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Diminished reward circuit response underlies pain avoidance learning deficits in problem drinkers

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A B S T R A C T

Individuals engaging in problem drinking show impaired proactive pain avoidance. As successful pain avoidance is intrinsically rewarding, this impairment suggests reward deficiency, as hypothesized for those with alcohol and substance misuse. Nevertheless, how reward circuit dysfunctions impact avoidance learning and contribute to drinking behavior remains poorly understood. Here, we combined functional imaging and a probabilistic learning go/nogo task to examine the neural processes underlying proactive pain avoidance learning in 103 adult drinkers. We hypothesized that greater drinking severity would be associated with poorer avoidance learning and that the deficits would be accompanied by weakened activity and connectivity of the reward circuit. Our behavioral findings indeed showed a negative relationship between drinking severity and learning from successful pain avoidance. We identified hypoactivation of the posterior cingulate cortex (PCC), a brain region important in avoidance, as the neural correlate of lower learning rate in association with problem drinking. The reward circuit, including the medial orbitofrontal cortex, ventral tegmental area, and substantia nigra, also exhibited diminished activation and connectivity with the PCC with greater drinking severity and learning deficits. Finally, path modeling suggested a pathway in which problem drinking disengaged the reward circuit. The weakened circuit subsequently induced PCC hypoactivation, resulting in poorer pain avoidance learning. As the learning dysfunction worsened alcohol use, the pathway represents a self-perpetuating cycle of drinking and distress. Together, these findings substantiate a role of reward deficiency in problem drinkers' compromised proactive avoidance, thus identifying a potential target for intervention aimed at mitigating harmful alcohol use.

1. Introduction

Drinking to avoid pain is considered maladaptive as it only provides temporary symptomatic relief. Moreover, chronic drinking aggravates pain sensitivity over time, worsening consumption (Zale et al., 2015). Despite these negative consequences, problem drinkers continue to engage in this coping method, suggesting they may be impaired in avoidance learning. While the altered pain response likely contributes to this impairment, both clinical and preclinical evidence has also implicated a potential role of alcohol-induced changes in the reward circuit (Borsook et al., 2007). As pain avoidance is intrinsically rewarding and has been found to activate this circuit in neurotypical individuals (Kim et al., 2006; Leknes et al., 2011; Navratilova et al., 2012), drinkers' attenuated reward response to pain relief may be central to their impaired pain avoidance learning. Indeed, various studies have demonstrated that substances of abuse, including alcohol, acutely elevate dopamine transmission in reward-related brain regions, and yet prolonged consumption produces the opposite effect (Elman et al., 2013; LeBlanc et al., 2015; Wiech and Tracey, 2013). These changes are thought to reflect allostasis, with the reward thresholds ramped up and the reward circuit progressively desensitized (Koob, 2015). A major outcome of this neuroadaptation is the diminished rewarding properties of pain relief (Borsook et al., 2016; Elman and Borsook, 2016). In problem drinkers, such devaluation of successful pain avoidance likely leads to poor avoidance learning and perpetuates alcohol use. However, the neural mechanisms of avoidance learning deficit and their relationship with the weakened reward response have not been systematically investigated as part of the pathophysiology of alcohol misuse.

Previous research suggests a role of the medial orbitofrontal cortex (mOFC) in the effects of alcohol use on the reward response to pain avoidance. The mOFC encodes the values of primary reinforcers, including pleasant taste, touch, and monetary gains (Rolls, 2000). Importantly, successful avoidance of aversive outcomes such as monetary loss also activated the mOFC (Kim et al., 2006). Additionally, placebo treatment of pain elicited endogenous opioid activity in the mOFC in positron emission tomography imaging (Wager et al., 2007). In

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contrast, mOFC lesions resulted in impaired reward-guided decision making (Noonan et al., 2017, 2010) and learning (Clarke et al., 2008) in both humans and non-human primates. Anatomically connected with the mOFC, the dopaminergic midbrain represents another key reward-related region (Gabbott et al., 2005; Hoover and Vertes, 2011) that may potentially be involved in avoidance learning. Neurons in the ventral tegmental area (VTA) (Morales and Margolis, 2017) and substantia nigra (SN) (Zaghloul et al., 2009) have been reported to be activated by unexpected rewards and reward-predicting cues, indicating their function in learning. In rodents, activation of both VTA (Schifirnet et al., 2014) and SN neurons also alleviated nociceptive responses (Yin et al., 2022). Despite the evidence for an important role of the reward circuit in pain relief, it remains unclear how alcohol-induced changes in the mOFC, VTA, and SN may contribute to impaired avoidance learning in problem drinkers.

In addition to the reward circuit, behavioral avoidance also engages the posterior cingulate cortex (PCC). Imaging studies showed PCC activation to avoidance of monetary loss or physical harm in neurotypical adults (Roy et al., 2011; Schlund et al., 2010). Our previous work suggested the PCC as a neural correlate of avoidance dysfunction in problem drinkers (Le et al., 2019). In animal research, the PCC has been found to respond to both avoidance of potential threats (Fiddick, 2011; Gabriel et al., 1991) and reward contingencies (Hayden et al., 2008; McCoy et al., 2003). The region may thus interact with the reward circuit to influence pain avoidance learning. However, whether the PCC also exhibits alcohol use-related dysfunctions in activity and/or connectivity with the reward circuit in alcohol users to affect drinking behavior via avoidance learning is not well understood.

The current study sought to identify the neural correlates of proactive avoidance learning in drinkers and examine their relationship with alcohol use. A probabilistic learning go/nogo task (PLGT) was employed to operationalize proactive avoidance. We hypothesized that drinking severity would be positively associated with proactive avoidance learning deficit. Importantly, we confirmed via a reinforcement learning model that this deficit was related to poor learning from positive outcomes, reflecting blunted reward response to pain relief. To identify and characterize the underlying neural processes of this reward response weakening, we examined the activity as well as connectivity of reward-related regions, including the mOFC, VTA, and SN. We anticipated that the diminished reward processing during proactive avoidance learning would be associated with impaired avoidance learning and ultimately greater drinking severity. Finally, we established the inter-relationship between alcohol use and behavioral as well as neural measures of proactive avoidance learning via path models.

2. Methods

2.1. Participants

One hundred and three adult drinkers (40 females, 35.5 ± 11.0 years in age) were recruited from New Haven, CT and surrounding areas via advertisement. Participants were screened to exclude major medical, neurological, and Axis I psychiatric disorders. Exclusion criteria also included MR contraindications and history of seizures, traumatic brain injury or concussions. No participants were currently on psychotropic medications, and all tested negative for illicit substances and alcohol use via drug and breathalyzer tests on the day of the visit. Subjects provided written informed consent after details of the study were explained following a protocol approved by the Yale Human Investigation Committee.

Participants completed the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993). AUDIT scores are calculated from the sum of 10 self-report questions involving quantity of alcohol use, alcohol-related problems and adverse reactions, and drinking behavior. A higher score indicates greater risk for having or developing an AUD. Participants reported an average AUDIT score of 8.3 ± 8.4, which indicated a group average of moderate problem drinking severity. Of the 103 subjects, 43 reported AUDIT scores of 7 and greater indicating problem drinking.

To control for individual differences in sex, age, years in education, and smoking status, we included these variables as covariates in all regression analyses. All significant results survived Bonferroni correction for multiple comparisons unless otherwise noted.

2.2. Behavioral task

Participants underwent fMRI while performing the PLGT (Fig. 1) (Guitart-Masip et al., 2012; Le et al., 2024; Oba et al., 2019). In each run of this event-related design, a cue (fractal) image was presented at the beginning of a trial to signal one of the four contingencies: go to win $1, nogo to win $1, go to avoid a painful shock, or nogo to avoid shock. There were 8 images, 2 per cue category, with cue-outcome mappings randomized across participants. The cue was displayed for 2 s and participants were instructed to decide whether to press a button (go) or not (nogo) before it disappeared. After a randomized interval of 1 to 5 s, feedback of reward (win trials), shock (avoid trials), or "null" (both win and avoid trials) was delivered. The inter-trial interval varied randomly from 2 to 8 s. The randomization and intervening time intervals enabled modeling of distinct regional responses to anticipation and feedback. The outcome was probabilistic, with 80 %/20 % of correct/incorrect responses in the win trials rewarded and the remaining 20 %/80 % of correct/incorrect responses leading to a null outcome. In avoid trials, electric shocks were avoided (a null outcome) on 80 %/20 % of correct/incorrect responses, with the remainder leading to electric shocks. In reality, despite the feedback display of the shock image, shocks were randomly delivered only half of the times to minimize head movements. Each shock was followed by a 20-s rest window to allow neural and physiological responses to return to baseline.

With four 10-minute runs, there were approximately 50 trials for each cue. Participants won ~$72 on average (plus a base payment of $25) and experienced a total of 15 actual shocks and 15 omitted shocks on average. Prior to MRI, the appropriate pain intensity level was calibrated for each participant so that the shocks would be painful but tolerable (*Supplemental Methods*). Participants also practiced on a version of the task with identical rules but different visual cues. To ensure the subjects' efficient task comprehension, there was one image per cue category in the practice version.

2.3. Reinforcement learning (RL) models

We constructed RL models of the participants' behavioral data (*Supplemental Methods*). A detailed description of the models can be found in our previous work (Le et al., 2024; Oba et al., 2019) and elsewhere (Guitart-Masip et al., 2012). Briefly, all models assigned an action value to each action in a given trial. Action value was updated based on the learning rate which, in turn, was distinguished by trial type and the sign of prediction error (*See below*). We further included the subjective impact of outcomes, a free parameter representing the effect size of reinforcement for a subject. The subjective impact of outcomes could also differ between win and avoid trials. To better explain behavioral performance, we finally included two other parameters validated in prior studies (Guitart-Masip et al., 2014, 2012): the action bias, a tendency to press a button regardless of learning, and the Pavlovian factor, which expresses the effect of a stimulus value independent of learning. In sum, we examined a total of 12 parameters and identified the best combination of these parameters in modeling the behavioral data.

To assess learning associated with proactive avoidance, we examined the models' output of learning rate which refers to the degree to which the agent changes action in response to unexpected outcomes. Learning rate can be separated according to the sign of prediction error (PE), with positive and negative PE indicating learning from positive and negative

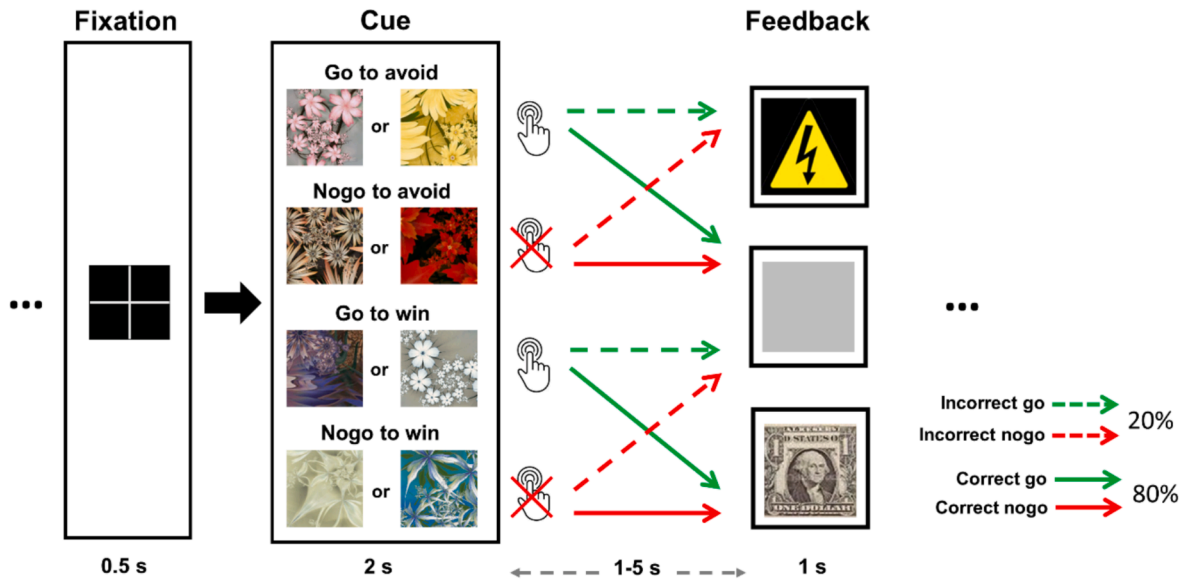

Fig. 1. Probabilistic learning go/nogo task (PLGT): Participants learned to respond to four cue categories to avoid electric shocks (i.e., go-to-avoid, nogo-to-avoid) and gain monetary rewards (i.e., go-to-win, nogo-to-win), with two different images per cue category. Correct responses yielded favorable outcomes 80% of the times whereas incorrect responses yielded unfavorable outcomes 80% of the times. Shocks were only delivered in 50% of the shock feedback instances to reduce head movement.

outcomes, respectively. Models that produce the learning rates for the signed PE allow an asymmetric effect of better or worse (than expected) outcome on learning (Cazé and van der Meer, 2013). Furthermore, the learning rates can be modeled separately for each trial type. Here, we focused on the Go-to-avoid trials.

Free parameters were estimated for each participant via a hierarchical type II maximum likelihood procedure, as with previous studies (Guitart-Masip et al., 2012; Huys et al., 2011). To perform the estimation, the likelihood was maximized by the expectation–maximization procedure using the Laplace approximation to calculate the posterior probability. We used the *Rsolnp* package in R to optimize the likelihood functions. These models were evaluated with the integrated Bayesian information criterion (iBIC). The iBIC values approximated the log marginal likelihoods with a penalty for the number of free parameters. A smaller iBIC value represents a better model.

2.4. Imaging protocol and data preprocessing

Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3 T scanner (Siemens Trio). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC–PC line with (TR) = 1900 ms, echo time (TE) = 2.52 ms, bandwidth = 170 Hz/pixel, FOV = 250 × 250 mm, matrix = 256 × 256, 176 slices with slice thickness = 1 mm and no gap. Functional blood oxygenation level-dependent (BOLD) signals were acquired using multiband imaging (multiband acceleration factor = 3) with a single-shot gradient echo echoplanar imaging sequence. Fifty-one axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 1,000 ms, TE = 30 ms, bandwidth = 2,290 Hz/pixel, flip angle = 62∘, field of view = 210 × 210 mm, matrix = 84 × 84, with slice thickness = 2.5 mm and no gap.

Imaging data were preprocessed using SPM12 (Wellcome Trust Centre for Neuroimaging). Subjects with BOLD runs with significant motion (>3-mm translation peak-to-peak movement and/or 1.5-degree rotation) were removed. Furthermore, we calculated framewise displacement (FD) for each task run and removed subjects with averaged FD of greater than 0.2 mm. Images from the first five TRs at the beginning of each run were discarded to ensure only BOLD signals at steady-state equilibrium between RF pulsing and relaxation were included in analyses. Physiological signals including respiration and heart rate were regressed out, together with 6 motion parameters, to minimize the influence of these sources of noise. T1 images were corrected for intensity bias field and a local means denoising filter and segmented into cerebrospinal fluid, gray, and white matter. Images of each subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation. The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Images were resampled to 2.5 mm isotropic voxel size. Finally, the images were smoothed with a Gaussian kernel of 4-mm FWHM.

2.5. Imaging data modeling and group analyses

As with previous work (Le et al., 2024), we constructed a general linear model (GLM) to examine the brain processes underlying the initiation of an action to avoid painful shocks. To this end, we focused on two trial types, Go-to-avoid and Nogo-to-win, with the cue onsets of individual trials convolved with a canonical HRF and with the temporal derivative of the canonical HRF and entered as regressors in the GLM. We used the contrast Go-to-avoid > Nogo-to-win (proactive avoidance, hereafter) to identify regional activities during proactive avoidance for individual subjects. This contrast enabled us to examine the neural processes involved in the initiation of an action to avoid a negative outcome, in comparison with the opposite behavior of action inhibition. Serial autocorrelation caused by aliased cardiovascular and respiratory effects were corrected by the FAST model. Next, the data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts. Finally, to ensure head motion did not influence our imaging findings, we applied stringent data quality control and ruled out the possibility of significant relationship between the degree of head motion and the neural correlates of proactive avoidance learning (*Supplementary Results*).

To identify the neural correlates of proactive avoidance learning, we

used whole-brain multiple regressions with the rate of learning from positive outcomes as the predictor of brain activity during proactive avoidance in the cue period. The results of all whole-brain analyses were evaluated with voxel $p < 0.001$ in combination with cluster $p < 0.05$, corrected for family-wise error of multiple comparisons, according to current reporting standards (Eklund et al., 2016; Woo et al., 2014). All peaks of activation were reported in MNI coordinates.

2.6. Region-of-interest analysis

To test the hypothesis of the reward circuit's decreased involvement during proactive avoidance learning, we conducted an ROI analysis of brain regions implicated in reward processing. Specifically, we obtained masks of the medial orbitofrontal cortex (mOFC) from an imaging *meta*-analysis of reward response (Bartra et al., 2013) and ventral tegmental area-substantia nigra (VTA-SN) from the AAL3 atlas (Rolls et al., 2020). These regions have not only been implicated in reward processing (Ranaldi, 2014; Rolls, 2000; Schultz et al., 1993) but also found to exhibit structural and functional changes with problem alcohol use (Juhás et al., 2017; Margolis et al., 2008; Miguel-Hidalgo et al., 2006; Moorman, 2018). Parameter estimates were extracted for the regions in each subject using the Go-to-avoid > Nogo-to-win contrast. As the results were similar across the three regions, we opted to average the parameter estimates to reduce the number of comparisons.

We also examined the functional connectivity between the mOFC/VTA/SN and the PCC (see *Results*), using the psychophysiological interactions (PPI) via the gPPI toolbox (McLaren et al., 2012). A PPI model was created for each subject with three components: the physiological term which represents the time series from the seed region, the psychological term which represents the task conditions (i.e., Go-to-avoid, Nogo-to-win), and the psychophysiological interaction term. The PPI was computed as the element-by-element product of the deconvolved time series of the seed region and a task condition vector. Again, we averaged the connectivity strength across the three seeds. The two cue conditions were included in the model. The PPI of proactive avoidance condition was calculated by contrasting the Go-to-avoid and Nogo-to-win conditions.

2.7. Path analysis

We employed path analysis to examine the relationship between activations in the mOFC, VTA-SN, PCC, drinking severity, and proactive avoidance learning rate. Path analysis involves a set of exogenous variables with variance not accounted for by the model and endogenous variables with variance explained in part by other variables in the model (Le et al., 2021; Streiner, 2005). Path analysis is conducted with regression analysis which predicts the effects of all other variables on the endogenous variables. The beta weights (β) from these multiple regressions represent the path coefficients. Standardized path coefficients convey assumptions about the directionality of interactions between variables. Model fit is assessed with fit indices including the Root Mean Square Estimation of Approximation (RMSEA, ≤0.08 for an acceptable fit), Chi-square (χ^2/df, ≤3), Comparative Fit Index (CFI, ≥0.9), and Standardized Root Mean Square Residual (SRMR, ≤0.08) (Chen et al., 2008; Hu and Bentler, 1995). We applied bias-corrected bootstrap with 10,000 resamples to estimate the confidence intervals for all effects in the model. Paths connecting variables are assessed for significance using $p < 0.05$ as the threshold.

3. Results

3.1. Behavioral results

We conducted a 2 (motivational goal: avoid vs. win) × 2 (response type: go vs. nogo) repeated-measures ANOVA of performance accuracy (Fig. 2**A**). The results showed a significant main effect of response type ($F_{(1,101)} = 12.66, p < 0.001$) but not motivational goal ($p = 0.48$). There was also a significant interaction effect ($F_{(1,101)} = 19.9, p = 0.002$). Post

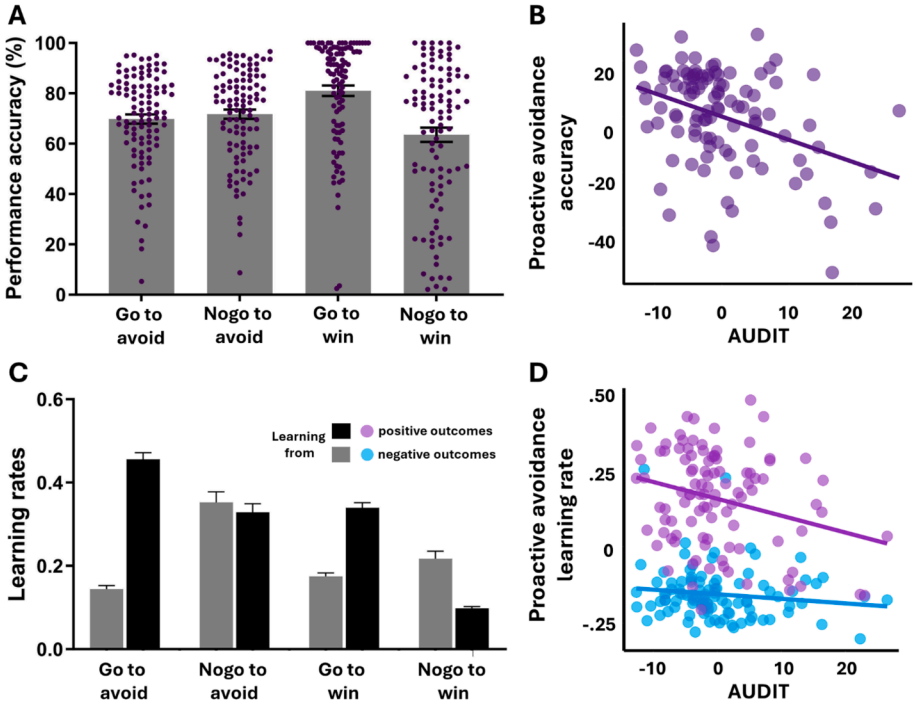

Fig. 2. Behavioral results. (**A**) Performance accuracy across the four task conditions. (**B**) Proactive avoidance performance accuracy was significantly correlated with drinking severity. (**C**) Learning rates from positive and negative outcomes across the four task conditions. (**D**) Proactive avoidance learning from positive outcomes (in purple), but not from negative outcomes (in blue), was significantly correlated with drinking severity. Note that the scatterplots show regression residuals after the effects of sex, age, years of education, and smoking status were removed. Error bars show standard error. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hoc analyses revealed that performance accuracy was significantly higher for go than nogo condition ($p = 0.002$). In contrast, avoid and win trials did not significantly differ in performance accuracy ($p = 0.46$). Performance accuracy on proactive avoidance (i.e., Go-to-avoid condition) was significantly lower than that of Go-to-win ($p < 0.001$) but higher than that of Nogo-to-win ($p = 0.02$) though the latter did not survive correction for multiple comparisons.

Examining the relationship between behavioral performance and alcohol use, we found a significant negative relationship between Go-to-avoid performance accuracy and AUDIT scores ($r = -0.37$, $p < 0.001$, Fig. 2**B**). Performance accuracy from other conditions were not significantly correlated with drinking severity (p's > 0.12).

3.2. RL model of performance

To characterize subjects' avoidance learning and determine whether alcohol use was associated with poor learning from negative or positive outcomes, we first identified RL model that optimally described behavioral data. In total, 12 models were constructed with different combinations of free parameters. Using a stepwise procedure for model comparison and selection, we added one free parameter to a model, calculated the iBIC, and accepted the parameter that decreased the iBIC the most at each step. We found that the Pavlovian factor reduced the iBIC of the basic model (one learning rate and one subjective impact of outcomes) over the other parameters. The iBIC value decreased further with learning rates computed separately for learning from positive and negative outcomes in each trial type. The subjective impact of outcomes was separated for win and avoid trials. Finally, the action bias parameter reduced the iBIC. Thus, the optimal model included eight different learning rates (two per trial type), two subjective impact of outcomes, action bias, and the Pavlovian factor.

With the eight learning rates (Fig. 2**C**), we conducted a 2 (valence: positive vs. negative PE) × 4 (trial types) ANOVA which showed a significant main effect of valence ($F_{(1,101)} = 56.59$, $p < 0.001$) and of trial type ($F_{(3,99)} = 50.26$, $p < 0.001$), as well as a significant interaction effect ($F_{(3,99)} = 75.45$, $p < 0.001$). Post hoc comparisons revealed that learning rate was significantly higher for positive than negative outcomes ($p < 0.001$). Learning rate was also significantly higher for avoid than win trials ($p < 0.001$). Importantly, we found that the rate of learning from positive outcomes in Go-to-avoid trials was significantly correlated with AUDIT scores ($r = -0.27$, $p = 0.005$, Fig. 2**D**). Learning from negative outcomes in Go-to-avoid trials did not show a significant relationship with drinking severity ($p = 0.18$).

3.3. Imaging results

3.3.1. Neural correlates of proactive avoidance learning rate

As drinking severity was inversely associated with the rate of learning from positive outcomes during proactive avoidance, we sought to identify the neural correlates of this relationship. First, to determine the brain processes involved in proactive avoidance learning, we conducted a whole-brain multiple regression in which the rate of learning from positive outcomes predicted brain activation during proactive avoidance (i.e., Go-to-avoid > Nogo-to-win contrast). We found that the learning rate was positively associated with activation in the posterior cingulate cortex (PCC), right superior frontal gyrus, right superior parietal lobule, left postcentral gyrus, and right cerebellum (warm color, Fig. 3, Table 1).

3.3.2. Neural correlates of drinking severity

Next, we conducted a second whole-brain multiple regression in which the AUDIT scores predicted brain activation during proactive avoidance. The results showed that drinking severity was negatively associated with activation in the PCC and left superior temporal sulcus (Fig. 3).

3.3.3. Shared brain processes of learning rate and drinking severity

As the PCC was identified in both of the multiple-regression results, the region may represent a shared neural correlate of both learning rate and drinking severity during proactive avoidance. To confirm, we assessed the overlap between the multiple-regression findings and indeed found the PCC to be a shared correlate (Fig. 3).

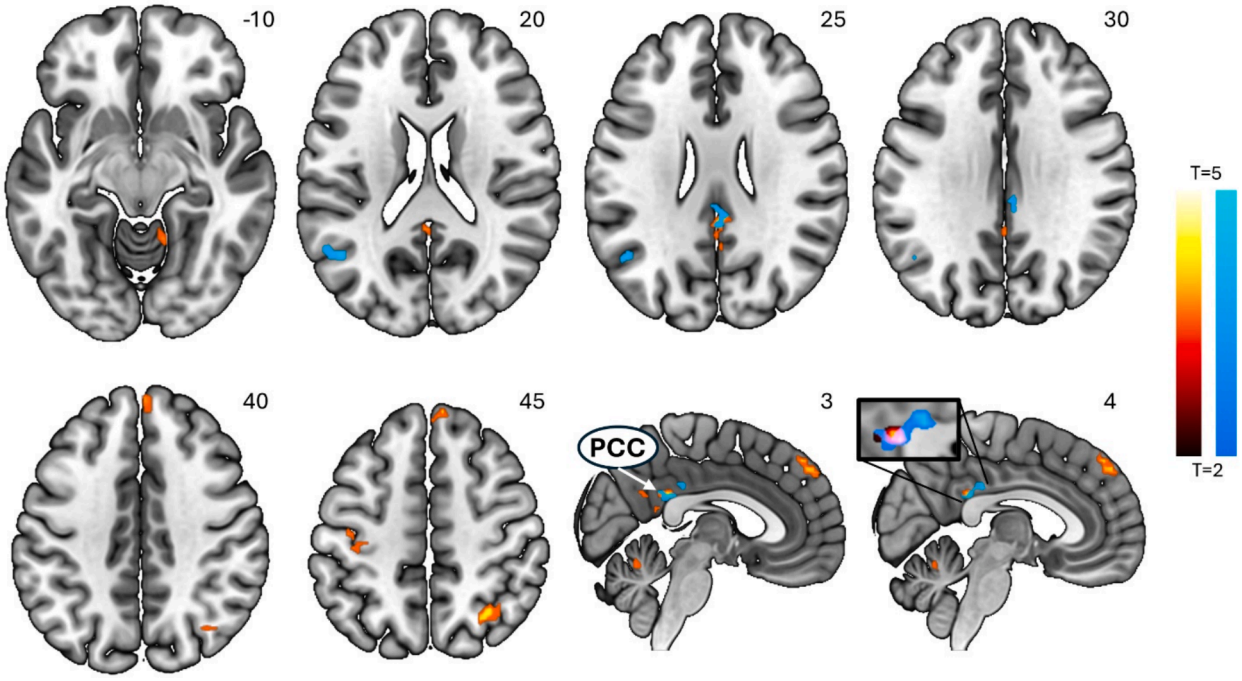

Fig. 3. Multiple-regression results during proactive avoidance. Learning rate was positively associated with activation in the posterior cingulate cortex (PCC), right superior frontal gyrus, right superior parietal lobule, left postcentral gyrus, and right cerebellum (warm color). AUDIT score was negatively associated with activation in the PCC and left superior temporal sulcus (cool color). The two regressions showed clusters spatially overlapped in the PCC (inset).

Table 1
Multiple regressions of proactive avoidance.

		MNI coordinates (mm)			Voxel	Cluster
	Region	x	y	z	T	k
Learning rate as predictor	Posterior cingulate cortex	0	−48	28	4.16	40
		2	−41	26	4.09	
		2	−48	18	3.64	
	Cerebellum	25	−61	−24	5.07	83
		10	−80	4.08		
	Postcentral gyrus	−35	−26	66	4.82	126
		−32	−38	66	4.38	
		−25	−26	73	4.01	
		−32	−48	38	4.59	47
	Superior frontal gyrus	8	46	50	4.45	37
		5	52	43	3.95	
	Superior parietal lobule	32	−61	53	4.38	59
		38	−68	46	4.21	
AUDIT as predictor	Posterior cingulate cortex	0	−44	26	4.05	30
		5	−31	30	3.86	
	Superior temporal sulcus	−48	−58	23	4.39	41
		−55	−56	18	3.94	
		−48	−61	33	3.65	

3.3.4. Region-of-interest analysis

Our behavioral results showed that learning rate during proactive avoidance was impaired in those with more severe drinking and this impairment was specific to learning from positive outcomes. This finding suggested the potential involvement of the reduced reward response during learning to avoid painful electric shocks in those with greater drinking severity. To explore whether the brain regions implicated in reward processing exhibited downregulation, we independently obtained masks of the medial orbitofrontal cortex (mOFC) and ventral tegmental area-substantia nigra (VTA-SN) (Fig. 4**A)** and extracted their activation during the cue period of proactive avoidance. We found that the lower the averaged parameter estimates (i.e., β) from the regions the higher the drinking severity ($r = -0.27$, $p = 0.007$) and lower learning rate ($r = 0.26$, $p = 0.009$) (Fig. 4**B and C**).

These ROI findings suggested there may be a bi-directional relationship between drinking severity and impaired proactive avoidance via the attenuated reward response to successful avoidance of pain. To test this hypothesis, we conducted a path analysis (Fig. 4**D**) in which the degree of drinking severity, as measured by AUDIT scores, was negatively predictive of activation level of the mOFC and VTA-SN as well as the PCC. Hypoactivation of the mOFC and VTA-SN further led to diminished PCC activity during proactive avoidance learning, which contributed to lower learning rate and accuracy. As poor proactive avoidance promoted alcohol use, the model represented a loop with mutual reinforcement between drinking and proactive avoidance dysfunction. The model showed a good fit (Fit indices: RMSEA = 0.00 [90 % CI: 0.00 0.115], $\chi 2/df = 0.58$, SRMR = 0.028, and CFI = 1.00). All paths were significant (p's ≤ 0.031).

Our path model suggested connectivity between the mOFC/VTA/SN and the PCC and this connectivity affected learning rate. To substantiate this possibility, we conducted a functional connectivity analysis (gPPI) for these regions during the cue period of proactive avoidance. The connectivity strength between the reward-related regions and the PCC indeed showed a significant positive relationship with learning rate ($r = 0.25$, $p = 0.01$, Fig. 4**E**). Nevertheless, drinking severity was not significantly correlated with the connectivity strength ($p = 0.43$).

4. Discussion

We found that greater drinking severity was associated with increased impairment of proactive avoidance learning. Importantly, this impairment was observed for learning from positive but not negative outcomes, suggesting a weakened reward response to successful pain relief. Indeed, this behavioral deficit was coupled with hypoactivation of brain regions implicated in reward processing including the mOFC, VTA, and SN. These regions also exhibited reduced connectivity with the PCC, a brain structure previously implicated in proactive avoidance. Such reduction was further associated with poorer avoidance learning rate. Adding to the literature, these findings highlight diminished reward circuit response to successful pain avoidance as a potential mechanism of proactive avoidance dysfunction in problem drinking. Using path modelling, we further characterized how weakened reward processing may have contributed to the mutually reinforcing interactions between impaired avoidance learning and alcohol misuse.

To investigate the neural processes underlying proactive avoidance learning, we employed a probabilistic go/nogo task. This task design allowed us to potentially identify the brain mechanisms associated with pain and avoidance behavior. There is evidence from the literature suggesting the involvement of several brain regions. For instance, *meta*-analyses of imaging studies in humans showed robust activations in the insula and periaqueductal grey to pain induction and anticipation (Duerden and Albanese, 2013; Palermo et al., 2015; Xu et al., 2020). The two regions were also found to increase activation to active avoidance and threats in fear and monetary incentive delay paradigms (Lefler et al., 2020; Samanez-Larkin et al., 2008; Wendt et al., 2017). Similarly, the anterior cingulate cortex has been shown to be involved in both pain and avoidance (Gao et al., 2004; Lee et al., 2022). It is worth nothing that while the avoidance behavior in these studies involved the initiation of an action to avoid aversive outcomes, they were not always contrasted with action inhibition. Several investigations have further used the go/nogo task to examine avoidance behavior. For instance, two EEG studies characterized the neural processes of action inhibition and initiation in response to emotional cues (pain/fearful, neutral, happy, faces) (Pidal-Miranda et al., 2019; Pornpattananangkul et al., 2014). Another study focused on the behavioral performance of both go and nogo trials after displaying videos of painful stimulation (Morrison et al., 2007). However, to our knowledge, no previous work has combined pain and the go/nogo paradigm to delineate proactive avoidance of pain. A number of studies did use versions of the incentive delay task featuring pain to investigate goal-directed actions during pain avoidance (Gandhi et al., 2022; Grodin et al., 2018). Particularly, Grodin and colleagues found that greater insula-nucleus accumbens connectivity during threats was associated with increased alcohol use severity (Grodin et al., 2018). They further reported heightened compulsive alcohol use despite aversive outcomes in problem drinkers, supporting the current findings of impaired avoidance learning.

We tested the hypothesis that poor avoidance learning in drinkers was underlined by the weakened reward response to pain relief, as reflected by diminished reward-related regional activities during proactive avoidance learning. This hypothesis aligns with the "reward deficiency syndrome" reported in users of alcohol and other substances of abuse (Kenny, 2007). As the reward response can serve to valuate successful pain avoidance and thus support learning from behaviors that produce pain relief (Jepma et al., 2022), this deficit likely plays an important role in drinkers' avoidance learning failure. Specifically, chronic alcohol exposure leads to blunted valuation of successful pain avoidance, undermining learning from this rewarding experience. As drinkers become impaired in integrating reinforcements to guide future behaviors, unchecked alcohol use as a coping method escalates.

While no work to our knowledge has directly examined drinkers' reward processing during avoidance learning, there is ample evidence for reduced reward response associated with harmful alcohol use in both animal and human literature. Individuals with alcohol use disorders

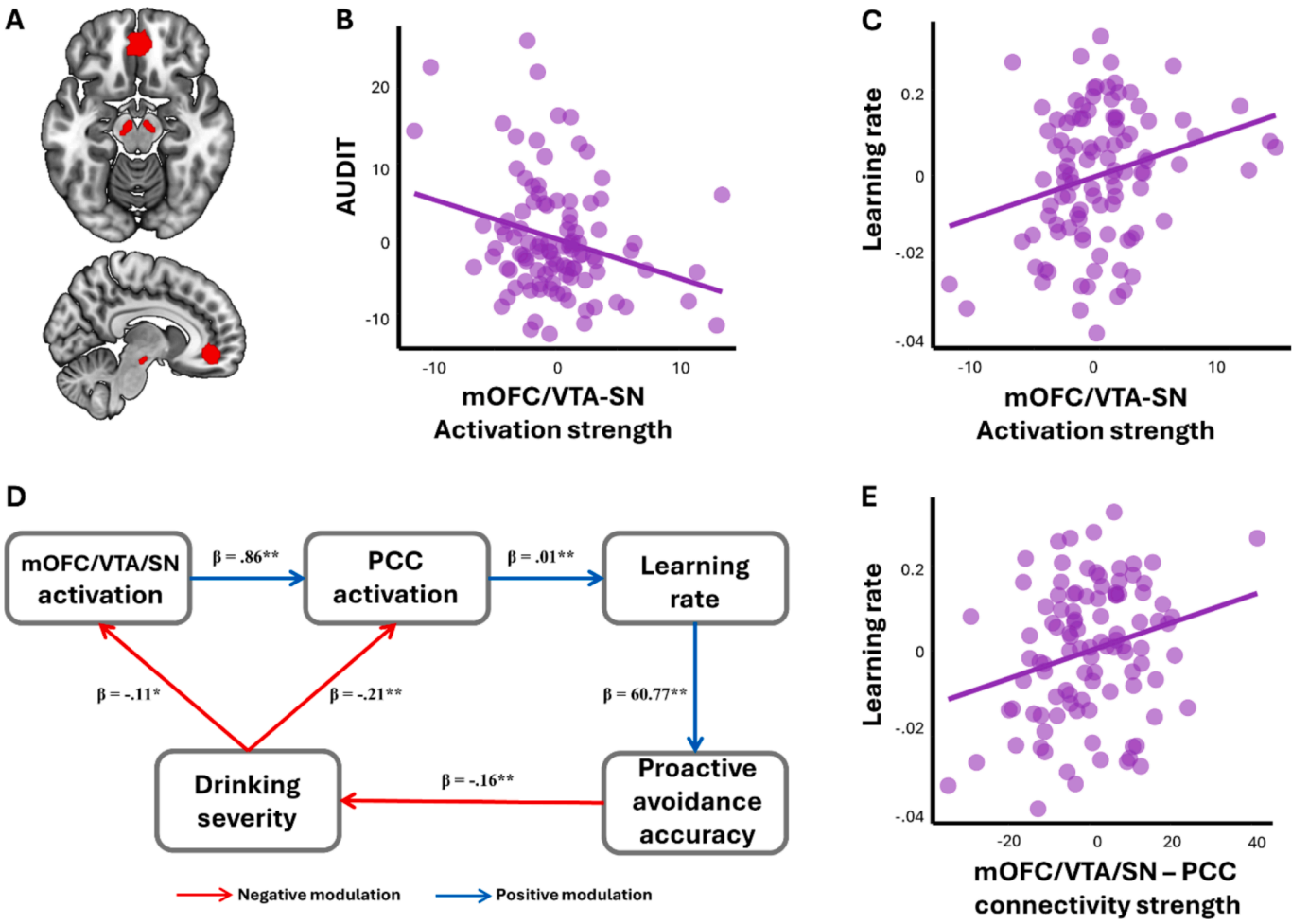

Fig. 4. Hypoactivity and connectivity of reward-related regions during proactive avoidance were associated with increased drinking severity and decreased learning rate. (**A**) Masks of the medial orbitofrontal cortex (mOFC), ventral tegmental area (VTA), and substantia nigra (SN) were independently obtained. Their activation during proactive avoidance was significantly correlated with drinking severity (**B**) and learning rate (**C**). (**D**) Path model suggests that alcohol use reduced activations in the mOFC and VTA-SN as well as the PCC which then led to lowered proactive avoidance learning from positive outcomes. Diminished learning rate was associated with impaired proactive avoidance which worsened alcohol use. (**E**) mOFC/VTA-SN connectivity with the PCC was positively associated with learning rate.

(AUD) have been consistently found to exhibit anhedonia – an inability to experience reward – and the degree of which was associated with drinking severity (Ardinger et al., 2022; Heinz et al., 1994). Compared to healthy controls, those with AUD have been shown to be deficient in dopamine receptors, a neural transmitter critical for both reward processing and learning (Martinez et al., 2005; Volkow et al., 1996). In a study of patients with Parkinson's disease, reduced dopamine availability led to impaired learning from positive but not negative outcomes, a deficit that was subsequently reversed by dopamine medication (Frank et al., 2004). In rodents, chronic ethanol intake decreased the baseline sensitivity of brain reward systems, resulting in elevated reward thresholds (Schulteis et al., 1995). Thus, it is plausible that reward deficiency promotes drinking not only because of ethanol's reinforcing properties but also through failure to recognize and/or learn the benefits of alternative pain-relieving strategies. Our behavioral and neural findings support this proposition. Hypoactivation of the reward-related mOFC, VTA, and SN was associated with poorer learning from positive outcomes during proactive avoidance and both metrics showed a significant relationship with drinking severity.

Abundant evidence implicates the mOFC in reward valuation (Noonan et al., 2012; Wallis, 2007). Several studies have further highlighted blunted mOFC's response to reward in problem drinkers. For instance, reduced mOFC activation to acute alcohol intake was reported in binge drinkers (Blaine et al., 2023), and weakened mOFC connectivity during reward feedback in the monetary incentive delay task was associated with greater drinking severity (Jia et al., 2021). This loss of reward sensitivity may be related to diminished gray matter volumes (Durazzo et al., 2011; Wang et al., 2016) and neuronal packing density (Miguel-Hidalgo et al., 2006) of the mOFC in those with AUD. As the mOFC is implicated in the reward response to both pain relief (Kim et al., 2006; Wager et al., 2007) and learning (Noonan et al., 2012), its structural and functional changes likely affect the valuation of successful pain avoidance during avoidance learning. Similarly, ethanol administration in rodents altered functional properties of dopaminergic neurons in the VTA (Brodie and Appel, 1998) as well as dopamine transporter sites in the SN (Jiao et al., 2006). In humans, postmortem studies revealed neurochemical changes in the VTA and SN in drinkers with AUD (Lee et al., 2017; Skuja et al., 2022). Taken together, there is robust evidence supporting our finding that the reward circuit is negatively affected by alcohol use, leading to avoidance learning dysfunctions.

Proactive avoidance is a complex behavior that involves multiple brain substrates, including not only those critical for motivational processes but also those supporting actions related to fear, avoidance, and escape (Cain, 2019; Manning et al., 2021). The PCC in particular has been found to be important in avoidance of aversive stimuli, as previously reported in animals learning to avoid foot shocks (Duvel et al., 2001; Souza et al., 2002; Vogt, 2005). In humans, PCC activation was associated with avoidance of fear-inducing cues (Barke et al., 2012;

Schlund et al., 2010). In monkeys performing gambling tasks, PCC neurons signaled the initiation of reward-related actions (Pearson et al., 2009) as well as learning from reward outcomes (Hayden et al., 2008). These findings are consistent in demonstrating a role of the PCC in linking reward, motivational, and motor processes to support proactive avoidance and learning (Rolls, 2019; Vogt, 2019). Extending current literature, we tested the hypothesis that the PCC, a brain structure involved in avoidance behavior, is negatively affected by alcohol use, as reflected in its hypoactivity during avoidance learning. Consistent with this hypothesis, our multiple-regression results showed PCC reduced activation in association with both drinking severity and impaired proactive avoidance learning from positive outcomes. We also demonstrated that PCC's attenuated function was likely modulated by the diminished reward circuit response during avoidance learning, as evidenced by their weakened functional connectivity in heavier drinkers.

Our path model additionally indicated that reduced activity from the reward-related regions weakened their connectivity with the PCC, which, in turn, hampered proactive avoidance learning from positive outcomes. Given past evidence for the intrinsic reward value of pain relief and pain avoidance (Kim et al., 2006; Navratilova and Porreca, 2014; Wager et al., 2007), these results strongly suggest that harmful alcohol consumption compromises the reward response in successful pain avoidance, a condition reflective of reward deficiency. A likely consequence is that drinkers become less sensitive to adaptive pain-relieving strategies which are a core component of proactive avoidance. With deficits in proactive avoidance learning, drinkers progressively resort to alcohol use as a maladaptive coping method in response to pain, thus becoming trapped in this self-perpetuating cycle of drinking and distress.

As observed in chronic, heavy drinkers, the reward deficiency syndrome promotes alcohol use to compensate for increased reward thresholds and changes in homeostasis (Koob, 2015). The current work adds to an accumulating body of evidence and suggests an additional pathway in which diminished reward function motivates drinking via proactive avoidance learning dysfunction. The characterization of this pathway may provide clinical implications for the treatment and prevention of AUD. Behavioral therapies could potentially benefit from incorporating coping strategies that encourage proactive and minimize reactive avoidance. Evidence of the disengagement of the reward circuit may further inform pharmaceutical interventions and non-invasive brain stimulation treatment of more selective targeting of the reward circuit.

5. Limitations

Findings from the current study should be examined with consideration of its limitations. First, we did not identify the reward-related regions in our whole-brain multiple regression results. While the use of ROI analysis helped shed light on a potential contribution of the neural underpinnings of reward deficiency in proactive avoidance dysfunction, we cannot rule out the possibility of false positives. In contrast, we examined activity during proactive avoidance in the nucleus accumbens (*Supplementary Results*) as the region is commonly implicated in reward processing. Nevertheless, its activation did not show a significant relationship with either drinking severity or learning rate. This finding indicated that alcohol use severity may not have had a direct relationship with the region's involvement in proactive avoidance learning in the current sample. While the region plays a critical role in reward response and learning, imaging *meta*-analyses have reported inconsistent findings on the structural changes in the nucleus accumbens in those with AUD (Li et al., 2021; Spindler et al., 2021; Yang et al., 2016). It is also worth noting that 60 of our subjects were considered social drinkers. Further work using samples of more individuals with severe drinking is required to validate the current findings. Despite these limitations, our study highlights proactive avoidance deficit as an important component of the AUD pathophysiology, thus presenting a promising avenue for further clinical and neurocognitive research.

Author contributions

T. M. L. and C. R. L. conceptualized and designed the study, T. M. L. collected the data. T. M. L. analyzed the data. T.O. conducted the modeling work. T. M. L. wrote the manuscript, with contributions from all other authors. All authors approved the final version of the manuscript.

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CRediT authorship contribution statement

Thang M. Le: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Investigation, Data curation, Formal analysis. **Takeyuki Oba:** Writing – review & editing, Formal analysis. **Chiang-Shan R. Li:** Writing – review & editing, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103762.

Data availability

Data will be made available on request.

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