Predicting alcohol-related memory problems in older adults: A machine learning study with multi-domain features

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Abstract

Memory problems are common among older adults with a history of alcohol use disorder (AUD). Employing a machine learning framework, the current study investigates the use of multi-domain features to classify individuals with and without alcohol-induced memory problems. A group of 94 individuals (ages 50-81 years) with alcohol-induced memory problems (*Memory* group) were compared with a matched *Control* group who did not have memory problems. The Random Forests model identified specific features from each domain that contributed to the classification of Memory vs. Control group (AUC=88.29%). Specifically, individuals from the Memory group manifested a predominant pattern of hyperconnectivity across the default mode network regions except some connections involving anterior cingulate cortex which were predominantly hypoconnected. Other significant contributing features were (i) polygenic risk scores for AUD, (ii) alcohol consumption and related health consequences during the past 5 years, such as health problems, past negative experiences, withdrawal symptoms, and the largest number of drinks in a day during the past 12 months, and (iii) elevated neuroticism and increased harm avoidance, and fewer positive "uplift" life events. At the neural systems level, hyperconnectivity across the default mode network regions, including the connections across the hippocampal hub regions, in individuals with memory problems may indicate dysregulation in neural information processing. Overall, the study outlines the importance of utilizing multidomain features, consisting of resting-state brain connectivity collected ~18 years ago, together with personality, life experiences, polygenic risk, and alcohol consumption and related consequences, to predict alcohol-related memory problems that arise in later life.

Key Words: Alcohol use disorder (AUD); EEG source functional connectivity; default mode network; alcohol-related memory problems; random forests.

1. Introduction

Alcohol use disorder (AUD) is a chronic, relapsing disorder [1,2] with a range of neurocognitive anomalies, including memory deficits [3]. Memory impairments due to heavy drinking, among other cognitive impairments, have been widely reported [4,5], and may interfere with social and occupational performance [6,7]. Since the etiology of AUD and related memory problems involves multiple domains, including the combination of neurocognitive, personality, behavioral, and genomic factors [8-10], a better understanding of these potential predictors may aid in prevention and treatment strategies.

Brain oscillations representing electrical signals of neural activity, as recorded by electroencephalogram (EEG), index specific circuit-level mechanisms during cognitive processing [11]. Oscillatory signals in different EEG frequency bands representing communications between specific brain regions underlie memory processes, including encoding, consolidation, storage, and retrieval processes [12,13]. Studies have indicated that memory processes are supported by oscillatory dynamics and communication across the hippocampus, entorhinal cortex and other cortical regions [13-15]. Both human and animal studies have implicated the theta band, generated within the hippocampus and also prevalent in the cerebral cortex, as the major frequencies associated with various memory processes [16,17]. Hippocampal theta rhythm is also involved in communication with other higher frequencies (e.g., beta and gamma oscillations) through various coupling mechanisms, including neural synchrony during sensory and cognitive processing [18-21].

Recent studies have used source localization methods, such as the exact low-resolution brain electromagnetic tomography (eLORETA) [22] to compute *functional connectivity* a measure of temporal synchrony or correlation between signals of two or more spatially separated brain regions representing functional integration between these areas [cf. 23]. These studies have used *lagged connectivity* [24] to overcome volume conduction artifacts [23,25]. While the eLORETA-based functional connectivity method has been utilized to study cognitive functioning in neuropsychiatric disorders [23,26-29], very few studies have utilized these approaches to investigate AUD [30] and none of these studies have examined alcohol-induced neurocognitive outcomes, such as memory. Since the default mode network supports memory functions [31-34], we will employ functional connectivity across the default mode network regions to examine

alcohol-induced memory problems.

AUD is a multi-factorial disorder, and therefore it is important for the predictive models of alcohol-related neurocognitive outcomes such as memory impairment to include features from multiple domains, including polygenic risk scores (PRS) [35,36] and personality dimensions [36-41]. Therefore, the goal of the present study was to identify a set of multi-domain factors that can differentiate individuals with alcohol-related memory impairments from those without, using (i) resting EEG-based functional connectivity measures of default mode network as derived from eLORETA, (ii) PRS related to alcohol outcomes, (iii) personality and life experience measures derived from established questionnaires, and (iv) measures of alcohol consumption and associated health consequences from the recent follow-up interview. Identifying specific default mode network functional connections underlying alcohol-induced memory problems may be useful for early preventive measures and for brain-based treatment strategies such as neuromodulation therapies for addiction [42] and memory/cognitive impairment or decline [43]. Similarly, other domains, including PRS, behavioral, personality, and clinical features, may have implications for prevention and treatment of alcohol-induced memory problems (e.g., cognitive-behavior therapy, brain stimulation, cognitive remediation, etc.).

2. Material and Methods

2.1. Sample

The sample for the present study was drawn from a recent follow-up assessment study [44,45] of participants from the Collaborative Study on Genetics of Alcoholism (COGA) [46-48]. Participants aged 50 or older who met lifetime criteria for alcohol dependence, as assessed with the Semi-Structured Assessment for the Genetics of Alcohol (SSAGA) [49,50], were drawn from data collected at six COGA sites. Details on screening and selection of participants for the current study are described the supplemental material [see *Section 1.1. Sample Description* and *Fig. S1* in the *Supplementary Material*]. The *Memory* and *Control* groups were also matched for age at assessments, sex, self-reported race, genetic ancestry, and the following alcohol use patterns assessed by their last SSAGA interview conducted ~18 years prior to the recent telephone interview (see **Table 1**): (i) continued high-risk drinking (men with 5+ drinks/day or

15+ drinks/week and women with 4+ drinks/day or 8+ drinks/week) and meeting criteria for DSM-5 AUD diagnosis derived from SSAGA items (N=68/group), (ii) low-risk drinking (fewer than 5 drinks/day for men and 4 drinks/day for women) without meeting criteria for AUD diagnosis (N=9/group), and (iii) abstinence from drinking (N=17/group).

Table 1: Demographic characteristics, AUD remission status during the latest SSAGA interview before the follow up telephone interview, and details of alcohol consumption from the recent telephone interview for the EEG functional connectivity analysis.

Variable	Measure / Category	Parameter	Study Group	
			***Memory* (N=94)**	***Control* (N=94)**
Age during assessment	EEG*	Min–Max	29.21–60.71	28.17–62.19
		Mean (SD)	39.42 (6.18)	40.11 (6.74)
	Follow-up Interview	Min–Max	50.55–81.86	50.34–81.49
		Mean (SD)	57.84 (5.77)	58.75 (6.07)
Sex	Male	N (%)	52 (55.30)	52 (55.30)
	Female	N (%)	42 (44.70)	42 (44.70)
Self-reported race	White	N (%)	67 (71.30)	67 (71.30)
	Black	N (%)	24 (25.50)	24 (25.5)
	Other	N (%)	3 (3.20)	3 (3.20)
Genetic ancestry	European	N (%)	63 (50.40)	62 (49.60)
	African	N (%)	23 (47.92)	25 (52.08)
	Other	N (%)	8 (53.33)	7 (46.67)
Alcohol use pattern during the latest SSAGA interview*	AUD diagnosis	N (%)	68 (72.30)	68 (72.30)
	Low Risk Drinking	N (%)	9 (9.60)	9 (9.60)
	Abstinence	N (%)	17 (18.10)	17 (18.10)
Time lag**	Years	Mean (SD)	18.42 (3.84)	18.63 (3.90)

*The latest SSAGA interviews were also closer in time to the EEG recording used for the current study. Note that the SSAGA interview is longer and more comprehensive than the recent follow-up phone interview.

** Time lag (years) between the latest past (baseline) assessments (EEG, SSAGA, and clinical/personality) and the recent follow-up telephone interview.

2.2. Recent Telephone Interview

The recent follow-up telephone interview (10-20 minutes) was designed to collect information regarding participants' alcohol use and current social and health status using a 31-items questionnaire [45] administered via the REDCap system [51,52]. Details about this interview items are available in *Section 1.2 of the Supplementary Material*. Three items that elicited self-reported alcohol-related memory problems have been listed in **Table 2**. Memory impairment was coded if the participant endorsed at least two of the three items (**Table 2**): the first item and

either the second or third item.

Table 2: Items related to memory problems in the follow-up interview questionnaire.

Domain	Question	Memory-related response*
Alcohol-related memory problems	Compared to most people your age, is your memory currently better, about the same, or worse than theirs?	○ Worse
	**There are several other health problems that can result from heavy drinking. In the last 5 years did drinking. (Check all that apply)	○ Impair your memory even when you were not drinking (not including blackouts)?
	**There are several other health problems that can result from heavy drinking. In the last 10 years did drinking. (Check all that apply)	○ Impair your memory even when you were not drinking (not including blackouts)?

* Response option related to memory problems.
** These items are the same for the categories eliciting alcohol use during the past 5 years and past 10 years.

2.3. EEG Data Acquisition and Preprocessing

Details of assessments and EEG recording in COGA, which is identical at all sites, can be found in our previous reports [46,53,54]. The EEG session that was closest to the latest SSAGA interview was used for this study. Detailed descriptions of EEG data acquisition and preprocessing steps are available in *Section 1.3* of the *Supplementary Material*.

2.4. EEG Functional Connectivity Analysis using eLORETA

EEG functional connectivity was computed using the eLORETA software [22,55], a validated tool for localizing the electrical activity in the brain. Detailed descriptions of EEG functional connectivity analysis using eLORETA are available in the *Section 1.4* of the *Supplementary Material*.

2.5. Functional Connectivity Across the Default Mode Network

The default mode network regions analyzed in the study are posterior cingulate cortex (PCC), anterior cingulate cortex, inferior parietal cortex, prefrontal cortex, lateral temporal cortex, and hippocampal formation [see **Table 3** below and **Fig. S2** in the *Supplementary Material*], in line with the functional connectivity studies of both fMRI and EEG [28,56,57] and our previous work on default mode network [58,59].

Table 3. Regions of interest (ROI), region code/abbreviation, Brodmann area (BA) and the MNI coordinates for the default mode network are listed.

ROI	Region Name	Region Code	BA	MNI (X)	MNI (Y)	MNI (Z)
1	Left posterior cingulate cortex	L.PCC	23	-10	-45	25
2	Right posterior cingulate cortex	R.PCC	23	10	-45	25
3	Left anterior cingulate cortex	L.ACC	32	-10	45	10
4	Right anterior cingulate cortex	R.ACC	32	10	45	10
5	Left inferior parietal lobule	L.IPL	40	-55	-55	20
6	Right inferior parietal lobule	R.IPL	40	55	-55	20
7	Left prefrontal cortex	L.PFC	46	-45	25	25
8	Right prefrontal cortex	R.PFC	46	45	25	25
9	Left lateral temporal cortex	L.LTC	21	-55	-15	-20
10	Right lateral temporal cortex	R.LTC	21	55	-15	-20
11	Left parahippocampal gyrus	L.PHG	36	-25	-30	-20
12	Right parahippocampal gyrus	R.PHG	36	25	-30	-20

2.6. Assessment of Temperament, Personality, and Alcohol Experience

The temperament, personality, and life experiences data included scores from seven questionnaires and their subscales, and scores included for the current study are described in *Section 1.6* of the *Supplementary Material.* These data were collected during the previous interviews (~18 years ago) at/around the same time as the SSAGA assessment.

2.7. Genomic Data and Polygenic Risk Scores (PRS)

Genotyping, imputation, and quality control of COGA genomic data have been described previously [48] and in the *Section 1.7* of the *Supplementary Material*. The publicly available Genome-wide Association Studies (GWAS) for alcohol use phenotypes, derived from studies including both individuals of European ancestry (EA) and African ancestry (AA), that were used in PRS calculations in this study are listed in **Table 4**.

Table 4. List of Polygenic Risk Scores (PRS) datasets from recently published GWAS

Phenotype	Discovery Sample/Consortium	Sample Size	
		EA	AA
AUD diagnosis (ICD-9/ICD-10)	MVP [60]	202,004	56,648
AUDIT-C symptoms	MVP [60]	200,680	56,495
Max alcohol intake	MVP [61]	126,936	17,029
Alcohol Dependence (DSM-IV)	PGC [62]	46,568	6,280

We created PRS using PRS-CSx [63-67], which is a recent, validated method for cross-ancestry polygenic prediction [68]. The PRS-CSx computation method is detailed elsewhere (https://github.com/getian107/PRScsx) and also briefly described in the *Section 1.7* of the *Supplementary Material*.

2.8. Feature selection of EEG functional connectivity variables

In keeping with recent machine learning approaches, including our previous study [69], we used a two-stage approach consisting of feature selection followed by a predictive algorithm using selected sets of variables [70-74]. A detailed description of this method is available in *Section 1.8* of the *Supplementary Material.*

2.9. Random Forests classification model and parameters

The Random Forests classification analysis was performed using R-packages "randomForest" [75], "caret" [76], and "randomForestExplainer" [77] to classify *Memory* vs. *Control* group using multi-domain predictors. The details of these predictors, which include 29 functional connectivity, 27 personality and life experience, 12 alcohol outcomes, and 4 PRS variables, are listed in the *Materials and Methods* section of the *Supplementary Material*. The random forests model, as implemented in the current study, has been detailed in *Section 1.9* of the *Supplementary Material.*

3. Results

3.1. Feature Selection of EEG functional connectivity variables

The input data for the feature selection included a total of 330 EEG functional connectivity

variables consisting of 66 connectivity features for each of five frequency bands. The model identified a total of 29 functional connectivity variables from multiple frequency bands connecting across the twelve default mode network seeds (Refer **Table 3** in *Methods* section and **Fig. S2** in *Supplementary Material*)**.** These connections included Delta – 12 connections, Theta – 6 connections, Alpha – 4 connections, Beta – 5 connections, and Gamma – 2 connections. The 10-fold cross-validation for the λ_{1se} threshold included all the 29 selected features, which were included in the subsequent implementation of the Random Forests classification model. The classification performance (to differentiate individuals with memory problems from those without) of the selected features as indicated by the area under the ROC curve (AUC) was 88.48%.

3.2. Random Forests Classification Accuracy

The overall prediction accuracy of the Random Forests model to classify *Memory* and *Control* group using functional connectivity, PRS, behavioral and clinical predictors, as estimated by the AUC, was 88.29%. The 72 predictors inputted in the model include 29 functional connectivity, 27 personality and life experience, 12 alcohol outcomes, and 4 PRS variables (see *Materials and Methods* section of the *Supplementary Material*). Additional details about the classification accuracy are available in *Section 2.2.* of the *Supplementary Material.*

3.3. Top Significant Features Contributed to the Classification

Out of the 72 input variables of the Random Forest model (see *Materials and Methods* section of the *Supplementary Material* for details), 29 significant features that contributed to classifying *Memory* group from those from the *Control* group were identified: 21 default mode network connections, 4 alcohol-related items, 3 personality and life experience factors, and 1 PRS (**Table 5**).

Table 5. Random Forest importance parameters and direction of significance for the top significant variables ($p < 0.05$) are shown. The variables are sorted based on Gini decrease. Details of these features are available in *Materials and Methods* section of the *Supplementary Material*.

Feature	Measure / Source	Gini Decrease	Accuracy Decrease	# Trees	# Nodes	Times a Root	Min. Depth	P value	Direction
AlcHlthProb5yrs	FU Interview	7.7281	0.0449	545	610	111	2.3303	8.26E-47	MEM > CTL
AlcWthSx5yrs	FU Interview	4.8291	0.0196	430	459	109	3.8230	4.09E-13	MEM > CTL
AlcExp5yrs	FU Interview	4.8134	0.0176	417	468	95	4.0144	1.42E-14	MEM > CTL
Drk24Hr	FU Interview	2.7318	0.0097	385	440	70	5.0280	2.75E-10	MEM > CTL
***NEO_N**	Questionnaire	1.9701	0.0029	334	382	47	5.6475	6.84E-04	MEM > CTL
FC_Ga_2_10	R.PCC–R.LTC	1.9574	0.0019	402	486	5	5.5047	1.02E-17	MEM > CTL
FC_Th_2_11	R.PCC–L.PHG	1.8902	0.0020	377	463	11	5.7415	9.38E-14	MEM > CTL
FC_Be_1_4	L.PCC–R.ACC	1.8699	0.0030	378	463	6	5.8232	9.38E-14	CTL > MEM
FC_Th_2_5	R.PCC–L.IPL	1.7564	0.0039	356	424	16	5.8446	3.53E-08	MEM > CTL
FC_Th_9_11	L.LTC–L.PHG	1.7206	0.0010	362	437	17	5.8282	7.15E-10	MEM > CTL
FC_De_1_5	L.PCC–L.IPL	1.6655	0.0011	346	412	12	6.0057	9.11E-07	MEM > CTL
***TPQ_HA**	Questionnaire	1.6312	0.0026	318	363	37	6.1333	1.44E-02	MEM > CTL
FC_Al_2_5	R.PCC–L.IPL	1.6034	0.0013	376	455	9	5.9314	1.72E-12	MEM > CTL
FC_De_2_5	R.PCC–L.IPL	1.5614	0.0004	366	437	18	5.8339	7.15E-10	MEM > CTL
FC_De_1_6	L.PCC–R.IPL	1.5384	0.0009	310	383	27	6.2101	5.68E-04	MEM > CTL
FC_Be_4_9	R.ACC–L.LTC	1.4901	0.0009	344	402	12	6.2038	1.05E-05	CTL > MEM
FC_Ga_4_12	R.ACC–R.PHG	1.4605	0.0016	376	451	3	5.6709	6.99E-12	CTL > MEM
FC_De_7_11	L.PFC–L.PHG	1.4543	0.0019	342	407	13	6.1891	3.19E-06	MEM > CTL
***DHU_UPL**	Questionnaire	1.4497	0.0021	315	368	15	6.4736	7.06E-03	CTL > MEM
FC_Th_4_10	R.ACC–R.LTC	1.4211	0.0006	345	422	8	6.2084	6.21E-08	CTL > MEM
FC_De_8_12	R.PFC–R.PHG	1.3844	0.0010	333	394	15	6.0851	6.29E-05	MEM > CTL
FC_Al_2_11	R.PCC–L.PHG	1.3805	0.0006	360	443	3	6.2337	1.04E-10	MEM > CTL
PRS_MVP_AUD	PRS	1.2987	0.0002	363	432	1	6.2696	3.35E-09	CTL > MEM
FC_De_5_6	L.IPL–R.IPL	1.2964	0.0009	320	378	11	6.4012	1.40E-03	MEM > CTL
FC_De_6_11	R.IPL–L.PHG	1.2959	-0.0001	317	381	10	6.3433	8.21E-04	MEM > CTL
FC_Th_4_6	R.ACC–R.IPL	1.2955	0.0002	342	404	2	6.3120	6.59E-06	CTL > MEM
FC_De_2_12	R.PCC–R.PHG	1.2581	0.0007	319	380	9	6.4407	9.83E-04	MEM > CTL
FC_De_4_8	R.ACC–R.PFC	1.1741	0.0015	315	364	6	6.5837	1.26E-02	MEM > CTL
FC_De_3_7	L.ACC–L.PFC	1.1278	0.0000	319	391	6	6.7618	1.18E-04	CTL > MEM

Abbreviations: FC–Functional Connectivity; De–Delta; Th–Theta; Al–Alpha; Be–Beta; Ga–Gamma; Numbers in functional connectivity variables: 1-12 of the default mode network; AlcHlthProb5yrs–Alcohol-related health problems in the past 5 years; AlcWthSx5yrs–Alcohol withdrawal symptoms in the past 5 years; AlcExp5y–Alcohol related negative experiences (symptoms) related to alcohol consumption in the past 5 years; Drk24Hr–The largest number of drinks in 24 hours during the past 12 months; PRS_MVP_AUD–PRS derived from the MVP GWAS of AUD; *Measures from personality and life experience questionnaires: TPQ_HA–Harm avoidance assessed by TPQ questionnaire; DHU_UPL–Uplift assessed by DHU questionnaire; and NEO_N–Neuroticism assessed by NEO questionnaire [See **Table 3** in Methods and **Fig. S2** *in* the *Supplementary Material* for the details of the ROIs of the default mode network]. MEM–*Memory group;* CTL–*Control group*

The multi-way importance plot [**Fig. 1**] displays all significant variables (labeled and marked with black circles) that contributed to the classification of the *Memory* group from the *Control* subjects and ranked based on the importance for classification as derived from Gini decrease, number of trees, and p-value. A chart showing distribution of minimal depth in classification against number of decision trees [see **Fig. S4** in the *Supplementary Material*]**.** While both multi-way importance plot and distribution plot can be created for any set of random forest parameters, the importance ranking for the features is likely to be similar owing to high correlations among these parameters (see **Fig. S5** in *Supplementary Material*).

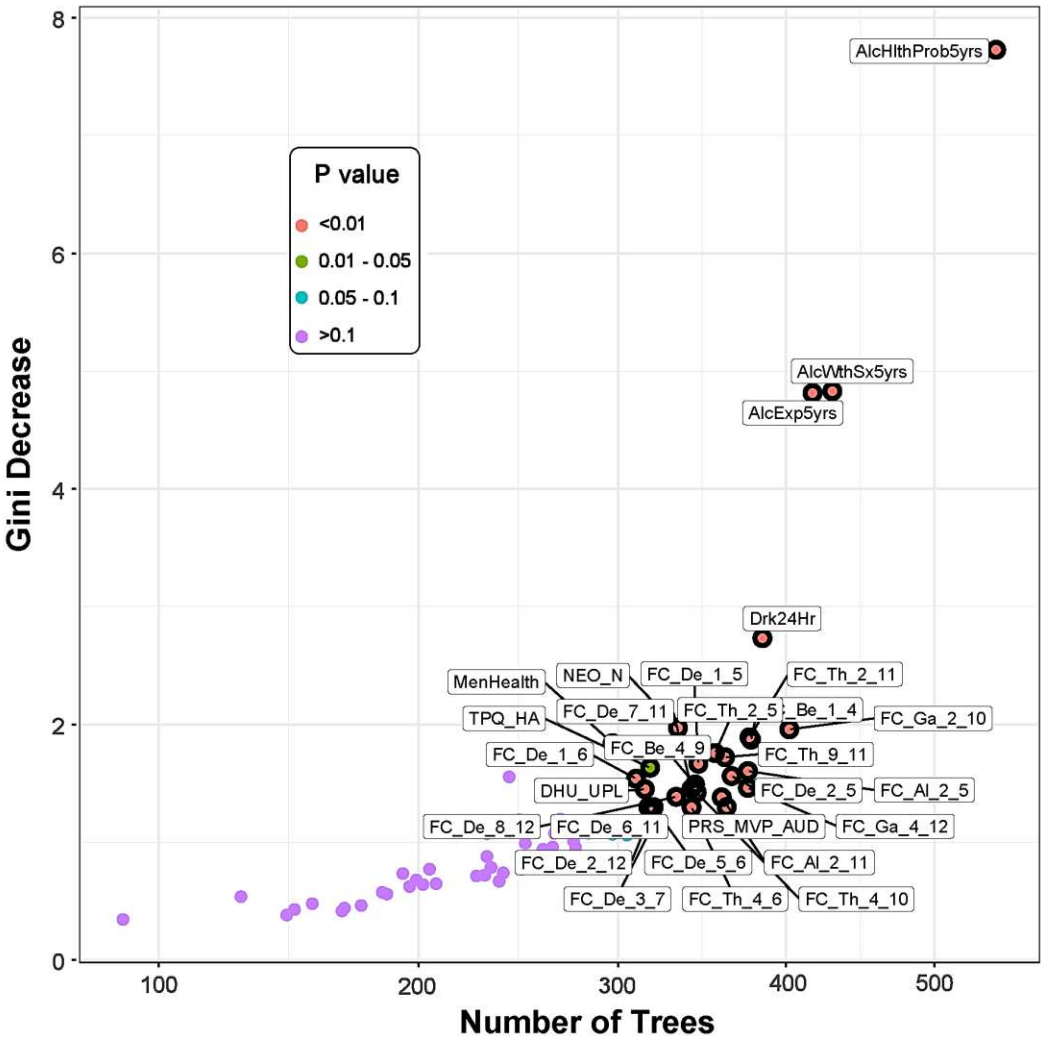

Fig. 1. The multi-way importance plot showing the top significant variables (labeled and marked with black circles) that contributed to the classification of the *Memory* group from the *Control* subjects based on the measures Gini decrease, number of trees, and p-value: Features related to alcohol-related

clinical/health outcomes stood top in the importance list, followed by functional connectivity, personality, and PRS measures. Note that the variables that were not significant (purple dots) are not highlighted. [See footnote of **Table 5** for the list of abbreviations for the measures shown here].

3.3.1. EEG Source Functional Connectivity of the Default Mode Network

Significant default mode network connections which contributed to the Random Forest classification of the *Memory* group from *Control* individuals have been illustrated in **Fig. 2**. *Memory* group showed a predominant pattern of hyperconnectivity across the default mode network regions, primarily contributed by delta band (10 connections) followed by theta band (5 connections) band, along with fewer hypoconnectivity (1 in delta band and 2 in theta band). Other significant functional connectivity features specific to each frequency band are (i) 9 hyperconnected paths and 1 hypoconnected path in delta band, (ii) 3 hyperconnected and 2 hypoconnected paths in theta band, (iii) 2 hyperconnected paths with no hypoconnected paths in alpha band, (iv) 2 hypoconnected paths with no hyperconnected paths in beta band, and (v) 1 hyperconnected path and 1 hypoconnected path gamma band (**Fig. 2, Panels A-E**). Number of significant connections from each ROI node (in descending order) was as follows: R.PCC = 7; R.ACC = 6; L.PHG = 5; L.IPL = 5; R.IPL = 4; L.PCC = 3; R.PHG = 3; L.PFC = 2; R.PFC = 2; L.LTC = 2; R.LTC = 2; L.ACC = 1. The number of significant connections for the ROIs involving both hemispheres (in ascending order) was: PCC = 10; IPL = 9; PHG = 8; ACC = 7; PFC = 4; LTC = 4. Individuals from *Memory* group showed predominant hyperconnectivity between hippocampal region (PHG) and other default mode network regions involving multiple frequencies except beta band compared with the *Control* group (**Fig. 2, Panel F**). Only a single hippocampal connection (R.PHG–R.ACC) of the gamma band oscillation was hypoconnected in the *Memory* group.

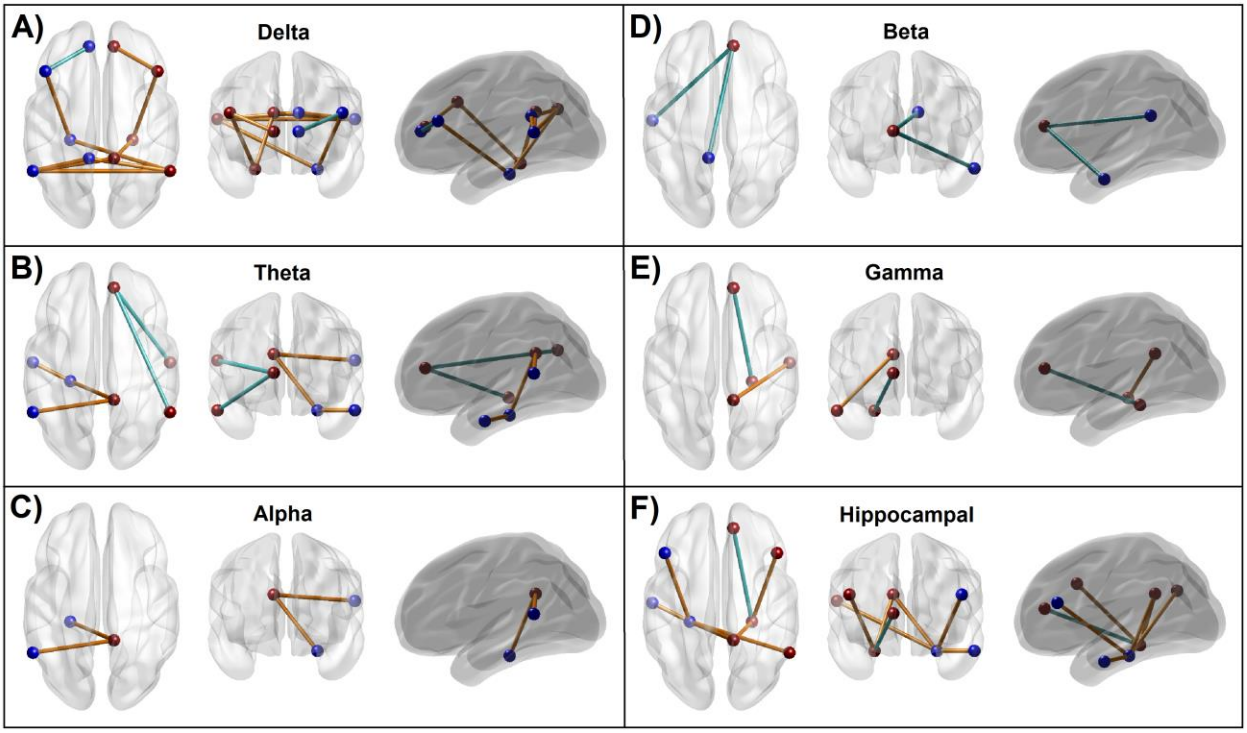

Fig. 2: ***Panels A-E:*** Significant default mode network connections within each frequency band, which contributed to the Random Forest classification of *Memory* group from *Control* individuals. The blue and brown beads represent ROIs of the left and right hemisphere, respectively, while the blue and brown lines represent hypoconnectivity and hyperconnectivity, respectively, in the *Memory* group. ***Panel F:*** Significant hippocampal connections that contributed to the *Memory* vs. *Control* classification. Seven of the eight hippocampal connections showed hyperconnectivity in the *Memory* group. Note that all hypoconnected networks involved an anterior cingulate node. Refer to *Fig. S2* in the *Supplementary Material* for the ROI locations and anatomical views/axes.

3.3.2. Recent Alcohol Consumption and Health Outcomes

Significant alcohol-related health outcome variables that contributed to classifying *Memory* individuals from the *Control* subjects included (i) alcohol-related health problems in the past 5 years ($Memory_{mean}$=0.77; $Control_{mean}$=0.01), (ii) alcohol withdrawal symptoms in the past 5 years ($Memory_{mean}$=1.20; $Control_{mean}$=0.11), (iii) negative experiences related to alcohol consumption in the past 5 years ($Memory_{mean}$=2.65; $Control_{mean}$=0.78), and (iv) the largest number of drinks within 24 hours during the past 12 months ($Memory_{mean}$=13.64; $Control_{mean}$=6.00). Interestingly, the features concerning alcohol-related outcomes over the past 10 years, physical health outcomes, other drinking patterns, and demographic variables were not significant.

3.3.3. Measures of Personality, Behavior, and Life Experiences

Out of 27 variables of personality and behavioral features, only the following three variables significantly contributed to the *Memory* vs. *Control* classification: (i) Harm avoidance representing internalizing traits and negative mood states as assessed by TPQ ($Memory_{mean}$=16.16; $Control_{mean}$=12.61), (ii) Uplift experience indicating "feel good" aspects as assessed by DHU ($Memory_{mean}$=51.25; $Control_{mean}$=58.99), and (iii) Neuroticism represented by dysregulated emotions and maladjusted behaviors as assessed by NEO ($Memory_{mean}$=59.00; $Control_{mean}$=52.11), and higher scores mean more neurotic traits.

3.3.4. Polygenic Risk Scores

PRS for the AUD diagnosis (based on the ICD codes) created using GWAS data from the MVP [60] was a significant contributor to the classification of *Memory* vs. *Control* group ($Memory_{mean}=8.25 \times 10^{-7}$ and $Control_{mean}=7.87 \times 10^{-7}$). PRSs for the other phenotypes, i.e., AUDIT-C scores from the GWAS of MVP dataset [60], Maximum habitual alcohol intake from the GWAS of MVP dataset [61], and DSM-IV alcohol dependence diagnosis from the GWAS of PGC dataset [62], were not significant contributors in the classification.

3.4. Correlations across Significant Predictors

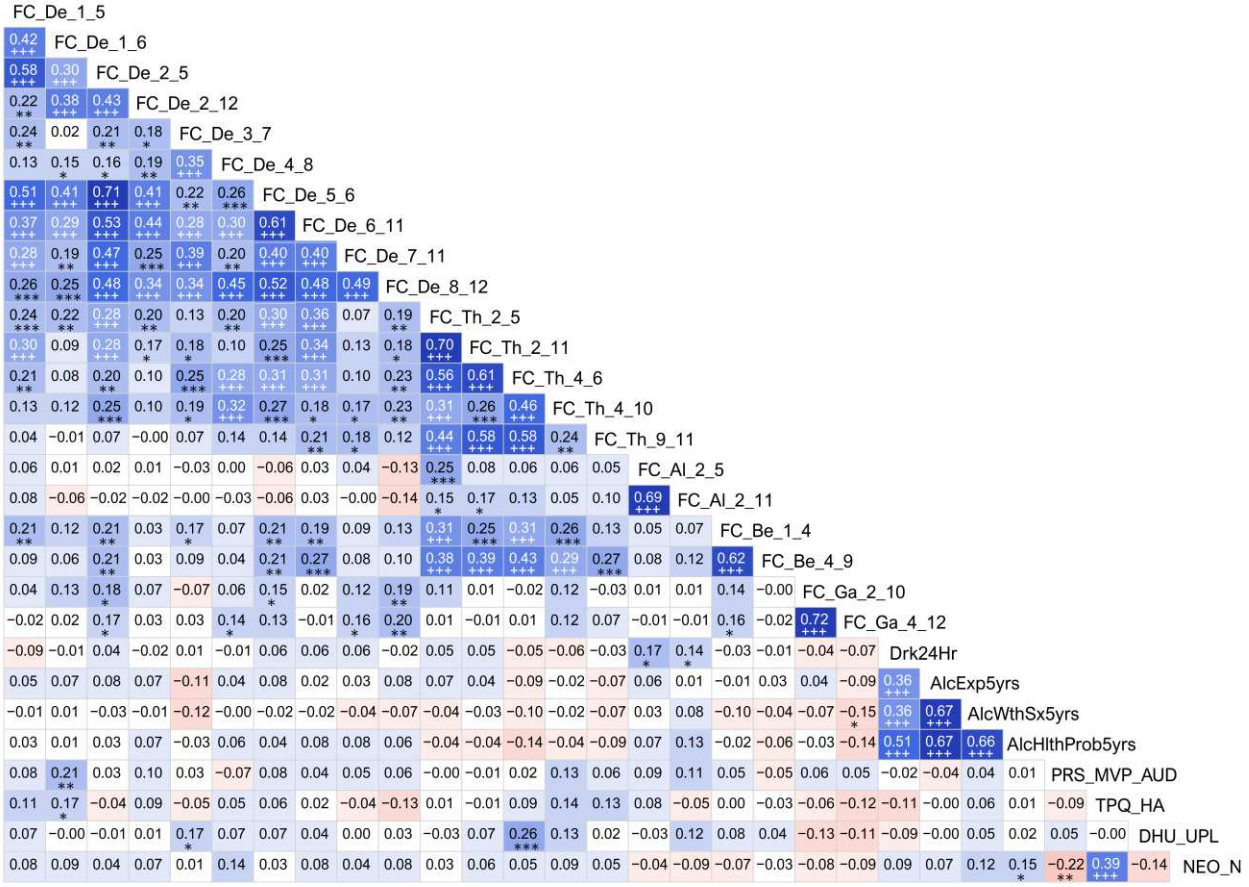

Fig. 3: Correlation matrix showing associations among the top significant variables. Values of the cells in red/pink shades represent negative r-values, and those in blue/cyan shades indicate positive r-values between variables that correspond to the vertical and horizontal axis. Darker color represents a higher magnitude of r-values. Significant correlations (before Bonferroni correction) have been marked with asterisks in black font [*p < 0.05; **p < 0.01; and ***p < 0.001], and those survived Bonferroni correction have been marked with a triple plus sign (+++) in white font. For the abbreviations in the variable labels, see the footnote of **Table 5**.

Exploratory (descriptive) analysis of correlations among the top significant variables is shown in **Fig. 3**. As shown in the correction matrix, there were significant positive correlations relationships among the functional connectivity variables within and between different frequency bands. Overall, most of the low-frequency connections in the delta and theta frequencies were highly correlated with one another. Specifically, those connections that shared a common node showed much higher correlations with each other than with other connections, regardless of their frequency band. Beta band connections had significant positive correlations between themselves

as well as with low-frequency connections, especially that of theta band connections. However, alpha and gamma band connections showed significant correlations only within the frequency but not across the frequencies. Highly significant positive correlations were observed among the alcohol-related health consequences. Among the personality factors, there was a significant positive correlation between neuroticism and harm avoidance. However, no significant correlations were observed across the domains (e.g., functional connectivity vs. personality, or functional connectivity vs. alcohol-related features).

4. Discussion

The current study suggests that alcohol-related memory problems can be predicted using a multi-domain set of features from neural, behavioral, genomic, and alcohol-related measures in a machine learning framework. It was found that the *Memory* group showed a predominant pattern of hyperconnectivity across the default mode network regions, including the hippocampal subnetworks, while showing hypoconnected anterior cingulate cortex subnetworks based on the EEG recorded about 18 years ago. Features from other domains that significantly contributed to the classification were (i) higher counts of alcohol-related consequences during the past 5 years, such as health problems, other alcohol-related adverse past negative experiences, withdrawal symptoms, and higher max number of drinks (the largest number of drinks per day), (iii) personality factors such as high neuroticism, high harm avoidance, and low positive/uplift experience, and (iv) high genetic liability, as reflected in variations in PRS for AUD across the *Memory* and *Control* groups. It should also be noted that the classification accuracy was better for the *Control* individuals (85/94 = 90.43%) than for the *Memory* group (68/94 = 72.34%). Although the reasons could be many, we speculate that the *Memory* group may have high variability in their clinical presentations and/or neurocognitive functioning.

4.1. Altered Functional Connectivity in the Memory group

Findings of resting-state EEG connectivity showed that those with alcohol-related memory problems, relative to matched controls, showed (i) a predominant pattern of hyperconnectivity of low-frequency (delta and theta) oscillations across most of the default mode network cortical regions, (ii) hyperconnected hippocampal sub-networks in multiple frequency bands, and (iii)

hypoconnectivity in subnetworks involving anterior cingulate cortex hub regions. In general, alterations in brain networks (in both low and high frequencies) due to alcohol-induced memory deficits could be interpreted as compromised memory engrams and changes in neural plasticity during encoding and recall processes. The neural basis of memory processes was first theorized by Richard Semon's *engram theory* [78] and Donald Hebb's *synaptic plasticity theory* [79] and here is a vast literature spanning several decades on memory functions. The connectivity differences observed between *Memory* and *Control* groups are discussed below in light of findings from the literature as well as our previous studies.

4.1.1. Predominant hyperconnectivity of low-frequency oscillations in the Memory group

The finding that individuals with alcohol-induced memory problems during their recent interview (i.e., *Memory* group) manifested a predominant pattern of hyperconnectivity across the default mode network nodes in their resting state EEG [**Fig. 2**] may indicate aberrations in neural communication. Specifically, EEG hyperconnectivity may indicate a brain signature related to an early stage of cognitive decline possibly leading to dementia [80]. While the EEG-based functional connectivity findings attributable to a specific diagnosis or outcome is far from clear, increased EEG connectivity during the resting state may be a sign of abnormal brain communication, since studies have reported this feature in several neuropsychiatric disorders. For example, individuals with schizophrenia had increased EEG coherence in delta and theta bands relative to controls [81]. Similarly, patients with major depressive disorder exhibited significantly higher EEG coherence as compared to controls in several frequencies, including delta and theta bands [82]. Such alterations in resting-state EEG connectivity in slow rhythms (delta and theta) has also been reported in childhood developmental disorders, such as autism spectrum disorders [83] and specific learning disorders [84]. On the contrary, healthy aging is marked by decreased slow frequency activity (band power) in the delta and theta bands during the resting state [85] as well as by reduced EEG network connectivity [86]. On the other hand, during the task performance, both delta and theta band oscillations predominantly contribute to the generation of P300 or P3 [87], a prominent event-related potential (ERP) component that is a marker of contextual neural processing, the amplitude of which is reduced abnormal in individuals with and/or at risk for AUD, who have shown reduced amplitudes [9]. Interestingly, the slow delta and theta oscillations are often found to be attenuated during task performance in individuals with chronic AUD relative to healthy individuals [88], while these slow theta

oscillations are also involved in episodic memory maintenance processes during cognitive processing [89].

At the neural level, it is possible that the hyperconnectivity seen in the *Memory* group may contribute to aberrant synaptic pruning in specific cortical regions [90] in these individuals who have also reported having increased alcohol-related consequences compared to the comparison group. It is also possible that damage to a specific network can enhance connectivity across other regions that are anticorrelated to the damaged network, such as that as it happens in neurodegenerative conditions [91]. Physiologically, alcohol can impact pre- and postsynaptic mechanisms during secretion/recycling of neurotransmitters, leading to the disruption of excitatory and inhibitory neurotransmission [92,93], potentially caused by detrimental effects of alcohol on glial cells [94]. Recent animal studies confirm that chronic and heavy alcohol consumption can cause aberrant synaptic pruning and substantial loss of excitatory synapses in the prefrontal cortex, resulting in disruption of brain connectivity and dysregulated neural communication across the cortical networks [95]. However, it remains to be confirmed whether the connectivity differences observed in the *Memory* group are the direct consequence of alcohol consumption or indicators of predisposed genetic risk in these individuals, or the interaction of both.

4.1.2. Hyperconnectivity across the hippocampal-cortical networks in the Memory group

Findings reveal that individuals who endorsed alcohol-related memory problems have also shown a predominant pattern of hyperconnectivity across the hippocampal network in their resting EEG, which was recorded about 18 years ago. Specifically, these hyperconnected hippocampal networks (7 out of 8 connections) involved bilateral PHG, bilateral PFC, left LTC, right PCC, and right IPL nodes, spanning delta, theta, and alpha bands [**Fig 7, Panel F**]. Further, majority of the hyper-connected paths (6 out of 7 connections) represented low-frequency (delta/theta) oscillations. Although direct evidence linking EEG-based hyperconnectivity of parahippocampal-cortical network to alcohol-related memory problems is lacking in the literature, some of the available findings may help interpret the findings of the present study. Interestingly, intracranial EEG recordings at the hippocampus and medial temporal regions revealed the existence of independent delta/theta rhythms in different subregions of the human hippocampus and surrounding cortical regions associated with memory encoding and retrieval

[96]. Therefore, it is possible that dysregulation (i.e., hyperconnected low frequency paths) in the hippocampal-cortical network, which underlies memory processing [97], may have directly contributed to the alcohol-related memory problems in the *Memory* group. At the neural level, elevated hippocampal resting-state connectivity may be associated with age-related decline in white matter integrity of the fornix as well as deficient neurocognitive function in human adults [98]. Converging findings indicate that memories for recent events underlie dynamic interplay across multiple cortical brain regions and networks, in which the hippocampus acts as a hub integrating information from these subnetworks [99]. Recent studies reveal hippocampal involvement in the default mode network activity. default mode network may mediate interactions between the hippocampus and the neocortex in memory formation and replay [100]. A large neuroimaging study revealed that subregions within default mode network contain fornix fibers from the hippocampus, and thus relating the network to its memory functions [101]. Specifically, the hyperconnected bilateral hippocampal-prefrontal network of slow frequency (delta band) may indicate a dysregulated long-range neural communication involving learning and memory processes, as these networks are crucial for the coordination of activity during memory-guided decision making [102]. Further, the theta band hyperconnectivity of left hippocampal with left temporal cortex and right PCC in *Memory* group may indicate disturbances in verbal [103] and episodic memory [104], respectively. This finding in theta band hippocampal connectivity is important as hippocampal theta rhythm is critical for the optimal functionality of memory networks [105]. It may also be interesting to note that theta band hyperconnectivity across cortical regions was also observed in the APOE-4 carriers of patients with Alzheimer's disease [106]. Lastly, it needs to be mentioned that a single connection with decreased connectivity at the gamma band in the *Memory* group was observed between ACC and PHG in the right hemisphere. Weaker resting-state connectivity between the hippocampus and ACC may suggest disruption of mood regulation [107], possibly due to compromised structural connectivity between these major structures [108]. Another explanation for lower connectivity between hippocampus and ACC in the *Memory* groups, as it happens in patients with traumatic axonal injury [109], is alcohol-induced microstructural alterations in neuronal fiber tracts connecting brain structures in AUD individuals [110], causing damage to axonal fiber tracts across and within the hemispheres including the hippocampal-cortical bundles [111]. As mentioned earlier, given that the *Memory* group has reported more occasions of heavy drinking

and alcohol-related health consequences than the *Control* group, it is expected that neuronal damage, including the compromised hippocampal-cortical connectivity, is more pronounced in these individuals resulting in memory problems along with other neurocognitive and health issues. In sum, it is possible that alcohol-induced hippocampal atrophy [112] may underlie the disruption of cortical hippocampal network subserving memory formation and retrieval processes [113,114].

4.1.3. Hypoconnectivity across the anterior cingulate hub networks in the Memory group

Findings of the present study have also revealed that the *Memory* group, in addition to the predominant hyperconnectivity across the default mode network nodes in multiple frequencies, manifested six hypoconnected paths (i.e., reduced connectivity strength) across bilateral ACC and other cortical regions (left PFC, bilateral LTC, R.IPL, left PCC, and right PHG) in all frequency bands except the alpha band. All except the connections in the beta band were intra-hemispheric. Broadly, since ACC hub networks within the default mode network are associated with the prediction of outcome for a given choice [115], planning of future actions [116], and social cognition [117], hypoconnectivity of ACC with other cortical regions, including the hippocampal region, may indicate disrupted neural communication leading to less efficient action plans and decision making. ACC also contributes to reward-based action selection or decision-making [118-120] as well as monitoring of action, conflict, error, and outcome [121-124]. In our previous study on EEG source connectivity in abstinent AUD individuals [58], we had also reported hypoconnected prefrontal nodes (PFC and ACC) relaying other cortical regions (LTC, IPL, and PHG) suggesting weaker top-down processing.

Specifically, the hypoconnected ACC–PFC subnetwork in the *Memory* group may suggest compromised top-down cognitive control mediated by the PFC as it happens in individuals addicted to drugs [125]. On the other hand, reduced connectivity of ACC with LTC in the *Memory* group may represent impaired semantic memory processing related to personally relevant action plans in these individuals, as the LTC is related to short-term verbal memory and language processes [126,127] as well as conceptual representations of actions and behaviors [128,129]. Further, hypoconnectivity between ACC and IPL in the right hemisphere may indicate a lack of spatial and computational processing for the task at hand, as dictated by the role of right IPL in spatial attention and mathematical cognition [130]. Taken together, these

alterations in the brain network may underlie alcohol-induced memory deficits in individuals from the *Memory* group, who have also shown more health problems due to their chronic and/or hazardous alcohol consumption (see Section 4.2. below).

4.2. Alcohol Consumption and Health Problems in the Memory group

The top-most predictors of memory problems as revealed by the Random Forests model were alcohol-related consequences during the past 5 years, such as health problems, past negative experiences, withdrawal symptoms, and the largest number of drinks per day. This finding indicates that the individuals with alcohol-related memory problems not only consumed larger quantities of alcohol during the last five years, but also suffered drinking-related adverse consequences such as withdrawal symptoms, negative experiences, and health issues. It is quite possible that the memory problems endorsed by the individuals from the *Memory* group could be one of the health and neurocognitive outcomes due to chronic and/or hazardous alcohol consumption as supported by relevant literature [131-133]. Relatedly, there is also a vast literature documenting alcohol-induced brain damage and cognitive impairments, including memory deficits, in chronic and hazardous drinkers [134-136]. Taken together, alcohol-induced memory problems could be a part of the larger picture of a gross brain damage in chronic and/heavy users of alcohol. Future longitudinal studies combining both structural and functional MRI, along with various EEG and neuropsychological measures, may clarify the exact nature of alcohol-induced neurocognitive deficits.

4.3. Personality Features in the Memory group

Among the host of personality and life experience factors included in the Random Forests model, only three factors, namely, harm avoidance, neuroticism, and uplift experiences, were identified as key features that contributed to classifying the *Memory* group from the controls. Our finding suggests increased harm avoidance in the *Memory* group, evidenced by higher endorsement of internalizing traits and negative mood states by these individuals. Although the past studies have shown mixed findings for the harm avoidance subscale of the TPQ in predicting AUD/SUD and risk [38,137], some of the latter studies have associated these internalizing traits with harmful use of alcohol and other substances [138,139] and with risk to develop AUD [140-142]. Interestingly, alcohol and other psychoactive substances are often used to self-medicate the

negative mood states such as depression [143,144]. Further, higher neuroticism in the *Memory* group may be related to a variety of alcohol-related outcomes, including relapse [145]. Further, neuroticism has been associated with ineffective use of coping strategies [146], while also mediating the relationship between AUD and neural connectivity [147]. Empirically, neuroticism was has also been found to be associated with internalizing factors related to lifetime diagnosis of mood and anxiety [148]. On the other hand, individuals from the *Memory* group also endorsed fewer uplifting experiences than comparison controls, reflecting less pleasurable experiences at work and home. Lack of adequate uplifting experiences represents a lower buffer against stress and coping [149], which can also contribute to both AUD [146,150] and internalizing outcomes such as depression [151,152]. Alternatively, negative mood states may lead to the assessment of fewer experiences as uplifting. Taken together, it is clear that personality and life experience-related factors are important determinants in alcohol-related outcomes, possibly mediated by neural as well as stress-coping dyad mechanisms. However, further studies are necessary to disentangle specific mechanisms involved in the complex etiological pathways of risk, symptoms, and recovery in AUD and related disorders.

4.4. Genomic Risk in the Memory group

The only significant PRS measure in the Random Forests model to classifying *Memory* and *Control* groups was derived from the MVP study of DSM-5 AUD, suggesting the importance of AUD-PRS, rather than the consumption related PRS, in predicting neurocognitive outcomes such as alcohol-induced memory problems. This could be partly because individuals from both *Memory* and *Control* groups had a lifetime diagnosis of DSM-IV alcohol dependence. While the DSM-IV alcohol dependence PRS derived from the PGC was not found to be significant, it is possible that it could be because of its relatively smaller GWAS sample size, compared to that of the MVP dataset, and fewer participants of non-European ancestry in the discovery GWAS (see **Table 4**), and/or the more inclusive diagnosis of DSM-5 AUD versus DSM-IV AD. Nevertheless, the finding that AUD-PRS significantly contributed to the classification suggests that alcohol-induced memory, at least in part, is associated with genomic liability. In general, family studies, twin studies, and GWAS have all demonstrated the heritability of AUD [153-155], and utility of PRS to identify and quantify the risk of developing AUD and related outcomes [65,67,156]. Recently, Lai et al. [67] reported that individuals with AUD had higher

PRS than controls and the PRS magnitude increased as the number of DSM-5 diagnostic criteria increased. Further, PRS for alcohol dependence was found to be associated with neural connectivity [36,157] and cognitive functions, such as verbal fluency, vocabulary, digit-symbol coding, and logical memory [158], as well as brain structure [159]. Unfortunately, PRS related to neurocognitive phenotypes, which could have improved the predictive model, were not included in the study due to a lack of neurocognitive GWAS on AA populations for calculating PRS-CSx for the study sample. Further studies using neurocognitive PRS in multi-ethnic samples are needed to ascertain and quantify the genomic contribution of alcohol-induced memory problems for predictive purposes.

4.5. Correlations among the Significant Features

It may be of interest to understand how the significant features, which contributed to the classification of *Memory* individuals from controls, are related to each other. As shown in **Fig. 3**, the correlation matrix revealed some interesting associations. Most obviously, most of the low-frequency connections in the delta and theta frequencies were highly correlated with one another. As mentioned earlier (Section 4.1.2), hippocampal EEG oscillations are mainly represented by delta and theta frequencies, which interact with each other in the memory processes, such as mnemonic encoding and retrieval [96]. Empirically, it is known that delta and theta rhythms are not only correlated with each other but involved in hippocampal-prefrontal communication, which underlies memory and other higher-order cognitive functions such as executive functions [160,161]. Another interesting finding was that the connections that shared a common node (brain region) between themselves were also significantly correlated with each other, regardless of their frequency band. It is possible that the common node forms a subnetwork that can facilitate information flow across the regions of the subnetwork as well as other connected regions in the brain [162]. Further, correlational results also showed that the beta band connections had highly significant correlations with other connections within the same frequency as well as among low-frequency connections ($p < 0.001$), especially with the theta band connections ($p < 0.001$ and survived Bonferroni correction). This could be because low-frequencies (delta/theta) synchronously work together with high-frequencies (beta/gamma) during cognitive processing, including working memory processes [163-165]. However, alpha and gamma band connections showed only within frequency correlations but no cross-frequency

correlations, partly because the magnitude of correlations is smaller warranting more statistical power to identify meaningful alpha-gamma associations.

Correlations among the alcohol-related outcome variables were also found to be highly significant with one another, which is in line with the research showing heavy and high-intensity drinking is associated with alcohol-related negative consequences such as withdrawal symptoms and health issues [166,167]. Further, the significant positive correlation between the two personality traits, namely, neuroticism and harm avoidance, is also backed by the evidence that both traits underlie negative emotions such as fear, shyness, and worry and are regulated by serotonin and opiate pathways [168]. Lastly, it was a rather unexpected finding that there were no highly significant correlations across the domains (e.g., functional connectivity vs. personality), likely because of very low correlation across the domains due to lack of adequate statistical power to detect the subtle associations among features from different categories of predictors.

4.6. Limitations and Suggestions

While this is the first multi-modal study including EEG based source connectivity to examine alcohol-related memory problems, which is an important alcohol-related neurocognitive outcome, it has some limitations: (i) the sample size of the study groups is rather small and the findings are therefore only preliminary, (ii) while the groups are matched based on important variables, stratified analyses based on age, sex, and self-reported race, and genetic ancestry, may identify more relevant features specific to each category; (iii) some of the variables were not considered for matching (e.g., memory status during baseline, relatedness among group members, comorbid diagnoses such as substance use, anti-social personality disorder, attention-deficit hyperactivity disorder, etc.), which may have impacted the results; (iv) the memory problems reported by the study sample can be heterogeneous and the assessment of alcohol-related memory problems was only based on oral self-report and not a psychometric measure; studies are currently underway in this sample with comprehensive neurocognitive assessments including memory function and will be more objective and quantitative; (v) the study has not considered genomic or other trait related baseline effects which could have influenced the results, and future large scale studies may consider this aspect into the study design; (vi) recent EEG recordings and neurocognitive assessments, including memory function, in the same

sample, which are missing in the current study, but are underway in our lab will further add to predictive modeling; (vii) other specific networks and regions related to memory (e.g., attention and memory networks) have not been explored in the current study, although studies are underway in our lab to explore these networks; (viii) PRS for neurocognitive phenotypes including memory functions have not been included due to lack of availability of multi-ethnic GWAS data. Future studies may attempt to overcome the shortcomings of the study by using a larger sample size and stratified analyses, longitudinal design, multimodal imaging (e.g., fMRI, DTI), and neurocognitive PRS data.

5. Conclusions

Our study has elucidated key multimodal features of brain connectivity, personality, life experiences, genomic, and alcohol-related measures that can serve as predictors of later occurring alcohol-related memory problems after about 18 years. Dysregulated brain connectivity, computed from the EEG data collected 18 years ago, in the form of hyper- and hypo-connectivity in specific subnetworks, including the hippocampal-cortical connections, represents potential neural correlates of alcohol-related memory problems. Personality and life experience features such as higher neuroticism and excessive harm avoidance, and fewer uplifting experiences in daily life also contributed to identifying individuals with memory problems from the controls. Importantly, alcohol-related negative consequences during the past 5 years, such as health problems, past negative experiences, withdrawal symptoms, and the largest number of drinks in a day during the past 12 months were the top-most predictors of memory problems. These findings will require confirmation in future studies to: (i) validate these multi-domain features for the use of early identification of individuals who may develop alcohol-induced memory problems in chronic and/or heavy drinkers; and (ii) use EEG-source connectivity measures to further identify/validate specific targets of brain networks underlying AUD related outcomes in general and memory deficits in particular for planning neuromodulation-based treatments (e.g., transcranial magnetic stimulation) as guided by the neural signatures related to dysregulated brain networks in affected individuals. However, in conclusion, the study has many limitations, and the results are only preliminary, warranting large-scale future studies to confirm the current findings by adopting better experimental designs within predictive modeling.

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