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Neural correlates of visual attention in alcohol use disorder

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ABSTRACT

Numerous studies have documented cognitive impairments in multiple domains in patients with an alcohol use disorder (AUD), including perceptuomotor, executive, and visuospatial functions. Although the neural underpinnings of cognitive deficits in AUD have been studied extensively, the neural basis of attention deficits in AUD remains relatively unexplored. Here, we investigated neural responses to a visual attention task (VAT) in 19 recently abstinent patients with AUD and 23 healthy control participants (HC) using functional MRI (fMRI). AUD had a mean number of 62 ± 34SD drinks per week and 29 ± 13 years' history of alcohol use. Results show that there were no behavioral differences (accuracy or reaction time) between groups during the VAT. For both groups, the VAT activated brain areas associated with visual attention load (i.e., parietal and prefrontal cortices) and visual processing (i.e., occipital cortex), which is in line with previous reports on the same task in healthy volunteers. Despite similar behavioral performances, AUD participants showed decreased VAT activation in regions of the dorsal and ventral attention networks, including parietal and prefrontal cortices, and in the insula as compared to controls. These findings corroborate differences in attention networks in AUD compared to HC that might underlie attention deficits in AUD, whereas impairments in the insula could reflect a disruption of interoception processing as found in other addictions.

1. Introduction

Alcohol use disorder (AUD) is associated with impairments in multiple functional domains, including cognitive, motivational, and social domains (Freeman et al., 2018; Kopera et al., 2012; Loeber et al., 2010; Pitel et al., 2012; Townshend and Duka, 2003) as well as in motor, visuospatial, and executive functions including working memory, attention control, and response inhibition (Kopera et al., 2012). Prior studies have given evidence of significant recovery of cognitive function with abstinence from alcohol (Fein et al., 2006), even within weeks of abstinence (Mann et al., 1999). Visuospatial deficits and tests of executive function appear to persist longer than other cognitive impairments (Fein et al., 2006; Munro et al., 2000; Sullivan et al., 2000). These cognitive deficits seem to be associated with disrupted brain structure (Harris et al., 2008; Pfefferbaum et al., 2009, 1998; Pitel et al., 2012; Wiers et al., 2015) and function (Kim et al., 2018; Orban et al., 2013; Shokri-Kojori et al., 2017; Wiers et al., 2014), predominantly in the prefrontal cortex (PFC) (Goldstein et al., 2011; Goldstein and Volkow, 2011), and with decreased cortical brain glucose metabolism (Volkow et al., 2017, 2013, 1992).

Attention engages both a dorsal attention network (DAN: including the bilateral intraparietal sulcus and frontal eye fields for top-down voluntary control of attention to stimuli) and a ventral attention network (VAN: including the temporoparietal junction and the ventral frontal cortex for detecting unattended or unexpected stimuli and shifting attention) (Corbetta and Shulman, 2002; Vossel et al., 2014). Attention is also associated with deactivation in regions of the default-mode network (DMN), which disengages during purposeful cognitive tasks (Raichle, 2015). Unexpected salient stimuli can activate the VAN (Corbetta and Shulman, 2002) and shift attention, leading to distractions when performing a task (Corbetta and Shulman, 2002; Raichle, 2015). The effect of chronic alcohol use on attention networks is understudied. During functional MRI (fMRI) of attention-demanding inhibitory tasks, AUD participants showed disrupted brain activation in parietal cortex and PFC (Ahmadi et al., 2013; Norman et al., 2011; Oscar-Berman and Marinkovic, 2007; Zahr et al., 2017), and

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adolescents with a high risk of developing AUD showed decreased activation in frontal and parietal regions in similar attention-demanding fMRI tasks (Rangaswamy et al., 2004).

Here, we studied fMRI activation in AUD participants and healthy controls (HC) using a visual attention task (VAT) with parametric increases of attentional load that required continuous tracking of moving targets in the visual field (Culham et al., 1998; Jovicich et al., 2001; Tomasi et al., 2007, 2004). Since the VAT requires responding or not responding to moving targets, the task also measures executive components of attention (Posner et al., 1984; Tomasi et al., 2016) and, hence, has similarities with cognitive control tasks such as the go/no-go and stop signal task (SST) (Ahmadi et al., 2013 and Li et al., 2009). We hypothesize that AUD participants compared to HC have poorer performance accuracy as well as disrupted activation in parietal and frontal brain areas involved in orienting attention and executive control during the VAT.

2. Methods

2.1. Participants

Nineteen participants with AUD and 23 HC completed the study. All participants gave written informed consent to participate in the study 14-AA-0192 that was approved by the Institutional Review Board at the NIH. Participants were medically screened to exclude for ferromagnetic implants, major medical problems, chronic use of psychoactive medications, or head trauma. Participants were also excluded if they met criteria for current psychiatric or neurological diagnoses (apart from AUD) or past psychiatric diagnoses that required medication treatment for more than 1 month as assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-5) (First et al., 2015, 2002). AUD participants met DSM-IV criteria for alcohol dependence or DSM-5 criteria for moderate or severe AUD, consumed at least 15 alcoholic drinks per week (mean = 62.1 ± 34.3SD drinks per week, range 17–117), and had at least a 5-year history of heavy drinking (i.e., binge drinking on 5 or more days in the past month) (mean = 20.1 ± 10.5, range 6–39 years). Patients were recently abstinent from alcohol– MRI was completed within 2 weeks of their last alcoholic drink, except for one patient who completed MRI 21 days after the last drinking day (see Table 1 for demographics and clinical characteristics). HC participants were either light drinkers who consumed less than 15 alcoholic drinks per week (mean = 0.9 ± 1.5 drinks per week, range 0–5) and who did not have a six-month history of binge drinking (4 drinks for women and 5 drinks for men on one occasion) or non-drinkers. On the screening day, participants completed the Timeline Followback (TLFB) to assess daily alcohol consumption in the 90 days prior to the study (Sobell and Sobell, 1996, 1992), the Lifetime Drinking History (LDH) to assess lifetime alcohol consumption (Koenig et al., 2009), the Wechsler Abbreviated Scale of Intelligence (WASI-II) subtests Matrix Reasoning and Vocabulary as a proxy for general intelligence (Wechsler, 1999), the Spielberger State–Trait Anxiety Inventory (STAI; Spielberger, 2010), and the Beck Depression Inventory (BDI; Beck et al., 1996). Participants were free of psychoactive medications within 24 h of study procedures (an exception was made for 5 AUD participants who received benzodiazepines during the first two to four days of detoxification to control withdrawal) and tested negative on an alcohol breathalyzer test and urine tests for drug screening and pregnancy (for women). Brain structural data from the same cohort of AUD patients were recently reported in Kim et al. (2018), indicating no group differences in overall brain gray matter volume.

Table 1
Demographics and clinical characteristics (mean ± SD) of AUD participants and healthy controls. Abbreviations - AUD: Alcohol Use Disorder, HC: Healthy Control. STAI: State-Trait Anxiety Interview, BDI: Beck Depression Inventory. IQ assessed using WASI 2-Scale, drinking assessed using TLFB: Timeline Followback Interview.

	AUD (n = 19)	HC (n = 23)	*p*-value*
Gender	5f 14 m	10f 13 m	.25
Mean Age	47.1 ± 9.9	46.7 ± 8.1	.89
Years of Education	12.2[a] ± 3.0	15.8 ± 2.7	< .001
Mean IQ	89.8 ± 17.0	101.6 ± 17.1	.031
Total drinks in past 90 days (TLFB)	798.3 ± 441.4	11.3 ± 19.7	< .001
Drinking Days in past 90 days (TLFB)	76.8 ± 18.9	6.3 ± 9.2	< .001
Drinks per drinking day in past 90 days (TLFB)	11.7 ± 9.7	0.8 ± 1.0	< .001
Drinks per week (TLFB)	62.1 ± 34.3	0.9 ± 1.5	< .001
Total drinking years (LDH)	29.5 ± 13.4	18.5 ± 15.2	.019
Heavy drinking years	20.1 ± 10.5		
ADS	14.6 ± 9.1	0.4 ± 0.8	< .001
STAI Trait	38.9 ± 11.9	28.4 ± 8.1	< .01
BDI	7.8 ± 10.2	1.4 ± 1.8	< .01

* p-values are from two sample *t*-test or $\chi 2$ test.
[a] n = 18.

2.2. Visual attention paradigm

Participants performed a blocked non-verbal VAT that involved alternating blocks of tracking moving targets or fixating on a cross (Culham et al., 1998; Jovicich et al., 2001; Tomasi et al., 2007, 2006, 2004). "TRACK" epochs were composed of five 12-second-long periods (See Fig. 1) in which the target balls (2, 3, or 4 out of 10 balls) were initially highlighted. One second after the highlight disappeared, all the balls started moving randomly across the screen. Participants were asked to mentally track the moving targets while fixating on a cross at the center of the visual field. Once the all the balls stopped moving, a new set of targets was highlighted for 0.5 s. Participants were instructed to press a button if these balls matched the original set of targets. After a 1 s response window, the original target set was re-highlighted for 0.5 s to re-focus participants' attention and the balls began to move again. During the "DO NOT TRACK" epochs, the 10 balls moved and stopped in the same manner as the "TRACK" epochs, but no balls were highlighted; during this condition, participants were instructed to fixate on the center cross and ignore the moving balls. This condition was used to control for the confounding effect of visual input activation. All subjects performed 3 runs of the VAT (2-, 3- and 4-ball tracking), each one comprising 3 "TRACK" and 3 "DO NOT TRACK" epochs and lasting 6 min. The stimuli were presented to the subjects on MRI-compatible goggles (VisuaStim Digital; Resonance Technology Inc., Northridge, CA) connected to a personal computer synchronized with the MR acquisition using an MRI trigger pulse. Button press responses were recorded with the Lumina response pad LSC-400 (Cedrus Co., San Pedro, CA). Performance accuracy was obtained as the difference between hits and false alarms. All participants completed a training session of a shortened version of the VAT to ensure task comprehension and performance > 70% outside the scanner.

2.3. Functional MRI acquisition

Participants underwent MRI on a 3 T Magnetom Prisma scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) equipped with a 20-channel head coil. T1-weighted 3D magnetization-prepared gradient-echo (Mugler and Brookeman, 1990) (MP-RAGE, TR/TE = 2200/4.25 ms; FA = 9°, 1 mm isotropic resolution) and T2-weighted spin-echo multi-slice (TR/TE = 8000/72 ms; 1.1 mm in-plane resolution; 94 slices, 1.7-mm slice thickness; matrix = 192) pulse sequences were used to acquire high-resolution anatomical brain images, which were assessed by a radiologist to rule out brain abnormalities. A standard echo-planar imaging (EPI) sequence with interleaved slice acquisition (TR/TE = 1500/30 ms, flip angle = 70°, 64 × 64 matrix, 36 slices, slice thickness 4 mm, voxel dimensions $3 \times 3 \times 4\,mm^3$, field of view

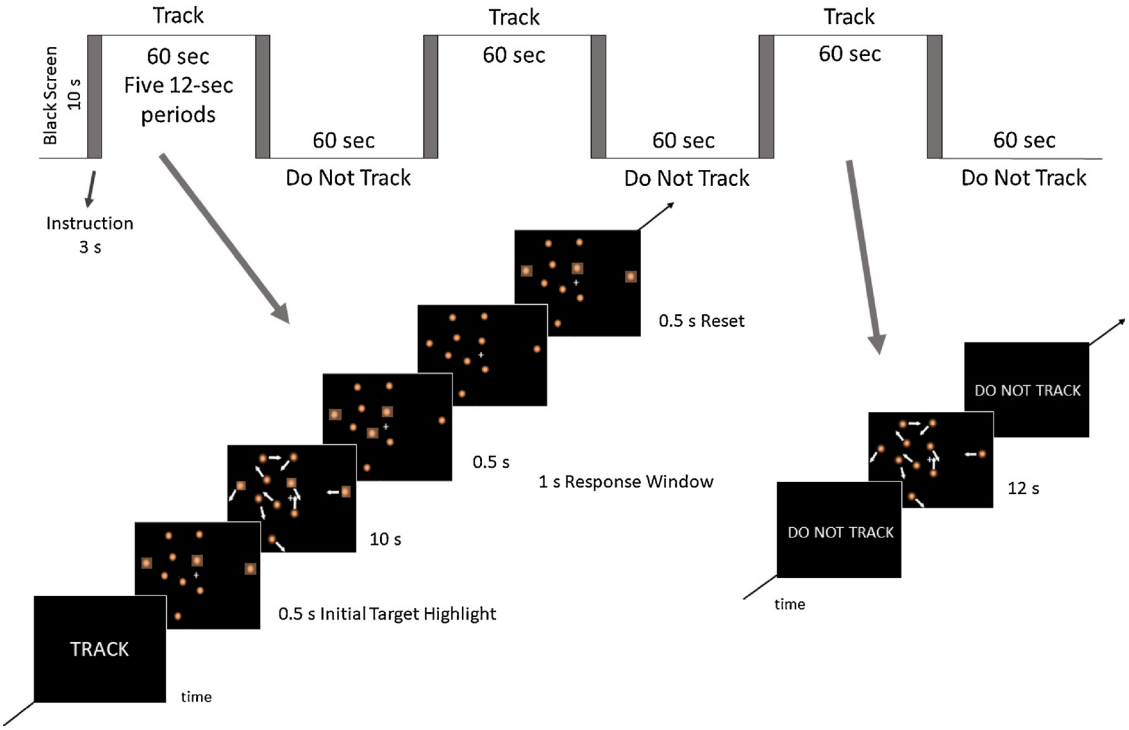

Fig. 1. Visual Attention Task. Example trial for the VAT based on (Tomasi et al., 2007, 2006, 2004). The task consisted of three 1-min long "TRACK" and three "DO NOT TRACK" epochs for each 2-, 3-, and 4-ball tracking. The figure also shows an example of two 12-s periods within a 3-ball tracking epoch.

192 × 192 mm^2) was used to record blood-oxygen level dependent (BOLD) responses in the brain. Padding was used to minimize head motion. Only scans with head motion less than 1-mm translations and 1°-rotations were included in the analysis (Tomasi et al., 2007).

2.4. Data processing

The first four volumes in the time series were discarded to avoid non-equilibrium effects in the fMRI signal. We used the minimal pre-processing pipelines (Glasser et al., 2013) of the Human Connectome Project (HCP) for the realignment and spatial normalization of the structural and functional scans to the stereotactic space of the Montreal Neurological Institute (MNI). Spatial smoothing was carried with the statistical parametric mapping software version 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK) using a 6 mm full width at half-maximum Gaussian kernel.

2.5. Statistical analysis

A 2-way analysis of variance (ANOVA) was used to assess statistical effects of group (AUD and HC) and load (2-, 3-, and 4-ball targets) on reaction time and accuracy using SPSS version 25. For fMRI, first-level voxel-wise analyses, carried out with the general linear model in SPM8, were used to estimate brain activation responses to the VAT for each fMRI run and subject. We used a blocked analysis based on a box-car design convolved with the canonical hemodynamic response function (HRF) and low-pass and high-pass (cut-off frequency: 1/256 Hz) filters. Second-level voxel-wise analyses were performed in SPM8 using a mixed design ANOVA model with group (AUD and HC) as a between-subject factor and task load (2-, 3-, and 4-ball targets) as a within subject factor. Because AUD participants had lower IQ scores than HC (Table 1), the group comparisons were corrected for IQ scores. Thus, IQ scores were added as a covariate. SPM8 multilinear regression was used to assess the association between VAT activation and accuracy in both groups. Furthermore, we performed exploratory multilinear regression analyses to assess potential associations between VAT activation and depression scores, anxiety scores, and drinking behavior (regressors) within the AUD group only. AUD is frequently comorbid with anxiety and depressive disorders (Craske and Stein, 2016; Sugarman et al., 2017), and through these exploratory analyses we wanted to assess whether VAT effects in AUD were associated with anxiety, depression, and drinking behavior. Brain activation clusters were corrected for multiple comparisons using the continuous random field calculation implemented in SPM8. Statistical significance was set at $p < 0.05$, corrected for multiple comparisons with a family-wise error (FWE), computed using a cluster defining threshold $p < 0.005$ uncorrected and a minimum cluster size of 100 voxels. The AAL atlas in Xjview was used for anatomical labeling of activations.

3. Results

3.1. Demographics and drinking history

Although groups were matched for age, BMI, and gender, HC had higher IQ scores ($t = 2.3$, $p = 0.03$) and more years of education ($t = 3.9$, $p < 0.001$) than AUD participants (see Table 1). AUD participants had a mean 29.5 ± 13.4SD year history of drinking (range 10–63), whereas HC had a mean 18.5 ± 15.2SD year history of drinking (range 0–55) ($p < .001$) (see Table 1). AUD participants also had higher anxiety ($t = 3.4$, $p < 0.002$) and depression scores than HC ($t = 3.1$, $p < 0.005$) (see Table 1).

3.2. Behavioral performance

Behavioral measures from the VAT are presented in Fig. 2. Performance accuracy and reaction times did not differ between groups. Nonetheless, there was a main effect of load ($F_{2,39} = 7.21$, $p = 0.002$): 4-ball tracking had lower accuracy than 2-ball tracking ($t_{41} = 3.17$, $p = 0.003$) or 3-ball tracking ($t_{41} = 3.85$, $p = 0.0004$). There was no difference in accuracy between 2 and 3 targets. There was no effect of load on reaction times. There was no main effect of group or interaction effect of load × group on accuracy or reaction times. There were no

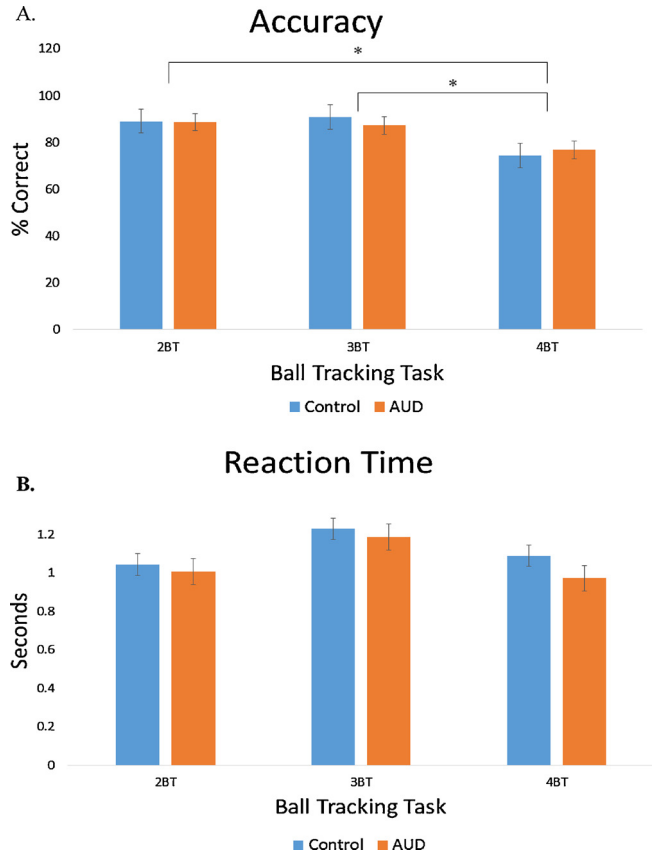

Fig. 2. Average performance accuracy and reaction times during fMRI: A. Participants had lower accuracy in the 4-ball trial compared to both the 3-ball and 2-ball trials. There was no difference in accuracy between 2-ball and 3-ball trials or between the two groups. B. Reaction times were not different between groups or trials. Sample size: 19 AUD participants and 23 controls. Error bars are standard errors.

effects of group on number of hits or false alarms in either condition.

3.3. VAT and fMRI activation and decreases in activation (deactivation)

All three conditions of the VAT produced similar activation and deactivation patterns in both groups (Table 2; Fig. 3A). The VAT activated brain regions of attention networks which included middle (MFG; Brodmann Areas [BA]: 6, 46) and superior (SFG; BA: 8) frontal gyri, precentral gyrus (BA: 6), inferior (IPL; BA: 40) and superior (SPL; BA: 7) parietal lobe, middle occipital gyrus (BA: 19), insula (BA: 48), and subcortical regions including the thalamus and caudate nucleus (Table 2, Fig. 3). The VAT decreased activation (referred to as deactivation) in regions of the DMN including posterior (PCC; BA: 31) and anterior (ACC; BA: 32) cingulate cortex, precuneus (BA: 23 and 31), angular gyrus (BA: 39, 19), postcentral gyrus (BA: 3, 4), superior (BA: 10 and 32) and middle (BA: 9) frontal gyri, precentral gyrus (BA: 6), insula and rolandic operculum (BA: 48), and superior temporal gyrus (Table 2, Fig. 3). This pattern of increases in activation and decreases in activation (deactivation) is in agreement with previous studies with the VAT (Tomasi et al., 2007, 2006, 2004). VAT-evoked activations were also mapped on DAN and VAN activation networks, based on DAN and VAN coordinates reported in Fox et al. (2006) (Fig. 3).

3.4. AUD < HC

Voxel-wise ANOVA revealed an effect of group such that VAT activation in parietal (IPL, SPL and angular gyrus) areas was lower in AUD than HC ($p_{FWE} < 0.05$) and largely driven by group differences in the 3-ball condition (Fig. 4). AUD participants also had lower activation in frontal (middle and inferior frontal gyri) areas of the DAN and VAN and insula compared to HC ($p_{FWE} < 0.05$) (see Table 2).

Table 2
Location of major areas of brain activation and deactivation in MNI space and statistical significance of BOLD responses and their association with performance accuracy in these regions at $p < 0.005$ uncorrected, $p < 0.5$ FWE, cluster size > 100.

Brain Region	BA	Peak MNI Coordinates (*x, y, z*)			Cluster size	*t*-value
1. Activation on 2, 3, and 4 ball trials						
Precentral Gyrus, Middle Frontal Gyrus, Superior Frontal Gyrus	6, 8	32	−4	50	4965	19.09
Inferior Parietal Lobule, Superior Parietal Lobule, Middle Occipital Cortex	40, 7, 19	−32	−54	52	14,932	18.19
Middle Frontal Gyrus, Precentral Gyrus	6	−26	−8	52	2394	17.34
Insula	48	−36	16	6	604	14.24
Thalamus, Caudate		16	−22	14	524	10.92
Thalamus		−16	−18	18	646	10.07
Posterior Cingulate Cortex	23	−2	−26	28	187	9.32
2. Deactivation on 2, 3, and 4 ball trials						
PCC, Precuneus	31, 23	−8	−46	34	1922	9.17
Superior Medial Frontal Gyrus, ACC	10, 32	−8	54	0	631	7.51
Rolandic Operculum, Insula	48	38	−16	18	294	7.39
Angular Gyrus	39, 19	−48	−70	34	187	5.76
Insula	48	−38	−14	16	188	5.30
Postcentral Gyrus	4, 3	−52	−16	48	130	5.23
Rolandic Operculum, Superior Temporal Gyrus	48	−54	−6	8	193	5.07
Postcentral Gyrus, Precentral Gyrus	6, 4	32	−28	64	251	4.58
Superior Frontal Gyrus, Middle Frontal Gyrus	32, 9	−18	34	40	125	4.55
3. AUD < HC (corrected for IQ)						
Inferior Parietal Lobule	40, 46	46	−44	52	300	4.43
Insula	47, 48	38	24	4	313	4.38
Middle Frontal Gyrus, Inferior Frontal Gyrus	48, 45	40	32	20	302	4.24
4. Positive Correlation with Accuracy on 2, 3, and 4 ball trials						
Precentral Gyrus	6	28	−10	56	338	4.42
Superior Frontal Gyrus, Supplementary Motor Area, Middle Frontal Gyrus	6	−22	−6	66	200	4.23*

* $p = 0.058$ FWE.

3.5. Effect of attentional load

The parametric analysis did not reveal a significant effect of load (number of tracked targets) on BOLD responses at $p_{FWE} < 0.05$. However, there was an effect of load on BOLD signals in parietal (SPL) and occipital regions (middle occipital and lingual gyri) at a more liberal threshold of $p < 0.005$ uncorrected $k > 100$ (See supplementary Table), which is in agreement with previous VAT studies (Tomasi et al., 2007, 2004).

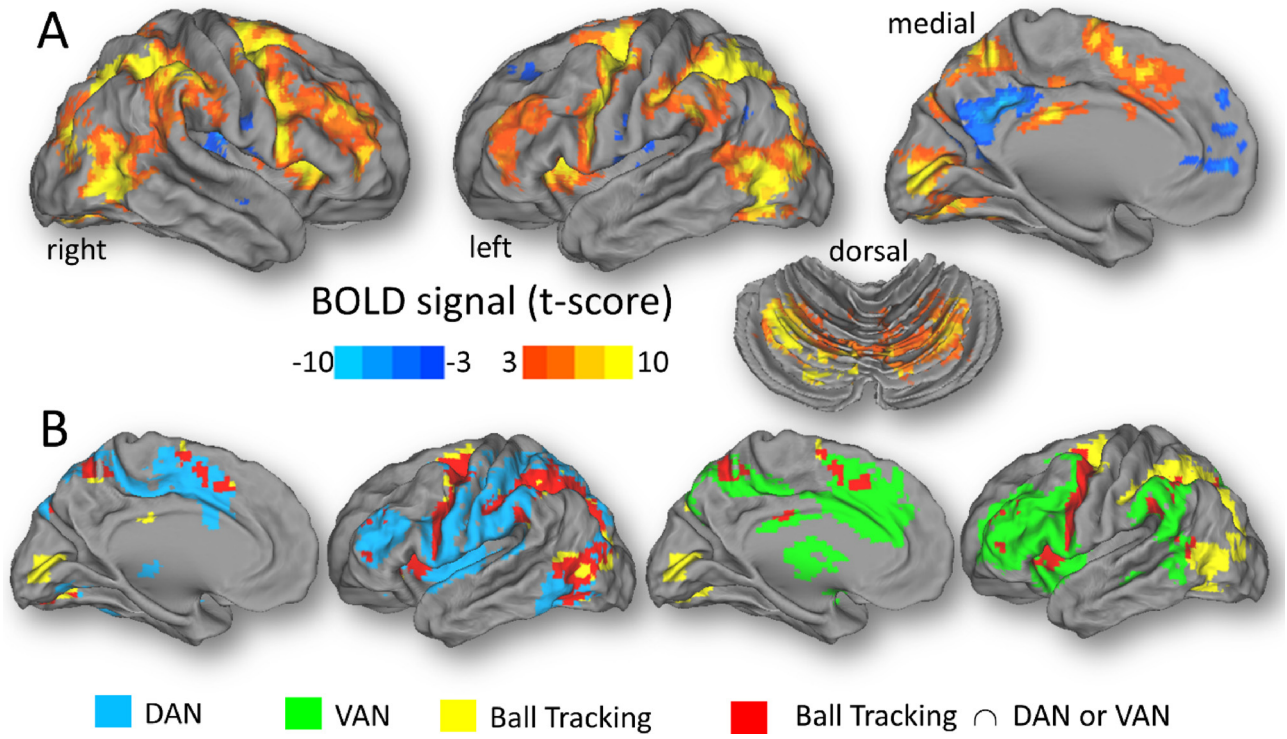

Fig. 3. Panel A: Statistical maps of the average BOLD signal across conditions (2-, 3-, and 4-ball tracking tasks) for 19 AUD participants and 23 controls, superimposed on the cerebral surface of the PALS_B12 template. Panel B: VAT-evoked activations for 19 AUD participants and 23 controls mapped on DAN and VAN activation networks, based on DAN and VAN coordinates reported in Fox et al., 2006.

3.6. Correlation between behavioral and clinical measures and fMRI activation

The voxel-wise regression revealed significant correlations between subjects' performance accuracy and VAT activation in frontal regions (precentral gyrus, SFG, MFG, and supplementary motor area; $p_{FWE} < 0.005$) such that greater accuracy in each trial was correlated with greater activation in these areas (Table 2). The analysis, however, did not reveal any group differences in brain activation associated with performance accuracy. The analysis also revealed no significant correlations between reaction time and activation during the VAT. Within the AUD group, there were no significant correlations between activation/deactivation during the VAT and depression and anxiety scores or with drinking behavior (i.e., heavy drinking years, total drinking years, or number of drinks per week).

4. Discussion

Here we find decreased activation in parietal and frontal cortical regions during a VAT in AUD versus HC despite no differences in behavioral performance. This pattern of lower activation in AUD in prefrontal (especially the IFG) and parietal regions is congruent with findings in previous fMRI studies of cognitive control tasks (Ahmadi et al., 2013; Gan et al., 2014; Li et al., 2009). Similar to our findings, Ahmadi et al. (2013) and Li et al. (2009) found decreased activation in AUD during a go/no-go task in parietal and frontal areas despite no group differences in reaction time. Lower activation in parietal and frontal regions during a go/no-go task may be a vulnerability for AUD as suggested by an fMRI study of adolescents who would subsequently transition to heavy drinking who showed lower task-induced activation in IPL, SPL, and frontal regions when compared to adolescents who did not transition to heavy drinking (Norman et al., 2011). Additionally, our findings extend previous electroencephalography (EEG) and fMRI studies with a visual oddball task. In the EEG study, despite no differences in behavioral task performance, abstinent AUD participants had reduced evoked theta power, which is a putative marker for genetic vulnerability to AUD (Gilmore and Fein, 2012). In an fMRI study with adolescents performing the visual oddball task, adolescents with a higher genetic risk for developing AUD had lower activation in the IPL and IFG compared to adolescents with a lower risk for developing AUD (Rangaswamy et al., 2004).

We also found decreased activation in the insula during the VAT in AUD versus HC participants. The insula is implicated as a hub of interoception, or the sense associated with the integration of body-relevant signals and external stimuli to influence ongoing motivated behavior (Paulus and Stewart, 2014). Previous neuroimaging studies with individuals with substance use disorder show that the insula is hypoactive during cognitive control processes (Courtney et al., 2013; Paulus and Stewart, 2014; Sullivan et al., 2013). Specifically, neuroimaging studies have shown altered connectivity between the insula and frontoparietal control networks in participants with AUD during resting state (Sullivan et al., 2013) and inhibitory control processes during a Stop-Signal Task (SST) (Courtney et al., 2013); furthermore, Sullivan et al., using fMRI, showed decreased perfusion to the insula during resting state and a spatial working memory task (2013). As such, our findings suggest that AUD is associated with impairments in the function of the insula that may contribute to deficits in interoception processing.

Previous structural MRI studies in AUD also revealed lower gray matter density and volume in the IFG and insula (Mechtcheriakov et al., 2007; Wiers et al., 2015), which correspond to regions where we found decreased activation in AUD. These studies along with our findings corroborate the involvement of the PFC in addiction, for which its disruption has been associated with impairment in self-regulation and salience attribution and with a risk for AUD or other addictions (Goldstein et al., 2011; Goldstein and Volkow, 2011; Müller-Oehring and Schulte, 2014; Parvaz et al., 2011; Zahr et al., 2017). Nonetheless, our study is the first to use a VAT in AUD participants in an fMRI

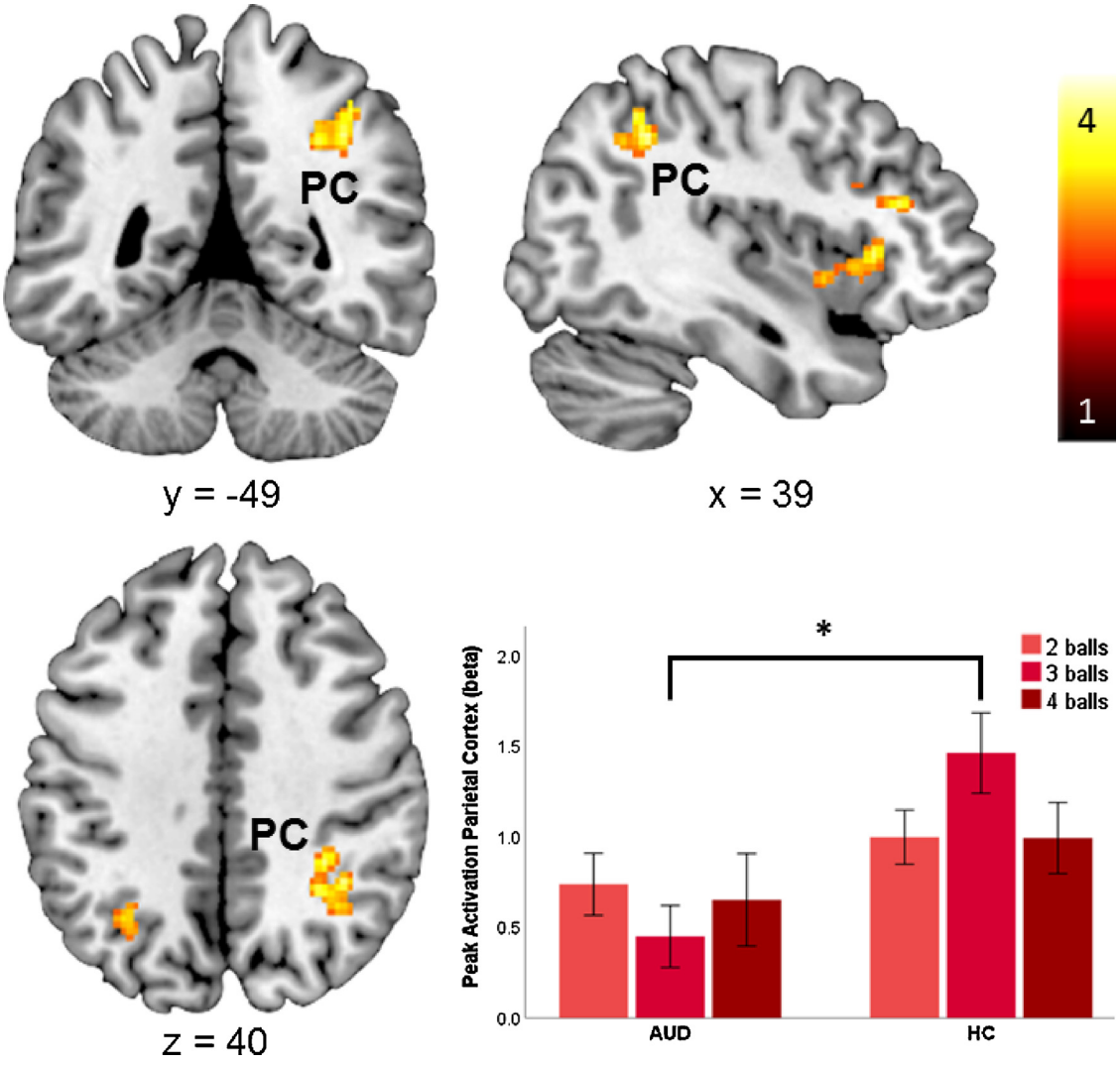

Fig. 4. Statistical group differences in VA activation: The statistical maps show brain areas that had lower VA activation in AUD (n = 19) compared to HC (n = 23) ($p_{FWE} < .05$). The colored bar shows the T-score window. The bar plot shows the average BOLD signal for each condition (2-, 3-, and 4-ball tracking) and group (AUD and HC) at the coordinates of peak group differences in VA activation in the parietal cortex ($p_{FWE} < .05$). Group differences in the parietal cortex were largely driven by activation in the 3-ball condition.

setting, which is important in light of previous findings that revealed alcohol's deleterious effects on selective attention and processing of goal-relevant information (Müller-Oehring and Schulte, 2014; Zahr et al., 2017).

Overall, activation patterns during the VAT were in line with previous studies with this task in healthy volunteers (Culham et al., 1998; Jovicich et al., 2001; Tomasi et al., 2007, 2006, 2004). These findings indicate that despite the lower frontal and parietal activation in AUD participants, the task consistently activated both a dorsal goal-directed attentional network (DAN) involving the IPL and SFG as well as a ventral signal detection attentional network (VAN) involving the temporoparietal cortex and IFG (Corbetta et al., 2008; Corbetta and Shulman, 2002). Unlike previous studies with the VAT (Tomasi et al., 2004), we found a positive correlation between performance accuracy and activation in frontal regions. This finding was not driven by group differences in AUD versus HC, since accuracy did not differ between groups (Fig. 2), and there were no group differences in the association of accuracy with activation in frontal regions. This, nevertheless, reflects that worse task performance was associated with lower frontal activation.

Previous studies with healthy volunteers have shown that abnormalities in the insula and PFC were associated with insight and behavioral control (Parvaz et al., 2011); furthermore, one fMRI study showed that difficulty in stopping during the stop-signal task (SST) was associated with greater activation in the IFG and insula (Hughes et al., 2013). Additionally, inhibition in the SST has been shown to be disrupted in people with damage to the right IFG (Aron et al., 2003), and in AUD patients IFG gray volume losses correlated negatively with response times on SST (Wiers et al., 2016).

Despite our hypothesis, we found no group differences in behavioral performance on the VAT. Previous studies found impairments in patients with AUD on attentional tasks including attentional set shifting (e.g., Wisconsin Card Sorting Test; Kopera et al., 2012; Ratti et al., 2002). Moreover, fMRI studies of attention-demanding tasks found disrupted brain activation in parietal cortex and PFC in AUD (Ahmadi et al., 2013; Goldstein and Volkow, 2011; Norman et al., 2011; Oscar-Berman and Marinkovic, 2007; Zahr et al., 2017) and often also found no behavioral group differences on the attentional task used for fMRI (e.g., Norman et al., 2011). The lack of effect on behavior may be due to the small sample size of our study. Thus, we see our results as exploratory and preliminary and in need of replication. Our study is the first to investigate the neural underpinnings of attention deficits on VAT in AUD, and further research is necessary to parse the specific effects of AUD on attention. As such, future studies should investigate attention

impairments in AUD participants both inside and outside a scanning environment. Additionally, future studies should investigate whether AUD and HC participants display differences in connectivity between nodes of the DAN and VAN and whether these differences are related to the duration and severity of AUD.

Limitations of our study include, first, that our findings show that the insula and IFG are disrupted in AUD but do not reveal whether this preceded AUD and might be a vulnerability factor or whether they reflect an outcome of AUD. Thus, future studies should investigate whether these disruptions are present before the onset of AUD or only appear afterwards. Moreover, our sample groups were not matched for IQ or years of education, which is why we added IQ as the most recent measure of intelligence as a covariate to our analyses. Anxiety and depression scores were higher in AUD than HC. However, these measures were not associated with VAT activation and thus are unlikely to contribute to our group findings. Furthermore, 5 out of 19 patients were prescribed benzodiazepines to treat their withdrawal symptoms in the days preceding the MRI scan, which may have influenced the results. In addition, our findings are limited because our AUD sample included only 5 females (26%), whereas there were 10 females in the HC sample (43%). Although the gender imbalance was statistically non-significant and may be representative of gender distributions observed in AUD (since women are less likely to develop AUD), this may have introduced a sampling bias in our study, since women who develop AUD tend to have more medical problems than AUD males (Erol and Karpyak, 2015), and we excluded participants with a history of major medical problems besides AUD. Nonetheless, we found no gender effects on BOLD responses during the VAT.

In conclusion, our study found that despite similar behavioral performance on a VAT and significant differences in years of education and IQ, AUD participants had decreased BOLD responses to a VAT in IPL, SPL, IFG, MFG, and insula. Our study is the first to investigate the changes in neural correlates of attention deficits in AUD. Our findings contribute specifically to previous literature on cognitive impairments seen in AUD in that we use an fMRI task that primarily engages attention networks and allows isolated investigation of neural signatures of attention in AUD. Our findings suggest lower brain activation in areas involved in dorsal and ventral attention networks in AUD that might underlie attentional deficits reported in AUD.

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Nothing declared.

Contributors

All authors contributed to the design and interpretation of the work. AZ, EL, CEW, CF, GM, VR, LT, and GJW collected MRI and behavioral data; AZ, EL, CEW, ESK, DT, and NDV analyzed MRI and behavioral data. AZ, EL, CEW, DT, and NDV drafted the manuscript, and all authors provided critical revisions for important intellectual content for the final version. All authors agreed to be accountable for all aspects of the work, and all authors have approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.10.032.

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