Behavioural Brain Research 317 (2017) 122–131

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Learning and generalization from reward and punishment in opioid addiction

Catherine E. Myers[a,b,*], Janice Rego[c], Paul Haber[d], Kirsten Morley[d], Kevin D. Beck (PhD)[a,b], Lee Hogarth[e,f], Ahmed A. Moustafa[a,g]

[a] Department of Veterans Affairs, New Jersey Health Care System, East Orange, NJ, USA
[b] Department of Pharmacology, Physiology & Neuroscience, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, NJ, USA
[c] School of Social Sciences and Psychology, Western Sydney University, Sydney, NSW, Australia
[d] NHMRC Centre of Research Excellence in Mental Health and Substance Use, Discipline of Addiction Medicine, Central Clinical School, The University of Sydney, NSW, Australia
[e] School of Psychology, University of New South Wales, Sydney, NSW, Australia
[f] School of Psychology, University of Exeter, Exeter, UK
[g] Marcs Institute for Brain and Behaviour, Western Sydney University, Sydney, NSW, Australia

HIGHLIGHTS

- Opioid-addicted individuals, and controls, performed an acquired equivalence task.
- The training phase interleaved reward-based and punishment-based learning.
- The addicted group was impaired on discriminating punishing vs. ambiguous outcomes.
- The groups did not differ on reward-based learning, or subsequent generalization.
- Impaired learning from punishment could support behavior that promotes addiction.

ARTICLE INFO

Article history:
Received 18 March 2016
Received in revised form 24 August 2016
Accepted 12 September 2016

Keywords:
Opioid addiction
Heroin
Reward learning
Punishment learning
Generalization
Acquired equivalence

ABSTRACT

This study adapts a widely-used acquired equivalence paradigm to investigate how opioid-addicted individuals learn from positive and negative feedback, and how they generalize this learning. The opioid-addicted group consisted of 33 participants with a history of heroin dependency currently in a methadone maintenance program; the control group consisted of 32 healthy participants without a history of drug addiction. All participants performed a novel variant of the acquired equivalence task, where they learned to map some stimuli to correct outcomes in order to obtain reward, and to map other stimuli to correct outcomes in order to avoid punishment; some stimuli were implicitly "equivalent" in the sense of being paired with the same outcome. On the initial training phase, both groups performed similarly on learning to obtain reward, but as memory load grew, the control group outperformed the addicted group on learning to avoid punishment. On a subsequent testing phase, the addicted and control groups performed similarly on retention trials involving previously-trained stimulus-outcome pairs, as well as on generalization trials to assess acquired equivalence. Since prior work with acquired equivalence tasks has associated stimulus-outcome learning with the nigrostriatal dopamine system, and generalization with the hippocampal region, the current results are consistent with basal ganglia dysfunction in the opioid-addicted patients. Further, a selective deficit in learning from punishment could contribute to processes by which addicted individuals continue to pursue drug use even at the cost of negative consequences such as loss of income and the opportunity to engage in other life activities.

Published by Elsevier B.V.

1. Introduction

Addiction can be thought of as a disorder in which addicted individuals continue to seek out and use the addictive substance despite negative consequences, such as loss of income and loss of

* Corresponding author at: Research Service, VA New Jersey Health Care System, East Orange, NJ 07018-1023, USA.
E-mail address: Catherine.Myers2@va.gov (C.E. Myers).

http://dx.doi.org/10.1016/j.bbr.2016.09.033
0166-4328/Published by Elsevier B.V.

the opportunity to engage in other activities [1,2]. It is possible then that addiction is not merely about heightened reward-seeking, but rather an imbalance between the ability to adjust behavior to maximize reward while simultaneously avoiding punishment.

Of particular societal concern are the highly-addictive opioid drugs. Due to an increasing use of medically-prescribed opioid painkillers, accidental addiction to prescription opiate drugs is estimated to affect approximately 2 million people in the U.S. alone [3], and abuse of these drugs often leads to use of illegal opiates such as heroin, once access to the prescriptions drugs is withdrawn. Opioid addiction is extremely difficult to overcome, even when the addicted individual strongly desires to stop using the drug, and there is a high relapse rate for individuals who have undergone detoxification treatment [4]. One option for individuals who have tried and failed to overcome opioid addiction is maintenance treatment, involving medically-supervised use of opioids such as methadone. However, a recent review of outcomes following maintenance therapy reported that, one month after discontinuation of treatment, rates of relapse to illicit opioid use exceed 50% [5]. Given these figures, it is of great importance to understand reinforcement-based learning processes in opioid-addicted individuals, in order to develop more effective therapies to aid these individuals in overcoming their drug dependence.

1.1. Opiate addiction and reward processes

Numerous prior studies have examined how opioids affect reward pathways in the brain [6–8], including studies suggesting that opioid-addicted individuals are particularly impaired at temporal discounting tasks that require foregoing a small immediate reward in favor of a larger delayed reward [9,10]. However, few studies have attempted to examine the balance between reward-based and punishment-based learning in opioid-addicted individuals, or how this learning might generalize when familiar stimuli are presented in new ways.

In a prior study, Myers et al. [11] used a categorization task that interleaved trials on which participants learned to avoid negative consequences (point loss) with trials on which they learned to obtain positive consequences (point gain). There was also an ambiguous "no-feedback" outcome, which could signal either missed opportunity for reward or else successful avoidance of punishment. The category mappings were probabilistic, such that a particular stimulus belonged to one category on 80% of the trials on which it appeared and to the other class on 20% of trials. Thus, expectancies were sometimes violated even for a subject who had learned the category mappings well. The optimal strategy was therefore to choose the most-often correct category for each subject ("probability maximizing"), and to continue to execute this strategy throughout the task, despite the occasional trials on which the response would fail to pay off. Results from this prior study showed that opiate-addicted individuals and never-addicted controls performed comparably in terms of total points accrued on the task. However, the addicted participants exhibited an increased tendency to shift response strategies after an unexpected loss (either a punishment or an omission of expected reward). In other words, the addicted group tended to "chase reward" by altering their response strategy whenever they experienced a negative outcome, while controls were more likely to "stick with" a stable response strategy that maximized long-term gain. However, another interpretation of the results is simply that opioid-addicted individuals were better at learning from punishment than controls, resulting in them being more able to adjust responding after a loss than controls. In the particular context of a probabilistic categorization task, this led to suboptimal behavior – but in a deterministic task, it might result in superior punishment-based learning.

The current task is designed to investigate this issue further, by considering a reward- and punishment-learning task where cue-outcome mappings are deterministic. If opioid-addicted individuals are simply better than controls at learning to adjust responding based on punishment, then they should similarly outperform controls on punishment-based trials in this deterministic task. On the other hand, if the results from the prior study were specifically due to the probabilistic nature of the task, then the opioid-addicted group might not outperform controls on a deterministic task. In addition, the prior study left open the question of whether learning would generalize in the same fashion in opioid-addicted and never-addicted groups, and if so, whether generalization was equivalent to stimuli that had previously been associated with reward versus those that had previously been associated with punishment.

To explore these questions, we adapted a widely-studied learning paradigm, acquired equivalence, in which prior training to treat two stimuli as equivalent increases generalization between them [12–14]. In one, widely-used version of the paradigm, participants learn via trial and error to pair each of several antecedents with a consequent; some antecedents are implicitly equivalent in the sense that they should be paired with the same consequent. Subsequently, a subset of antecedents are paired with new consequents. Prior work has shown that healthy controls reliably generalize this new learning, tending to pair equivalent antecedents with the same consequents, even though these pairings were never explicitly trained [15].

1.2. Brain substrates of acquired equivalence

A computer-based version of acquired equivalence has previously been used to demonstrate qualitative differences in learning vs. generalization in a number of psychiatric and neurological patient groups (for review, see [16]. For example, the learning of stimulus-response pairs appears to depend on frontostriatal circuits, and is disrupted in individuals with frontostriatal dysfunction, such as patients with Parkinson's disease tested on normal dopaminergic medication [15,17], who show slow learning followed by successful generalization.

On the other hand, generalization appears to depend on medial temporal (hippocampal) function; thus, amnesic patients with bilateral hippocampal destruction [18] and nondemented elderly with hippocampal atrophy consistent with prodromal Alzheimer's disease (AD) [15] both spared learning followed by impaired generalization. Patients symptomatic for early (AD) show similar deficits on generalization, although they also show slower learning than age-matched controls, consistent with a more diffuse pattern of accumulating brain pathology in early AD [19]. Disrupted generalization on acquired equivalence tasks is also seen in other psychopathologies that commonly involve hippocampal-region volume reductions, including schizophrenia [20,21] and post-traumatic stress disorder [22].

Together, these studies suggest that the acquired equivalence paradigm provides a platform to dissociate frontostriatal-dependent associative learning from medial temporal-dependent generalization. Further evidence for this dissociation comes from functional neuroimaging (fMRI) studies in healthy young adults, which show a positive relation between caudate activity and performance on the initial feedback-based learning, while increasing activation in the hippocampus during training correlates with performance on subsequent generalization tests [23].

The importance of the hippocampal region for generalization in the acquired equivalence paradigm is consistent with theories suggesting that the hippocampal region helps establish stimulus representations that support later flexible use of the learned information [24,25]. On the other hand, the role of the basal gan-