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Elevated thalamic glutamate levels and reduced water diffusivity in alcohol use disorder: Association with impulsivity

Corinde E. Wiers, PhD[1,*], **Samantha I. Cunningham, PhD**[1,*], **Dardo G. Tomasi, PhD**[1], **Thomas Ernst, PhD**[3,4], **Linda Chang, MD**[3,4,5], **Ehsan Shokri-Kojori, PhD**[1], **Gene-Jack Wang, MD**[1], **Nora D. Volkow, MD**[1,2]

[1]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA

[2]National Institute on Drug Abuse, Bethesda, MD, USA

[3]Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

[4]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD. USA

[5]Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Alcohol induces neuroinflammation but its role in cognitive impairment and impulsivity in alcohol use disorder (AUD) has been poorly investigated. We used proton magnetic resonance spectroscopy to measure brain glutamate levels and diffusion-weighted imaging to measure functional anisotropy (FA) in the thalamus and ventral anterior cingulate cortex (vACC) in 15 recently detoxified patients with AUD and 14 matched controls. Compared to controls, AUD patients showed higher glutamate levels (p=0.04) and lower FA in the thalamus (p=0.04) but not in the vACC. In AUD, thalamic glutamate levels (r=0.62, p=0.019) and FA (r=−0.55, p=0.034) were associated with severity of drinking (drinks/week). Compared to controls, AUD patients showed higher scores on Conners' Adult ADHD Rating Scale for impulsivity (p=0.03), which correlated with glutamate levels in the thalamus (r=0.58, p=0.03) and vACC (r=0.55, p=0.036). In a second cohort of AUD patients (n=32), Glu in dorsal ACC (dACC) also correlated with Barrett Impulsiveness Scale total score (r=.43, p=0.014). We interpret the elevated thalamic glutamate levels and the parallel reduction in FA in AUD—which correlated with drinking severity

Correspondence: Corinde E. Wiers, Ph.D. 10 Center Dr, Rm B2L124, Bethesda, MD 20892-1013, Phone: 301 451-3021, corinde.wiers@nih.gov, Nora D. Volkow, MD, 6001 Executive Boulevard, Bethesda, MD 20892, Phone: 301 443-6540, nvolkow@nida.nih.gov.

*Authors contributed equally

Contributors

CEW, SIC, DGT, TE, LC, ESK, GJW and NDV were responsible for study concept and design. CEW and GJW managed data acquisition. SIC, CEW, DGT, TE, LC and ESK analyzed data. CEW, SIC and NDV drafted the manuscript. All authors criticially reviewed content, approved the final version for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

All authors declare they have no competing interests.

—as possible evidence of neurotoxicity from neuroinflammation. The association of Glu with impulsivity suggests that neurotoxic effects of chronic alcohol exposure in the thalamus and dACC may contribute to impulsivity.

Keywords

Inflammation; neurotoxicity; withdrawal; abstinence; neuroimaging

1. Introduction

Alcohol use disorder (AUD) is associated with impairments in multiple cognitive domains, including response inhibition and impulsivity (Freeman et al., 2018; Goldstein et al., 2001; Kopera et al., 2012; Loeber et al., 2010; Zehra et al., 2019). These cognitive deficits in AUD have been associated with alterations in brain structure (Gropper et al., 2016; Pfefferbaum et al., 2009; Tomasi et al., 2019; Wiers et al., 2015) and function (Kim et al., 2018; Shokri-Kojori et al., 2017; Volkow et al., 2017).

AUD affects several neurotransmitter systems, including dopamine (Volkow et al., 2006; Volkow et al., 1996), GABA, and glutamate (Glu) (Hillmer et al., 2015; Prisciandaro et al., 2019). In animal models of alcohol dependence, microdialysis studies reported elevated brain Glu in various brain regions including the cortex and thalamus (Fliegel et al., 2013), with greater increases during acute than prolonged alcohol withdrawal. Clinical studies of Glu levels using proton magnetic resonance spectroscopy (^{1}H-MRS) (Hillmer et al., 2015) have generally shown higher Glu (Hermann et al., 2012) or glutamate + glutamine (combined: Glx) levels (Yeo et al., 2013) in the anterior cingulate cortex (ACC) of AUD patients studied during withdrawal compared to controls. However, some studies found either no differences (Bauer et al., 2013; Cheng et al., 2018) or lower ACC Glu in AUD patients compared to controls (Mon et al., 2012; Thoma et al., 2011). Interestingly, ACC Glu levels in AUD patients correlated inversely with the number of heavy drinking days in the 14 days preceding the MRS scan (Cheng et al., 2018). Glu changes in other brain regions have been reported in AUD including elevated Glu in the nucleus accumbens (Bauer et al., 2013) and reduced Glx in the occipital cortex (Bagga et al., 2014). Binge drinking in rats induced neuroinflammation (i.e., active microglia) in the hippocampus, which was found to be mediated by elevated extracellular Glu levels (Ward et al., 2009). Nevertheless, administration of N-acetylcysteine (NAC), which restores glutamate homestasis in the synapse, was shown to protect against the neuroinflammatory changes from chronic alcohol exposure in rats (Schneider et al., 2017). In humans, elevated Glu levels have been associated with neuroinflammatory markers—such as cytokines and C-reactive protein—in mood disorders (Haroon et al., 2017).

Diffusion MRI has also been used to assess alcohol's effects on the brain (Chen et al., 2017). In healthy individuals, a study using diffusion tensor imaging (DTI) reported that acute alcohol administration reduced mean diffusivity in the frontal lobe, thalamus, and middle cerebellar peduncle (Kong et al., 2012). In non-smoking individuals with AUD, 1-month of abstinence was associated with increased fractional anisotropy (FA) in temporal white

matter and with decreased diffusivity throughout the cortex suggestive of microstructural recovery (Gazdzinski et al., 2010). In treatment-seeking AUD patients, those who resumed heavy drinking showed lower FA and higher diffusivity in the frontal lobes compared to those who maintained abstinence, suggesting that white matter injury increased the risk for relapse (Sorg et al., 2012).

Functional consequences of DTI changes in AUD were shown on an alcohol cue reactivity task (Monnig et al., 2013). Specifically, FA values of nine white matter tracts (including the corpus callosum and cingulate gyrus) in heavy drinkers were inversely correlated with BOLD activation in several brain regions including the thalamus and ACC. These results suggest that impaired white matter integrity in frontoparietal and corticolimbic networks is associated with an individual's frontal lobe function, which would impact their ability to control their alcohol consumption. DTI-based measures have been associated with impulsive behavior in other substance use disorders (SUD). For instance, chronic marijuana smokers exhibited lower FA in frontal white matter compared to non-smokers and this decreased fiber integrity was associated with higher impulsivity (Gruber et al., 2011). Methamphetamine (Meth)-dependent patients similarly displayed high levels of impulsivity that correlated with FA and axial and radial diffusivity in frontal white matter tracts (Uhlmann et al., 2016). In addition, current Meth users had greater impulsivity than past users and their brain microstructural abnormalities differed, which could reflect different stages of neuroinflammation or iron-induced neurodegeneration (Andres et al., 2016).

In the current study, we aimed to assess (1) the effect of chronic alcohol exposure on brain Glu levels in the ACC and thalamus using ^{1}H-MRS and their association with impulsivity, (2) the effect of chronic alcohol exposure on FA using diffusion-weighted imaging (DWI) in the same brain regions, and (3) the association between Glu concentrations and FA in the ACC and thalamus. We hypothesized that, in both brain regions, patients with AUD compared to healthy controls (HC) would show (1) elevated concentrations of Glu which would positively correlate with impulsivity, (2) lower FA, and (3) negative associations between Glu and FA indicating underlying inflammation related to chronic alcohol use.

2. Methods

2.1. Study 1

2.1.1 Participants—Fifteen patients with AUD and 14 HC completed the first study. The two groups did not differ in age, gender proportion, or BMI (Table 1). Patients were screened to exclude major medical, neurological and psychiatric disorders, head trauma with loss of consciousness greater than 30 minutes, chronic use of psychoactive medications, current or past diagnosis of SUD (other than alcohol abuse and/or dependence in the AUD group, or current tobacco smoking in either group) as assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000) or DSM-5 (American Psychiatric Association, 2013), and metallic implants which are contraindicated for MRI. Women were neither pregnant nor breastfeeding and were studied in the mid follicular phase. AUD patients were abstinent from alcohol an average of 3.5 days at the time of the scans (range 1–7 days). All patients had a negative urine drug screen on the days of testing and were free of

psychoactive medications within 24 hours of study procedures (except for benzodiazepines used to relieve withdrawal symptoms in 4 AUD patients). All patients provided written informed consent to participate in the study, which was approved by the Institutional Review Board at the National Institutes of Health (Combined Neurosciences White Panel) and were scanned between June 2015 and April 2017.

On the day of screening, patients completed the Timeline Follow-Back (TLFB) to assess daily alcohol consumption in the 90 days prior to the study (Sobell and Sobell, 1996), the Lifetime Drinking History (LDH) to assess total lifetime alcohol consumption (Skinner and Sheu, 1982), the Alcohol Dependence Scale (ADS) to assess the severity of dependence (Skinner and Allen, 1982), and the Wechsler Abbreviated Scale of Intelligence (WASI-II) subtests Matrix Reasoning and Vocabulary as a proxy for general intelligence (Wechsler, 1999).

Patients completed the Conners Adult ADHD Rating Scale (CAARS) long version as a measure of inattention, hyperactivity and impulsivity (Conners, 1998).

2.1.2 Image Acquisition and Processing

2.1.2.1 MRI: Patients underwent MRI on a 3.0T Magnetom Prisma scanner (Siemens Healthineers USA, Inc., Malvern, PA) equipped with a 20-channel head coil. T1-weighted 3D magnetization-prepared gradient-echo (MP-RAGE, TR/TE = 2200/4.25 ms; FA = 9°, 1 mm isotropic resolution) and T2-weighted multi-slice spin-echo (TR/TE = 8000/72ms; 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.

We used the minimal preprocessing pipelines (Glasser et al., 2013) of the Human Connectome Project (HCP) for the spatial normalization of the structural scans to the stereotactic space of the Montreal Neurological Institute (MNI). Freesurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu) was used to automatically segment the anatomical MRI scans into cortical and subcortical gray matter regions of interest (ROIs). Standard preprocessing steps were adopted in the Freesurfer pipeline (Fischl et al., 2002; Fischl et al., 1999; Ségonne et al., 2004).

2.1.2.2 DWI: Patients also underwent diffusion-weighted imaging (TR/TE = 7.4s/73ms, 2.2 mm isotropic voxels; 70 slices; Field-of-view = 240mm; GRAPPA phase encoding acceleration factor = 2; bandwidth = 2391 Hz/pixel) consisting of 2 runs (PA and AP) each of which contained a total of 45 volumes (3 volumes of b=0, 6 volumes of b = 200, 6 volumes of b = 500, and 30 volumes of b=1100 s/mm^2). Diffusion data were preprocessed in FSL (Jenkinson et al., 2012) and according to Andersson et al., 2003, including: intensity normalization across runs, EPI distortion correction, eddy current and motion correction, and gradient nonlinearity correction. The resulting diffusion images were registered to the MNI152 standard space with 2×2×2mm isotropic resolution. For each ROI, the mean FA value was calculated.

2.1.2.3 ^{1}H-MRS: Localized proton magnetic resonance spectroscopy (^{1}H-MRS) was performed in two ROIs: the ventral ACC (vACC) and thalamus (Fig. 1). Dimensions were

2×2×2cm for the vACC and 3×1.3×2cm for the thalamus. A Point Resolved Spectroscopy (PRESS) pulse sequence (TE/TR=30/3000sec, 64 averages) was used to acquire water-suppressed spectra. The PRESS sequence (TR=10s, 1 average) was also used to collect 7 water-unsuppressed data at different TEs (0.03, 0.05, 0.08, 0.12, 0.20, 0.50, 1.00 s). The water-unsuppressed spectra were used to measure the T2 decay of the water signal and correct the metabolite concentrations for the partial volume of cerebrospinal fluid (Ernst et al., 1993; Kreis et al., 1993). Spectral fitting of the MRS datasets was carried with the LCModel program (Provencher, 1993) to determine absolute and relative metabolite concentrations for Glu and total creatine (tCr). There were no group differences for tCr and absolute Glu measures were used for further analysis. The results from LCModel spectral analysis were inspected for nonrandom residuals as well as baseline fitting and a Cramér–Rao lower bound (CRLBs) of 20% for each individual peak was used as a quality criterion (Provencher, 1993). One Glu spectrum in the vACC (HC participant) and one in the thalamus (AUD patient) did not meet this criterion and were excluded from analyses. The CRLBs for Glu in all participants were between 5–13% (vACC) and 7–19% (thalamus). Additional spectral quality measures included mean±SD signal-to-noise ratio (vACC: 23.9±6.9; thalamus: 12.4±3.9) and full width at half maximum (FWHM) (vACC: 0.07±0.04 ppm; thalamus: 0.09±0.02 ppm).

2.1.3 Statistical Analyses—

There were no >3SD of the mean outliers for Glu, FA or impulsivity measures. All measures were normally distributed as per K-S test (all $p>0.07$). Two-sample t-tests were used to compare Glu concentrations and FA values between healthy controls and AUD patients to test our hypothesis that Glu levels would be elevated and FA reduced in the ACC and thalamus of AUD patients. Pearson's correlations were used to test our hypothesis that Glu levels and FA in the vACC and thalamus would be associated with the CAARS score of impulsivity (with a significance threshold of $p<0.05$). Moreover, within the AUD group, we explored associations between Glu and FA measures with CAARS inattention and restlessness, and with alcohol history measures (i.e., days since last alcohol use, lifetime drinking in kg, and drinks/day).

2.2 Study 2

2.2.1 Participants—

We aimed to study the association between brain Glu and impulsivity in a second replication cohort of n=32 AUD patients, who were scanned between October 2017 and March 2020. Clinical characteristics of the study population can be found in Supplementary Table 1. Exclusion crtieria were the same as reported for the AUD participants in study 1. All patients were treatment-seeking AUD patients undergoing detoxification in the NIAAA treatment center. AUD patients were abstinent from alcohol an average of 4.8 days at the time of the scans (range 1–11 days). All patients had a negative urine drug screen on the days of testing and were free of psychoactive medications within 24 hours of study procedures (except for benzodiazepines used to relieve withdrawal symptoms in n=7 AUD patients). All patients provided written informed consent to participate in the study, which was approved by the Institutional Review Board at the National Institutes of Health (Combined Neurosciences White Panel).

2.2.2 Impulsivity scale—Participants underwent the same study questionnaires as cohort 1, except for the Barrett Impulsiveness Scale (BIS-11; Patton et al., 1995). The BIS-11 consists of 30 items and assesses general impulsivity (total score) as well as the subfactors Attentional, Motor and Nonplanning impulsivity.

2.2.3 ^{1}H-MRS—The same ^{1}H-MRS scanning procedures were used as in study 1. The 2×2×2cm cm voxel was placed in the dorsal ACC (dACC), rather than in the vACC used in study 1 (see Supplementary Figure 1 for voxel position of the dACC).

2.2.4 Statistical Analyses—There were no >3SD of the mean outliers for Glu or BIS-11 impulsivity. We correlated Glu measures with the BIS-11 total score using Pearson's correlations, and post-hoc with the BIS-11 second order factors to explore the contribution of subfactors of impulsivity (i.e., Attentional, Motor and Nonplanning) to variance in Glu. Alpha was set at 0.05

3. Results

3.1 Glu concentrations and impulsivity

3.1.1 Cohort 1—AUD: 8.2±2.1 SD, mean HC: 6.9±1.0 SD; t(26)=2.2, p=0.04) but not in the vACC (p=0.3) (see Fig. 2A). AUD patients had higher scores than controls on the CAARS impulsivity scale (t(26)=2.2, p=0.03). Within the AUD group, Glu levels in thalamus and vACC correlated positively with CAARS impulsivity (r=0.58 p=0.03 and r=0.55 p=0.036) (Fig. 2B). CAARS inattention and hyperactivity/restlessness scores were also higher in AUD patients than HC (Table 1), but did not correlate with Glu measures in the thalamus or vACC.

3.1.2 Cohort 2—In the n=32 AUD patients in cohort 2 Glu concentrations in dACC correlated with BIS-11 total score (r=.43, p=.014; Fig. 2C), which was driven by a significant effect of the subscales Attentional (r=.51, p=0.003) and Motor impulsivity (r=.42, p=.020), but not Nonplanning impulsivity (r=.25, p=.17) (data not shown).

3.2 FA in vACC and thalamus

FA was lower in AUD patients than HC in the thalamus (AUD: 0.29±0.026, HC: 0.31±0.015; t(df)=2.1, p=0.04) but not in the vACC (p=0.3) (Fig. 3A). The assocations between FA and impulsivity in the thalamus or ACC were not significant in either group (all p > 0.5).

3.3 Relationship between Glu and FA

Within the AUD group only, Glu levels and FA correlated at trend level in the thalamus (r=−0.52, p=0.058) but not in the vACC (r=−0.43, p=0.11) (Fig. 3B).

3.4 Correlations with drinking behavior

Within the AUD group, the number of drinks per week in the last 90 days correlated with both Glu concentrations (r=0.62, p=0.019) and FA (r=−0.55, p=0.034) in the thalamus (Fig. 4). Moreover, LDH in kilograms correlated with Glu in the thalamus (r=0.54, p=0.049) (data

not shown). There were no associations between Glu measures and days of abstinence. Moreover, within the AUD group, neither smoking status nor cigarettes per day was associated with Glu or FA.

4. Discussion

The main findings of our study are: 1) AUD patients showed higher Glu levels and lower FA in the thalamus compared to HC, 2) Glu in thalamus and in dACC (but not vACC) were positively associated with measures of impulsivity, and 3) both elevated Glu and lower FA in the thalamus in AUD patients were associated with the severity of alcohol drinking behavior in the weeks preceding the study. Elevated Glu levels have been associated with alcohol-induced neurotoxicity and neuroinflammation (Frischknecht et al., 2017) whereas reductions in thalamic FA have been associated with degenerative changes (Cavallari et al., 2014; Santos et al., 2019). Therefore, we suggest our findings reflect neurotoxic changes in the thalamus that are possibly triggered by chronic alcohol exposure due to neuroinflammation. In an exploratory analysis, we found that the higher thalamic Glu levels are associated with higher impulsivity scores in AUD patients, which suggests that alcohol-induced neurotoxic changes in the thalamus may contribute to impulsivity in AUD. Although we had hypothesized that elevated Glu levels and lower FA would occur in the ACC as well, we did not find any group differences in this region. Nevertheless, we found that in a larger, independent cohort of n=32 patients with AUD Glu in dACC was associated with increased impulsivity as well.

To our knowledge, this is the first study in humans to report elevated levels of Glu and lower FA in the thalamus of recently detoxified AUD patients compared to controls. Our thalamic results are consistent with preclinical findings of elevated Glu in the thalamus of alcohol-dependent animals studied during acute withdrawal (Fliegel et al., 2013). A recent clinical study showed that in moderate drinkers, acute alcohol administration elevated Glx in the thalamus relative to baseline (Monnig et al., 2019). However, the latter study did not evaluate if Glx remained elevated post-intoxication and withdrawal. Our study did not find an association with days since last intoxication (ranged 1–7 days), which indicates that elevated Glu levels persisted for at least one week of detoxification. On the other hand, both elevated Glu and reductions in FA in the thalamus were associated with the severity of recent drinking behavior, which suggest that these abnormalities were related to alcohol exposures. Lower FA has been reported in AUD in various white and gray matter structures (Monnig et al., 2013; Pandey et al., 2018; Wang et al., 2016) including the thalamus (Monnig et al., 2013), although one study reported higher thalamic FA in AUD patients compared to controls (Pandey et al., 2018). Acute alcohol exposure was also found to reduce the apparent diffusion coefficient—a measure of the magnitude of mean diffusion (Kong et al., 2012).

Since both increased Glu levels and reduced FA have been associated with neuroinflammation, including in an animal model of alcohol dependence (Fliegel et al., 2013), our findings may reflect neuroinflammatory changes associated with chronic alcohol exposure to the thalamus. Indeed, using autoradiography, we previously showed that chronic alcohol exposure in rodents was associated with increases in thalamic binding of the TSPO ligands [^{3} H]PBR28 and [^{3} H]PK11195, which are markers of inflammation (Tyler et al.,

2019). Other imaging methods, including resting state functional connectivity, have also documented that acute and chronic alcohol administration significantly affects the thalamus (Shokri-Kojori et al., 2017; Wang et al., 2016). Therefore, the thalamus may be particularly vulnerable to the effects of alcohol.

Glu levels in both the thalamus and dACC (but not vACC) of the AUD patients correlated positively with impulsivity. This finding is consistent with studies that found positive associations between Glu in the ACC and impulsivity in neuropsychiatric disorders that are characterized by high impulsivity, including cocaine use (Schmaal et al., 2012) and borderline personality (Hoerst et al., 2010) and attention-deficit-hyperactivity disorders (Ende et al., 2016). Impulsive behavior in AUD patients may follow a similar mechanism in which acute and chronic alcohol use alters Glu neurotransmission. This in turn may serve as a biomarker (or predictor) of AUD-related behaviors. Indeed, elevations in impulsivity (Gropper et al., 2016) as well as Glu (Hermann et al., 2012) were observed during acute alcohol withdrawal in AUD patients compared to controls. While Glu levels normalized after a few weeks of abstinence in AUD patients (Hermann et al., 2012), future research is needed to investigate whether this is accompanied by decreased impulsivity. Pharmacological intervention with NAC normalizes Glu levels and decreased neuroinflammation in alcohol-dependent rodents (Schneider et al., 2017), as well as alcohol self-administration, extinction responding, and relapse (Lebourgeois et al., 2019). In human cocaine abusers, NAC also normalized elevated Glu levels, and impulsivity at baseline was a predictor for medication-induced reductions in Glu. However, impulsivity was not assessed after treatment (Schmaal et al., 2012). Future studies are needed to investigate whether NAC may also decrease Glu levels in AUD and whether it has an impact on impulsive behavior.

Despite previous findings of elevated Glu and Glx levels in the ACC of AUD patients (Hermann et al., 2012; Yeo et al., 2013), in the current study we did not find any group differences in Glu levels in thr ACC. The reason for these discrepancies is unclear but might involve low power due to the small sample size of our study or differences in the clinical and demographic characteristics of the patients. However, other than a younger age for the AUD group in Yeo et al., 2013 (mean age is 31, rather than 47 in our study and 46 in Hermann et al., 2012), we could not identify any other group differences between our study and previous studies.

Study Limitations

Given our limited sample size, we see our first study as exploratory and in need of further replications. All results from study 1 were presented without corrections for multiple comparisons and although all data were normally distributed and we removed > 3SD outliers, the correlationsal measures of thalamic Glu with impulsivity and thala mic FA would lack significane if 2SD outliers were removed. The small sample size may have also have limited the power to detect group differences in the vACC, or associations with impulsivity. Nevertheless, we were able to replicate the association between elevated brain Glu and impulsivity in AUD in an independent and larger cohort of 32 AUD patients – although in a different brain area (dACC) and with a different scale used (i.e., BIS-11 rather than CAARS). In addition, our measurement of Glu using the PRESS sequence may have

suffered from glutamine contamination; future studies using edited MRS sequences that can measure glutamate separate from glutamine (e.g., TE-averaged PRESS or HERMES) are needed to replicate our findings. Moreover, a higher proportion of AUD patients than HC were tobacco smokers which confounds the interpretation of our findings. Although we did not find an association between FA or Glu and smoking status or quantity, we cannot completely rule out the contribution of smoking to our findings. Finally, we did not obtain peripheral markers of neuroinflammation, which would have allowed us to assess associations with Glu and FA.

In conclusion, we found elevated Glu and decreased FA in the thalamus, but not in vACC, associated with impulsivity (Glu in thalamus and dACC) and severity of drinking behavior in AUD patients, which we interpret as evidence of thalamic neurotoxicity. These findings suggest that the thalamus and dACC are vulnerable to the neurotoxic effects of chronic alcohol use and implicate these effects in impulsivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Patients with Alcohol Use Disorder show higher glutamate (Glu) and lower FA in the thalamus than controls
- Chronic alcohol exposure in the thalamus may contribute to impulsivity
- Past drinking behavior correlated with higher Glu and lower FA in the thalamus

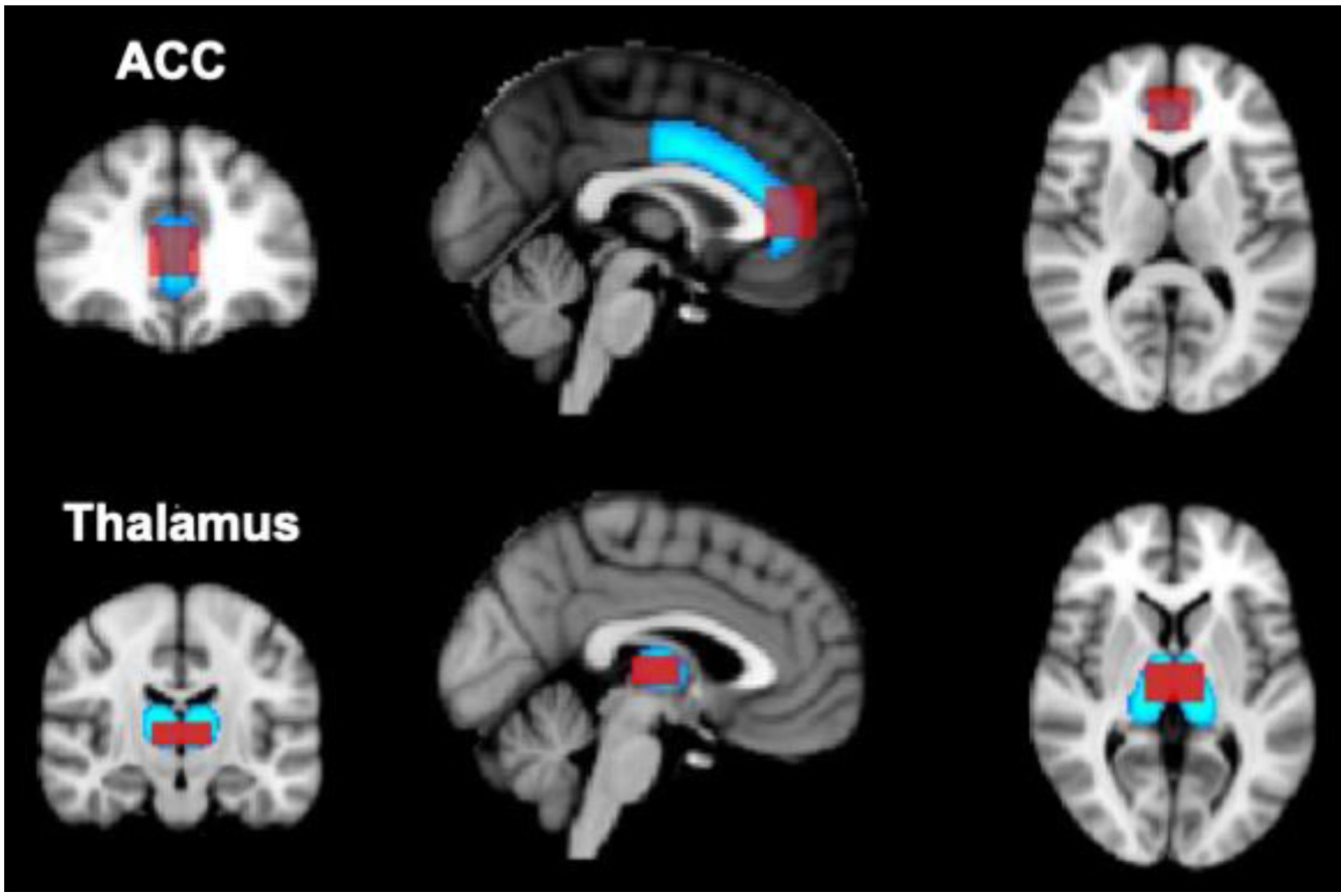

Fig. 1. ^{1}H-MRS voxel locations projected on to FA ROIs in the ACC and thalamus.
MPRAGE images and anatomical landmarks were used to prescribe isotropic 8-mL MRS voxels in the ACC and thalamus (in red). These custom ROIs were used for subsequent MRS analyses. Bilateral FA ACC and thalamus ROIs (in blue) were selected for the DWI data analysis from FSL's Harvard–Oxford Cortical and Subcortical Structural probabilistic atlases (Desikan et al., 2006). Both DWI ROI masks were thresholded in FSL at 50% signal intensity.

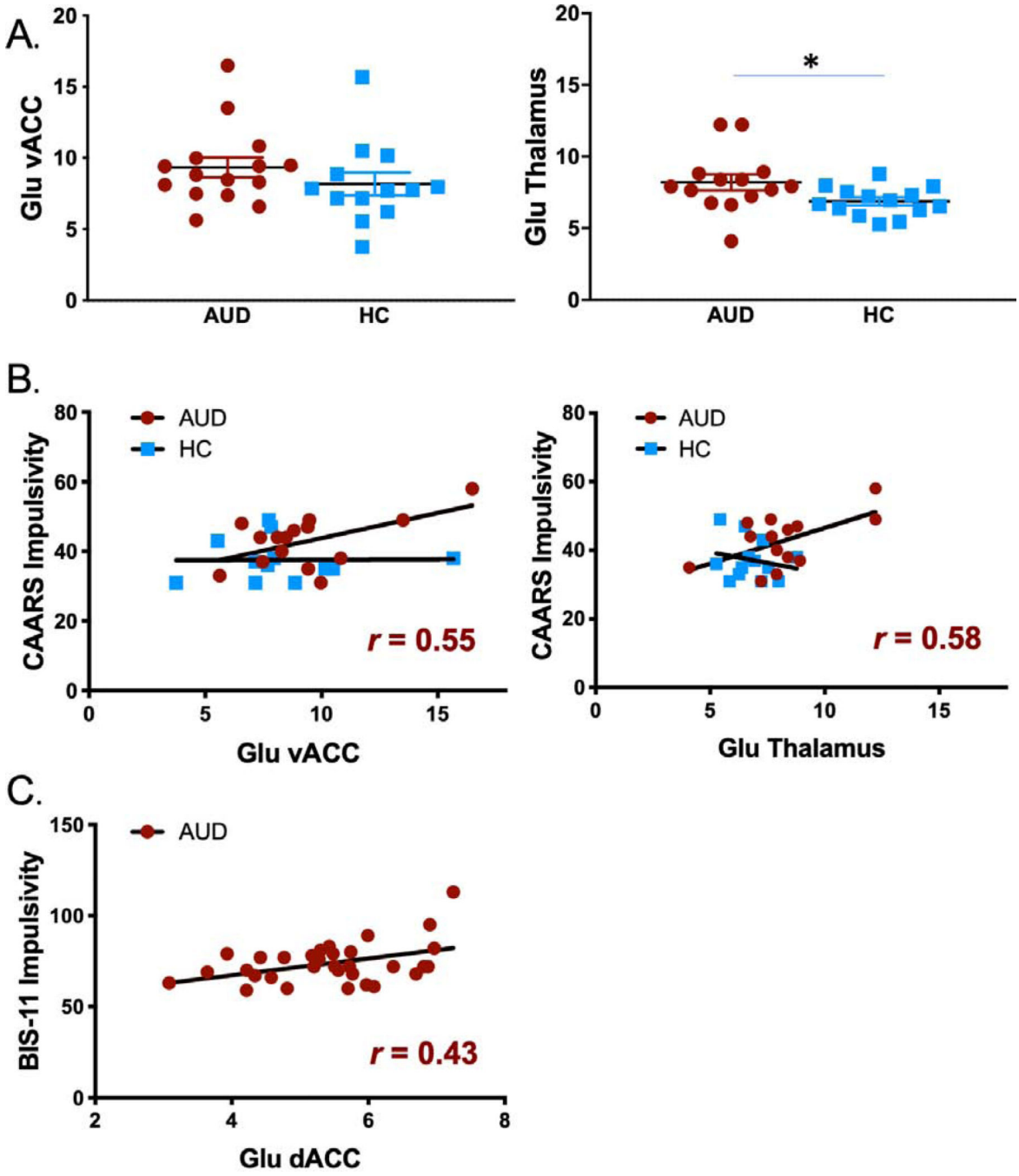

Fig. 2. Comparison of Glu concentrations and subject impulsivity.

(A) Group comparisons of Glu concentrations in the ACC and thalamus. **(B)** Correlations between Glu concentrations and impulsivity across healthy and AUD patients in the ACC and thalamus (* $p < 0.05$).

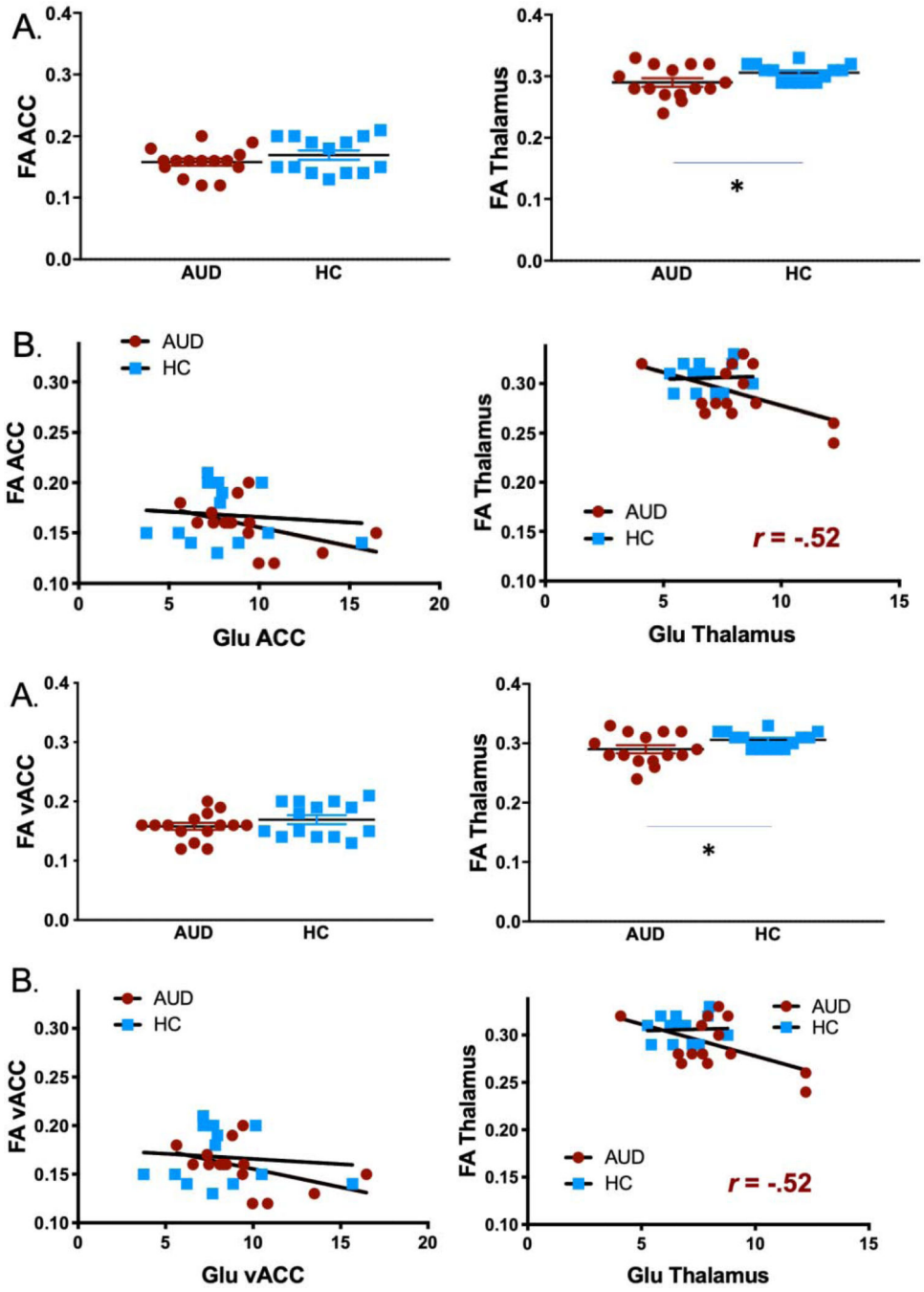

Fig. 3. Comparison of Glu concentrations and FA measures.

(A) Group comparisons of FA in the ACC and thalamus. Thalamic FA was lower in AUD patients compared to HC (p=0.04). **(B)** Correlation between Glu concentrations and FA values across healthy and AUD patients in the ACC and thalamus. Glu and FA in the thalamus correlated at trend level in the AUD group (r=−0.52, p=0.058).

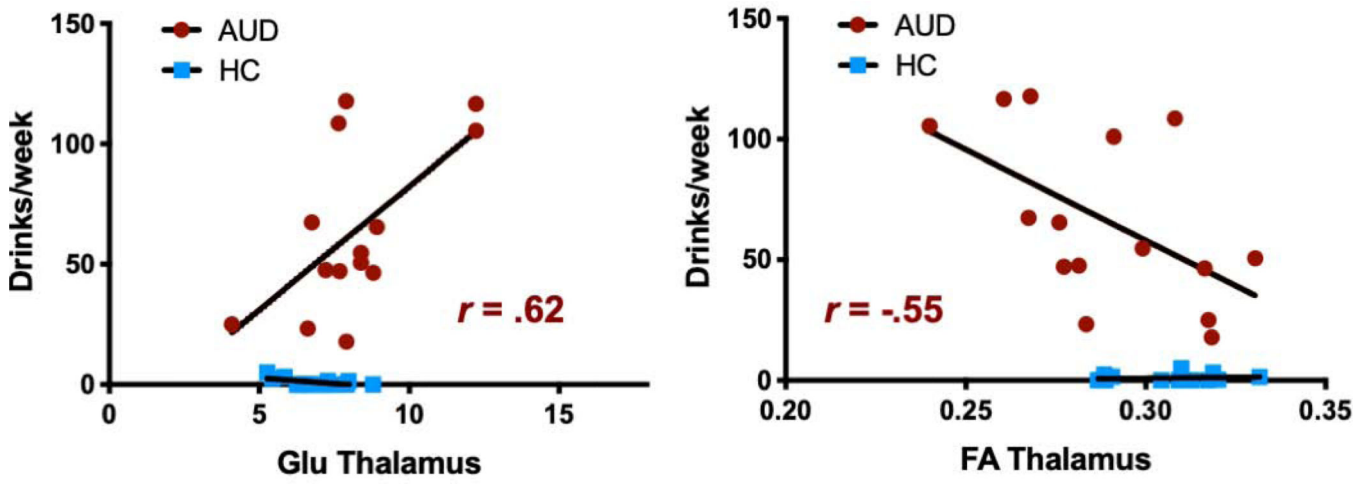

Fig. 4. Correlation of drinking severity with Glu concentrations and FA.

Within the AUD group, number of drinks per week in the last 90 days correlated positively with Glu concentrations (r=0.62, p=0.019) and negatively with FA (r=−0.55, p=0.034) in the thalamus.

Table 1.

Demographics and clinical characteristics of AUD and HC groups.

	AUD (*n*=15)	Controls (*n*=14)	P-value
Age (years)	47.1 (9.7)	48.0 (11.4)	0.8
Years of education	12.3 (2.3)	15.1 (2.3)	0.002
WASI IQ	90.2 (15.8)	99.4 (16.1)	0.13
BMI	26.4 (3.7)	29.0 (4.7)	0.11
Gender	4 females	4 females	0.9
Smoking status	8 smokers 2 ex-smokers 5 non-smokers	0 smokers 1 ex-smoker 13 non-smokers	<0.0001
LDH (kg)	1526 (1420)	33 (52)	0.001
TLFB Drinks/week	66.3 (34.9)	1.0 (1.6)	<0.0001
TLFB # Drinking days	79.3 (15.2)	6.6 (9.2)	<0.0001
ADS	14.1 (8.5)	0.2 (0.4)	<0.0001
CAARS A inattention	46.7 (9.9)	38.2 (5.7)	0.01
CAARS B hyperactivity	47.1 (8.2)	44.3 (8.7)	0.01
CAARS C impulsivity	42.9 (7.2)	37.2 (5.9)	0.03

Abbreviations: ADS Alcohol Dependence Scale, BMI body mass index, CAARS Conners' Adult ADHD Rating Scale, IQ intelligence quotient, LDH lifetime drinking history, TLFB Timeline Follow-back, WASI Wechsler Abbreviated Scale of Intelligence.