Alcohol and Alcoholism, 2017, 52(5) 617–624
doi: 10.1093/alcalc/agx037
Advance Access Publication Date: 14 June 2017
Article

OXFORD

Article

Development, Initial Testing and Challenges of an Ecologically Valid Reward Prediction Error FMRI Task for Alcoholism

Anita Cservenka[1], Kelly E. Courtney[2], Dara G. Ghahremani[3], Kent E. Hutchison[4], and Lara A. Ray[3,5,6,*]

[1]School of Psychological Science, Oregon State University, 2950 SW Jefferson Way, Corvallis, OR 97331, USA, [2]Department of Psychiatry, University of California, 9500 Gilman Drive #0862, La Jolla, San Diego, CA 92093, USA, [3]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, 37-356 Semel Institute, Box 951759, Los Angeles, CA 90095-1759, USA, [4]Department of Psychology and Neuroscience, University of Colorado, Boulder, Muenzinger Psychology, 345 UCB, Boulder, CO 80309-0345, USA, [5]Department of Psychology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA, and [6]Brain Research Institute, University of California, Box 951761, Los Angeles, Los Angeles, CA 90095-1761, USA

*Corresponding author: Department of Psychology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA. Tel.: +310-794-5383; Fax: +310-206-5895; E-mail: lararay@psych.ucla.edu

Received 20 December 2016; Revised 26 May 2017; Editorial Decision 26 May 2017; Accepted 6 June 2017

ABSTRACT

Aims: To advance translational studies of the role of reward prediction error (PE) in alcohol use disorder, the present study sought to develop and conduct an initial test of an alcohol-specific PE task paradigm using functional magnetic resonance imaging in humans.

Methods: Alcohol dependent or social drinkers received small tastes of their preferred alcohol beverage or control beverage, with preceding visual cues indicating whether alcohol (or water) would be delivered. To assess both positive and negative PE signals, expectancies were systematically violated in both positive (i.e. expecting water and receiving alcohol) and negative (i.e. expecting alcohol and receiving water) directions. Exploratory trial-by-trial analyses were conducted to explore temporal fluctuations of activation within a priori-defined regions of interest that have been implicated in cue reactivity and PE processing.

Results: Across the entire sample of participants, positive PE-related brain activation was found in a large cluster comprised of frontal lobe regions, as well as insular cortex, and motor/sensory cortices. Compared to social drinking subjects, alcohol dependent subjects had greater positive PE-related brain activity in left superior parietal lobule, lateral occipital cortex and postcentral gyrus. Exploratory trial-by-trial analyses indicated differences in activation specific to type of taste, mostly at earlier trials.

Conclusions: This task-development oriented pilot study found that PE signaling may not be detected in expected brain regions when image analyses average across all PE trials of the task. Rather, a trial-by-trial analysis approach may help detect sparse, temporally distinct PE signaling in expected reward processing regions.

Short Summary: This fMRI study of reward prediction error found greater positive prediction error-related activity (i.e. expecting water taste, receiving alcohol taste) in alcohol dependent individuals relative to social drinkers in parietal and occipital cortices. Trial-by-trial analyses may be able to better detect sparse prediction error signaling in expected reward processing regions.

INTRODUCTION

One of the defining clinical features of alcoholism is the inability to stop using alcohol despite a host of negative physical and psychosocial consequences (Kalivas and Volkow, 2005). Neurobiological models suggest impairments associated with alcohol dependence may be subserved by deficits in the ability to adapt behavior to changes in reward contingencies (Park *et al.*, 2010; Vanes *et al.*, 2014). Reward prediction error (PE) signals in the brain are thought to reflect this adaptive behavior (Schultz and Dickinson, 2000) and failure to learn from reward PEs (i.e. discrepancies between expected and obtained outcomes) may, in part, contribute to the maintenance of behavioral patterns, such as alcohol seeking, despite negative consequences.

Although PE has been well studied in preclinical models (Schultz *et al.*, 1997; Schultz and Dickinson, 2000), fewer studies have applied this approach to human clinical samples, and in particular, to those with an alcohol use disorder (AUD). Further, studies that have examined PE have mainly used instrumental or reversal learning paradigms, as opposed to Pavlovian conditioning tasks (Garrison *et al.*, 2013). This is important as there are differences in learning requirements and learning rates across these different paradigms. For example, a study by Park *et al.* (2010) employed a reinforcement learning task during functional magnetic resonance imaging (fMRI) to compare males with alcoholism and healthy control participants on PE-related neural responses (Park *et al.*, 2010). During the reward-based decision-making task participants had to select between two abstract stimuli that were associated with probabilistic reward outcomes. Correct selection resulted in wins, while incorrect selections resulted in losses. Response-outcome contingencies changed unexpectedly during the task (resulting in PEs) and participants had to learn the new rules based on the reward feedback they received. Using functional connectivity analyses, with the ventral striatal clusters from the PE analysis as seeds, this study found an association between weaker functional connectivity between the ventral striatum and dorsolateral prefrontal cortex (dlPFC) in males with an AUD. This weaker functional connectivity across all participants was also associated with impairments in learning speed during the task (mean number of trials needed to reach four correct responses in a row), as well as alcohol craving. These findings may suggest inefficient communication between reward-related brain regions and those associated with executive functioning during reinforcement learning in individuals with an AUD.

A number of error-monitoring, reward and emotion-associated brain regions respond to PE across both animal and human studies. For example, previous research in animal models has implicated the anterior cingulate cortex (ACC), basolateral amygdala and dopaminergic neurons in reward PE (Bissonette and Roesch, 2016). Human neuroimaging studies translating this preclinical work indicate PE-related brain activation in similar regions, including reward-related, salience and cognitive control regions such as the ventral striatum (VS), dorsal striatum, medial prefrontal cortex (mPFC), insula and ACC (Garrison *et al.*, 2013). This meta-analysis indicated that the striatum (dorsal and ventral regions) is a primary region that shows activation in response to positive PEs, while the insula is an important region that responds to aversive PEs (Garrison *et al.*, 2013), and is also active during unexpected absence of positive outcomes (Gu *et al.*, 2016).

A common theme across PE studies in humans using fMRI is the reliance on cognitive tasks in which participants learn contingencies for reward that may be changed during the task (reversal learning). These types of probabilistic reversal learning tasks probe participants' ability to integrate reinforcement contingencies over time to guide future behavior (Xue *et al.*, 2013; Hauser *et al.*, 2015). Additionally, some studies have investigated whether reward PE is dysregulated when individuals with an addiction perform reward-related decision-making tasks. For example, a study by Tanabe *et al.* (2013) investigated whether decision-making deficits on the Iowa Gambling Task in substance-dependent individuals were related to PE processing, which could influence how participants learn from the feedback they receive on the task (Tanabe *et al.*, 2013). The authors found that in substance-dependent individuals, the VS and medial orbitofrontal cortex (mOFC), a region within the mPFC, did not track PE as strongly as in healthy controls, which suggested that maladaptive decisions with regards to substance use are related to aberrant reward PE in these individuals. While this task used visual representations of secondary rewards (i.e. monetary), the seminal work by Schultz *et al.* (1997) demonstrated that in a Pavlovian conditioning experiment firing of midbrain dopaminergic neurons correlates with PE in animals using tangible, primary rewards (e.g. juice) (Schultz *et al.*, 1997). One study investigated the use of tangible primary rewards in a healthy human sample and observed similar PE signaling in the caudate nucleus in response to juice delivery and a pictorial representation of monetary reward (Valentin and O'Doherty, 2009).

As widely discussed in the preclinical literature, through chronic use, and putatively via neuroadaptation in the brain, alcohol and drugs serve as primary reinforcers to motivate addictive behavior in individuals with addiction. Therefore, the presentation of alcohol itself within the context of a Pavlovian conditioning PE paradigm offers unique opportunities to probe for impairment in integration of reinforcement learning contingencies and underlying circuitry associated with reward processing in alcoholism without the requirement for instrumental responses to complete the task. While not using oral alcohol administration, a positron emission tomography study in humans demonstrated that unanticipated intravenous (IV) infusion of alcohol after presentation of a neutral cue induced an increase in striatal dopaminergic activity (Yoder *et al.*, 2009). In another condition, the authors presented alcohol cues, but did not deliver alcohol, and this resulted in a decrease in dopaminergic activity. Thus, the authors interpreted the results of these two phases of the experiment as positive and negative PE, respectively. A subsequent study found that pairing novel geometric shapes as conditioned stimuli (CS) with either IV alcohol or saline infusion elicited differential brain responses to CS+ and CS− during fMRI when no infusions were delivered, counter to subject expectations (Kareken *et al.*, 2012). Specifically, presenting CS+ without alcohol delivery resulted in significant negative activation in medial superior frontal gyrus and ACC, suggesting reduced response in medial frontal regions when reward was expected, but withheld (negative PE). This suggests that the mPFC is an important region to be examined in studies of alcohol PE, but the presence of conditioned stimuli with oral alcohol administration may result in stronger PE-related brain activity due to both conditioned taste cues and neuropharmacological effects. The former two IV alcohol PE studies provide an important foundation for the development of the current novel paradigm, which examined PE-related brain activation using oral alcohol tastes as reward reinforcers in humans using fMRI.

To that end, the present study sought to develop and conduct an initial test of an alcohol-specific PE task using fMRI and oral administration of alcohol. Specifically, participants in this study received small tastes of their preferred alcohol beverage or control beverage (water), which in turn were paired with preceding visual cues

indicating whether alcohol (or water) would be delivered. Consistent with the PE model, after learning the task, expectancies were systematically violated in both positive (i.e. expecting water and receiving alcohol) and negative (i.e. expecting alcohol and receiving water) directions. Through this novel associative learning fMRI task using alcohol tastes (i.e. tastes of one's preferred alcoholic beverage) as the rewarding stimuli, this pilot study examined the potential for measuring PE signals in the brain using this task paradigm. Importantly, an associative learning alcohol taste PE paradigm uses actual alcohol taste cues familiar to individuals with AUD and allows for the examination of brain response to both positive and negative expectation violations that may in part help explain the maintenance of alcohol seeking to unexpected positive outcomes and the persistence of maladaptive behaviors in the presence of negative outcomes. Thus, this information may be used clinically to assist with the extinction of conditioned responses to alcohol-associated cues. Based on previous research implicating VS (Garrison *et al.*, 2013), mOFC (Tanabe *et al.*, 2013), and more generally mPFC (Kareken *et al.*, 2012; Garrison *et al.*, 2013) in PE processing, we hypothesized that trials designed to elicit positive reward PE (water expected, but alcohol delivered) would produce increased VS and mOFC (a region within mPFC) activity, while diminished activation would be seen in these regions during negative reward PE, which we defined as absence of something positive expected, and receipt of an alternative less positive reinforcer (alcohol expected, but water delivered). As a secondary aim of this pilot study, we explored differences in PE signaling between alcohol dependent (AD) individuals and social drinkers. Importantly, these efforts in task development are discussed in the context of clinical translational neuroscience as a PE task in humans that specifically uses oral alcohol tastes may be an effective assay of the clinical phenomenology of alcoholism.

MATERIAL AND METHODS

Participant recruitment and screening procedures

Participants for this study were recruited through community advertisements. Interested individuals called the laboratory and completed a telephone-screening interview to determine initial eligibility. Exclusionary criteria included < 21 or >35 years of age; visual/reading problems; left-handedness; treatment for an alcohol or substance use disorder in the past 30 days or currently seeking treatment for alcohol-related problems; self-reported current use of non-prescription drugs (e.g. heroin, morphine, methamphetamine, cocaine) or recreational use of prescription drugs other than marijuana or cigarettes (DSM-IV cannabis dependence exclusionary); self-reported psychiatric problems; nursing, or plans to become pregnant; current treatment with psychotropic medications; and fMRI contraindications (i.e. irremovable metal from the body, claustrophobia). Detailed screening criteria are included in the Supplementary Material.

Inclusion criteria in the AD group ($N = 9$) were meeting DSM-IV criteria for current alcohol dependence, an Alcohol Use Disorders Identification Test (AUDIT) (Saunders *et al.*, 1993) score >15, and drinking ≥14 or ≥7 drinks/week at least once in the past month for males and females, respectively. Participants in the Social Drinking (SD) group ($N = 9$) could not meet DSM-IV criteria for alcohol dependence, had to have an AUDIT score <8, and had to consume <14 (males) or <7 (females) drinks/week in the past month. No subjects reported ≥5 (males) or ≥4 (females) drinks/occasion more than once in the past month in the SD group. Participants were instructed to abstain from using alcohol or drugs for 24 h prior to their scheduled MRI scan. All procedures were approved by the University of California, Los Angeles (UCLA) Institutional Review Board and were in accordance with the Declaration of Helsinki.

Demographics and individual differences measures

Demographic information including age, sex and ethnicity were collected during the in-person screening visit and are presented in Table 1. Furthermore, Table 1 includes scores from the AUDIT, drinks per drinking day as well as percent drinking days in the past month. The Fagerström Test for Nicotine Dependence (FTND) (Heatherton *et al.*, 1991) was administered to participants to assess the number of daily smokers (>10 cigarettes/day) in the AD and SD groups. Only one participant in each of the groups was considered a daily smoker based on this criterion.

fMRI scanning visit

Pre-scan measures

At the start of the scanning visit, participants were required to have a breath alcohol concentration (BrAC) of 0.00 g/dL and a urine toxicology screen negative for all drugs (excluding tetrahydrocannabinol), while female participants completed a pregnancy test.

Image acquisition

Scanning took place at the UCLA Center for Cognitive Neuroscience on a 3.0T Siemens Magnetom Tim Trio scanner. A T2-weighted, high resolution matched-bandwith (MBW) anatomical scan (Time to Repetition (TR) = 5000 ms, time to echo (TE) = 34 ms, flip angle = 90 degrees, voxel size: 1.5 mm × 1.5 × 4 mm, field of view (FOV) = 192 mm^2, 34 slices, ~1.5 min) and a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR = 2530 ms, TE = 1.74 ms, Time to Inversion (TI) = 1260 ms, flip angle = 7 degrees, voxel size: 1 mm^3, FOV = 256 mm^2, ~6.2 min) were acquired for co-registration to the functional data. A T2*-weighted echo planar imaging scan (TR = 2000 ms, TE = 30 ms, voxel size: 3 mm × 3 mm × 4 mm, FOV = 192 mm^2, 325 TRs, ~10.83 min/run) was acquired to examine the blood oxygen level-dependent (BOLD) signal during two runs of the Alcohol Prediction Error (APE) Task (total time: ~22 min). The first six TRs were discarded to allow for steady-state longitudinal magnetization to be reached.

Table 1. Sample demographics

Variable	Frequency or mean (SD)		
	SD ($n = 6$)	AD ($n = 9$)	All ($n = 15$)
Age	26.67 (4.93)	27.22 (4.55)	27.00 (4.54)
Sex—male/female	3/3	6/3	9/6
Ethnicity			
Caucasian	3	5	8
African American	3	3	6
Asian	0	1	1
Drinks per drinking day*	1.42 (0.79)	8.38 (5.34)	5.59 (5.39)
Percent drinking days*	12.8% (0.10)	57.0% (0.30)	39.3% (0.32)
AUDIT total score*	2.33 (1.37)	22.44 (9.53)	14.40 (12.51)
Daily smokers (>10 per day)	1	1	2

*$P < 0.05$; AD, Alcohol Dependent Group; SD, Social Drinking Group; AUDIT, Alcohol Use Disorders Identification Test (Saunders *et al.* 1993).

fMRI task

The APE Task was developed through modifications to the Alcohol Cues Task (Filbey *et al.*, 2008a,2008b), which has been previously used in our lab (Courtney and Ray, 2014; Courtney *et al.*, 2014, 2015; Ray *et al.*, 2014). During this event-related task (Fig. 1), each trial began with the presentation of a visual cue (alcohol or water; 2 s) such that the words *Alcohol* or *Water* were visually presented to participants (cues). This was followed by a fixation cross (jittered for an average of 3 s), delivery of the taste (2 ml alcohol or water; 5 s) and a fixation cross (jittered using an exponential distribution with a mean of 3 s and a range of 0.5–6 s). Alcohol and water tastes (outcomes) were delivered through Teflon tubing using a computer-controlled delivery system (Infinity Controller) as described by Filbey and colleagues (Filbey *et al.*, 2008a). Participants were instructed to press a button on a response box placed in their right hand to indicate the timing of swallowing, which was used as a covariate in the first-level analyses to account for variance associated with motor activity involved in swallowing. Alcohol tastes consisted of participants' preferred alcoholic beverages (wine or liquor). Beer could not be administered due to incompatibility of the alcohol administration device with carbonated liquids. The presentation of visual cues and response collection were programmed using MATLAB (Mathworks, Natick, MA) and the Psychtoolbox (www.psychtoolbox.org) on an Apple MacBook running Mac OSX (Apple Computers, Cupertino, CA), and visual cues were presented using MRI-compatible goggles (Resonance Technologies, Van Nuys, CA).

The APE Task was administered over the course of two runs with 50 trials/run, 16 of which were violation trials designed to elicit positive (presentation of water cue and receiving alcohol taste) or negative (presentation of alcohol cue and receiving water taste) PEs. Thus, there were a total of 16 positive PE, 16 negative PE and 68 non-PE trials across the two runs of the task (i.e. 32% of trials included expectation violations). The first 10 trials of the task were constrained to be congruent (non-PE) trials, after which expectation violations were introduced (representing 32% of all trials) and no more than 2 consecutive expectation violations were allowed. All cue presentations resulted in a subsequent delivery of liquid that was either congruent or incongruent with the visual cue, such that no cue presentation resulted in absence of an outcome. After completing the fMRI task, participant sobriety (0.00 g/dL BrAC) was confirmed with a breathalyzer and participants were compensated before they were released from the study visit.

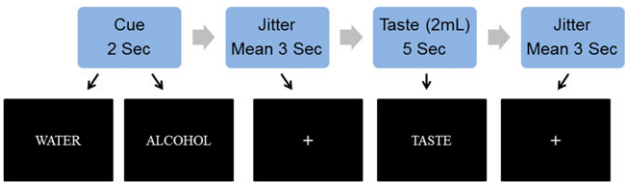

Figure 1. Task design. Each trial of the reward PE fMRI task began with the presentation of a visual cue (alcohol or water; 2 s) such that the words Alcohol or Water were visually presented to participants, followed by a fixation cross (jittered for an average of 3 s), delivery of the taste (2 ml alcohol or water; 5 s) and a fixation cross (jittered using an exponential distribution with a mean of 3 s and a range of 0.5–6 s). A total of 50 trials/run were included over the course of two runs of the task. For each run, 16 trials were violation trials designed to elicit positive or negative PEs. For the two runs there were a total of 16 positive PE, 16 negative PE and 68 non-PE trials.

Image processing and PE analysis

Preprocessing of data followed conventional procedures implemented in FMRIB's Software Library (FSL 4.1) (www.fmrib.ox.ac.uk/fsl). This included motion correction [Motion Correction Linear Image Registration Tool (McFLIRT, Version 5.0)], high-pass temporal filtering (100 s cutoff) using FSL's FMRI Expert Analysis Tool (FEAT, Version 5.63), and smoothing with a 6 mm full width half maximum Gaussian kernel. FSL's Brain Extract Tool (BET) was used to remove skull and non-brain tissue from both the structural and functional scans. Two subjects from the SD group were excluded from analyses due to excessive head motion (>3 mm maximum translation), and another subject from the SD group was excluded due to insufficient data (only 27% of volumes were collected) as a result of excessive head motion (17 TRs >3 mm, 15 of which >18 mm and maximum of 22 mm translational motion). Thus, the final analyses include 6 SD subjects and 9 AD subjects.

All first-level analyses of imaging data were conducted within the context of the general linear model (FSL's FEAT), modeling the 2 s cue period and 5 s period of taste delivery convolved with a double-gamma hemodynamic response function (HRF), and accounting for temporal shifts in the HRF by including the temporal derivative. Button press times, corresponding to time of swallowing, were used as covariates to account for motor activity associated with swallowing. Six motion regressors representing translational and rotational head movement were also entered as regressors of no interest. Data for each subject were registered to the MBW, followed by the MPRAGE using affine linear transformations, and then normalized to the Montreal Neurologic Institute (MNI avg152) template. Registration was further refined using FSL's nonlinear registration tool (FNIRT) (Andersson *et al.*, 2007). *Z*-statistic images were thresholded with cluster-based corrections for multiple comparisons based on the theory of Gaussian Random Fields with a cluster-forming threshold of $Z > 1.96$ and a cluster-probability threshold of $P < 0.05$ (Worsley, 2001).

To explore PE-related signals and task-related activation, in general, three analyses were conducted to examine brain activity during taste delivery (outcome phase of the task): (a) average activation differences between task conditions, (b) a standard model-based approach using model-based computations of PE values as weights in a whole-brain parametric modulation analysis and (c) exploratory trial-by-trial analyses of activation within PE-relevant regions of interest (ROIs). The first two methods are detailed below, while the exploratory trial-by-trial analysis is included in the Supplemental Material.

For the analysis designed to evaluate direct contrasts across task conditions, separate regressors for each of the three conditions (positive expectation violations: receiving alcohol taste when cued for water, negative expectation violations: receiving water taste when cued for alcohol, and congruent trials) were included in the same model, for both cue and taste (alcohol or water) delivery. Contrasts representing alcohol vs. water (congruent only), positive expectation violations and negative expectation violations across all participants and in AD vs. SD subjects were evaluated.

For model-based parametric modulation analyses of PE-related activation, PE was calculated on a trial-by-trial basis using the Rescorla-Wagner Model (Rescorla and Wagner, 1972). Similar to previous neuroimaging studies [e.g. (Hare *et al.*, 2008; Cohen *et al.*, 2010)], we used the following equations: $PE(t) = O(t) - V(t)$; $V(t+1) = O(a) + \alpha * PE(t)$, where PE is the prediction error, t is the trial number, α is the learning rate, O is the outcome (alcohol or

water) of the current trial and V is the expected value of the current trial. We examined several learning rates (i.e. 0.2, 0.5 and 0.8) which produced similar results. For the sake of brevity, we present results from $\alpha = 0.8$ here. Three regressors of interest were included: cues, taste delivery (mean) and taste delivery with HRF height weighted by trial-specific PE values [parametric modulation analysis, e.g. (Buchel *et al.*, 1998)]. Positive and negative PE were evaluated via positive and negative contrasts (1, −1), respectively, for the parametric modulation regressor. Higher-level analyses examined positive and negative PE trials across all subjects, and group differences in positive and negative PE trials. An exploratory model that included additional trials in the second run resulted in no significant PE-related regions of activation; however, given that the artifact in the second run data was frequently directly related to the task itself (i.e. delivery of the taste cue), the unaffected trials in the second run were deemed likely to be nonrepresentative of the intended PE signal and thus were not included in the final model.

RESULTS

Sample characteristics

Demographic characteristics for the SD and AD groups as well as the total sample are presented in Table 1. There were no significant group differences in age, sex, ethnicity or the number of daily smokers. However, as expected, the AD group had significantly greater drinks per drinking day and percent drinking days in the past 30 days compared to the SD group ($P < 0.05$). The mean AUDIT score of the AD group was also significantly higher than the mean AUDIT score of the SD group ($P < 0.05$).

Direct contrasts across task conditions: Whole-brain activity

Congruent contrasts

Significant clusters from the whole-brain congruent alcohol taste vs. water taste contrast for the entire sample are presented in Table S1A and Fig. S1. Greater activity in the cerebellum and lingual gyrus, as well as in parietal lobe regions, including precuneus was found in the congruent alcohol taste vs. water taste contrast. Greater activation for the AD vs. SD group was observed in the left putamen and bilateral caudate (Table S1C, Fig. S2B).

Incongruent contrasts

No areas of significant activation were observed averaged across all subjects, or contrasting the AD and SD subject groups for the positive or negative expectation violation incongruent contrasts.

PE: Whole-brain activity

Significant clusters from the whole-brain positive PE analysis are presented in Table 2A and Fig. 2.

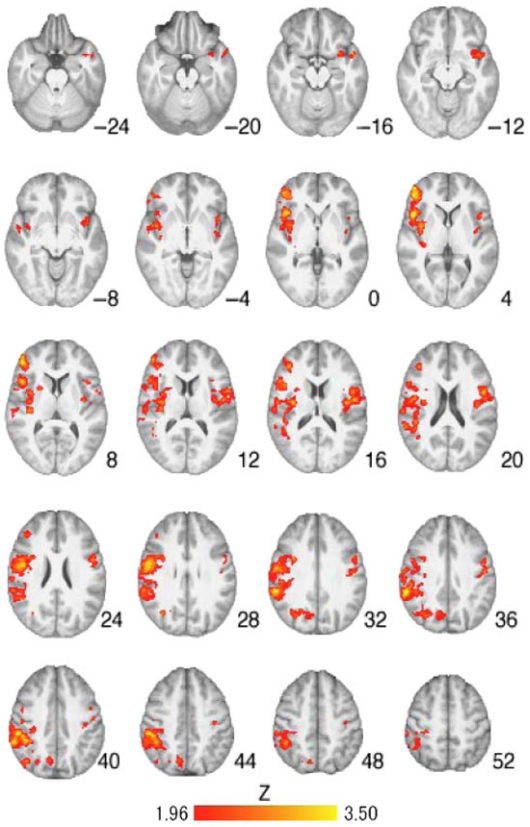

Figure 2. Positive PE in entire sample. Brain regions showing greater activation to positive expectation violation in all participants include frontal, insular and parietal regions ($Z > 1.96$, $P < 0.05$).

Table 2. Brain activation for positive PE trials

Brain region	Hemisphere	Cluster voxels	Max Z	X	Y	Z
(A) Positive PE—all subjects						
Posterior supramarginal gyrus/insula/precentral gyrus/postcentral gyrus/middle frontal gyrus/angular gyrus	R	6765	3.50	60	−38	32
Dorsolateral prefrontal cortex	R		3.46	48	50	4
Inferior frontal gyrus	R		3.45	48	16	6
Anterior supramarginal gyrus	R		3.40	54	−32	40
Frontal opercular cortex	R		3.30	46	20	2
Precentral gyrus/insula/temporal pole	L	1567	3.10	−48	2	22
Central opercular cortex	L		3.00	−52	−8	16
(B) Positive PE—AD vs. SD						
Superior parietal lobule/lateral occipital cortex	L	1192	3.47	−20	−58	64
Postcentral gyrus	L		2.81	−46	−30	58

Locations of significant activation for the positive PE trials (A) averaged across all subjects and (B) for the AD vs. SD subjects. No areas of significant activation were observed for the negative PE trials. All analyses were whole-brain cluster-corrected at $Z > 1.96$, $P < 0.05$. AD, Alcohol Dependent Group; SD, Social Drinking Group; L, Left; R, Right.

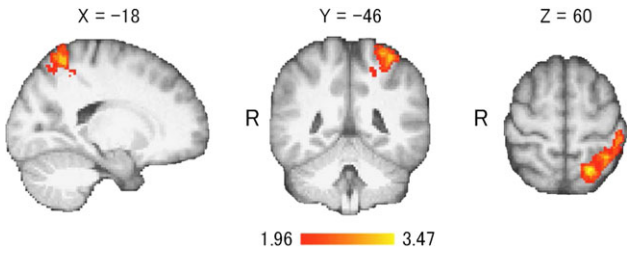

Figure 3. Positive PE in AD vs. SD participants. Brain regions showing group differences in positive expectation violation in AD vs. SD subjects include regions of the parietal lobe ($Z > 1.96$, $P < 0.05$).

Across the entire sample of participants, greater positive PE-related brain activation was found in a large cluster comprised of frontal lobe regions, including middle frontal gyrus, inferior frontal gyrus and dlPFC, as well as insular cortex, and motor/sensory cortices, including precentral and postcentral gyrus. Comparison of AD vs. SD participants during positive PE indicated that AD subjects had greater brain activity in left superior parietal lobule, left lateral occipital cortex and left postcentral gyrus during positive PE compared to SD subjects (Table 2B/Fig. 3). No significant whole-brain negative PE-related activation was found.

DISCUSSION

The concept of reward PE has been widely applied to the study of addiction, primarily from a preclinical vantage point. Translating such rich literature to human and clinical samples with alcoholism represents a promising area for significance and impact. To that end, developing a fMRI task that can effectively mirror the phenomenology of a positive and negative reward PE using a primary, 'real-world' reward and, in particular, reward indexed by a substance of abuse has important face validity for translating preclinical findings to clinical populations. The present study sought to develop an fMRI-based reward PE task using orally-delivered alcohol as the rewarding stimuli. The initial results reported herein demonstrate some successes as well as many challenges in task development, which in turn highlight the intricate nature of translational efforts that are meaningful at both preclinical and clinical levels.

The starting point for the task developed in this study was the alcohol taste cues task developed and validated by Filbey *et al.* (2008a) and employed by multiple research groups, including ours (Filbey *et al.*, 2008b; Ray *et al.*, 2014). The task was originally designed for each taste (alcohol vs. control) presentation to last 24 s, whereas the current study delivers the taste in 5 s. The shorter duration of taste presentation allows for a larger number of trials to be included in the task, which was required to establish an expectation that cues would be associated with delivery of the stated taste and set the stage for cue-taste violations (i.e. positive and negative reward PEs). Given the marked reduction in the length of each trial compared to the original task, it is important to consider the primary contrast of alcohol taste vs. water taste for all congruent trials in this study in order to offer initial validation of the shorter trial application of the task. Results indicated greater activity in the cerebellum and lingual gyrus, as well as in parietal lobe regions, including precuneus, in the congruent alcohol taste vs. water taste contrast across the entire sample of participants. Importantly, in the AD group alone, greater brain activation was observed during congruent alcohol taste vs. water taste in the insula and striatum, including the caudate and putamen, as well as in several frontal lobe regions, including the middle frontal gyrus and ACC. In addition, the AD group exhibited greater brain activation in the caudate and putamen as compared to the SD group. We were unable to detect significant findings in the SD group alone for the congruent alcohol taste vs. water taste contrast, which may have been limited by the smaller sample size of this group. These initial findings, albeit in a small sample and in the context of task development, are consistent with the expected pattern of activation for this task (Filbey *et al.*, 2008a), as well as with the literature on neural bases of alcohol cue reactivity more broadly (Schacht *et al.*, 2013).

The next step consisted of examining the positive and negative PE effects in the whole sample in addition to contrasting the AD and SD groups. Across the entire sample, greater positive PE-related brain activation was present in a large cluster comprised of frontal lobe regions, including middle frontal gyrus, inferior frontal gyrus and dlPFC, as well as insular cortex, and motor/sensory cortices, including precentral and postcentral gyrus. Comparison of AD vs. SD participants indicated that AD subjects had greater positive PE-related brain activation in left superior parietal lobule, left lateral occipital cortex and left postcentral gyrus compared to SD participants. While these results show an interesting pattern of positive PE-related activation, there was a notable absence of differential activation in the VS and mOFC, regions robustly implicated in the PE literature (Pessiglione *et al.*, 2006; Park *et al.*, 2010; Garrison *et al.*, 2013; Tanabe *et al.*, 2013).

Based on these results, the task could not be convincingly validated in its current format and additional exploration of the patterns of activation during the task appeared warranted. Thus, we employed an exploratory trial-by-trial design to further inform our efforts and elucidate patterns of activation in response to the task. In particular, these analyses were centered on four ROIs, namely VS, mOFC, amygdala and anterior insula. Results indicated greater activation in the VS during the second trial of the task for congruent alcohol taste vs. water taste delivery. One might infer that participants had difficulty distinguishing alcohol vs. water delivery in the first trial of the task, but following this, the tastes themselves increased in salience, such that alcohol itself elicited more activation of regions related to reward than did water in the second trial of the APE task. In terms of PE signaling, the first incongruent trial for alcohol (positive expectation violation: water expected, but alcohol delivered) and for water (negative expectation violation: alcohol expected but water delivered) showed significant differences in mOFC activation, such that positive expectation violations showed increased response in the mOFC compared with negative expectation violations. Although not exactly equivalent to model-based PE computations which take into account trial history, trial-by-trial expectation violations may be considered an approximate proxy for PE phenomena.

The fact that subsequent trials largely showed no significant differences in mOFC activation may suggest that repeated violations of the expected cue-reward relationship do not carry the same significance, and/or neural correlates, as early PE trials in which priors for the reliability of cues have not yet been established. If this is the case, averaging across all expectation violation trials may effectively washout the PE effect in areas such as the VS and mOFC, and model-based PE approaches may not include enough dynamic range in PE signals to adequately detect corresponding signals in these regions. An APE task with fewer PE trials, but with ones significantly spaced out from each other across the task may ultimately be more sensitive to detecting expected PE effects and could be more easily applied to a much larger sample.

As noted above, several challenges were encountered and should be carefully addressed in future task-development efforts. First, the salience of the alcohol tastes and the history that each participant may have had with their preferred beverage taste cannot be entirely controlled for. Second, there is a possibility for aversive effects of alcohol taste or aversive effects of non-preferred beverage in the SD and AD group as beer was not an option for alcohol delivery due to constraints with the liquid delivery system, which does not allow for carbonated liquids to be used. Furthermore, preferred beverages may have been distinct from those participants had most experience with or had most recently consumed, and thus may not have elicited the expected reward PE that other more frequently or recently consumed beverages would have. Third, data was lost due to excessive motion that we believe was a result of several factors, including: delivering liquid across many trials within a short time frame; trial and error to make the equipment function properly with the new task (e.g. leaking of delivery tubes, tubes falling out during scanning); and participant difficulties receiving certain types of alcoholic beverages lying down. Future improvements to the task set to reduce the movement could include: practicing the task with the participant prior to scanning (i.e. receiving liquid lying down), imposing a single alcoholic beverage that is suitable to most participants, reducing the amount of liquid that is delivered during each trial (e.g. from 2 ml to 1 ml) and ensuring the tubes are secure and properly placed. Fourth, it is uncertain whether SD and AD subjects found the alcoholic beverages to be equally rewarding, which could have confounded the PE results. Future work may consider a pre-assessment of the alcoholic beverage's value to the participant and using a button press to rate the pleasure associated with delivery of the tastes. Fifth, there is likely individual variability in the learning rate for the task among participants, even though the task design included no more than two expectation violations that followed each other. Sixth, task-development efforts will need to attend to optimal trial sequences such that dynamic range of PE is maximized to detect adequate signal when only a few trials may index the PE effect. In turn, PE modeling approaches may be optimized to better capture situations in which fewer trials are available for robust PE calculation. One might also consider longer trial durations to fully capture more robust PE effects during the early trials of the task. Lastly, since model-based PE signals have traditionally been computed within reinforcement learning paradigms that often include action-outcome learning, future PE task paradigms may consider including an instrumental conditioning component using alcohol as reinforcement, similar to paradigms used in the original studies by Schultz (1998).

In conclusion, the current reward PE task-development study for alcoholism found that positive and negative PE signaling may not be detected in expected brain regions when image analyses average across all PE trials of the task. Rather, a trial-by-trial analysis approach may help detect sparse PE signaling in expected reward processing regions, but many task considerations, including beverage choice, task length, number and sequence of trials, trial length, and type of learning will need to be carefully examined in future task designs to improve upon the current task that was piloted in this small study. An APE fMRI task for alcoholism holds promise for understanding the neurobiological correlates of AUD and associated reward learning deficits that may in part contribute to the clinical course of this disorder.

SUPPLEMENTARY MATERIAL

Supplementary data is available at *Alcohol and Alcoholism* online.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Luke Change for helpful discussions on the prediction error fMRI analyses.

FUNDING

This work was supported by seed funds from the UCLA Department of Psychology and pilot scans provided by the UCLA Center for Cognitive Neuroscience (CCN) to L.A.R.; the National Institute on Drug Abuse [F31 DA035604 to K.E.C. and T32 DA024635 to support training for A.C.]; and the National Institute on Alcohol Abuse and Alcoholism [T32 AA013525 to support training for K.E.C.].

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

Andersson, J, Jenkinson, M, Smith, S (2007) Technical report TR07JA2. Non-linear registration. FMRIB.

Bissonette GB, Roesch MR. (2016) Neurophysiology of reward-guided behavior: correlates related to predictions, value, motivation, errors, attention, and action. *Curr Top Behav Neurosci* **27**:199–230.

Buchel C, Holmes AP, Rees G, *et al.* (1998) Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *NeuroImage* **8**:140–8.

Cohen JR, Asarnow RF, Sabb FW, *et al.* (2010) A unique adolescent response to reward prediction errors. *Nat Neurosci* **13**:669–71.

Courtney KE, Ghahremani DG, London ED, *et al.* (2014) The association between cue-reactivity in the precuneus and level of dependence on nicotine and alcohol. *Drug Alcohol Depend* **141**:21–6.

Courtney KE, Ghahremani DG, Ray LA. (2015) The effect of alcohol priming on neural markers of alcohol cue-reactivity. *Am J Drug Alcohol Abuse* **41**:300–8.

Courtney KE, Ray LA. (2014) Subjective responses to alcohol in the lab predict neural responses to alcohol cues. *J Stud Alcohol Drugs* **75**:124–35.

Filbey FM, Claus E, Audette AR, *et al.* (2008a) Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology* **33**:1391–401.

Filbey FM, Ray L, Smolen A, *et al.* (2008b) Differential neural response to alcohol priming and alcohol taste cues is associated with DRD4 VNTR and OPRM1 genotypes. *Alcohol Clin Exp Res* **32**:1113–23.

Garrison J, Erdeniz B, Done J. (2013) Prediction error in reinforcement learning: a meta-analysis of neuroimaging studies. *Neurosci Biobehav Rev* **37**: 1297–310.

Gu Y, Hu X, Pan W, *et al.* (2016) Neural activities underlying the feedback express salience prediction errors for appetitive and aversive stimuli. *Sci Rep* **6**:34032.

Hare TA, O'Doherty J, Camerer CF, *et al.* (2008) Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. *J Neurosci* **28**:5623–30.

Hauser TU, Iannaccone R, Walitza S, *et al.* (2015) Cognitive flexibility in adolescence: neural and behavioral mechanisms of reward prediction error processing in adaptive decision making during development. *NeuroImage* **104**:347–54.

Heatherton TF, Kozlowski LT, Frecker RC, *et al.* (1991) The fagerstrom test for nicotine dependence: a revision of the fagerstrom tolerance questionnaire. *Br J Addict* **86**:1119–27.

Kalivas PW, Volkow ND. (2005) The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* **162**:1403–13.

Kareken DA, Grahame N, Dzemidzic M, *et al.* (2012) fMRI of the brain's response to stimuli experimentally paired with alcohol intoxication. *Psychopharmacology (Berl)* **220**:787–97.

Park SQ, Kahnt T, Beck A, *et al*. (2010) Prefrontal cortex fails to learn from reward prediction errors in alcohol dependence. *J Neurosci* **30**:7749–53.

Pessiglione M, Seymour B, Flandin G, *et al*. (2006) Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* **442**:1042–5.

Ray LA, Courtney KE, Hutchison KE, *et al*. (2014) Initial evidence that OPRM1 genotype moderates ventral and dorsal striatum functional connectivity during alcohol cues. *Alcohol Clin Exp Res* **38**:78–89.

Rescorla RA, Wagner AR. (1972) A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In Black AH, Prokasy WFs (eds). *Classical Conditioning II: Current Research and Theory*. New York: Appleton Century Crofts, 64–99.

Saunders JB, Aasland OG, Babor TF, *et al*. (1993) Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption —II. *Addiction* **88**:791–804.

Schacht JP, Anton RF, Myrick H. (2013) Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addict Biol* **18**:121–33.

Schultz W. (1998) Predictive reward signal of dopamine neurons. *J Neurophysiol* **80**:1–27.

Schultz W, Dayan P, Montague PR. (1997) A neural substrate of prediction and reward. *Science* **275**:1593–9.

Schultz W, Dickinson A. (2000) Neuronal coding of prediction errors. *Annu Rev Neurosci* **23**:473–500.

Tanabe J, Reynolds J, Krmpotich T, *et al*. (2013) Reduced neural tracking of prediction error in substance-dependent individuals. *Am J Psychiatry* **170**: 1356–63.

Valentin VV, O'Doherty JP. (2009) Overlapping prediction errors in dorsal striatum during instrumental learning with juice and money reward in the human brain. *J Neurophysiol* **102**:3384–91.

Vanes LD, van Holst RJ, Jansen JM, *et al*. (2014) Contingency learning in alcohol dependence and pathological gambling: learning and unlearning reward contingencies. *Alcohol Clin Exp Res* **38**:1602–10.

Worsley KJ. (2001) Statistical analysis of activation images. In Jezzard P, Matthews PM, Smith SMs (eds). *Functional MRI: An Introduction to Methods*. New York, NY: Oxford University Press.

Xue G, Xue F, Droutman V, *et al*. (2013) Common neural mechanisms underlying reversal learning by reward and punishment. *PloS one* **8**:e82169.

Yoder KK, Morris ED, Constantinescu CC, *et al*. (2009) When what you see isn't what you get: alcohol cues, alcohol administration, prediction error, and human striatal dopamine. *Alcohol Clin Exp Res* **33**:139–49.