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ARTICLE

Acute depletion of dopamine precursors in the human brain: effects on functional connectivity and alcohol attentional bias

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Individuals who abuse alcohol often show exaggerated attentional bias (AB) towards alcohol-related cues, which is thought to reflect reward conditioning processes. Rodent studies indicate that dopaminergic pathways play a key role in conditioned responses to reward- and alcohol-associated cues. However, investigation of the dopaminergic circuitry mediating this process in humans remains limited. We hypothesized that depletion of central dopamine levels in adult alcohol drinkers would attenuate AB and that these effects would be mediated by altered function in frontolimbic circuitry. Thirty-four male participants (22–38 years, including both social and heavy drinkers) underwent a two-session, placebo-controlled, double-blind dopamine precursor depletion procedure. At each visit, participants consumed either a balanced amino acid (control) beverage or an amino acid beverage lacking dopamine precursors (order counterbalanced), underwent resting-state fMRI, and completed behavioral testing on three AB tasks: an alcohol dot-probe task, an alcohol attentional blink task, and a task measuring AB to a reward-conditioned cue. Dopamine depletion significantly diminished AB in each behavioral task, with larger effects among subjects reporting higher levels of binge drinking. The depletion procedure significantly decreased resting-state functional connectivity among ventral tegmental area, striatum, amygdala, and prefrontal regions. Beverage-related AB decreases were mediated by decreases in functional connectivity between the fronto-insular cortex and striatum and, for alcohol AB only, between anterior cingulate cortex and amygdala. The results support a substantial role for dopamine in AB, and suggest specific dopamine-modulated functional connections between frontal, limbic, striatal, and brainstem regions mediate general reward AB versus alcohol AB.

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INTRODUCTION

Attentional bias (AB) towards alcohol-related stimuli predicts alcohol craving [1], relapse risk [2–4], and future alcohol drinking [5]. Although the latter clinical predictive relationships are inconsistent [6], AB does appear to measure an underlying addiction state or trait. One such trait that is closely related to AB is a susceptibility to reward conditioning [7]. The development of AB to addiction-related cues is thought to reflect Pavlovian learning, such that drug reward-predicting cues eventually acquire the capacity to initiate drug seeking and use [8, 9]. Indeed, AB is greater among heavier drinkers [10]. AB to non-drug rewards is also heightened in the context of addiction, suggesting that substance misuse more generally associates with sensitivity to reward conditioning [11, 12]. However, whether alcohol-related AB relies on the same brain circuits as non-drug reward conditioning and AB is uncertain.

Human neuroimaging studies have begun to examine the neural correlates of alcohol AB. Testing individuals recovering from alcohol use disorder (AUD) on a dot-probe task, researchers identified positive correlations between alcohol AB and activations in the inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), anterior insula, and striatum [13]. Individuals with AUD also displayed heightened nucleus accumbens (NAc) and medial prefrontal cortex activation during an implicit alcohol approach bias task [14]. Evidence from an alcohol word Stroop task indicates prefrontal hypoactivation associated with alcohol AB in AUD [15]. These prior studies highlight a role for frontal and limbic brain regions in AB to addiction-related cues. However, human fMRI studies of addiction AB have not yet identified the functional neurocircuitry mediating this behavior.

Given the limitations of current non-invasive human neuroimaging methods, rodent studies have been instrumental in probing the neural circuits of behavior. While AB is difficult to model in rodents, much is known about Pavlovian conditioned responses to reward-predictive cues. For example, mesolimbic dopamine projections from the ventral tegmental area (VTA) to the NAc play a critical role in both Pavlovian conditioning and the expression of conditioned responses [16, 17]. In addition, fast dopamine release events (dopamine transients) commence at the onset of a conditioned cue [18, 19]. Pavlovian conditioned responses to alcohol cues in rodents provide a model of alcohol AB that allows direct measurements and mechanistic manipulations of the neural circuitry underlying AB [20–22]. Taken together, preclinical evidence indicates a key role for dopaminergic pathways in mediating responses to alcohol-related cues [23–25]. Moreover, work in non-human primates highlights a role for the prefrontal cortex in reward signaling [26], and human fMRI studies show that prefrontal cortex drives phasic cue responses in the VTA

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[27, 28]. However, the dopaminergic circuitry mediating AB to alcohol cues in humans––and the extent to which this circuitry overlaps with the circuitry mediating conditioned responses to non-drug rewards––remains unclear.

The goal of the current study was to map the dopaminergic functional circuitry underlying alcohol AB in human subjects. To do so, we transiently reduced dopamine in human subjects by administering an amino acid beverage deficient in the dopamine precursors phenylalanine and tyrosine (P/T) [29, 30] prior to resting-state fMRI and testing on three AB tasks. In event-related fMRI procedures, dopamine depletion decreases reward-related brain activation [31–33] and reduces AB to smoking cues [34]. Thus, we hypothesized that acutely lowering dopamine via P/T depletion would reduce AB to both alcohol cues and non-drug, reward-conditioned cues and would do so in proportion to changes in the functional connectivity (FC) between prefrontal and subcortical brain regions. Furthermore, we predicted greater reductions in AB among subjects reporting heavier alcohol use. Because adolescent and recent alcohol use differentially impact the mesolimbic dopaminergic system [25, 35–38], we tested for both effects on AB. As behaviors modulated by PFC dopamine show ovarian cycle-dependent variance in females [39–46], here we tested adult males ($n = 34$) in two separate sessions: a P/T depletion session and a control session, in a double-blind, counter-balanced design.

METHODS

Participants

Thirty-four healthy male participants (ages 22–38 years; mean = 26.3) were recruited from the University of North Carolina, Chapel Hill (UNC) campus and surrounding communities. Although our statistical tests utilized continuous measures of alcohol use, to ensure a broad distribution of alcohol use, we recruited participants into two groups that were guided by the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) definitions for moderate drinking and binge drinking [47]. The moderate, social drinking group ($n = 15$) self-reported <14 alcoholic drinks/week, <10 lifetime binge episodes, and no binge episodes in the past 12 months. The frequent binge drinking group ($n = 15$) self-reported ≥14 alcoholic drinks/week and ≥12 binge episodes (≥5 drinks/2 h) in the past 12 months. Participants had no current or past neurological or psychiatric diagnoses, no contraindications for MRI or the amino acid depletion manipulation. Additional exclusion criteria were current psychoactive drug use (including medications), history of treatment for a substance use disorder, or lifetime substance use disorder based on a structured clinical interview using DSM-IV criteria [48]. One participant reported light, non-dependent vaping. No participants reported any lifetime regular use of psychoactive medications (see Supplementary Materials). For individuals enrolled as heavy drinkers, current or past AUD was not exclusionary. All participants were native English speakers, right-handed, and had at least a high school education (or equivalent). Negative breathalyzer tests (FC-10, Lifeloc Inc., Wheat Ridge, CO) and urine drug screens for cocaine, THC, amphetamines, methamphetamine, and opiates (Biotechnostix, Inc., Markham, ON) were obtained at the beginning of each session; participants were instructed not to drink alcohol for 24 h before the session. Participants gave written, informed consent, as approved by the UNC Office of Human Research Ethics.

General procedure

We used a double-blinded, within-subjects, counter-balanced design consisting of two laboratory visits of ~8 h each; visits were separated by ≥72 h. The visits were identical and began with urine, alcohol, and health screening. Following screening, participants were given up to 30 min to consume the amino acid-containing beverage (see "Dopamine Depletion Procedure"). Following beverage consumption, participants completed questionnaires (see "Alcohol Use Inventories" and Supplementary Materials) and relaxed in the lab; 4–5 h after beverage consumption, they underwent a resting-state fMRI scan, then completed computerized behavioral tasks outside the scanner (see "Behavioral Tasks"). Participants were dismissed after being offered a high protein snack and were compensated for participation after completing the second visit.

Dopamine depletion procedure

The P/T depletion method has been safely used for many years, and its effects on brain dopamine levels are well established [49, 50]. As in our previous studies [29, 30], prior to each test session, subjects followed a low protein (<20 g) diet for 24 h and fasted from midnight until session onset (~8 A.M.). After participants provided a written account of their diet in the previous 24 h, they consumed either a control amino acid beverage or one deficient in the dopamine precursors, phenylalanine (P), and tyrosine (T) (see Supplementary Materials), to initiate the acute dopamine depletion process [51]. Under typical brain P/T concentrations, T is the preferred substrate for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, but T-depletion without P-depletion is not sufficient to reduce brain dopamine [52]. Amino acid beverages lacking P and T decrease brain P/T concentrations [53–55] after 4–5 h [50]. Although brain norepinephrine synthesis is also reduced by P/T depletion [56] the dopamine system seems to be disproportionately affected [57], a distinct advantage of this method over administering the tyrosine hydroxylase inhibitor α-methyl-para-tyrosine (AMPT) [58], which also requires multiple doses and can cause motor and urinary side effects [59] and is generally used in an in-patient setting.

Alcohol use inventories

We quantified current alcohol use with the Alcohol Use Questionnaire [AUQ; 60] from which we calculated a "binge drinking score" [60]. This score was log transformed to provide a Gaussian distribution suitable for parametric statistics. The Carolina Alcohol Use Patterns Questionnaire (CAUPQ [61]) was used to estimate a total number of adolescent (0–21 years) binge episodes (see Supplementary Materials) and quarter-root transformed before statistical analysis.

Resting-state fMRI

We acquired resting-state fMRI data as 243 blood oxygenation level-dependent (BOLD) images on a Siemens 3 T Prisma scanner equipped with a 32-channel TEM send–receive radio frequency (RF) head coil (Siemens Healthineers, Erlangen, Germany), using a 1-shot gradient-echo EPI pulse sequence (TR = 2 s, TE = 25 ms, flip angle = 50°, 35 slices tilted at 30° from horizontal plane; FoV = 192 × 192 mm; voxel size = 3 × 3 × 4 mm with a 0.5 mm inter-slice gap). The fMRI acquisition was preceded by 11 s of dummy gradient RF pulses to achieve steady-state tissue magnetization. We also acquired a low-resolution T1-weighted co-planar image and a high-resolution magnetization-prepared rapid gradient-echo (MPRAGE) T1-weighted image (see Supplementary Materials). Participants were directed to stay awake, look at the fixation crosshair on a screen, and "let their minds wander" without focusing on particular thoughts.

Behavioral tasks

Dot-probe task. We assessed selective attention capture using a dot-probe task modified from our previous studies assessing AB toward smoking cues in cigarette smokers [62, 63] (See Supplementary Materials). Faster response times (RT) in trials in which the target was congruent with the alcohol image versus the neutral image indicates AB toward alcohol-related cues via selective attention capture.

Modified attentional blink task. To measure extended attention hold, participants completed a modified attentional blink task based on the emotional blink of attention paradigm [64–68] (See Supplementary Materials for details). Trials contained a rapid serial presentation of upright landscape or house images [69, 70], except for two images: the critical distractor (either neutral or alcohol-related images) and the target stimulus. Targets were house photos rotated 90° left or right and occurred 2 or 8 images after the distractors. Participants indicated the target orientation by button press. Reduced lag 2 accuracy relative to lag 8 accuracy indicates a greater attentional blink, and a greater blink following an alcohol distractor relative to neutral distractor is interpreted as greater AB to alcohol cues.

Reward task. We assessed reward conditioning sensitivity using a value-driven attention capture task identical to one described elsewhere [11] (Supplementary Materials). Briefly, participants were first trained to implicitly associate the colors red and green with a high or low reward (counterbalanced across subjects). In a separate test of reward conditioning, participants were instructed to ignore colors. However, 50% of trials included non-target red or green stimuli, representing conditioned distractors. Prolonged RTs in trials containing a distractor stimulus previously associated with reward indicates AB to reward-conditioned cues.

Behavioral analyses. We assessed whether measures of current or adolescent binge drinking moderated effects of dopamine depletion on AB using repeated-measures linear mixed models with PROC MIXED in SAS 9.4. We opted to use linear mixed models (LMM) rather than repeated-measures (RM) analysis of variance (ANOVA) here, as linear mixed models are better suited to handle missing data, among other advantages over RM-ANOVA [71]. All models included beverage order, as well as both current binge score and adolescent binge drinking as independent variables. Based on the hypothesis that heavier drinking would be associated with greater effects of dopamine depletion on AB, we specifically tested for interacting effects of beverage type and task parameters with binge drinking (independently for both current and adolescent) on performance in each task.

For the dot-probe task, the dependent measure was RT from correct trials. AB is measured by effects of cue type (neutral or alcohol). We excluded trials in which the RT was >2 standard deviations above the individual's mean RT for that trial type or <200 ms. One participant was missing data from one session. In the LMM for this task we tested for significant interacting effects of both beverage type × cue type × current binge drinking, and beverage type × cue type × adolescent binge drinking.

For the attentional blink task, the dependent measure was the accuracy of target responses. AB is measured by the interaction of the lag (2 or 8) and distractor type (neutral or alcohol). Trials in which the RT was <200 ms were excluded. One participant was missing data from both sessions. In the LMM for this task we tested for significant interacting effects of both beverage type × cue type × lag × current binge drinking, and beverage type × cue type × lag × adolescent binge drinking.

For the reward task, the dependent measure was RT from correct responses during the test phase. To measure AB, a linear variable modeling the distractor trial type (high = 2, low = 1, no reward = 0) was created [72]. We excluded trials in which the RT was >3 standard deviations above the individual's mean RT for that trial type or <200 ms. Thirteen participants only completed the task during their first session. In the LMM for this task we tested for significant interacting effects of both beverage type × distractor type × current binge drinking, and beverage type × distractor type × adolescent binge drinking.

We examined the behavioral evidence for overlapping mechanisms of alcohol and non-drug reward AB by conducting pairwise Spearman's partial correlations among the three AB tasks, covarying for beverage effects. AB values were residual values from the linear regression analysis with the beverage effect added back; because this calculation provides a separate adjusted value for each trial type, a mean value was calculated to get a single AB score for each session.

Neuroimaging analyses. FMRI preprocessing included the following steps using Analysis of Functional Neuroimages (AFNI [73], version 19.3.07): slice time correction; realignment; co-registration to the low-resolution T1 image; MPRAGE segmentation; regression of nuisance time series corresponding to white matter, cerebrospinal fluid, and subject-specific realignment parameters; and normalization to a standard template in Montreal Neurological Institute (MNI) space. Images were resampled back into the original 2 mm^3 voxel resolution and spatially smoothed with a 5 mm Gaussian kernel. A temporal filter of 0.008–0.1 Hz was applied. Data were "scrubbed" using a framewise displacement threshold of >0.3 mm, resulting in the removal of the flagged time point along with one preceding and two following [74]. Furthermore, two participants exhibiting an average framewise displacement of >0.2 mm for at least one session were omitted from FC analyses due to the likelihood of persistent motion artifacts [75].

Regions-of-interest analysis. An a priori-selected neural circuit of dopaminergic pathways predicted to underlie alcohol AB included the VTA, striatum, amygdala, and prefrontal cortical regions that are anatomically connected to the VTA and involved in motivated behaviors [76–81]. Mean time series were extracted from a priori regions of interests (ROI) selected from published research findings (Table 1). For each beverage condition, Pearson correlation values of the 11 ROI time series were calculated and Fisher-Z transformed. FC values were assessed for main effect of P/T depletion via general linear model covarying for beverage order, FC on placebo to account for individual differences in baseline FC/dopamine levels [29], and global FC of each of the two ROIs to account for motion induced FC effects [82]. Results were corrected for

Table 1. Regions of interest for functional connectivity analysis.

Region of interest	MNI coordinates	Sources
Ventral tegmental area (VTA)	Probabilistic atlas	[120]
Dorsolateral prefrontal cortex (dlPFC)	Left: −48, 18, 44 Right: 48, 18, 44	[121]
Anterior cingulate cortex (ACC)	−8,24,34	[121]
Fronto-insular cortex (FIC)	Left: −38, 24, −8 Right: 34, 24, −8	[121]
Inferior frontal gyrus pars opercularis (IFGop)	Structural atlas	Harvard–Oxford cortical and subcortical atlases [122]
Medial orbitofrontal cortex (medOFC)	Left: −6, 37, −12 Right: 6, 37, −12	[123]
Amygdala (Amy)	Left: −20, 6, 10 Right: 20, 6, −12	[123]
Lateral orbitofrontal cortex (latOFC)	Left: −27, 39, −6 Right: 27, 39, −6	[123]
Limbic striatum (striatum L)	Probabilistic atlas	[124]
Executive striatum (striatum E)	Probabilistic atlas	[124]
Sensorimotor striatum (striatum S)	Probabilistic atlas	[124]

multiple comparisons using a false discovery rate correction (FDR, $q = 0.05$).

Whole-brain VTA seed-based analysis. Because a priori ROI selection may miss potentially significant FC changes among regions not included in the analysis, we also conducted an exploratory seed-based FC analysis to examine whole-brain changes in VTA FC in a voxel-wise manner. Main effects of P/T depletion were tested via general linear model covarying for beverage order, FC on placebo [29], and global VTA FC [82]. Results were FDR corrected for multiple comparisons ($q = 0.05$).

Mediation Analyses. Mediation analyses using the Multilevel Mediation and Moderation (M3) Matlab Toolbox [83] identified functional connections that mediated the effects of P/T depletion on AB for each of the AB tasks. We limited mediation testing to those ROI–ROI connections for which the depletion effects survived a threshold of $p < 0.05$, uncorrected, since these connections were most likely to contribute to significant indirect effects. FC values (i.e., the mediators) in these analyses were residual values from the linear model described above ("*Regions-of-Interest Analysis*"). Likewise, AB values (i.e., the outcome variables) were also adjusted values identical to those used in the task behavioral correlation analysis (see "*Behavioral Analyses*"). Significance testing was performed with 100,000 bootstrap iterations and a 95% CI, one-tailed distribution. Due to multiple tests performed across 10 ROI–ROI connections and three tasks, results were FDR-corrected ($q = 0.05$). Only participants with complete FC and AB data for the given task were included for each analysis.

RESULTS

Demographic and psychometric data

Drinking groups were similar in age, years of education, and familial alcoholism (Supplementary Table 2). Individuals recruited to the heavy drinking group reported higher rates of current and adolescent binge drinking, although these measures were only modestly correlated across groups ($\rho = 0.36$, $p = 0.037$)

Effects of P/T depletion on AB measures

As detailed below, linear mixed models (LMMs) of performance in each behavioral task indicated that P/T depletion diminished AB to a greater extent among subjects reporting higher levels of binge drinking. For the dot-probe task, the LMM found significant interacting effects of beverage type, cue type, and current binge drinking on RT ($t_{(30)} = -2.28$, $p = 0.030$; Fig. 1a); however, adolescent binge drinking did not significantly interact with beverage type and cue type ($t_{(30)} = 1.57$, $p = 0.12$). In other words, current binge drinking significantly moderated the change in AB after P/T depletion. Specifically, the difference in RT between alcohol and neutral cues on placebo was greater for those reporting greater current binge drinking, but this AB effect was diminished by P/T depletion.

For the attentional blink task, the LMM found significant interacting effects of beverage type, cue type, lag, and adolescent binge drinking on accuracy, indicating that adolescent binge drinking significantly moderated the change in AB after P/T depletion ($t_{(30)} = -2.52$, $p = 0.017$; Fig. 1b). Specifically, adolescent binge drinking was associated with lower alcohol lag 2 accuracy, and this AB effect was rescued by P/T depletion. The LMM did not find a statistically significant interaction of current binge drinking with beverage type, cue type, and lag ($t_{(30)} = 1.35$, $p = 0.19$).

For the reward task, the LMM found significant interacting effects of beverage type, distractor type, and adolescent binge drinking on RT, again finding that adolescent binge drinking significantly moderated the change in AB after P/T depletion ($t_{(30)} = 3.93$, $p < 0.001$; Fig. 1c). The significant interaction reflected a larger non-drug reward AB on placebo among those reporting more frequent adolescent binge drinking, which was diminished following P/T depletion. Again, the corollary interaction term that instead included current binge drinking was not statistically significant ($t_{(30)} = -0.48$, $p = 0.63$).

Covarying for P/T depletion effects, AB toward alcohol cues in the dot-probe task positively correlated with AB toward to alcohol cues in the blink task ($\rho_{(58)} = 0.34$, $p = 0.008$) and with AB toward conditioned non-drug cues in the reward task ($\rho_{(49)} = 0.32$, $p = 0.023$). Alcohol AB in the blink task also correlated with AB on the reward task ($\rho_{(47)} = 0.41$, $p = 0.003$).

P/T depletion effects on frontolimbic FC

Using an ROI-to-ROI approach, we assessed beverage-related changes in pairwise FC (Fig. 2). Ten connections showed altered FC ($p < 0.05$; these 10 were included in mediation analyses), six of which survived an FDR correction. Nine of these connections demonstrated reduced FC with P/T depletion, whereas only one connection demonstrated greater FC.

Dopamine depletion effects on VTA FC

As the VTA is a major nucleus of dopamine cell bodies, we explicitly assessed changes in connectivity with the VTA induced by depletion of dopamine precursors. In testing for voxels demonstrating significant changes in FC with the VTA following P/T depletion, we found decreased FC between the VTA and the OFC, NAc, intra-parietal sulcus and the superior frontal sulcus (Fig. 3; Supplementary Table 3), whereas increased FC was detected with the brainstem, temporal lobe, caudate tail, and cerebellum.

Mediation Analyses

Several ROI–ROI connections mediated the effects of P/T depletion on AB. For the blink task, P/T-depletion effects on AB were mediated by FC changes between both fronto–insular cortex (FIC)–limbic striatum and ACC–amygdala (Fig. 4a). Although these same two connections also demonstrated mediating effects of P/T depletion on dot-probe AB ($p_{uncorrected} < 0.05$), the effects did not survive an FDR correction. Similar to the alcohol AB tasks, depletion effects on reward task AB were mediated by FIC–limbic striatum FC changes; reward task AB was additionally mediated by FC changes between the FIC and both executive and sensorimotor subdivisions of the striatum (Fig. 4b).

DISCUSSION

Here we quantified AB toward alcohol and non-drug, reward-conditioned cues and their neural underpinnings after acute dopamine precursor depletion across a broad spectrum of alcohol users. P/T depletion significantly reduced AB across three different tasks, particularly in individuals who reported heavier drinking. P/T depletion altered FC between prefrontal and subcortical brain regions involved in reward processing and motivation, and these alterations predicted changes in AB.

AB behavior following dopamine depletion

P/T depletion reduced AB to both alcohol and non-drug, reward-conditioned cues in this study. This reduction is consistent with the one prior study that tested the effects of P/T depletion on smoking AB [34]. Animal studies demonstrate that mesolimbic dopamine projections from the VTA to the NAc play a critical role in both Pavlovian conditioning and expression of conditioned responses, which are often conceptualized as a preclinical model of AB [16, 17]. Human neuroimaging work also indicates a role of dopamine release, specifically within the anterior caudate, in generalized reward conditioning [84]. In addition to conditioned responding, the AB tasks employed in the current study also require attentional processes such as alerting, and orientating to

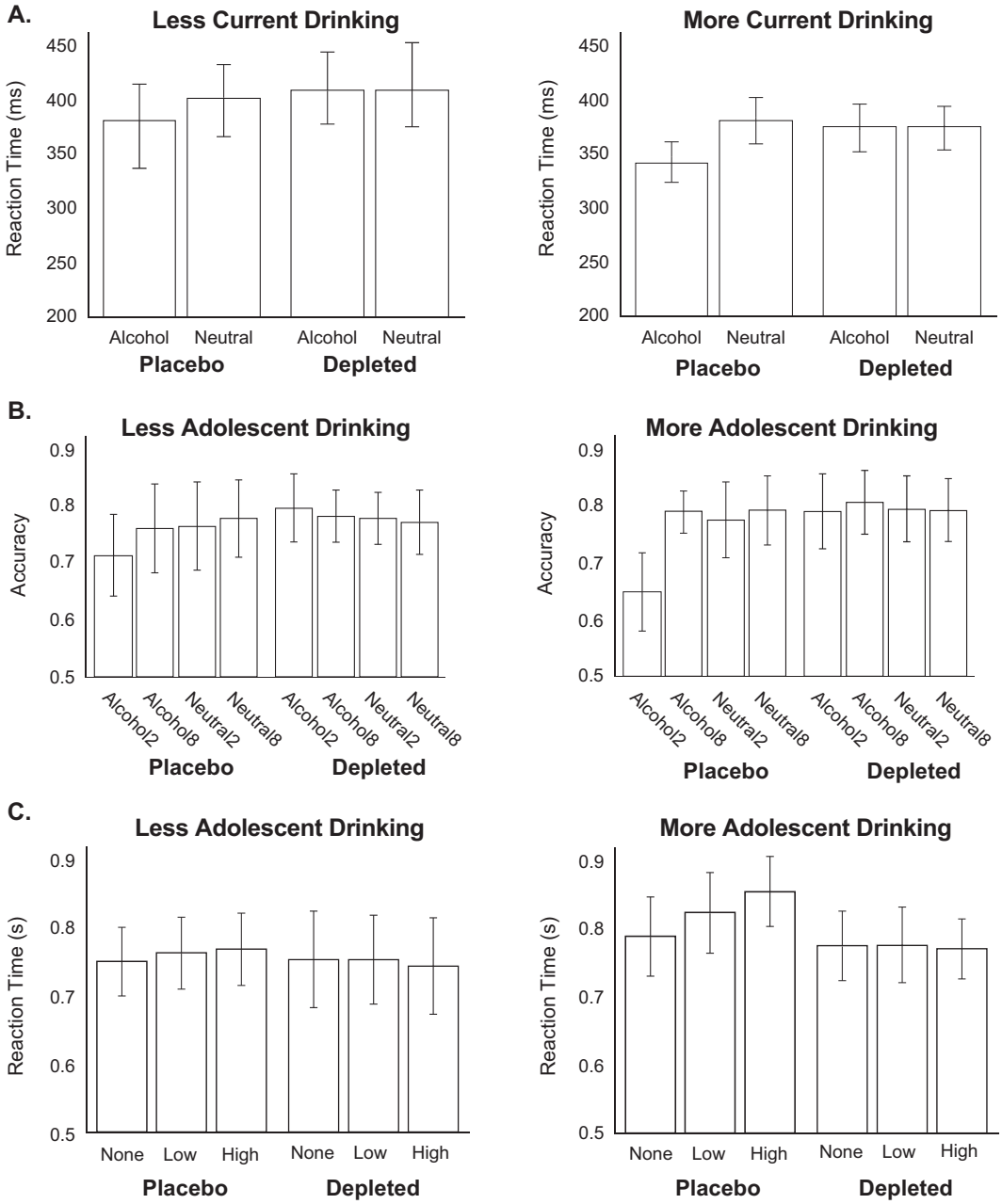

Fig. 1 Dopamine depletion attenuates attentional bias, dependent on binge drinking severity. A For the dot-probe task, a linear mixed model indicated a significant beverage type × cue type × current binge drinking interaction effect on RT. **B** For the attentional blink task, a linear mixed model indicated a significant beverage type × cue type × lag × adolescent binge drinking interaction effect on accuracy. **C** For the reward task, a linear mixed model indicated a significant beverage type × distractor type × adolescent binge drinking interaction effect on RT. Least squares means are presented. For display purposes, binge drinking was binarized: "More Current Binge Drinking" corresponds to an Alcohol Use Questionnaire binge score of >10, whereas "More Adolescent Binge Drinking" corresponds with >9 estimated binge episodes by the age of 21.

stimuli, and executive control function processes relying on dopamine [85]. Thus, the observed AB changes following P/T depletion reflect not only changes to dopamine transients [57] in response to conditioned cues [18, 19], but also changes to catecholamine systems involved in attention and cognitive control. While data suggest that P/T depletion affects dopamine more than norepinephrine [50, 58, 86, 87], changes to norepinephrine systems could contribute to the effects reported here.

The effects of P/T depletion on AB in this sample of light/moderate to heavy drinkers depended on binge drinking levels. Specifically, greater binge patterns of drinking during adolescence enhanced AB effects in the reward task and the blink task, whereas current binge drinking more strongly predicted AB effects in the dot-probe task. These findings were consistent with the enhanced AB present among heavier versus lighter drinkers [10], an association attenuated here by P/T depletion. Exposure to alcohol during adolescence is associated with persistent changes in brain function [88, 89]. Preclinical models of adolescent binge drinking demonstrate deleterious effects of alcohol exposure on neurogenesis [90] as well as on prefrontal function, leading to persistent changes in adult cognition [91–93]. Significant changes to reward neurocircuitry also occur during this period [94, 95]. Our findings of adolescent alcohol exposure moderating P/T

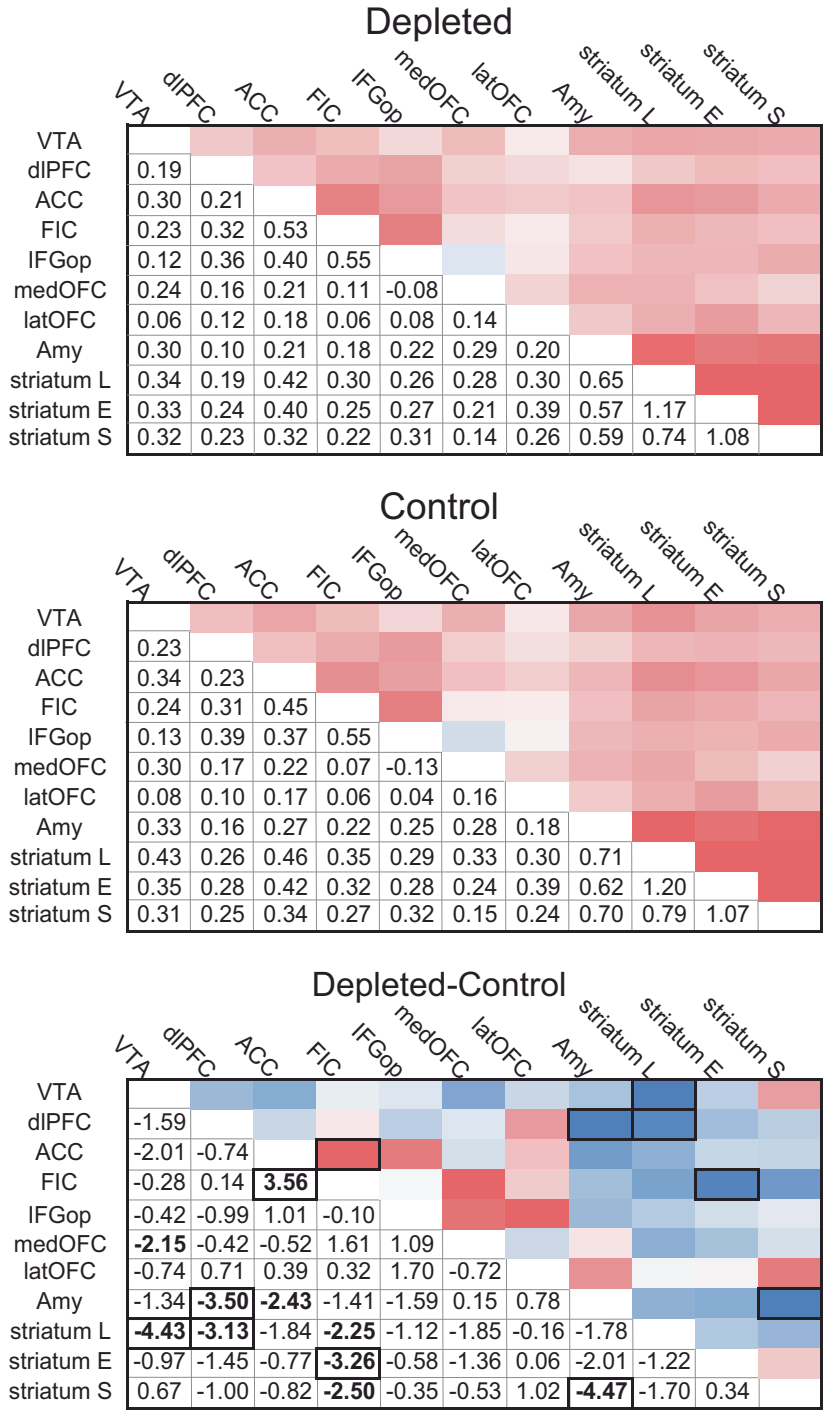

Fig. 2 Region-of-interest analysis results. Functional connectivity estimates (Fisher *Z*-transformed Pearson correlations) are displayed for the depleted (top) and control (middle) beverages and t-statistics are displayed for the contrast of depleted minus control (bottom). Bold text indicated $p < 0.05_{uncorrected}$, whereas outlined cells indicate connections surviving an FDR correction. VTA ventral tegmental area, dlPFC dorsolateral prefrontal cortex, ACC anterior cingulate cortex, FIC fronto–insular cortex, IFGop inferior frontal gyrus pars opercularis, medOFC medial orbitofrontal cortex, latOFC lateral orbitofrontal cortex, Amy amygdala, striatum L limbic subdivision of the striatum, striatum E executive subdivision of the striatum, striatum S sensorimotor subdivision of the striatum.

depletion-related changes in AB, even when controlling for current drinking, is consistent with the harmful consequences of alcohol on the developing brain. However, it is also possible that effects of adolescent binge drinking on AB reflect premorbid cognitive differences between those who initiated alcohol use in adolescence and those who did not; notably, impulsive behavior in childhood predicts adolescent misuse of alcohol and other substances [96, 97], and impulsivity further predicts AB [72]. We also found that current binge drinking levels predicted AB on the dot-probe task, covarying for adolescent alcohol binges. In adult rodents, binge-like drinking exposure leads to deficits [98] in prefrontal functions including reversal learning [99, 100]. Taken together, these findings emphasize the importance of both past and current binge drinking on AB and provide insight

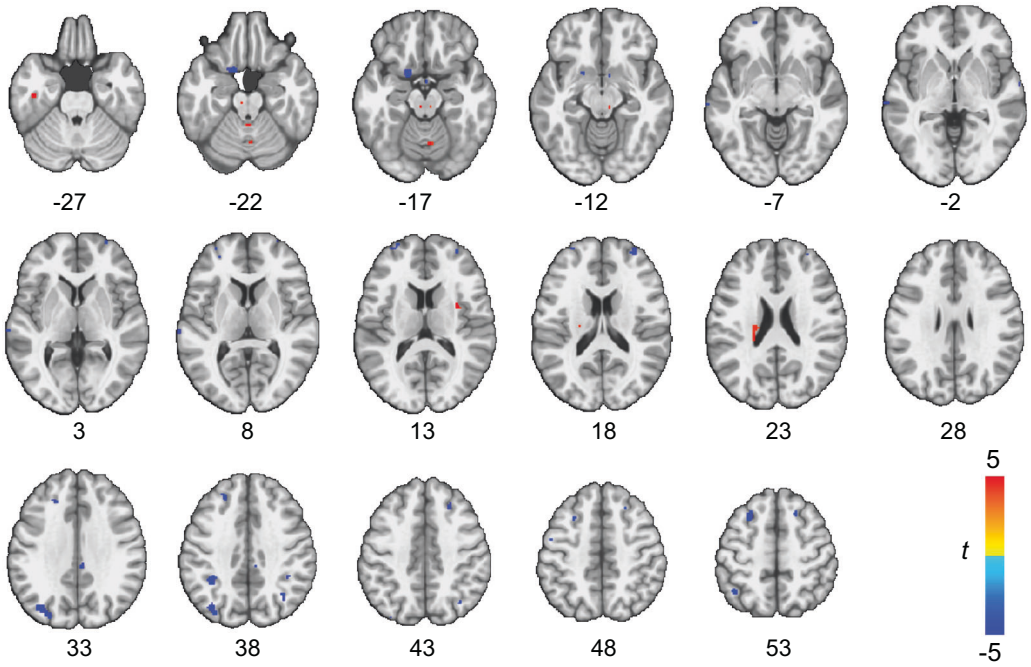

Fig. 3 Voxel-wise results of dopamine depletion effects on functional connectivity of the ventral tegmental area (VTA). Warm colors indicate increased connectivity following dopamine depletion, whereas cool colors indicate decreased connectivity following dopamine depletion. Significant voxels after false discovery rate (FDR) correction are displayed.

into developmental and acute impacts of alcohol on the dopamine system.

Beverage effects on FC

Although two previous studies reported changes in intrinsic FC associated with dopamine precursor depletion [101, 102], this is the first to link such changes to attentional control, as well as the first to show moderating effects of binge drinking history. This procedure mostly reduced FC between prefrontal (i.e., FIC, MFG) and subcortical (i.e., striatum, amygdala, VTA) brain regions. An increase in FC between ACC and FIC, two core regions of the "salience network" [103], was a notable exception. A seed-based approach enabled a whole-brain examination of VTA FC changes that was not restricted to a priori ROIs. This analysis revealed diminished VTA FC with both reward-related regions (e.g., OFC and NAc) as well as regions involved in visual attention (e.g., intra-parietal sulcus). These findings support the recent suggestion that dopamine may stabilize signaling within networks engaged when orienting attention towards behaviorally relevant stimuli [101].

FC mediation of AB

The consistent mediation of AB by FIC–limbic striatum across all three tasks (although not significant after FDR correction for the dot-probe task) indicates a general mechanism of processing reward-predicting cues, which may represent a trait marker of susceptibility to reward conditioning. The limbic striatum ROI is primarily centered in the NAc. Indeed, preclinical work emphasizes the role of NAc in stimulus-reward learning [17, 104], which extends to drug-related cues [22, 105–107]. This coherent FC relationship across AB tasks is also consistent with the significant correlations between behavioral measures of AB. Conversely, ACC–amygdala FC only mediated alcohol-related AB. Interactions between these two brain regions modulate responses to emotional stimuli [108–110] and may also underlie motivation for rewards [111]. The unique association of this connection with alcohol AB, but not generalized reward AB, suggests that alcohol cues become imbued with distinct emotional and motivational qualities beyond their ability to predict reward.

It is noteworthy that the ACC and FIC––the prefrontal brain regions for which increased FC following P/T depletion mediated AB in this study––are major hubs of the salience network that is involved in conditioning and assigning incentive salience to drugs and drug-related cues [112]. The FIC specifically facilitates access to attention and working memory resources when a salient event is detected and regulates reactivity to salient stimuli [113, 114]. Our findings support prior work indicating the importance of dopaminergic signaling in salience network FC [101, 115], and supporting a potentially key role for this functional network in AB [116].

Strengths and limitations

The within-subjects, repeated-measures study design afforded power to detect significant effects of dopamine depletion despite an otherwise modest sample size (34 individuals). A study limitation is that, although our results indicated P/T depletion effects on the brain and behavior, we did not directly measure dopamine or dopamine metabolite levels. Individual differences, such as baseline dopamine levels, sex, state factors, and genetic factors may play a role in the depletion effects as seen in previous studies [29, 117]. Our conclusions would have been strengthened by including plasma measurements of amino acids to confirm the effectiveness of the P/T depletion procedure. In addition, this study only included males due to sex differences in the dopamine system [118, 119]. Finally, preclinical studies demonstrate phasic dopamine release in response to conditioned reinforcers [23, 36], and P/T depletion suppresses spontaneous dopamine transients in the NAc of rats at rest [57]. However, in this study, the behavioral tasks were performed after the resting-state scan; future work pairing event-related fMRI AB tasks with the P/T depletion procedure may provide additional insight into the dopamine response to alcohol or non-drug reward cues.

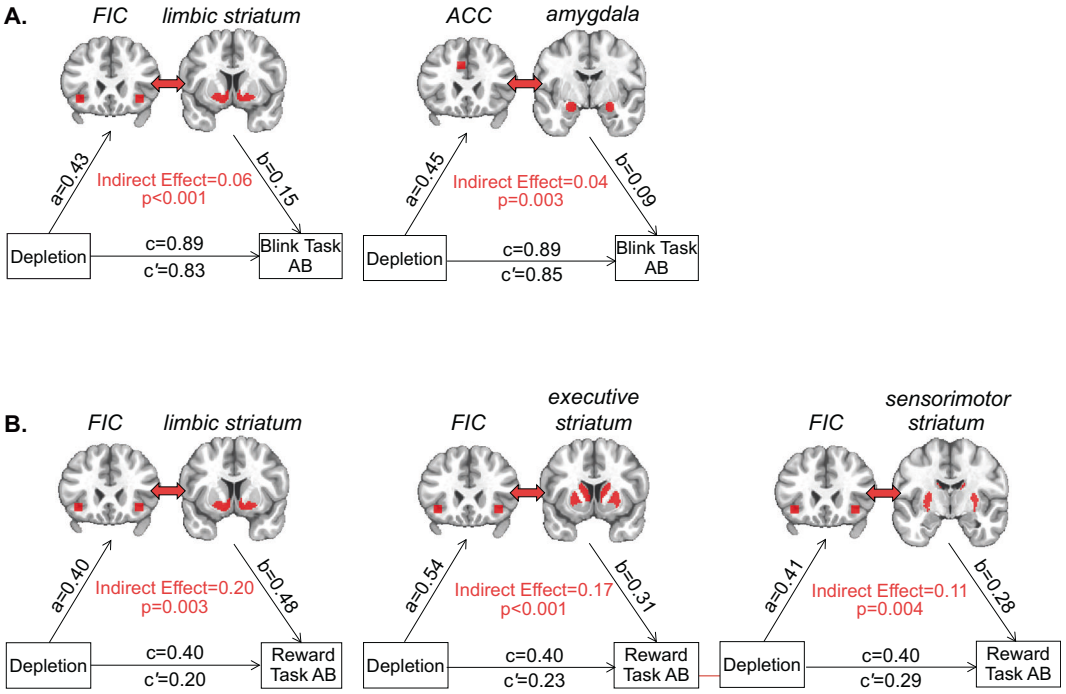

Fig. 4 Mediation analysis results. Functional connectivity mediation of dopamine depletion effects on (**A**) attentional bias on the blink task and (**B**) attentional bias on the reward task. Significant indirect effects indicate the functional connection significantly mediated the effect of beverage type on attentional bias. c is the direct effect without the mediator, and c′ is the effect after entering the mediator.

CONCLUSIONS

Our findings are the first to identify the dopamine-related functional connections underlying alcohol-related AB in humans. The results point to a significant role of dopamine for both alcohol and non-drug reward AB and indicate that specific dopamine-dependent functional connections between frontal, limbic, striatal, and brainstem regions mediate these behaviors.

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AUTHOR CONTRIBUTIONS

These authors contributed equally: Monica L. Faulkner, Amanda Elton. CAB, DLR and MLF designed the research. MLF performed the research. MLF and AE analyzed the data. All authors made a substantial contribution to interpretation of the data and drafting of the manuscript.

ADDITIONAL INFORMATION

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