value of the joined brain–NP coupling in characterizing AUD-related dysfunction.

The joint brain-NP analysis naturally facilitates investigation into how AUD-related neural pathways contribute to declines in cognitive and motor performance. Specifically, most important for the classification process was the 8th component, for which the loadings of the Temporal Attention Network and the Sensorimotor Network were of significance. Compared to controls, AUD participants had lower connectivity strength within the Temporal Attention Network, which included connections between the frontal and temporal regions (Fig. 3). We and others have shown that AUD is associated with smaller frontal and temporal lobes [13–16]. There is also converging evidence that their connections can be weakened by alcohol consumption, resulting in impaired inhibitory control [87, 88], as it slows attentional capture of infrequent stop signals and hinders subsequent action plan updates from response execution to inhibition [89, 90]. This diminished inhibitory control can affect the ability to actively maintain goal-relevant information in focus [91, 92] assessed by the Visual Span test of visual working memory and attention and cognitive regulation of motor responses [93] assessed by the Trail Making Test. Our analysis supports those findings as the effect of AUD on both tests was mediated by the Temporal Attention Network and replicated on the independent HIV data set. Furthermore, our prior studies and others have extensively characterized brain structural abnormalities associated with AUD, including frontal lobes, hippocampus, thalamus, and cerebellum [13–16, 94], and individuals with AUD have been shown to exhibit consistently larger white matter hyperintensity frames compared to controls [95]. Our findings complement these works by identifying functional disruptions in large-scale networks including frontal regions that may serve as systems-level pathways linking structural brain alterations to observed cognitive deficits in AUD.

Comporting with the existing literature [96, 97], connectivity strength within the Sensorimotor Network (i.e., the other predictive network) was higher in AUD than control participants (Fig. 3). In contrast with the Temporal Attention Network, greater connectivity in this network has been linked to worse Trail Making performance [98], which requires visual perception and motor execution ability controlled by precentral gyrus and visual cortex in the Sensorimotor Network. In line with this observation, our analysis found that the effects of diagnosis on the Trail Making Test were also mediated by this network. Here, we observed heightened connectivity, which may reflect a neural compensatory mechanism within the network, where stronger functional connectivity arises in response to alcohol-induced compromised functional connectivity to maintain cognitive or motor performance [99]. Previous studies also found that attention impairments were associated with greater connectivity in the sensorimotor network, indicative of compensatory mechanisms [98]. However, while this mechanism might temporarily support functionality, the altered network dynamics could eventually lead to impaired cognitive performance, possibly by usurping processing capacity served by the network used for compensation but required for a different function as observed in our mediation analysis and previous findings [37, 100, 101].

As the first effort to apply deep learning to identify brain functional substrates in AUD dysfunction, our work lays important groundwork for future studies to discern subtle, network-level patterns that underlie cognitive and motor impairments in individuals diagnosed with AUD. These neural profiles not only offer a systems-level explanation for cognitive impairments in AUD but also point to potential targets for future therapeutic strategies. For instance, if reliable and replicable, individualized neural signatures may help identify patients most likely to benefit from targeted interventions such as transcranial magnetic stimulation (TMS) [102] or neurofeedback [103]. Over time, such biomarkers could support predictive models for treatment response and recovery, advancing precision medicine for addiction.

Several limitations should be noted. First, we chose to analyze each NP test as representing a broad functional domain reflecting a hierarchical integration of multiple neurological processes rather than isolated components and sub-scales of dissociable functions. For example, in the Trail Making Test, Part A primarily engages visual scanning and motor speed, whereas Part B requires additional working memory and set-shifting skills. However, both parts share an underlying reliance on psychomotor speed, visual search, and attention [104] and motor function requiring eye-hand coordination. Moreover, by treating sub-scale NP tests as unified measures rather than dissecting them into dissociable cognitive components, we align our approach with real-world clinical practice to enhance the generalizability and translational relevance, where these selected tests are all widely used as standardized and interpretable measures of cognitive function.

Another limitation was setting the threshold for motion censoring during the fMRI analysis to 0.3 mm framewise displacement threshold, which is lenient compared to more stringent thresholds (e.g., 0.1–0.2 mm) adopted in some studies [105–107]. However, doing so ensured consistency with our prior publications [38, 108] and maintained longitudinal compatibility across our ongoing study. Finally, the mediation analysis was confined to a cross-sectional design as our relatively small study did not have enough power to investigate their temporal dynamics, i.e., how the mediating effects of brain networks evolve over time and relate to the potential of accelerated cognitive decline in the AUD population.

CONCLUSION

The fully data-driven, deep learning analysis advances understanding of the neural mechanisms underlying the effect of AUD on neuropsychological processes commonly affected in AUD. Specifically, the analysis found that the Temporal Attention Network and the Sensorimotor Network mediated the effect of AUD on aspects of goal-relevant information maintenance, motor response regulation, and motor control as measured in traditional tests of visual working memory and cognitive flexibility. The joint analysis of thousands of functional variables compared with relying on a one-to-one correlational approach yielded brain-behavior relations defining a neurofunctional signature of AUD.

DATA AVAILABILITY

The data supporting the results of this study are available upon request from the corresponding author.

CODE AVAILABILITY

The source code is available at https://github.com/Wangyixinxin/BrainCog.

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AUTHOR CONTRIBUTIONS

YW drafted the manuscript and performed the data analyses; EMM-O, SAS, KZS, AP, and EVS contributed to data collection, organization, and curation; YW, QZ and KMP conceptualized the study and reviewed and edited the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS STATEMENT

All participants gave written informed consent for partaking in the study, which was approved by the Stanford and SRI institutional review boards. The consenting process abided by The Code of Ethics of the World Medical Association (Declaration of Helsinki).

ADDITIONAL INFORMATION

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