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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE

Delay discounting and alcohol consumption correlate with dorsal anterior insula activation during choice in nontreatment-seeking heavy drinkers

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Abstract

Background: The anterior insular cortex (AIC), a prominent salience network node, integrates interoceptive information and emotional states into decision making. While AIC activation during delay discounting (DD) in alcohol use disorder (AUD) has been previously reported, the associations between AIC activation, impulsive choice, alcohol consumption, and connectivity remain unknown. We therefore tested AIC brain responses during DD in heavy drinkers and their association with DD performance, alcohol drinking, and task-based connectivity.

Methods: Twenty-nine heavy drinkers (12 females; mean (SD) age=31.5 ±6.1 years; mean (SD)=40.8 ±23.4 drinks/week) completed a DD task during functional MRI. Regions activated during DD decision making were tested for correlation with DD behavior and alcohol drinking. Psychophysiological interaction (PPI) models assessed the task-dependent functional connectivity (FC) of activation during choice.

Results: Delay discounting choice activated bilateral anterior insular cortex, anterior cingulate cortex, and left precentral gyrus. Right dorsal (d) AIC activation during choice negatively correlated with discounting of delayed rewards and alcohol consumption. PPI analysis revealed FC of the right dAIC to both the anterior and posterior cingulate cortices—key nodes in the midline default mode network.

Conclusions: Greater dAIC involvement in intertemporal choice may confer more adaptive behavior (lower impulsivity and alcohol consumption). Moreover, salience network processes governing discounting may require midline default mode (precuneus/posterior cingulate cortex) recruitment. These findings supporta key adaptive role for right dAIC in decision making involving future rewards and risky drinking.

KEYWORDS
alcohol use disorder, alcoholism, monetary discounting, psychophysiological interaction, task fMRI

INTRODUCTION

Alcohol use disorder (AUD) and other addictions are characterized by immediate reward-seeking and disregard of future rewards (Amlung et al., 2017; Bickel & Marsch, 2001). The delay discounting (DD) task quantifies immediate reward preference, differentiates AUD from controls (Petry, 2001), predicts alcohol consumption, (Fernie et al., 2013) and is associated with recovery self-efficacy and duration (Turner et al., 2021). Steep discounting (immediate reward preference) is a putative endophenotype for addiction disorders and likely underlies elements of addiction-related decision making (MacKillop, 2013), although the degree to which DD models addiction processes is currently debated (Bailey et al., 2021; Stein et al., 2022). Nonetheless, DD tasks clearly engage intertemporal decision making (making exclusive selections for rewards occurring at proximal or distant points in time) and present the opportunity to measure brain activity during this crucial process. However, the functional brain areas and circuits governing immediate or delayed reward preference in heavy drinkers are not well-understood. Elucidating the neurological underpinnings of DD and heavy drinking will help clarify the neurological mechanisms contributing to intertemporal decision-making dysfunction in AUD.

Unfortunately, although knowledge of how the brain makes intertemporal decisions is critical to addiction research, to date, only three studies have examined current heavy drinkers performing DD during fMRI (Amlung et al., 2014; Claus et al., 2011; Lim et al., 2017) (although for reports in abstinent AUD participants, see Boettiger et al., 2007, 2009). While showing qualitative agreement with DD findings in controls, these studies also show some divergent results, particularly in the insula. In the largest of these studies, Claus and colleagues demonstrated that left AIC activation in the [Delayed > Immediate] contrast correlated with immediate choice preference (Claus et al., 2011). Lim et al. (2017) found that [Immediate > Delayed] contrast activation in right AIC correlated with immediate choice preference, whereas Amlung et al. (2014) detected left AIC activation during both immediate ("impulsive") and delayed ("restrained") choice types. The AIC therefore appears to be central to intertemporal decision making in heavy drinkers, but its precise influence and associated networks have not been fully elucidated.

Prior functional magnetic resonance imaging (fMRI) work in healthy participants has shown that the DD task activates the salience network (insula and anterior cingulate cortex), posterior cingulate cortex, frontoparietal regions, temporal lobe, and basal ganglia (for review, see Frost & McNaughton, 2017), reflecting our recent findings in youth varying in risk for SUD (Butcher et al., 2021) Switching between the executive frontoparietal and introspective default mode networks is mediated by the right anterior insular cortex (AIC), as demonstrated in task and task-free states (Sridharan et al., 2008). AIC activation scales with adaptive intertemporal decision making that appears to be mediated by dopamine systems (elicited by tolcapone) and striatal activity (putamen coactivation) (Kayser et al., 2012). Right AIC engagement during decisions of greater uncertainty (Paulus et al., 2003) and its proposed role in interoceptive time marking (Craig, 2009) suggest its key involvement in integrating perceived value over the time domain. As the AIC is a salience network node altered in AUD (Halcomb et al., 2019) and implicated in DD (Frost & McNaughton, 2017), converging evidence points to it as a key locus underlying the neurobehavioral bases of the impaired decision making that is emblematic of AUD.

While the research outlined above indicates that the AIC plays a prominent role in DD task performance, decision making involves integration of input from multiple brain networks. Intertemporal decision making relies critically on the perception of the self, as the imagined future self is the recipient of delayed rewards. The midline default mode network (DMN) mediates self-focused thought, most prominently in the anterior and posterior cingulate cortices and precuneus (Northoff et al., 2006). Broadly, adaptive intertemporal decision making requires efficient management of brain systems dedicated to cognitive control, introspective thought, and subjective valuation. This integrative role is accomplished by the salience network generally (Sridharan et al., 2008), with frontoparietal-linked executive aspects (Janes et al., 2020; Sridharan et al., 2008) and introspective default mode elements (Li et al., 2021) that are mediated specifically by the dAIC. The DMN demonstrated compromised functional connectivity with cerebellar regions during rest and during a spatial working memory task, (Chanraud et al., 2011) and attentional networks at rest (Song et al., 2021) in abstinent AUD patients. Research in nontreatment seeking AUD participants revealed disrupted connectivity in left parietal and temporal regions, as well as white matter integrity impairments (Gerhardt et al., 2021). Both the DMN and insula are implicated in processing internal information and are dysregulated in heavy drinkers, but functional connectivity between these regions during intertemporal choice is yet unknown.

To understand both AIC function during choice in the DD task and the associations of AIC subregions with self-referential networks, we administered two runs of DD during fMRI and analyzed event-related activation and functional connectivity during choice. We hypothesized that (1) choice would activate regions within the salience network (bilateral insula and dorsal ACC) and prominent nodes of the frontoparietal network (dorsolateral prefrontal cortex [dlPFC], and inferior parietal lobule), (2) blood oxygenation level dependent (BOLD) response would correlate with both baseline levels of discounting and drinking history, and (3) the midline default mode network (DMN), given its role in introspection (Andrews-Hanna et al., 2010), future simulation (Benoit & Schacter, 2015), and manipulations that increase delayed reward preference (Oberlin et al., 2020) would show functional coupling with the regions engaged by the discounting task.

MATERIALS AND METHODS

Participants

Study procedures were approved by the Indiana University Institutional Review Board. Participants were recruited from the local community through online advertisements (Craigslist, university classified ads), newspaper ads, flyers posted in the community,

and referrals. Twenty-nine heavy drinkers were recruited, provided informed consent for study procedures, and were compensated with $240.00. Exclusionary criteria were: contraindications for MRI, positive urine pregnancy screen, positive urine toxicology screen for illicit substances (except marijuana), current use of any psychotropic medication, history or presence of any neurological or major medical disorders, and current treatment for any psychiatric disorder (including substance use disorder). Demographics and drinking characteristics are listed in Table 1, and drug use history is described in Tables S1–S4.

General study procedures

On the study day, participants' vital signs were recorded by nursing staff and sobriety was verified (BrAC of 0.000 g/dl). Visible signs of alcohol withdrawal prompted formal assessment (CIWA; Clinical Use Withdrawal Assessment of Alcohol Scale, Revised), and scores of 10 or greater (out of 67) (Sullivan et al., 1989) triggered exclusion and study day termination—although no participants were excluded by this assessment. Participants performed the adjusting DD task outside of the scanner (Oberlin et al., 2015), which provided indifference points for the DD task during fMRI (see below). They also completed several self-report measures (described below) for correlational analyses with drinking patterns, discounting behavior, and task-based fMRI neural activity. These results were culled from a larger study that incorporated post-fMRI alcohol administration, which will be reported elsewhere.

DD task

Prior to the fMRI session, DD was administered outside the scanner to quantify discounting behavior (adjusting task). During fMRI, a nonadjusting DD task was used to measure brain activation during intertemporal choice. The pre-scan, adjusting-amount DD task generated indifference points; titrated amounts for which preference was equal between the adjusted immediate and delayed options ($100 delayed by 2 days, 1 week, 1 month, 6 months, 1 year, or 5 years) using an adjusting procedure with five trials per delay (Oberlin et al., 2015), illustrated in Figure S1. Participants were instructed to make every choice according to their true preference and that some of their choices would be selected at random by the computer and paid according to the amount and delay chosen for that trial (the actual payout was an additional $20 at the end of the day, obfuscated by automated selection and rounding). Nonlinear regression derived the fitted parameter *k* (Mazur, 1987), which was used to calculate choice options close to participants' indifference points and maximize cognitive load for the fMRI DD task. The fMRI (nonadjusting) task targeted the middle of the discounting curve by presenting delays corresponding to 30%, 40%, 50%, 60%, and 70% of the value of the delayed option (in the outside-scanner adjusting task), to mitigate floor and ceiling effects. Calculated indifference points using delays and amounts equivalent to 30% to 70% discounting were presented during fMRI, and equality of immediate versus delayed choices was controlled by biasing trials, with 15 immediate-biased trials 50% to 60% above the indifference curve, and 15 delay-biased trials 50% to 60% below the curve, distributed across delays (3 immediate-biased and 3 delay-biased trials per amount, with 5 amounts, comprised 30 choice trials). Participants were allowed 6 s to make their choice; nonresponses were counted as omissions. DD behavior during the in-scanner task was quantified as a simple preference score, i.e., the proportion of immediate choices selected to total choices made (trial omissions were disregarded). To prevent repetitive visual presentation, amounts were randomized within the 10% window. Ten trials controlling for visual presentation and motor response were also included, which required participants to identify the larger of two amounts (Butcher et al., 2021). DD behavior (performed outside the scanner) was quantified by calculating the area under the curve (AUC) using the trapezoidal method. While *k* values were calculated for creating in-scanner amount/delay combinations, AUC is model-free and agnostic to the form of discounting, making it arguably a more objective measure (Myerson et al., 2001). Larger AUC values represent less impulsive choice, while smaller AUC values indicate greater impulsive choice—more preference for immediate rewards. Guided by Johnson and Bickel (2008), we assessed monotonically decreasing indifference points, with all but two participants demonstrating fully systematic discounting (these two made single errors, but otherwise showed systematic discounting).

TABLE 1 Demographics, $N = 29$

	Mean (SD) or *n* (%)	Range
Age	31.5 (6.1)	22 to 43
Female	12 (41)	
Caucasian	16[a] (55)	
Education years	13.3 (2.0)	11 to 18
Smoker[b]	19 (55)	
Drinks per week	40.8 (23.4)	16.4 to 116.3
Heavy drinking days per week[c]	3.5 (2.0)	0.6 to 7.0
Drinks per drinking day	8.1 (4.7)	2.6 to 21.3
AUDIT	17.8 (6.4)	8 to 34
DSM-IV counts[d]	5.1 (2.6)	1 to 10

[a]Plus 11 African American and 2 mixed-race.
[b]Seven female.
[c]Four or five drinks per day for females or males, respectively.
[d]DSM, Diagnostic and Statistical Manual AUD criteria met for lifetime.

Self-report measures

To detect associations between self-reported impulsivity, sensation seeking, and problem drinking, we administered the sUPPS-P Impulsive Behavior Scale (Cyders & Smith, 2007; Whiteside & Lynam, 2001). sUPPS-P subscales include negative urgency, lack of perseverance, lack of premeditation, sensation seeking, and positive urgency (Table S2).

Participants completed a 35-day timeline follow-back (TLFB; Sobell et al., 1986) for alcohol consumption to quantify their recent drinking, and verified that it accurately reflected their drinking pattern in the past 6 months. If participants claimed it did not, they were asked to complete a 90 day TLFB from which they would select the 35-day period most accurately reflecting their usual drinking pattern. All participants in this sample confirmed the representativeness of drinking in the 35-day TLFB, so were not given the 90-day version. Participants were also asked to complete the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) to assess alcohol-related problems, and were administered the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) to determine the number of DSM-IV alcohol abuse/dependence criteria that were met (criteria counts for lifetime). Hazardous alcohol drinking was defined as AUDIT scores ≥8 (Saunders et al., 1993). Of the 29 participants, 20 met DSM-IV criteria for alcohol abuse or dependence, as indicated by the SSAGA. Our recruitment targeted a range of heavy drinking patterns to facilitate correlational analyses.

Image acquisition

Imaging was performed on a Siemens 3T Prisma MRI scanner with a 32-channel head coil array. fMRI data were acquired during two, 7 min and 29 s runs using a multiband (MB) blood oxygenation level dependent (BOLD) contrast sensitive sequence as detailed in Xu et al. (2015). The imaging parameters were: 546 BOLD volumes, gradient-echo echo-planar imaging (EPI), MB slice acceleration factor = 4, TR/TE = 810/29 ms, flip angle = 56°, 2.5 × 2.5 × 2.5 mm^3 voxels, field-of-view: 220 × 220 mm, 48 axial slices. The first BOLD fMRI was preceded by two short (16 s) spin echo field mapping scans (TR/TE = 1370 ms/51.6 ms, 5 A-P and 5 P-A phase direction volumes) with the same coverage, voxel size, and slice acceleration as the BOLD acquisition. At the start of the imaging session, participants underwent a T1-weighted anatomical MRI with whole-brain coverage using a 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (5 min and 12 s duration, 176 sagittal slices, 1.05 × 1.05 × 1.2 mm^3 voxels, GRAPPA R = 2 acceleration).

Image preprocessing

BOLD fMRI data for each run were preprocessed using FSL (FMRIB's Software Library (Jenkinson et al., 2012). Specifically, we included BOLD volume distortion correction utilizing spin echo field mapping scans as implemented in *topup/applytopup*, motion correction with *mcflirt*, nonbrain removal with *bet*, spatial smoothing with a 6.0 mm full width at half maximum Gaussian kernel, and mean intensity normalization of volumes at each timepoint. Linear registration to high resolution structural and standard space images was carried out using *flirt* and was followed by *fnirt* nonlinear registration. Following recommendations for robust preprocessing (Eklund et al., 2016), the preprocessed data were presented to FSL's *MELODIC* to generate filtered data for independent component analysis (ICA)-based denoising with ICA-AROMA (Pruim et al., 2015). The denoised functional data were then projected in the standard Montreal Neurological Institute (MNI) space and interpolated to 2 mm isotropic voxels. Subsequent statistical analyses in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) were performed on the denoised data using voxel-level inferences (detailed below) that unlike cluster-defining threshold approaches reliably achieve nominal false positive rates (Eklund et al., 2016).

Statistical analysis

Imaging

Intertemporal decision-making choice trials (immediate and delayed) and control trials were presented in an event-related fMRI design with a mean intertrial interval of 11 s (see Figure S1 for trial design). Individual-level responses to each trial were modeled in SPM12 using canonical hemodynamic response function (HRF) and FAST autocorrelation modeling (Olszowy et al., 2019) appropriate for short TR data. Trials were modeled to capture the decision-making period, with the onset 400 ms after choice presentation (allowing for semantic comprehension, Hagoort et al., 2004) and duration ending 50 ms before response (to minimize motor-related signal, Pfefferbaum et al., 1985). In order to test the primary associations of interest between neural activation patterns, impulsivity, and alcohol consumption levels, we first identified brain regions robustly activated by choice trials (either delayed or immediate). Using the data from both fMRI runs, the [Choice > Baseline] contrast images from each participant were entered into one-sample group models in SPM12 with sex, age, and education as covariates (voxel-level significance $p_{FWE} < 0.05$, correcting for whole-brain family wise error; FWE) (Eklund et al., 2016). We then extracted mean contrast values from the significant clusters using the MarsBar toolbox (https://github.com/marsbar-toolbox/marsbar). These clusters served as the "choice-defined" regions of interest (ROIs). In addition, we assessed control trial activations and compared choice and control activations by extracting [Control > Baseline] and [Choice > Control] contrast values from the choice-defined ROIs. Discounting (AUC from the prescan adjusting DD) and drinking (drinks consumed per week and per drinking day) were tested for correlations with [Choice > Control] mean contrast values in the choice-defined ROIs using SPSS (v26; IBM).

To better understand how our findings relate to function in other key brain regions linked to relative individual valuation, we focused on connectivity with the DMN. The midline DMN correlates with reward value in intertemporal choice tasks (Kable & Glimcher, 2010), likely due to the personal relevance of imagined future rewards. The midline DMN largely comprises the core network supporting mental simulation of the future and autobiographical thought (Schacter et al., 2008) and self-referential processing (Northoff et al., 2006; Wen et al., 2020). We posited that the integration of DMN self-related processing and insular interoceptive monitoring made DMN-insula connectivity an important linkage for DD neural processing.

We conducted a psychophysiological interaction (PPI) analysis in SPM12 to identify regions functionally related to the AIC activation cluster that resulted from the intertemporal choice responses (detailed in Results). We selected the functional cluster from the right AIC ROI (Figure 1, Table S3), as it correlated with both intertemporal choice and drinking (see Results) and occupies a key role in AUD decision making. PPI analysis permits detection of *task-related* changes in functional connectivity between regions (O'Reilly et al., 2012) and is an essential tool for identifying synchronous regions at the network level that modulate specific behaviors. Using individual SPM models (described above), we extracted the first eigenvariate of BOLD signal from all 121 voxels in the right AIC ROI from each participant, run, and contrast of interest. We then performed a psychophysiological interaction procedure to create two regressors of no interest (original BOLD signal eigenvariate and psychological main effect described by an HRF-convolved task regressor), and a PPI regressor (estimated neuronal response after the hemodynamic response has been deconvolved). These multiple-regression models assessed voxel-wise associations with a PPI regressor in each participant. We then tested for positive slopes of the PPI regressor in each participant. In the group analysis, we conducted one-sample *t*-tests on the contrast images of the PPI terms obtained from these individual analyses with sex, age, and education as covariates. The PPI findings for each contrast of interest (e.g., [Choice > Control]) were assessed at a voxel-level significance ($p_{FWE} < 0.05$), FWE-corrected for multiple comparisons across all voxels within the DMN mask as detailed in Figure 3C.

To evaluate effects related to illicit drug use, participants were grouped according to recent use of any illicit drug, with Users ($n = 16$) reporting illicit use within the past 6 months, and Nonusers ($n = 11$) reporting no such use. Recent and lifetime use is summarized in Tables S1–S4. These groups were analyzed for differences in [Choice > Control] and [Choice > Baseline] contrasts for each choice-defined region of interest using independent samples *t*-tests in SPSS.

Behavior

Median reaction times were calculated for in-scanner delayed choice, immediate choice, and control trials and were subsequently compared using paired *t*-tests. Discounting behavior outside the scanner prescan DD, was quantified as AUC and normalized with natural log transform (*ln*AUC) for correlation with brain activity and behavior (the DD task during fMRI used individually tailored amount/delay choice sets for each participant). The in-scanner DD task preference scores did not differ between two fMRI runs (paired-*t*, $p = 0.89$), so those data were pooled. Subsequently, we tested if significant activations in our functionally defined ROIs (as indexed by mean regional values from the [Choice > Control] contrast of interest) were associated with baseline discounting behavior (DD *ln*AUC) or self-reported trait impulsivity (sUPPS-P). Finally, we also tested for associations between impulsive choice (DD *ln*AUC) and alcohol intake (drinks consumed per week), AUDIT scores, and DSM-IV counts.

RESULTS

Imaging results

Activation during intertemporal choice

Intertemporal choice (immediate or delayed rewards) relative to baseline elicited BOLD activation in four regions (Figure 1, Table S3): bilateral dorsal AIC, dorsal anterior cingulate cortex (dACC), and left precentral gyrus (PrG). There were no significant effects of sex, age, or education. There were no significant differences in activation between males and females (independent *t*-test). Extracted values from choice-activated regions in each of the three contrasts are illustrated in Figure S2.

Correlations with DD behavior

Right dAIC activation during choice (relative to control trials) correlated with prescan discounting ($r(27) = 0.37$, $p = 0.048$), such that greater dAIC activation corresponded with more delayed reward preference (Figure 2A). Activations in the left dAIC, dACC, and left PrG ROIs were not correlated with discounting behavior ($ps > 0.4$).

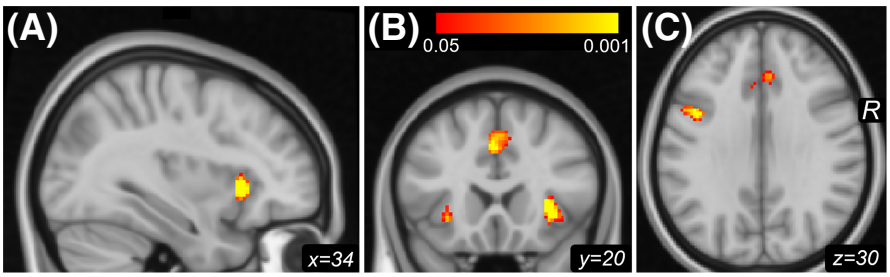

FIGURE 1 Intertemporal choice regions. Choice trials relative to baseline elicited activation in the left and right dorsal anterior insula (panels A, B), the dorsal anterior cingulate cortex (panels B, C), and left precentral gyrus (panel C). Illustrated activation foci contain significant peak voxels ($p_{FWE} < 0.05$, corrected for whole-brain multiple comparisons), displayed as a *p*-value heat map, $k > 15$

Correlations with alcohol intake

There was a significant negative relationship between the right dAIC activation during choice (relative to control trials) and the number of drinks consumed per drinking day ($r(27) = -0.41$, $p = 0.026$), and per week, ($r(27) = -0.54$, $p = 0.002$) (Figure 2B,C), wherein greater activation in the right dAIC was associated with fewer drinks consumed. Activation in the other ROIs did not significantly correlate with either drinks per drinking day or drinks per week ($ps > 0.2$). There were no significant correlations with other measures of alcohol-related problems (AUDIT scores or DSM-IV counts), $ps > 0.1$.

Correlations with self-reported impulsivity and sensation seeking

None of the contrast estimates from ROIs that were activated during choice (relative to control) were correlated with either impulsivity or sensation seeking measures from sUPPS-P ($ps > 0.06$).

Psychophysiological interaction analysis

As described in Materials and methods, the functionally defined right dAIC cluster was selected as a volume of interest in psychophysiological interaction analysis because of its associations with both DD and alcohol consumption, as outlined above. The [Choice > Control] contrast PPI analysis revealed functional coupling between the right dAIC and both the precuneus/posterior cingulate cortex (PCC) and pregenual ACC (Figure 3A; Table S4). Functional coupling for the [Choice > Baseline] contrast was present only between the right dAIC and the precuneus/PCC (Figure 3B; Table S4). The [Control > Baseline] contrast showed no significant functional coupling.

Recent drug use

Users did not differ from Nonusers in the [Choice > Control] contrast, $ps > 0.2$. Significant differences were detected in the [Choice > Baseline] contrast in the right dAIC ($t(25) = 2.52$, $p = 0.02$), the dACC ($t(25) = 2.12$, $p < 0.04$), and the left dAIC ($t(25) = 2.45$, $p = 0.02$). Data from two participants were excluded due to imprecise dates of recent use.

Behavioral results

Reaction times during fMRI

Median reaction times did not differ between immediate and delayed choice trials during fMRI, $ps > 0.3$. Control trial reaction times were faster than both immediate and delayed choice trials ($ts(28) = 8.00$ and 8.49, respectively, $ps < 0.001$). Control trial accuracy was 98.2%. Reaction times were not correlated with discounting behavior (*ln*AUC). There were no associations between reaction times and activation in any of the ROIs ($ps > 0.1$).

DD and alcohol intake

Discounting (*ln*AUC) and alcohol drinking were correlated, with greater immediate reward preference (smaller AUC) corresponding to more drinking (drinks per drinking day, $r(27) = -0.45$, $p = 0.016$ and drinks per week, $r(27) = -0.38$, $p = 0.042$). Results are depicted in Figure 4A,B. There were no significant correlations with other measures of alcohol-related problems (AUDIT scores or DSM-IV counts), $ps > 0.1$.

DD and impulsivity and sensation seeking measures

There were no significant correlations between discounting (*ln*AUC) and self-reported measures of impulsivity or sensation seeking, $ps > 0.2$.

DISCUSSION

This study is the first to link right dorsal anterior insula activation during temporal discounting with choice behavior, recent alcohol consumption history, and functional coupling to medial default mode network regions in heavy drinkers. More specifically, these findings propose a central role for the dAIC in problem drinkers as a putative protective influence, as greater dAIC activation during intertemporal choice is associated with less impulsive choice (temporal discounting) and alcohol intake. Further, we find dAIC activation during choice to be functionally coupled to medial default mode network nodes, which are key to introspection (Buckner et al., 2008), self-referential processing (Northoff et al., 2006), and heightened delayed reward preference (Oberlin et al., 2020). This is highly relevant, given that previous work has revealed that both introspection (e.g., evoked memories of previous drug experience) (Stacy, 1997) and self-referential thinking (e.g., self-discrepancy) predict alcohol consumption and contribute to excessive intake patterns (Poncin et al., 2015). These results are consistent with functional specialization in the subregions of the AIC and extend previous work that identifies the dorsal aspect as an important mediator of substance-use related drives (Janes et al., 2020) and decision making (Droutman et al., 2015). Additionally, the AIC activation region induced by intertemporal choice is within the previously defined subregion of the right dAIC (Gorgolewski et al., 2015) (Figure S3), a salience network node engaged by reward decision making.

Our results expand the growing body of literature delineating specialized functionality of the dAIC. The dAIC appears to be integral to adaptive decision making in the real world, particularly in

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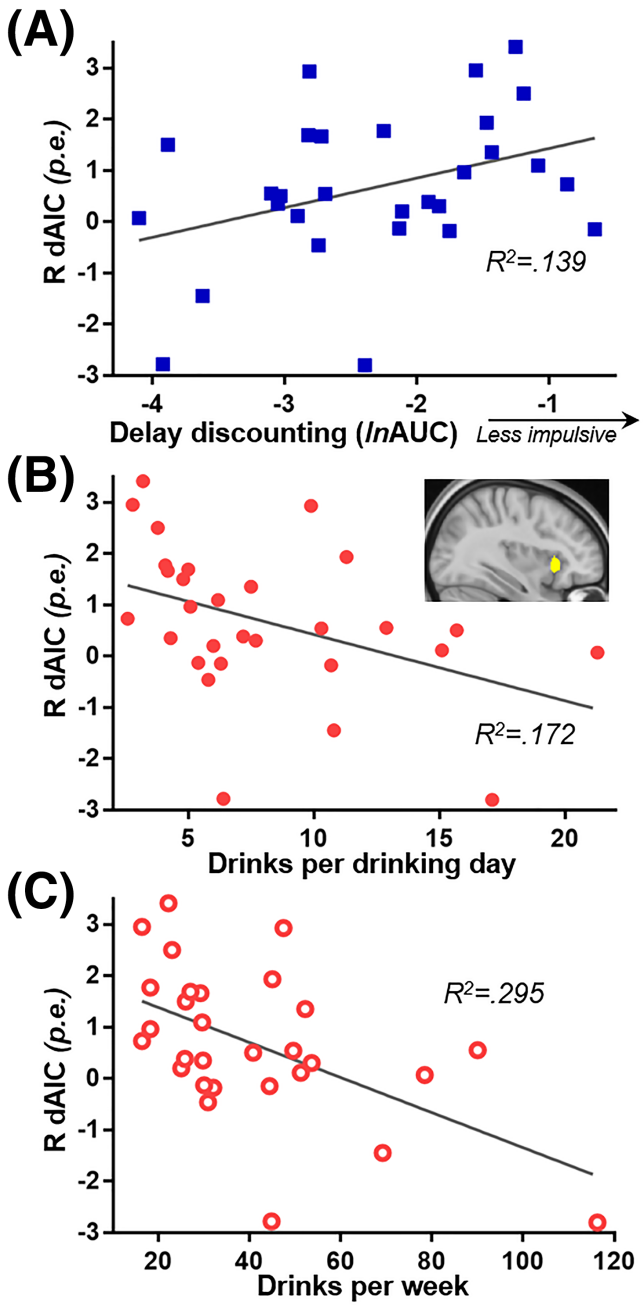

FIGURE 2 Dorsal anterior insula activation correlations with behavior. (A) Mean [Choice > Control] contrast values in the right dorsal anterior insula cortex (dAIC) cluster were positively associated with greater delayed reward preference during the pre-MRI DD and (B, C) negatively with alcohol consumption. Right dAIC cluster (yellow) is depicted in the middle panel inset. *p.e.*, parameter estimate

decision making under uncertainty (resembling decision making for rewards in uncertain futures). dAIC activation during risky choices correlated with postpunishment safe choice preference and trait harm avoidance (Paulus et al., 2003), and risk prediction (Gowin et al., 2014; Preuschoff et al., 2008). In those who use methamphetamine, the right AIC's aberrant response to risky decisions better predicted relapse than actual drug use (lifetime or recency) or trait risk-taking (Gowin et al., 2014). Together, these findings converge on the AIC's key role in modulating reward decision making in the face of uncertainty (varying delay or probability (Preuschoff et al., 2008), and its potential role in drug-related decision making.

One mechanism by which the insula impacts behavior is by integrating interoceptive states with the decision-making apparatus (e.g. the 'somatic marker hypothesis'; Damasio, 1994). In addition to its association with decision making, the insula also appears to govern interoceptive aspects of addiction maintenance, with insular lesions resulting in unplanned smoking cessation (Naqvi et al., 2007). Critically, some former smokers in that study noted that they no longer had an "urge" to smoke after stroke damage to the insula. Similarly, the right AIC in particular is recruited when suppressing powerful natural urges such as eyeblink (Lerner et al., 2009). Thus, our findings join two key insula functions identified from prior work—decision making (see above) and urge suppression. Both of these functions play key roles in alcohol consumption and relapse (De Wilde et al., 2013; Palfai et al., 1997). Further, prior work indicates that the insula may be a region of particular sensitivity to alcohol exposure (Sullivan et al., 2013, 2021), with reduced insular perfusion detected in AUD (vs. controls), and insular perfusion correlating with working memory function (Sullivan et al., 2021). Together with the present report, these findings suggest the possibility that alcohol impairs insula function, such that greater lifetime alcohol consumption compromises insula-mediated adaptive decision making and executive function.

To our knowledge, this study is the first to identify task-based connectivity changes during intertemporal choice in an AUD sample. While prior work shows AIC connectivity at rest correlated with tobacco craving (dAIC with the frontoparietal and vAIC with the default mode network; Janes et al., 2020), our task-linked connectivity reveals dAIC connectivity with the midline posterior default mode network *during* decision making. The precuneus/PCC is an extensive and heterogeneous midline structure with diverse functions, including moderation of internally directed cognition (Buckner et al., 2008). Mounting evidence indicates that the precuneus/PCC plays an active role in focusing attention (Gusnard et al., 2001) and regulating cognition (Pearson et al., 2011). Our findings establish a functional link between regions governing interoception, i.e., "how the brain senses and integrates signals originating from inside the body" (Khalsa & Lapidus, 2016, p. 2) and introspection (precuneus/PCC; Buckner et al., 2008) during decision making. Other work has found that decreased connectivity between the PCC and the right ventral attention network (of which our finding is a component) produced disturbances in participants' time orientation abilities (Yamashita et al., 2019), coinciding with the insula's purported role in subjective time perception (Craig, 2009). Time perception modulates discounting (Xu et al., 2020) and may underlie the steep discounting in AUD. Our data suggest that the connectivity of the AIC with the PCC potentially represents a candidate mechanism for how time perception interacts with intemporal choice behavior in AUD.

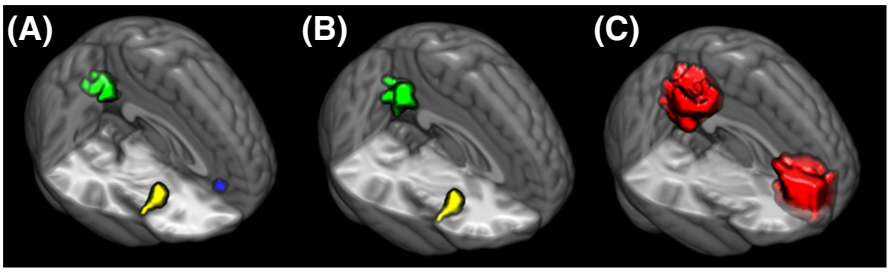

FIGURE 3 Psychophysiological interaction analysis. Illustration of connectivity clusters including significant peak voxels. (A) The right dorsal anterior insula seed (yellow) showed stimulus-dependent functional connectivity with precuneus/PCC (green) and pregenual ACC/medial prefrontal (blue) in [Choice > Control], and (B) precuneus/PCC alone in the [Choice > Baseline] comparison. Correction for multiple comparisons within a (C) medial default mode mask (45,074 mm^3, red) was performed using a small volume correction. Peak voxel $p_{FWE} < 0.05$; display threshold, $p < 0.001$, uncorrected. FWE, family-wise error corrected

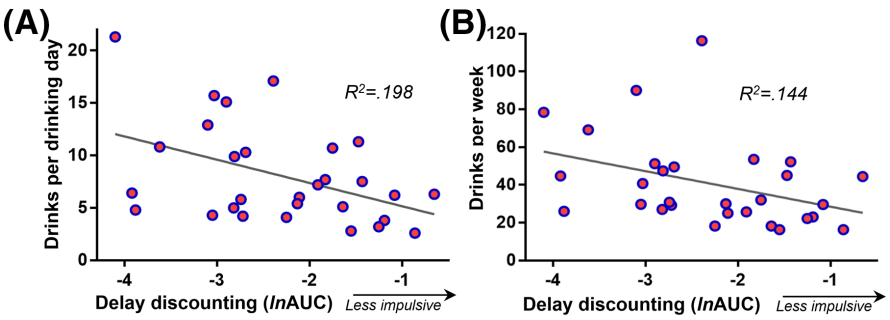

FIGURE 4 Discounting and drinking. Greater discounting was associated with higher alcohol consumption as illustrated by the negative correlation between DD (pre-MRI) discounting and (A) drinks consumed per drinking day and (B) per week

The present dAIC results, which suggest that insula activation correlates with adaptive decision making, may appear to contradict earlier findings that support the insula's role in reward drive. Although previous work showed that AIC activation correlated with immediate reward preference in heavy drinkers (Claus et al., 2011; Lim et al., 2017), AIC correlations in those DD studies were drawn from different contrasts, making their precise action less certain (e.g., possible inhibitory activity). AIC involvement in the overall intertemporal choice process is suggested by findings in Amlung et al. (2014), which showed left AIC activation during both immediate and delayed choice types in AUD. Our analyses maximized power by combining both decision types to capture brain responses broadly underlying intertemporal consideration. This discord may also be understood in terms of subregion functional specificity, with potentially different neural contributors within the same activation cluster (Cauda et al., 2011).

Previous findings derived from human stroke patients, where insula lesions reduced immediate monetary reward preference (Sellitto et al., 2016) and desire to smoke tobacco (Naqvi et al., 2007), included participants with large insular lesions showing substantial anatomic variability, making direct comparisons with the current findings difficult. For example, if the posterior insula—associated with primary emotional and sensory states—is ablated more than the AIC in a patient, we might reasonably expect different or even opposite effects than if the lesion was contained in the AIC. Similar outcomes might be expected with lesions that included both dorsal and ventral aspects of the AIC. Our correlational findings occur in the functionally distinct right dAIC and cannot necessarily be extrapolated to the insula *writ large*, and concur with prior work implicating the right dAIC in adaptive intertemporal choice (Kayser et al., 2012) and goal-directed responding (Wang et al., 2018).

Limitations of this study warrant consideration. The sample size was modest, and future work should replicate the design with a larger sample. Additionally, most participants had a history of co-use of other substances. Although we detected activation differences in participants who recently used illicit drugs, these differences were only present when compared to implicit baseline, and were not detected when compared to an active condition. The higher activation (vs. baseline) in the Nonuser group broadly supports the notion that stronger salience network activation corresponds to more adaptive behavior. While the polysubstance use observed in this sample potentially contributes to nonalcohol related variability, it reflects the more-likely real world phenotype (McLellan et al., 1994). This is consistent with the Collaborative Research on Addiction at NIH (CRAN) viewpoint, which acknowledges the common comisuse of alcohol and other drugs with concomitant pathology and mechanisms. Thus, the current sample may suffer from additional sources of variability but has greater generalizability to actual AUD populations.

By design, all participants were "problem drinkers", which limits interpretations regarding social drinkers, nondrinkers, past drinkers and potential group differences between such samples.

While results here are entirely within-subjects and not compared to controls, studies using group comparisons detect insula differences in both structure and function between heavy drinkers and controls (Demirakca et al., 2011; Momenan et al., 2012). In addition, nontreatment-seeking AUD participants show aberrant functional connectivity patterns from the anterior insula with multiple brain regions, contrasted with healthy participants (Halcomb et al., 2019). Additionally, AIC cortices showed lower volume and thickness relative to controls, with morphometric measures negatively correlated with trait and behavioral impulsivity (BIS and DD) in AUD participants (Grodin et al., 2017). These deficits may underlie the robust findings of executive impairment in AUD—most readily detected in bias toward immediate reward, cognitive flexibility, and response inhibition (Iowa Gambling Task, Wisconsin Card Sorting Task, and Hayling Test, respectively; Stephan et al., 2017 meta-analysis) and high levels of trait impulsivity (Coskunpinar et al., 2013).

Although restricting the sample to problem drinkers limits comparisons with controls, it provides more power to examine the group of greatest clinical relevance and interest. While there was considerable variability in participants' drinking patterns, this breadth permitted power for detection of drinking-related associations. Our findings should be interpreted with caution with respect to light drinkers. Although DD tasks using monetary reinforcers have a strong record in detecting group differences between those with addictions and healthy controls, single-commodity monetary DD does not precisely model alcohol-specific AUD decision making (involving the choice between intoxication and other future rewards). However, monetary choices appear to be a reasonable proxy for reward decision making for other commodities, as cross-commodity alcohol: money choices are strongly correlated with single-commodity monetary discounting, even while intoxicated (Oberlin et al., 2021), consistent with prior work suggesting a common underlying preference that underlies temporal discounting of many commodities (Odum, 2011).

The current findings are the first to report that activation of one specific subregion of the AIC during intertemporal choice is associated with better control over both impulsive behavior and alcohol consumption. We also identified alterations in AIC connectivity with self-referential default mode nodes. This emergent information about the role of the AIC in addiction-relevant behavior in heavy drinking populations provides a focused path for more targeted future investigations and perhaps novel therapeutic approaches. Understanding the neural substrates underlying impulsive choice is essential for understanding AUD pathology and should ultimately drive future progress in AUD treatment.

AUTHOR CONTRIBUTIONS

BO, MD conceived and designed, BO, YIS, MD acquired data for the study; BO, MD, MH, ZL, TJB performed processing, scripting, and analyses, MH wrote the initial draft, and MH, MD, YIS, ZL, TJB, KKY, and BO performed critical revisions and finalized the manuscript and approved the final version for publication.

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CONFLICT OF INTEREST

We have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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