Drug and Alcohol Dependence 218 (2021) 108391

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Diminished cortical response to risk and loss during risky decision making in alcohol use disorder

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ARTICLE INFO

Keywords:
Risk-taking
BART
Alcohol use disorder
fMRI
Prefrontal cortex

ABSTRACT

Background: Risky decision-making is an important facet of addiction. Individuals with alcohol dependence show abnormalities in gambling and other risk-taking tasks. In one such measure, the Balloon Analogue Risk Task (BART), participants sequentially choose to pump a virtual balloon to increase potential reward while the risk of explosion increases, or to cash-out and take earnings. In a prior study, alcohol-dependent participants differed from controls in brain activation during decision-making on the BART, but the relationship between risk/reward magnitude and brain activation was not studied, nor were participants compared to controls. Here we compared the degree to which risk and magnitude of reward influenced brain activation in alcohol-dependent participants vs. controls during decision-making on the BART.

Methods: Thirty-two participants (16 alcohol-dependent, 16 control; 5 females/group) performed the BART during fMRI. A parametric analysis tested for a relationship between risk/reward magnitude and activation in rDLPFC and bilateral striatum regions of interest when participants chose to take risk or to cash out. An exploratory whole-brain voxel-wise analysis of mean activation during pumping, cash-out, and explosion events was also conducted.

Results: Compared with controls, alcohol-dependent participants displayed less modulation of activation in the rDLPFC when taking risk. Exploratory analyses found that alcohol-dependent participants showed less activation than controls during explosions in a cluster including the insula. No differences were seen in striatal activation.

Conclusions: Insensitivity of the rDLPFC to risk and of the insula to loss may contribute to decision-making deficits in alcohol dependence.

1. Introduction

Decision-making abnormalities, linked to prefrontal cortical dysfunction, are a central facet of addiction (Bechara et al., 2001; Dao-Castellana et al., 1998). Individuals with alcohol dependence tend to make less advantageous decisions than controls in decision-making in situations that involve risk with or without ambiguity, generally leading to less reward (Brevers et al., 2014; Fein et al., 2004; Noël et al., 2007), and this abnormality is implicated in the development and maintenance of addictions (Bechara et al., 2001; Grant et al., 2000; Nasrallah et al., 2009). A better understanding of the neurobiological basis for these problems associated with alcohol dependence may help improve therapeutic approaches to this disorder.

Laboratory tests of risk-taking allow for the measurement of a specific facet of these executive function deficits associated with prefrontal cortical damage in long-term alcohol use, such as the failure to plan ahead or think adequately about the consequences of actions (Bowden-Jones et al., 2005). Acute alcohol administration increased risk taking and increased the probability of making consecutive losing risky responses, indicating an alcohol-induced insensitivity to loss (Lane et al., 2004). Alcohol-dependent individuals made disadvantageous decisions on the Iowa Gambling Task and took more risks on the Cups and Coin

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https://doi.org/10.1016/j.drugalcdep.2020.108391
Received 16 July 2020; Received in revised form 23 October 2020; Accepted 26 October 2020
Available online 1 November 2020

Flipping tasks than controls, showing poor decision-making under both ambiguity and risk. (Brevers et al., 2014). This disadvantageous decision-making has been linked to poor working memory processes. In another study, performance on both a gambling task and a odds-based prediction-making task predicted relapse within a sample of recently detoxified alcohol-dependent patients (Bowden-Jones et al., 2005); patients who relapsed within 3 months selected more cards from disadvantageous decks on the gambling task and risked more points across all odds on the decision-making task.

A well-established and commonly-used laboratory test of decision-making under ambiguous risk is the Balloon Analogue Risk Task (BART, Lejuez et al., 2002), in which participants sequentially choose to pump a virtual balloon to increase potential reward, while also increasing potential risk of explosion and loss, or to cash-out and take earnings. The BART has been used before in studies related to alcohol use; however, associations between performance on the BART and alcohol outcomes have been inconclusive. In one comparison of heavy-drinking or alcohol-dependent samples against healthy controls, alcohol-dependent patients, on average, took more risk (higher average adjusted pumps) than controls (Wang et al., 2016). Opposite results also have been reported, with individuals who had long-term alcohol use pumping less (Campbell et al., 2013). However, most relevant studies found no difference in risk-taking on the BART between participants with Alcohol Use Disorder (AUD) and healthy controls (Holmes et al., 2009; Sehrig et al., 2019; Thompson et al., 2012; Wang et al., 2018). Assessments that use neuroimaging are more sensitive to abnormalities in brain function than behavioral measures alone (Whitten, 2012). Understanding how alcohol-dependent and healthy participants differ in the neural correlates of disordered risk-taking behavior may allow for these neural substrates to be targeted therapeutically. Adapted for fMRI (Rao et al., 2008; Schonberg et al., 2012), the BART has been used in functional neuroimaging studies of substance use, including alcohol, tobacco, and methamphetamine (Claus et al., 2018; Galván et al., 2013; Kohno et al., 2014). In healthy control participants, risk-taking on the BART is associated with activation in mesolimbic-frontal regions, including the midbrain, ventral and dorsal striatum, anterior insula, dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex, anterior cingulate/medial frontal cortex, and regions of visual pathways (Congdon et al., 2013; Rao et al., 2008; Schonberg et al., 2012).

In a prior study of participants with DSM-5 Alcohol Use Disorder (criteria for which include alcohol dependence), the BART was used to compare brain activation when participants chose to take risk vs. cash out (Claus and Hutchison, 2012). The decision to take risk (i.e., pump) was associated with greater (compared to cashing out) activation in the dorsal anterior cingulate cortex (dACC), anterior insula, and striatum, whereas cashing out was associated with greater (compared to pumping) response in the caudate and inferior parietal lobe, and balloon explosions with increased activation in the middle temporal gyrus, lateral prefrontal cortex, insula, and ACC. The research participants were not compared to healthy controls, making it difficult to draw conclusions specific to alcohol dependence, and the relationship between the magnitudes of risk and reward, which increase together with each pump, and activation were not investigated.

Comparisons with control groups and association of activation with risk and reward were tested in two other studies of addiction – one in adolescent/emergent adult smokers (mean ± SD age 19.08 ± 1.15) (Galván et al., 2013) and another in adults with Methamphetamine Dependence (mean ± SD age 35.68 ± 1.64) (Kohno et al., 2014). Compared to nonsmoker control subjects, adolescents who smoked cigarettes daily showed greater modulation of activation by risk and reward in the right dorsolateral and ventrolateral prefrontal cortices when deciding to take risk (i.e., to pump the balloon) (Galván et al., 2013). In contrast, adult methamphetamine-dependent (DSM-IV criteria) research participants showed below-control modulation of right dorsolateral prefrontal cortex (rDLPFC) activation by magnitude of risk and reward when deciding to pump, but greater-than-control modulation of striatal activation when deciding to cash out and receive accumulated reward (Kohno et al., 2014).

In this study, we compared a group of alcohol-dependent individuals with healthy controls in an fMRI study using the BART. Based on prior observations in adolescents who smoked cigarettes and methamphetamine-dependent adults, we expected that participants with alcohol dependence would differ from controls in modulation of rDLPFC activation although we did not predict the direction of the difference. We also expected alcohol-dependent participants to show greater modulation of striatal activation when deciding to cash-out.

2. Methods

2.1. Participants

A total of 32 participants were recruited via newspaper and Internet advertisements and provided written informed consent as approved by the University of California Los Angeles Institutional Review Board. Exclusion criteria for both groups, as determined by physical examination, medical history, and laboratory blood tests, were: systemic, neurological, cardiovascular, or pulmonary disease; any MRI contraindications; current, recent, or seeking treatment for alcohol problems; current use of prescribed psychoactive drugs or illicit substances (other than marijuana), verified by toxicology screening; serious alcohol withdrawal symptoms; or current major psychiatric / Axis I diagnoses—other than Nicotine Dependence for either group and alcohol dependence for the alcohol-dependent group— within the last 12 months, assessed with the Structured Clinical Inventory for *DSM-IV-TR* (SCID (First et al., 1995)). Inclusion criteria for the alcohol-dependent group were: ages 21–55 years, and current alcohol dependence. Abstinence from alcohol at least 24 h prior to their scan time was also required, verified by a Breathalyzer test (Dräger, Telford PA). Demographic data (sex, age, race, and years of education) were collected from all participants via questionnaire at the first screening visit. Frequency of alcohol use was measured in control participants as part of a screening questionnaire developed in-house. Alcohol-dependent participants were assessed for a broader scope of alcohol-use measures using the alcohol abuse and dependence assessments of the SCID and the 30-day Timeline Follow-back (Sobell and Sobell, 1992).

The alcohol-dependent group included 16 non-treatment-seeking participants (5 female, 11 male; 11 smokers; mean ± SD age 31 ± 9.05) that met DSM-IV-TR criteria for current alcohol dependence. The control group was matched to the alcohol-dependent group on sex, age, and smoking status (5 female, 11 male; 12 smokers; mean ± SD age 30.94 ± 10.39) from a pool of participants used in previous fMRI studies (Galván et al., 2013; Kohno et al., 2015, 2014).

2.2. BART

A version of the BART adapted for event-related fMRI was used as described previously (Galván et al., 2013; Kohno et al., 2014; Schonberg et al., 2012). Active balloons were red or blue; control balloons were white. In active trials, participants pressed buttons either to pump a computer-simulated balloon image or to “cash-out”. Pumping increased the potential payoff of a trial, which accumulated in a temporary bank, but also increased the risk of the balloon exploding. Participants could cash-out and keep the amount accumulated at any point during a trial. If a balloon exploded, the trial provided no payoff, but earnings from previous trials were unaffected.

Prior to scanning, participants were informed that red and blue balloons were associated with monetary reward and that they would receive their winnings after scanning, but not that the number of pumps that would produce an explosion was predetermined. Colored balloons were assigned the same monetary payoff ($0.25/pump), but differed on their explosion points, which were randomly selected from a uniform distribution ranging from 1 to 8 and 1–12 pumps for red and blue

balloons, respectively. As pumping progressed during the trial, the conditional probability of an explosion increased. White balloons were associated with neither reward nor possible explosions, providing control for motor- and visual-related activation. Participants were instructed to press a button in response to each presentation of a white balloon until it disappeared from the screen; white balloons did not increase in size with each pump. The task followed a random presentation, such that the sequence and number of balloons presented differed from subject to subject as did the time intervals between balloon presentations. Within white-balloon trials, the number of balloons varied between 1 and 12, randomly sampled from a uniform distribution. Red, blue, and white-balloon trials were randomly interspersed throughout the 10-minute task. Trials started with the first presentation of a balloon and ended with either cash-out, resulting in a 2-s display of the total earned, or explosion, resulting in a 2-s display of an exploded balloon with the message "Total = $0.00." The numbers of trials and balloons presented within a trial varied between participants since the task is participant-directed and the variability in number of trials presented is due to response time and the decision to continue pumping before cashing-out and ending a trial. The inter-stimulus interval (time between balloon presentations within a trial) was 1–3 seconds, randomly sampled from a uniform distribution, and the inter-trial interval (time between offset of previous trial and onset of subsequent trial) was randomly sampled from an exponential distribution (mean 4 s; range 1−14 s).

2.3. fMRI data acquisition

Imaging was performed at 3 T on a Siemens Magnetom Trio MRI system at the UCLA Ahmanson-Lovelace Brain Mapping Center. 302 functional, T_2*-weighted, echoplanar images were acquired (slice thickness = 4 mm; 34 slices; repetition time = 2 s; echo time = 30 ms; flip angle = 90°; matrix = 64 × 64; field of view = 200 × 200 mm^2). High-resolution, T_2-weighted, matched-bandwidth, and magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scans were also acquired. The orientation for matched-bandwidth and EPI scans was oblique axial to maximize brain coverage. All data were acquired from the same scanner.

2.4. Data analysis

Behavioral data were analyzed using R (RStudio 1.2.5001) (RStudio Team, 2020). A general linear mixed model (Bates et al., 2015) was used with participant as random effect. The model included balloon color and group. The dependent variable, behavioral risk-taking, was measured by the "average adjusted pumps", a term that denotes the mean number of pumps across trials that ended in cash-out rather than balloon explosions. The rDLPFC region of interest (ROI) was sampled with a 10-mm sphere around the peak voxel (Montreal Neurological Institute coordinates: $x = 30$, $y = 36$, $z = 20$) from a cluster showing modulation of activation during pumping on the BART (Kohno et al., 2015; Rao et al., 2008). A bilateral striatum ROI (caudate head and putamen) was derived from the Harvard-Oxford Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Exploratory whole-brain voxel-wise analyses examining parametric and mean activation during pumping, cash-out, and explosion events were also conducted. Preprocessing of neuroimaging data followed conventional procedures implemented in the FMRIB Software Library (FSL 5.0.2.1, http://www.fmrib.ox.ac.uk/fsl). This included motion correction (Jenkinson et al., 2002), high-pass temporal filtering (100 s), spatial smoothing (5-mm full-width-at-half-maximum gaussian kernel), skull-stripping, and registration to Montreal Neurological Institute space using 12-parameter affine transformation and nonlinear image registration (using FSL's FNIRT) (Andersson et al., 2007). All MRI data from control participants had been used in previous studies (Galván et al., 2013; Kohno et al., 2015, 2014) and, as such, met criteria passed a level of quality control (exclusion criteria: >2 mm translational displacement, >1.5° rotation). Therefore, no control participants or images were dropped for quality control issues, including motion, as part of this study. Alcohol-dependent participants were assessed for the same criteria, and data from two of the original group of 18 subjects' scans were excluded for excessive motion, leaving 16. The general linear model (GLM) (implemented in FSL's FEAT) included the following event types: pumps on active balloons (red and blue balloons were collapsed into a single "active balloon" event type indicative of a condition that presented any risk at all), cash outs, balloon explosions, and pumps on control balloons. Separate regressors for each event type were included to obtain estimates of parametric modulation (Büchel et al., 1998) of activation by pump number and of mean activation for each event type. Thus, there were 7 total task-related explanatory variables: active balloon pumps (parametric and mean), cash-outs (parametric and mean), explosions (parametric and mean), and control balloon pumps (mean only, as participants were informed that these balloons carried no risk). Parametric regressors were used to test for a linear relationship between risk level and activation by assigning greater weight (higher amplitude of the hemodynamic response function) to events that carried greater risk and potential reward, operationalized by pump number. Parametric regressors were orthogonalized to their respective mean regressors. Regressors were created by convolving a set of delta functions, representing onset times of each event with a canonical (double-gamma) hemodynamic response function (HRF). The width of each event's HRF was determined by the duration from onset of the stimulus until the participant's response time to pump. Fixed-effects analyses were conducted for each participant. For within- and between-group mixed-effects analyses, with participant as random effect, all whole-brain voxel-wise fMRI statistics were corrected for multiple comparisons by using cluster correction with voxel height threshold of $Z > 2.3$ and cluster significance of $P < .05$. Analyses of group differences in the modulation of activation by pump number were conducted in R as two-sample t-tests between alcohol-dependent and control participants, restricted to the rDLPFC and striatal ROIs. Variables of interest were rDLPFC activation during decisions to pump and striatal activation during decisions to cash-out, both including pump number as a parametric regressor.

3. Results

3.1. Clinical characteristics

The control and alcohol-dependent groups did not differ on demographic measures, including race (White/Black/Asian/Latino: 12/2/1/1 alcohol; 10/2/2/2 control; p=0.838) and years of education (mean ± SD alcohol: 15.00 ± 2.56; mean ± SD control: 14.31 ± 1.45; p=0.359). The control group showed significantly less frequent alcohol use than the alcohol-dependent group (mean ± SD drinking days in last month: 19.44 ± 6.26 alcohol; 5.91 ± 6.57 control; $p < 0.0001$). Within the alcohol-dependent group, participants reported a mean of 6.45±2.06 drinks per drinking day in the last month and a mean of 2.31±1.49 days since last use, assessed on the day of the scan. Alcohol-dependent participants met a mean of 4.81±1.22 DSM-IV-TR alcohol dependence criteria.

3.2. Task performance

There was a significant main effect of risk level, represented by active balloon color (red vs. blue; i.e. more pumps on blue balloons, which had lower explosion probability) ($F = 12.824$, $p < 0.001$). However, there was no main effect of group (alcohol dependence vs. control) on pumping ($F = 0.100$, $p = 0.75$) and no group × balloon color interaction. There were no group differences in the average adjusted pumps (mean±SD alcohol: 2.95±1.960; control: 2.86±1.744) or in overall amount earned (mean±SD alcohol: $17.02±$4.65; control $16.44± $4.31). No group differences were seen in the number of trials presented in a 10-minute run (mean±SD alcohol: 31.69±6.32; mean±SD control:

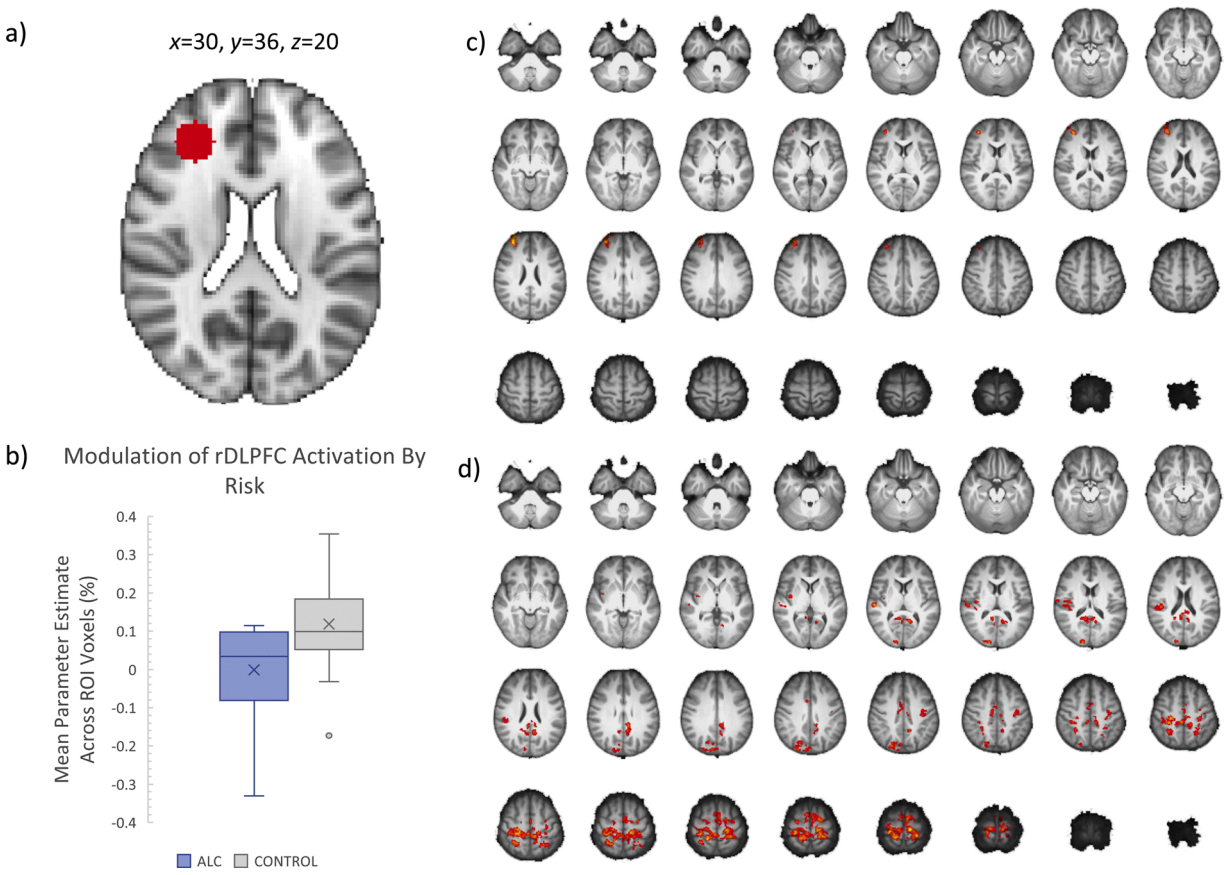

Fig. 1. ROI and Whole-Brain analyses. a) rDLPFC ROI, represented by a 10-mm radius sphere centered at $x = 30$, $y = 36$, z=20 (MNI coordinates). **b)** Modulation of rDLPFC activation by pump number for Alcohol Dependent and Control participants, extracted from pumping events with pump number as parametric regressor. Group means are represented by ×. **c)** Modulation of Activation by Risk During Pump Events: Control > alcohol dependence. Cluster is localized around and includes the rDLPFC. See Table 1 for more details. **d)** Mean Activation During Explosion Events: Control > alcohol dependence; Clusters include bilateral pre- and postcentral gyri and right insula. See Table 1 for more details. Brain maps are displayed in radiological convention (right = left).

Table 1
Whole-brain analysis clusters. Alcohol-dependent participants show lower-than-control modulation of activation during risk-taking in a cluster including the rDLPFC and lower-than-control mean activation during explosions in a cluster including the insula. Z-statistic maps were thresholded using cluster-corrected statistics with a height-threshold of Z > 2.3 and cluster-forming threshold of $p < 0.05$.

Brain Region	Cluster Voxels	Max Z-statistic	x	y	z
Control > alcohol dependence - Modulation of Activation by Risk During Pumping					
R Frontal Pole	667	3.92	32	62	24
Control > alcohol dependence - Mean Activation During Explosions					
L Precentral Gyrus	5041	4.24	−12	−26	72
R Postcentral Gyrus		4.03	28	−34	54
R Precuneus	810	3.53	10	−48	14
L Precuneus		3.44	−10	−54	8
R Occipital Cortex	659	3.42	24	−80	40
R Insular Cortex	447	3.72	40	−16	14

32.75±5.90); balloons of each type (mean±SD alcohol: 13.37±2.87 red, 12.56±3.50 blue, 5.75±1.29 white; mean±SD control: 13.75±3.08 red, 13.69±2.79 blue, 5.312±1.30 white); or explosions (mean±SD alcohol: 14.375±1.78; mean±SD control: 15.875±3.13).

3.3. fMRI

The control group showed greater modulation of activation by risk than the alcohol-dependent group in the rDLPFC during risk-taking, reflecting a stronger linear association of pump number with rDLPFC activation in controls than participants with alcohol dependence ($p < 0.01$, Cohen's $d = 0.915$; see Fig. 1). As the inclusion of white-matter in the spherical ROI could be a confound, a confirmatory analysis was conducted within an anatomical ROI derived from the Desikan-Killiany gyral based cortical atlas. The result using the anatomical ROI remained significant ($p < 0.05$). No significant group differences were found in modulation of bilateral striatal activation by reward level (Cohen's $d = 0.258$) during cashing out.

In exploratory whole-brain analyses, the group difference in parametric modulation of activation was observed in a cluster that included and extended beyond the rDLPFC (peak MNI coordinates: $x = 34$, $y = 50$, $z = 24$; extent: 479 voxels; Z statistic: 3.8; $P < 0.005$, whole-brain corrected; see Table 1); control participants showed greater modulation. Control participants also exhibited greater mean activation than the alcohol-dependent group in response to explosion events (regardless of pump number) in a cluster including the insula (peak coordinates: $x = 56$, $y = 2$, $z = 12$; extent: 402 voxels; Z statistic: 3.56; $p < 0.05$, whole-brain corrected; see Table 1).

4. Discussion & conclusion

Here we explored the relationship between risk magnitude and fMRI activation during decision-making on the BART. Participants with alcohol dependence displayed less modulation of activation by risk level in the rDLPFC when deciding to take risk compared to controls. This observation aligns with effects reported using the BART in methamphetamine-dependent participants (Kohno et al., 2014), but directly contrasts with findings in adolescent/emergent adults who

smoked cigarettes and showed greater-than-control modulation of rDLPFC activation by risk magnitude (Galván et al., 2013). Thus, while abnormalities in rDLPFC function may contribute to maladaptive choice selection by individuals with various substance use disorders, the nature of the abused substance or the stage of brain development may influence the findings.

These findings also align with a previous functional neuroimaging study, in which adolescents with a family history positive for alcoholism showed less activation in the rDLPFC than family history-negative peers during risky decision-making on the Wheel of Fortune decision-making task (Cservenka and Nagel, 2012). This observation in a brain region implicated in executive function is thought to reflect reduced cognitive control.

Participants with alcohol dependence also showed less mean activation than controls in response to explosion events in a cluster including the insula. This region has been associated with loss aversion and risk prediction error, as well as in biasing decision-making based on negative outcome representations (Bossaerts, 2010; Claus and Hutchison, 2012; Markett et al., 2016). In previous studies, control and alcohol-dependent research participants showed greater insula activation during explosion events as compared to cash-out events (Rao et al., 2008; Claus and Hutchison, 2012). The relative insula insensitivity to loss, observed here in participants with alcohol dependence, may contribute to decision-making abnormalities in this population.

Both the insula and DLPFC have been explored as targets of brain stimulation treatments for substance dependence (Zhang et al., 2019). Excitatory deep transcranial magnetic stimulation (dTMS) of the bilateral DLPFC and insula have reduced alcohol (Addolorato et al., 2017) and cigarette (Dinur-Klein et al., 2014) consumption. The current findings indicate that impairments in risky decision-making in alcohol dependence may benefit from dTMS targeting the insula and DLPFC as well.

Unlike the prior finding in a sample of methamphetamine-dependent participants that was larger than the sample size in the current study ($n = 53$) (Kohno et al., 2014), we found no group differences between alcohol-dependent participants and controls in modulation of striatal activation during cashing out. A notable limitation of the current study is its small sample size. With the small effect size (Cohen's $d = 0.258$) of the striatal result, we would need a substantially larger sample to find a statistically significant group difference. Additionally, the study is limited by the wide age range covered by the small sample size. Future studies would benefit from a larger sample or one with a narrower age range. Another limitation is that only frequency of drinking but not amount consumed was measured in the control group. Future studies should consider number of drinks consumed by the control sample.

While the current results primarily concern neuroimaging, the behavioral results should also be considered in the context of previous studies of the BART related to alcohol use. We found no group differences between participants with alcohol dependence and healthy controls in any aspect of task performance, consistent previous studies showing no differences in behavioral performance between participants with AUD and controls (Holmes et al., 2009; Sehrig et al., 2019; Thompson et al., 2012; Wang et al., 2018).

In conclusion, these findings support previous research indicating that the abnormalities in risky decision-making seen across addiction phenotypes are associated broadly with rDLPFC circuitry but differ directionally by disorder or developmental stage. Nonetheless, the modulation of rDLPFC activation by risk showcases a common neurobiological substrate of risky decision-making in addiction that extends across substances including methamphetamine, tobacco, and alcohol. Functional differences in the insula related to reward/loss prediction error also may contribute to decision-making abnormalities in alcohol dependence. Our findings suggest that the rDLPFC and insula may both be possible therapeutic targets for the development of alcohol dependence treatments, such as brain stimulation.

Funding sources

This research was supported by ABMRF, the Foundation for Alcohol Research. EMB is supported by NIAAAF31AA028976. ENG is supported by NIAAAF32AA027699. MK was supported by the Department of Veterans Affairs Clinical Sciences Research and Development Career Development AwardCX17008-CDA2, Oregon Health & Science University Collins MedicalTrust AwardAPSYC0249, Medical Research Foundation of OregonAPSYC0250 and Center for Women's Health Circle of GivingGPSYC0287A.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Elizabeth M. Burnette: Writing - original draft. **Erica N. Grodin:** Writing - original draft. **Dara G. Ghahremani:** Methodology, Writing - original draft. **Adriana Galván:** Conceptualization. **Milky Kohno:** Methodology. **Lara A. Ray:** Conceptualization, Methodology, Writing - original draft. **Edythe D. London:** Conceptualization, Methodology, Writing - original draft.

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