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# LATERAL HABENULA INTEGRATION OF PROACTIVE AND RETROACTIVE INFORMATION MEDIATES BEHAVIORAL FLEXIBILITY

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**Abstract**—The lateral habenula (LHb) is known to play an important role in signaling aversive or adverse events that have happened or are predicted by cues under Pavlovian conditions. In rodents, it is also required for behavioral flexibility when changes in reward outcomes signal that strategies should be changed. It is not known whether the LHb also controls appetitive behaviors when an animal is able to utilize external cues proactively to guide upcoming decisions. In order to test this, male Long–Evans rats were trained to switch between two arms of a figure eight maze based on the tone presented prior to the choice. Importantly, the tones were switched every three to six trials so rats were able establish a response pattern before being required to switch. This caused rats to rely on both proactive (tones) and retroactive information (reward feedback) to guide behavior. Inactivation of the LHb with the GABA agonists baclofen and muscimol impaired overall performance by increasing both errors when the tones are switched (switch errors) as well as on subsequent trials (perseverative errors) indicating that both proactive and retroactive information are utilized by the LHb to guide behavioral flexibility. Once a correct choice was made in a given block, LHb inactivated rats did not make more errors than controls. A control study revealed that the LHb is not required for tone or reward magnitude discrimination per se. These results demonstrate for the first time that the LHb contributes to behavioral flexibility through utilizing both proactive and retroactive information when performing appetitive tasks.

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**Key words:** cognitive flexibility, behavioral flexibility, reversal learning, habenula, set-shifting, reward prediction error.

## INTRODUCTION

The ability to rapidly and repeatedly switch from ongoing behaviors to new ones when contingencies change is critical across species. Both internally and externally generated cues such as hunger or negative reinforcement can signal that alternative behaviors should be engaged. The ability to switch behaviors based on changing contingencies is commonly known as behavioral flexibility. Behavioral flexibility encompasses many different types of behavioral switches ranging from reversal learning where rewards switch from one response to the opposite, to go/no-go tasks where pre-potent responses must occasionally be withheld based on the presence of a cue. In many common behavioral flexibility tasks, the subject learns of a change in reward retroactively and must update expectations on subsequent trials. However, in other tasks such as go/no-go or cued switching tasks, cues can be used to guide changes in ongoing behavior proactively in order to avoid the withholding of a reward due to choice errors.

A wide variety of both individual brain areas as well as neural systems have been implicated in the ability to perform tasks requiring behavioral flexibility, often dissociating between its various types (Reading et al., 1991; Ragozzino, 2007; Bissonette et al., 2008; Young and Shapiro, 2009; Kesner and Churchwell, 2011; Penner and Mizumori, 2012). For example, within the prefrontal cortex, reversal learning is thought to be controlled by the orbital frontal cortex while the medial prefrontal cortex (mPFC) is known to control the ability to switch sensory modalities such as from discriminations based on visual information to those controlled by odors (McAlonan and Brown, 2003; Ragozzino et al., 2003; Ragozzino, 2007). Less is known, however, about the role of many of these structures in behavioral flexibility when cues can be used to switch ongoing behaviors proactively.

In rodents, it has been found that when cues are available to guide switches between two choices both in an operant chamber and a maze, the mPFC is required for effective performance (Leenaars et al., 2012; Baker and Ragozzino, 2014a,b; Duan et al., 2015). Additionally, mPFC projections to both the dorsomedial striatum and subthalamic nucleus contribute to effective task switching performance (Baker and Ragozzino, 2014a,b). Across behavioral flexibility tasks, both the midbrain dopamine (DA) and serotonin (5-HT) monoamine systems have consistently been identified as necessary for effective

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performance making them likely contributors to proactive switching as well (Cools, 2006; Evers et al., 2007; Crockett et al., 2009; Robbins and Arnsten, 2009; Bari et al., 2010; Baker et al., 2011; Cools et al., 2011; Klanker et al., 2013; Hart et al., 2014; Logue and Gould, 2014). However, this has not been tested to date.

Recent work supports that the lateral habenula (LHb), a structure in the dorsal diencephalic conduction system, is a key modulator of the midbrain monoamine systems (Christoph et al., 1986; Ji and Shepard, 2007; Lecourtier and Kelly, 2007; Hikosaka, 2010; Proulx et al., 2014; Stopper et al., 2014). In addition to its influence on 5-HT and DA, the LHb also receives input from both the mPFC and basal ganglia (Herkenham and Nauta, 1977; Greatrex and Phillipson, 1982; Vincent and Brown, 1986; Kim and Lee, 2012), which contains both the striatum and subthalamic nucleus, raising the possibility that the LHb acts as a relay between forebrain and midbrain structures to coordinate behavioral flexibility. While the majority of studies conducted on the LHb have implicated it in the processing of aversive or adverse events (Matsumoto and Hikosaka, 2007; Hikosaka, 2010; Stamatakis and Stuber, 2012), recent work has demonstrated that the LHb likely also plays a more fundamental role in behavioral flexibility within complex environments (Stopper and Floresco, 2014; Baker et al., 2015; Mathis et al., 2015; Orsini et al., 2015; Zhao et al., 2015). In a study by Stopper and Floresco (2014), inactivation of the LHb using GABA agonists abolished any choice bias in both a delay discounting task and a probabilistic discounting task. In delay discounting tasks, rats are required to choose between a small reward delivered immediately and a large, delayed reward. Importantly, reward (either large or small) is always guaranteed in this paradigm, and therefore the task requires no aversive signal such as an anti-reward signal. Moreover, if LHb inactivation removed an anti-reward signal from probabilistic discounting, it should have biased choice for the large risky level rather than causing guessing behavior as was also observed in both tasks (Stopper and Floresco, 2014). A similar level of guessing behavior was observed in a repeated probabilistic reversal learning task with an increase in both lose-shift and a decrease in win-stay performance indicating that rats had ceased to use a strategy and tended to guess again suggesting a role for the LHb beyond providing an anti-reward signal (Baker et al., 2015).

These previous studies relied on immediately prior outcomes influencing upcoming decisions (retroactive switching) but they did not address a possible role for the LHb in using cues proactively to guide upcoming switches in behavior. We have proposed that during tasks requiring behavioral flexibility, the LHb serves to coordinate neural systems in order to perform learned behaviors suggesting it should also be required to utilize proactive information when switching behaviors (Baker et al., 2015). In order to directly test whether the LHb contributes to behavior when cues are used proactively to switch behavior, a cued switching task was employed in which tones presented prior to an animal's choice determined which of two maze arms would result in reinforcement.

If the LHb contributes to behavioral flexibility when cues signal an upcoming change in reinforcement contingencies, then LHb inactivation should increase errors immediately after a change in the tone presented. If however, the LHb is only important following negative reinforcement, then increases in errors should only be observed following a previous error regardless of when it occurred in the trial sequence. In addition to the cued switching task, an additional experiment was run in which the tone–arm contingencies were switched between instead of within a session. If the LHb is important for organizing behavior in a dynamic environment as has been suggested previously, then no effect on the between session discrimination should be observed. If, however, the LHb is generally required for performing tone discriminations or memory processes, then impairments would be expected in this task as well.

## EXPERIMENTAL PROCEDURES

### Subjects

A total of 22 adult, male Long–Evans rats (350–450 g, Charles River) across both experiments were housed individually in Plexiglas cages and maintained on a 12-hour light/dark cycle (lights on at 7:00 A.M.), in a temperature and humidity controlled environment. All behavioral experiments were performed during the light phase of this cycle. The rats were food restricted to 85 percent of their *ad libitum* body weight except during surgery and recovery and each rat was allowed access to water *ad libitum*. All animal care was conducted according to guidelines established by the National Institutes of Health and approved by the University of Washington's Institute for Animal Care and Use Committee.

### Apparatus and pre-training

In both experiments a figure eight maze (Fig. 1) was used which was 122 cm in diameter with 8 cm alleys, 84 cm off the ground. A center alleyway bisecting the maze served as the choice arm with the outer arms being goal arms. A series of sensors and doors were operated by z-basic that controlled rats' movement through the maze and recorded their behavior (z-basic, Elba corp., Beaverton, OR, USA). Animals were initially familiarized to the maze by training them to collect two 45-mg sucrose pellets (TestDiet, Richmond, IN, USA) from both feeders. Specifically, rats were allowed directed exploration of the maze by closing and opening doors, forcing them on to one or the other side of the maze (five trials per side). Following these 10 forced trials, 10 free choice trials were given to reveal any side preferences for a given rat. Once rats were able to complete the 20 training trials in fewer than 30 min on three consecutive days, they were advanced to the experimental training. No consistent bias was observed during the final three days of the initial training with animals often switching bias between days. Thus initial bias was not accounted for in any of the analyses.

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