Unawareness and Volition in Alcohol Consumption:
A Study using Functional Magnetic Resonance Imaging

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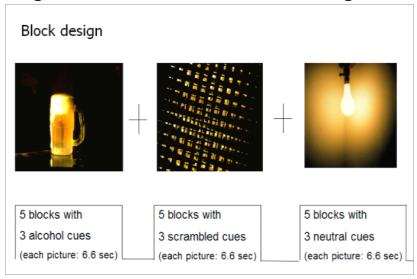
BACKROUND

According to the incentive salience theory of addiction (Robinson & Berridge, 1993), consumption is guided by the initial hedonic effects of the substance of abuse ('liking'). Everitt and Robbins (2016) have expanded the incentive sensitization theory to include the importance of habitual acts and a state of 'must do!'. According to this model, habitual consumption and automatisms can play a prominent role in later stages of dependence. In the present study we examined a) the dysfunctional brain regions and functional connectivities involved in alcohol-cue reactivity, and b) the association between dysfunctional neural activity and automated alcohol consumption, in order to find the neural basis of automated craving in alcohol use disorders.

METHODS AND STUDY DESIGN

We examined 50 recently detoxified male alcohol-dependent patients with functional Magnetic Resonance Imaging (fMRI), during a cue-reactivity task with visual alcohol stimuli (Figure 1; Vollstaedt-Klein et al., 2010). Automated alcohol craving was measured in 41 out of 50 participants, with the CAS-A questionnaire (Vollstaedt-Klein et al., 2015; Nakovics et al., 2012), which comprises five automated craving subscores related to different aspects of unawareness and non-volition. Data were acquired with a block design in a 3T scanner and preprocessed with SPM12 in Matlab. Psychophysiological interaction (PPI) analyses were performed to calculate the whole-brain connectivity, based on the hypothesized seed regions of the whole-brain data. Then one-sample t-tests were used for statistical analyses, with the FWE-cluster-wise $P < 0.05$. The voxel-wise-threshold was $P < 0.005$, combined with a cluster-extend-threshold determined by 10,000 Monte Carlo Simulations in AFNI's 3dClustSim. The results were obtained using the WFU Pickatlas tool in Matlab.

Figure 1. Cue-induced alcohol craving task



CAS-A Questionnaire

5 Factors:

1. ***only aware in hindsight*** (Fac1)
2. ***no deliberate decision*** (Fac2)
3. ***contrary to intention*** (Fac3)
4. ***no perception*** (Fac4)
5. ***no control*** (Fac5)

2 General Factors:

1. ***unaware*** (g-Factor 1): Fac1, Fac4, Fac5
2. ***nonvolitional*** (g-Factor 2): Fac2, Fac3

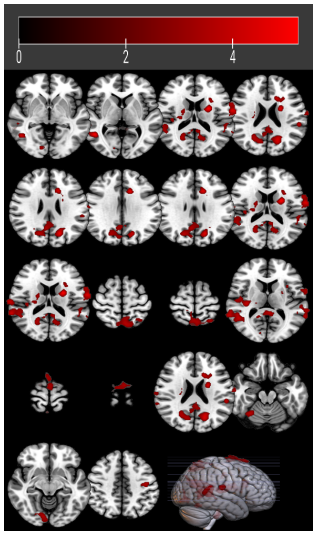
RESULTS

Table 1. Correlation of whole-brain activity with CAS-A

CAS-A	Description	Corr.	Clusters	Peak coordinates	Areas
Factor 1	only aware in hindsight	**neg.**	2	-32, -86, 24	L middle/superior occipital gyrus
				2, -6, 50	R/L SMA, R/ **L middle cingulum** (BA31)
Factor 2	no deliberate decision	no significant results			
Factor 3	contrary to intention	**pos.**	2	22, 20, 4	**R caudate**, R putamen
				-16, 36, 10	**L caudate**, L putamen, L pallidum
Factor 4	no perception	no significant results			
Factor 5	no control	**pos.**	1	-16, 36, 10	mostly white matter (94%), small portions of L caudate, putamen, and **dACC**
gFactor 1	unaware	**pos.**	1	-16, 36, 10	similar to Fac 5, but less white matter (82%) and more **L caudate** (24%)
		neg.	2	-32, -86, 24	L middle/superior occipital gyrus
				2, -6, 50	R/L SMA, R/ **L middle cingulum** (BA31)
gFactor 2	nonvolitional	no significant results			

Multiple regression, covariate age, N = 41 (p<0.005, 357 voxels)

Figure 2. Increased connectivity with the Inferior Frontal Gyrus



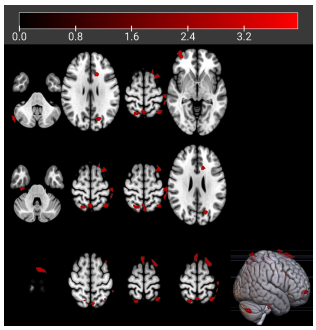
Side	Lobe	Brain regions	Cluster size	MNI coordinates x y z	tmax
Right	Temporal Lobe	Temporal_Mid_R Temporal_Sup_R	998	46 -56 0	5,366
Left	Frontal Lobe	**Putamen_L** **Caudate_L**	193	-22 -2 16	5,2819
Left & Right	Limbic Lobe Parietal Lobe Occipital Lobe Temporal Lobe Sub-lobar	Precuneus_R Cuneus_R Cuneus_L Cingulum_Post_L Precuneus_L Occipital_Sup_L Cingulum_Post_R	1424	-18 -68 26	4,8593
Left	Frontal Lobe Sub-lobar Limbic Lobe	Insula_L Cingulum_Ant_L	274	-14 18 28	4,7834
Left	Frontal Lobe Parietal Lobe Temporal Lobe	Postcentral_L Temporal_Sup_L	320	-64 -6 16	4,5335
Right	Parietal Lobe Temporal Lobe	SupraMarginal_R Temporal_Sup_R	149	66 -20 16	4,0838
Left & Right	Parietal Lobe Frontal Lobe	Precuneus_L Precuneus_R Parietal_Sup_L	789	-4 -62 64	4,0548
Left & Right	Frontal Lobe	**Supp_Motor_Area_L** Supp_Motor_Area_R	429	-4 -2 76	3,7768

Alcohol vs. neutral, p<0.005, uncorrected, extent voxel threshold: 99

Whole-brain PPI analyses

PPI analyses during the alcohol versus neutral condition were performed. The regions of interest (ROIs) analyzed included the dorsal and ventral striatum, the anterior, posterior and bilateral insula, the angular gyrus, the left and right middle cingulum, the left and right superior occipital gyri, the inferior frontal gyrus (IFG) and the right and left supplementary motor areas (SMA). Only the IFG (Figure 2) and the left SMA (Figure 3) significantly correlated with other voxels (p<0.005).

Figure 3. Increased connectivity with the Left Supplementary Motor Area



Side	Lobe	Brain regions	Cluster size	MNI coordinates x y z	tmax
Left	Limbic Lobe Frontal Lobe	**Cingulum_Mid_L** **Cingulum_Ant_L**	68	-14 20 28	3,7687
Left	Parietal Lobe	Postcentral_L	82	-48 -40 66	3,6211
Right	Frontal Lobe	Frontal_Mid_Orb_R Frontal_Mid_R	110	44 62 -4	3,4985
Right	Limbic Lobe Temporal Lobe	Fusiform_R ParaHippocampal_R	64	34 -22 -34	3,4511
Left	Parietal Lobe	Parietal_Sup_L	94	-34 -58 66	3,3951
Left	Frontal Lobe	Frontal_Mid_L Frontal_Sup_L	144	-36 18 64	3,3828
Left	Occipital Lobe Parietal Lobe Temporal Lobe	Occipital_Sup_L Cuneus_L **Precuneus_L**	59	-20 -72 26	3,3631
Right	Parietal Lobe	Parietal_Sup_R **Precuneus_R**	116	20 -60 68	3,117

Alcohol vs. neutral, p<0.005, uncorrected, extent voxel threshold: 51

DISCUSSION

In this study, we validated the CAS-A questionnaire on a neural basis as a tool for assessing components of automated craving. Lower activity in the middle cingulum and motor areas correlated with high 'unaware' scores, suggesting that abstainers have poor response inhibition after seeing alcohol-associated stimuli. A positive correlation between the CAS-A factor 'unaware' and the activity in the dorsal striatum indicates that in these users, habit responding is less inhibited, and hence they require more top-down control over their drinking behavior. The PPI results revealed strong coupling between the IFG and temporal, parietal and limbic regions during visual alcohol stimuli presentation, indicating potential top-down inhibitory control from the IFG to these regions. The SMA showed strong coupling with frontal regions, suggesting that, in users, the SMA is under tight inhibitory control from frontal areas, due to an increased need for response inhibition. Moreover, the correlation between the SMA and parietal areas, especially the precuneus, which is involved in attention switches, might point to an increased attention allocation to alcohol-related stimuli. Our findings, including subjective craving scores and neural imaging data, show that prolonged drinking results in automated craving. These patients could potentially benefit from additional treatment strategies, such as cognitive behavioral therapy, where the patient learns to avoid automated initiation of alcohol consumption.

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