

Supplementary Materials for

**Decoding fMRI alcohol cue-reactivity and its association with
drinking behavior**

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Supplementary Methods

Participants

The patients did not use other substances except nicotine, which was verified by a urine drug screening (nal von minden GmbH Drug-Screen® Diptest, Version 1.0). The healthy participants had no history of alcohol or drug addiction or any current psychiatric disorder, assessed by applying the Structured Clinical Interview for DSM-IV and -5 (SCID). Participants in both groups were excluded if they had any history of serious medical (including psychiatric or neurological) complications, brain injury, use of psychotropic medications (other than during the detoxification process), or did not meet magnetic resonance safety criteria for our imaging facility.

Before taking part in the scanning procedure, participants completed the following questionnaires: the Alcohol Dependence Scale (ADS, ¹), the Alcohol Urge Questionnaire (AUQ, ²), the Obsessive Compulsive Drinking Scale (OCDS, ^{3,4}), FORM 90 ⁵ and visual analogue scale (VAS) ranging from 0 (no craving) to 100 (extremely extensive craving). The calculation rules of OCDS was based on the study from Mann et. al ⁴.

Details of cue-reactivity tasks and RDMs

The alcohol cue-reactivity (ALCUE) task was block-designed, in which one block consisted of five stimuli, each presented for 4 seconds, resulting in a total duration of 20 sec per block. Alcohol stimuli were taken from an own alcohol picture series ⁶, while neutral cues were taken from the International Affective Picture Series ⁷. After each block participants were asked to indicate their subjective craving for alcohol on a visual analogue scale ranging from 0 ('no craving at all') to 100 ('severe craving'). Participants had to rate their subjective craving in a maximum period of 10 sec. Thereafter a black fixation cross was presented on a white background for a minimum of 10 sec. The data in this study were from previous projects, and there were three versions of cue-reactivity tasks, including ALCUE, ALCUE-short, and ALCUEPV. The version of ALCUE tasks had different numbers of blocks: ALCUE had 30 blocks (18 alcohol + 12 neutral), ALCUE-short had 20 blocks (12 alcohol + 8 neutral), and ALCUEPV had 24 blocks (12 alcohol + 12 neutral). All these versions had same picture presenting blocks, which consisted of five pictures, each presented for 4 seconds. The ALCUEPV version had no have craving rating parts, which was replaced with 20 seconds fixations. The percentages of ALCUE and ALCUEPV in AUD and Healthy groups were not significantly different.

For Visual Object Recognition, the dimensions of RDMs were 150x150, 100x100 and 120x120 for the three versions of the task, and the Reward Appraisal model only included the alcoholic pictures, the dimensions of RDMs were 90x90, 60x60 and 60x60. The RDMs of neural activity were in same dimensions respectively with the Visual Object Recognition and Reward Appraisal models.

Visual Object Recognition (VOR) model construction

For the VOR model, we used a pre-trained deep convolutional neural network (dCNN) to obtain the visual decoding information of the stimuli of the cue-reactivity task ^{8,9}. Previous studies demonstrated high layers of visual dCNN containing high-dimensional representations of objects and complex features in visual recognition ^{9,10}. In this study, the dCNN model based on the ImageNet dataset ¹¹, VGG19 ⁸, was used to recognize the stimulus pictures with the MatConvNet

toolbox (<https://www.vlfeat.org/matconvnet/>), and connected layers of the neural network were used to construct the model RDMs.

Connectivity analyses

Based on the identified regions of neural representations of alcohol cue-reactivity, seed-to-voxel psychophysiological interaction (PPI) analyses¹² were performed with the CONN toolbox v20.b (<https://web.conn-toolbox.org/>)¹³.

Supplementary Table 1. Information of included studies

Study name	Inclusion criterion *	Sample size		ClinicalTrials/ German Clinical Trials Register (DRKS)
		AUD	HC	
Transalc ¹⁴	1) alcohol use disorder according to DSM-5; 2) for heavy-drinker, at least 84g pure alcohol in the previous 90 day; 3) treatment-seeking and abstinent.	30	36	DRKS: DRKS00003357
SFB_Haupt/ NGFN13 ¹⁵	1) alcohol dependence according to the DSM-IV and ICD 10; 3) treatment-seeking and abstinent.	79	71	ClinicalTrials: NCT00926900
SFB_Folgestu die ¹⁶	1) alcohol dependence according to the DSM-IV and ICD 10; 3) treatment-seeking and abstinent.	80	52	DRKS: DRKS00003388
eMEDs ¹⁷	1) alcohol dependence according to the DSM-IV and ICD 10; 2) treatment-seeking and abstinent.	28	57	DRKS: DRKS00003341
NALCUE ¹⁸	1) alcohol use disorder according to the DSM-5; 2) at least 60g for men and 40g for women pure alcohol, at least 5 days/week; 3) non-treatment-seeking.	21	0	ClinicalTrials: NCT02372318
Oxytocin ¹⁹	healthy participants **	0	13	DRKS: DRKS00009253
Total sample size:		238	229	

Abbreviations: diagnostic and statistical manual of mental disorders (DSM), international classification of diseases (ICD), alcohol use disorder (AUD), healthy control (HC).

* General criterion of inclusion and exclusion:

These studies included AUD individuals who 1) between 18 and 75 years, 2) right-handed; and excluded AUD individuals who 1) comorbid axis-I disorders (other than nicotine dependence) in the last year, 2) treatment with psychotropic or anticonvulsive medications in the last three months, 3) severe neurological or physiological disease (i.e. liver cirrhosis), 4) positive drug screening, 5) ineligibility for MRI scanning (e.g. metal implants), 6) history of severe head trauma.

These studies included healthy participants/light to moderate drinkers who 1) were aged between 18 and 75 years, 2) right-handed, 3) had an average alcohol consumption below 14g pure alcohol;

and excluded healthy participants who 1) comorbid axis-I disorders (other than nicotine dependence) in the last year, 2) treatment with psychotropic or anticonvulsive medications in the

last three months, 3) severe neurological or physiological disease (i.e. liver cirrhosis), 4) positive drug screening, 5) ineligibility for MRI scanning (e.g. metal implants), 6) history of severe head trauma.

** light to moderate drinkers were classified as healthy participants.

Supplementary Table 2 Group characteristics of all participants (N=467)

	AUD Individuals	Healthy Controls	Statistics (T/ χ^2 -value)	df	p-value
N	238	229			
Sex (female)	53, 22.3%	50, 21.8%	0	1	0.999
Age (years)	47 \pm 10.8	45.7 \pm 12.7	1.139	465	0.255
ADS score	13.7 \pm 7	2.4 \pm 3.6	11.722	171	<0.001
AUQ score	12.8 \pm 5.7	10.1 \pm 3.5	4.936	328	<0.001
OCDS global ^a	15.4 \pm 6.8	2.9 \pm 4.1	16.63	279	<0.001
Cumulative amount of alcohol (gram in the last 90 days) ^b	13608.3 \pm 12462.5	1095.2 \pm 4035.4	8.824	260	<0.001

Abbreviations: Alcohol Dependence Scale (ADS), Alcohol Urge Questionnaire (AUQ) and the Obsessive Compulsive Drinking Scale (OCDS)

^aThe calculation rules of OCDS was based on Mann et. al. ⁴.

^bThe amount of drink was based on FORM90.

Supplementary Table 3. Different Neural Representation of VOR and RA between AUD and healthy individuals

ROI Names	AAL Label (size)	Brodmann Label (size)	Cluster size	MNI coordinate	tmax
VOR1	Supp_Motor_Area_R (111) Frontal_Sup_R (3)	BA6: premotor cortex and supplementary motor cortex (12)	114	10 -4 60	4.9028
VOR2	Precentral_R (74) Postcentral_R (46)	BA4: primary motor cortex (36) BA3: primary somatosensory cortex (27)	120	48 -18 48	4.8782
RA1	Occipital_Sup_L (140) Cuneus_L (67) Occipital_Mid_L (57)	BA18: secondary visual cortex_V2 (35) BA19: associative visual cortex (V3, V4 & V5) (32) BA31: cingulate cortex (5) BA7: visuo-motor coordination (3)	264	-16 -86 26	5.3685
RA2	Temporal_Mid_R (327) Temporal_Sup_R (136) Temporal_Pole_Mid_R (6) Amygdala_R (3) Temporal_Inf_R (1)	BA21: middle temporal gyrus (192)	543	68 -14 -14	5.1199
RA3	Frontal_Inf_Tri_L (185) Frontal_Inf_Orb_L (147) Frontal_Mid_Orb_L (83) Frontal_Mid_L (44)	BA47: pars orbitalis, part of the inferior frontal gyrus (58) BA11: orbitofrontal area (31) BA10: anterior prefrontal cortex (9) BA46: dorsolateral prefrontal cortex (2) BA45: part of Broca area (1)	495	-42 46 -12	4.8378
RA4	Putamen_R (91) Caudate_R (75) Pallidum_R (19) Hippocampus_L (16) Olfactory_R (12) Amygdala_L (12) Frontal_Mid_Orb_R (3) Frontal_Inf_Orb_R (2) Insula_R (2) Frontal_Sup_Orb_R (1) Pallidum_L (1)	BA25: subgenual area (12) BA47: pars orbitalis, part of the inferior frontal gyrus (3) BA11: orbitofrontal area (2) BA13: insular cortex (1) BA34: dorsal entorhinal cortex (1)	512	22 8 -4	4.8361
RA5	Precentral_R (114) Frontal_Inf_Oper_R (105) Rolandic_Oper_R (20) Insula_R (12)	BA6: premotor cortex and supplementary motor cortex (38) BA9: dorsolateral prefrontal cortex (13)	374	40 0 30	4.6263

	Frontal_Mid_R (7)	BA13: insular cortex (13) BA44: part of Broca area (6)			
RA6	Frontal_Mid_L (204) Precentral_L (165) Frontal_Sup_L (119) Frontal_Inf_Oper_L (111) Frontal_Inf_Tri_L (60) Frontal_Sup_Medial_L (26) Supp_Motor_Area_L (7)	BA8: frontal eye fields (193) BA9: dorsolateral prefrontal cortex (134) BA6: premotor cortex and supplementary motor cortex (13) BA46: dorsolateral prefrontal cortex (1)	721	-52 12 28	4.6095
RA7	Temporal_Mid_L (109) Temporal_Sup_L (9)	BA21: middle temporal gyrus (55)	121	-64 -4 -16	4.4758
RA8	Calcarine_L (81) Lingual_L (6) Precuneus_L (1)	BA21: middle temporal gyrus (55) BA30: cingulate cortex (30) BA18: secondary visual cortex_V2 (3)	88	-16 -64 6	4.3857
RA9	Lingual_R (57) Calcarine_R (45) Vermis_4_5 (13)	BA30: cingulate cortex (34) BA18: secondary visual cortex_V2 (12) BA29: cingulate cortex (1)	116	18 -54 4	4.3199
RA10	Occipital_Mid_R (67) Occipital_Sup_R (38)	BA19: associative visual cortex_V3, V4 & V5 (16)	105	30 -80 24	4.219
RA11	Lingual_R (77) Vermis_3 (5) Cerebelum_4_5_R (4) ParaHippocampal_R (2) Thalamus_R (2)	BA30: cingulate cortex (12) BA27: piriform cortex (9) BA19: associative visual cortex_V3, V4 & V5 (2)	142	10 -34 -2	4.1889
RA12	Frontal_Inf_Tri_R (114)	BA45: part of Broca area (45) BA46: dorsolateral prefrontal cortex (6)	114	56 38 8	4.0697

Two-sample t-tests were used between Alcohol Use Disorder (N = 238) and healthy (N = 229) individuals, combining voxel-wise- $p < 0.0005$ and FWE_c=108 voxels for VOR modelling and 88 voxels for RA modelling, corresponding to cluster- p FWE_c<0.05. See supplementary Table for the full table with cluster sizes, MNI coordinates and peak T-values of clusters, as well as labels under five voxels.

Supplementary Table 4. Compare of RDM-fc7 in Visual Object Recognition between AUD and individual

Lobe	Brain regions	Regions size	Cluster size	MNI coordinates	tmax
Frontal Lobe	Precentral_R	74	122	48 -16 50	4.579
Parietal Lobe	Postcentral_R	48			

Supplementary Table 5. Connectivity from the Neural Pattern

Seeds	AAI Label (size)	Brodman Label (size)	tmax
Positive Connectivity			
RA1	Angular_R(125) Lateral_Occipital_superior_R(100)	BA_40: supramarginal gyrus (50) BA_39: angular gyrus (7)	4.196
RA2	Postcentral_R(191) Supramarginal_anterior_R(50)	BA_2: primary somatosensory cortex (postcentral gyrus) (36) BA_40: supramarginal gyrus (19) BA_3: primary somatosensory cortex (postcentral gyrus) (7) BA_4: primary motor cortex (precentral gyrus) (39) BA_3: primary somatosensory cortex (postcentral gyrus) (8) BA_6: premotor cortex and supplementary motor cortex (7)	4.827
RA4	Inferior_Temporal_L(174) Inferior_Temporal_R(99) Lateral_Occipital_inferior_L(97) Temporal_Fusiform_posterior_L(78) Lateral_Occipital_inferior_R(29) Middle_Temporal_L(27) Temporal_Occipital_Fusiform_L(25) Inferior_Temporal_posterior_L(6) Middle_Temporal_R(4) Cerebellum_6_L(4) Occipital_Fusiform_L(3)	BA_37: fusiform gyrus (14) BA_19: associative visual cortex (V3, V4 & V5) (11) BA_37: fusiform gyrus (68) BA_20: inferior temporal gyrus (48) BA_19: associative visual cortex (V3, V4 & V5) (12)	4.701
RA5	Cingulate_posterior(253) Cingulate_anterior(4)	BA_23: cingulate cortex (87) BA_31: dorsal posterior cingulate cortex (10) BA_24: cingulate cortex (4)	4.622
RA6	Parietal_Operculum_L(129) Supramarginal_anterior_L(57) Planum_Temporale_L(22) Superior_Temporal_posterior_L(7)	BA_40: supramarginal gyrus (84) BA_42: primary auditory cortex (Heschl gyrus) (39) BA_13: insular cortex (10)	4.823
RA9	Angular_R(391) Middle_Frontal_R(328) Frontal_Pole_R(289) Cingulate_posterior(101) Supramarginal_posterior_R(61) Lateral_Occipital_superior_R(45) Cingulate_anterior(11)	BA_10: anterior prefrontal cortex (112) BA_9: dorsolateral prefrontal cortex (22) BA_24: cingulate cortex (32) BA_23: cingulate cortex (21) BA_8: frontal eye fields (72) BA_9: dorsolateral prefrontal cortex (71) BA_6: premotor cortex and supplementary motor cortex (4) BA_40: supramarginal gyrus (204) BA_39: angular gyrus (1)	5.146

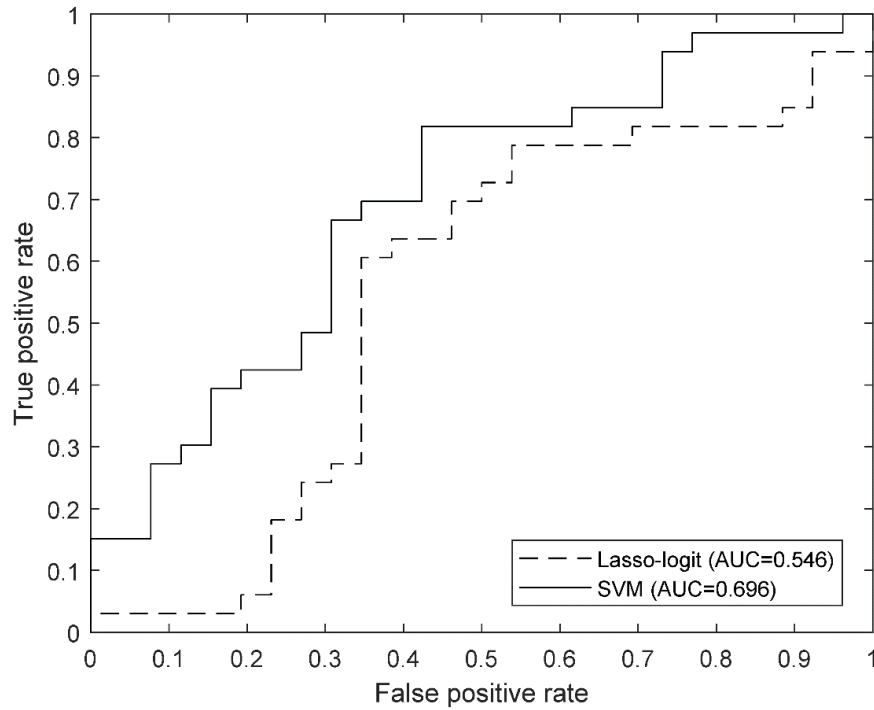
RA10	Cingulate_posterior(541) Precuneous(434) Lateral_Occipital_superior_L(154) Superior_Parietal_Lobule_L(1)	BA_7: visuo-motor coordination (superior parietal lobule) (212) BA_31: dorsal posterior cingulate cortex (168) BA_23: cingulate cortex (68) BA_24: cingulate cortex (17) BA_7: visuo-motor coordination (superior parietal lobule) (46) BA_39: angular gyrus (4) BA_19: associative visual cortex (V3, V4 & V5) (2) BA_40: supramarginal gyrus (2)	7.410
VOR1	Precentral_R(79) Postcentral_R(34) Central_Opercular_R(5)	BA_6: premotor cortex and supplementary motor cortex (39) BA_4: primary motor cortex (precentral gyrus) (16)	4.092
Negative Connectivity			
RA1	Lateral_Occipital_superior_R(357) Lateral_Occipital_inferior_R(29)	BA_19: associative visual cortex (V3, V4 & V5) (51) BA_18: secondary visual cortex (V2) (8) BA_31: dorsal posterior cingulate cortex (7) BA_7: visuo-motor coordination (superior parietal lobule) (2)	5.228
RA4	Supramarginal_posterior_R(118) Angular_R(37) Supramarginal_anterior_R(14)	BA_40: supramarginal gyrus (72) BA_2: primary somatosensory cortex (postcentral gyrus) (1)	4.316
RA5	Lateral_Occipital_inferior_L(192) Lateral_Occipital_inferior_R(92) Middle_Temporal_L(28) Middle_Temporal_R(24)	BA_37: fusiform gyrus (74) BA_39: angular gyrus (16) BA_19: associative visual cortex (V3, V4 & V5) (6) BA_37: fusiform gyrus (24) BA_19: associative visual cortex (V3, V4 & V5) (3)	5.280
RA8	Lateral_Occipital_superior_R(171) Lateral_Occipital_inferior_R(3)	BA_19: associative visual cortex (V3, V4 & V5) (3) BA_39: angular gyrus (3)	5.620
RA9	Cingulate_posterior(204) Lingual_R(189) Lingual_L(155) Vermis_4_5(105) Temporal_Fusiform_posterior_R(65) Parahippocampal_posterior_R(61) Parahippocampal_posterior_L(46)	BA_19: associative visual cortex (V3, V4 & V5) (83) BA_30: part of the cingulate cortex (66) BA_36: perirhinal cortex & entorhinal area (62) BA_37: fusiform gyrus (43)	5.214

	Temporal_Occipital_Fusiform_R(40)	BA_29: retrosplenial cingulate cortex (30)	
	Temporal_Fusiform_posterior_L(39)	BA_20: inferior temporal gyrus (11)	
	Precuneous(36)	BA_27: piriform cortex (6)	
	Cerebelum_4_5_L(27)		
	Temporal_Occipital_Fusiform_L(22)		
	Thalamus_r(17)		
	Hippocampus_r(14)		
	Cerebelum_4_5_R(14)		
	Hippocampus_l(8)		
	Vermis_3(1)		
RA11	Lingual_R(87)	BA_19: associative visual cortex (V3, V4 & V5) (33)	4.916
	Cingulate_posterior_(56)	BA_30: part of the cingulate cortex (19)	
	Temporal_Occipital_Fusiform_R(33)	BA_37: fusiform gyrus (15)	
	Precuneous(13)	BA_36: perirhinal cortex & ectorhinal area (8)	
	Parahippocampal_posterior_R(13)	BA_29: retrosplenial cingulate cortex (3)	
	Temporal_Fusiform_posterior_R(2)		
	Hippocampus_r(2)		

Supplementary Table 6. The support vector weights of ROIs in relapse prediction

ROI Names	Weight	AAL Label	Brodman Label
RA11	0.4802	Lingual_R (77) Vermis_3 (5) Cerebelum_4_5_R (4) ParaHippocampal_R (2) Thalamus_R (2)	BA30: cingulate cortex (12) BA27: piriform cortex (9) BA19: associative visual cortex_V3, V4 & V5 (2)
RA8	0.4131	Calcarine_L (81) Lingual_L (6) Precuneus_L (1)	BA21: middle temporal gyrus (55) BA30: cingulate cortex (30) BA18: secondary visual cortex_V2 (3)
RA9	0.4007	Lingual_R (57) Calcarine_R (45) Vermis_4_5 (13)	BA30: cingulate cortex (34) BA18: secondary visual cortex_V2 (12) BA29: cingulate cortex (1)
VOR1	0.2508	Supp_Motor_Area_R (111) Frontal_Sup_R (3)	BA6: premotor cortex and supplementary motor cortex (12)
VOR2	0.0816	Precentral_R (74) Postcentral_R (46)	BA4: primary motor cortex (36) BA3: primary somatosensory cortex (27)
RA7	-0.0501	Temporal_Mid_L (109) Temporal_Sup_L (9)	BA21: middle temporal gyrus (55)
RA4	-0.0809	Putamen_R (91) Caudate_R (75) Pallidum_R (19) Hippocampus_L (16) Olfactory_R (12) Amygdala_L (12) Frontal_Mid_Orb_R (3) Frontal_Inf_Orb_R (2) Insula_R (2) Frontal_Sup_Orb_R (1) Pallidum_L (1)	BA25: subgenual area (12) BA47: pars orbitalis, part of the inferior frontal gyrus (3) BA11: orbitofrontal area (2) BA13: insular cortex (1) BA34: dorsal entorhinal cortex (1)
RA1	-0.1233	Occipital_Sup_L (140) Cuneus_L (67) Occipital_Mid_L (57)	BA18: secondary visual cortex_V2 (35) BA19: associative visual cortex (V3, V4 & V5) (32) BA31: cingulate cortex (5) BA7: visuo-motor coordination (3)
RA12	-0.1446	Frontal_Inf_Tri_R (114)	BA45: part of Broca area (45) BA46: dorsolateral prefrontal cortex (6)
RA2	-0.1449	Temporal_Mid_R (327) Temporal_Sup_R (136) Temporal_Pole_Mid_R (6) Amygdala_R (3) Temporal_Inf_R (1)	BA21: middle temporal gyrus (192)
RA5	-0.2027	Precentral_R (114) Frontal_Inf_Oper_R (105) Rolandic_Oper_R (20) Insula_R (12) Frontal_Mid_R (7)	BA6: premotor cortex and supplementary motor cortex (38) BA9: dorsolateral prefrontal cortex (13) BA13: insular cortex (13) BA44: part of Broca area (6)

RA3	-0.3025	Frontal_Inf_Tri_L (185) Frontal_Inf_Orb_L (147) Frontal_Mid_Orb_L (83) Frontal_Mid_L (44)	BA47: pars orbitalis, part of the inferior frontal gyrus (58) BA11: orbitofrontal area (31) BA10: anterior prefrontal cortex (9) BA46: dorsolateral prefrontal cortex (2) BA45: part of Broca area (1)
RA10	-1.4421	Occipital_Mid_R (67) Occipital_Sup_R (38)	BA19: associative visual cortex_V3, V4 & V5 (16)
RA6	-1.9085	Frontal_Mid_L (204) Precentral_L (165) Frontal_Sup_L (119) Frontal_Inf_Oper_L (111) Frontal_Inf_Tri_L (60) Frontal_Sup_Medial_L (26) Supp_Motor_Area_L (7)	BA8: frontal eye fields (193) BA9: dorsolateral prefrontal cortex (134) BA6: premotor cortex and supplementary motor cortex (13) BA46: dorsolateral prefrontal cortex (1)

Supplementary Figure 1. Receiver operating characteristic (ROC) curves in relapse prediction

Supplementary Reference

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