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Cooperative and dissociable involvement of the nucleus accumbens core and shell in the promotion and inhibition of actions during active and inhibitory avoidance

Patrick T. Piantadosi, Dylan C.M. Yeates, Stan B. Floresco*

Department of Psychology and Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, B.C., V6T 1Z4, Canada

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ABSTRACT

The flexible implementation of active and passive strategies to avoid danger is critical to survival. Conversely, the inappropriate allocation of these behaviors may underlie pathological avoidance in neuropsychiatric illnesses. The present study investigated whether these two poles of avoidance may be differentially regulated by subdivsions of the nucleus accumbens, the core (NAcC) and shell (NAcS), which are known to bi-directionally control flexible action selection during reward-seeking. In so doing, we developed a novel cued active/inhibitory avoidance task conducted in operant chambers that entailed presentations of two distinct, 15 s auditory cues. One cue indicated that impending foot-shocks could be avoided by pressing a lever (active avoidance), whereas another cue signaled that shocks could be avoided by withholding presses (inhibitory avoidance). In well-trained rats, pharmacological inactivation of either the NAcC or NAcS impaired active avoidance. In contrast, inhibitory avoidance was disrupted by inactivation of the NAcS, but not NAcC, reflecting a deficit in response-inhibition that manifested as more inhibitory avoidance failures and lever-presses, as well as increased locomotion. Foot-shock sensitivity was unaffected by inactivation of either subregion. In a subsequent experiment, treatment with the monoamine releaser D-amphetamine (1 mg/kg) did not affect active avoidance, but disinhibited lever pressing during inhibitory avoidance trials. These results provide novel insight into the ventral striatal and monoaminergic regulation of flexible response allocation and inhibition that facilitates avoidance behavior and highlight the importance of different subregions of the NAc in action selection during aversively-motivated behaviors.

1. Introduction

When faced with a potential threat, animals may employ one of two main types of defensive behaviors: defensive reactions and defensive actions (LeDoux, 2012; Moscarello and Ledoux, 2014). Defensive reactions are designed to evade predator detection and, in rodents, include forms of behavioral suppression such as freezing. These reactions can facilitate the passive avoidance of threatening stimuli. Conversely, defensive actions are instrumental behaviors which enable active threat avoidance or escape. Both active and passive avoidance strategies serve adaptive functions, with their flexible application being critical to survival.

These dichotomous defensive strategies may be viewed analogously to processes that govern appetitive behavior. For example, Go/No-Go conditioning requires an active approach response to receive reward in the presence of one cue (a “Go” response), while another cue signals that suppressing approach (a “No-Go” response) results in reward delivery. It is well-established that different aspects of appetitively-motivated behavior are predicated on activity within meso-cortico-limbic-striatal circuitry. A particularly crucial node in this network is the nucleus accumbens (NAc), which integrates diverse affective, cognitive, and neuromodulatory input to control action selection (Calhoon and O'Donnell, 2013; Floresco, 2015; Gruber et al., 2009; Gruber and O'Donnell, 2009; Mogenson et al., 1980). The NAc can be further partitioned into a lateral core (NAcC) and medial shell (NAcS), based on neuroanatomical and functional differences (Heimer et al., 1997; Zahm and Brog, 1992), with these subregions often playing dissociable, yet complementary, roles in guiding motivated behavior.

The NAcC has been proposed to promote active approach

* Corresponding author.
E-mail address: floresco@psych.ubc.ca (S.B. Floresco).

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behaviors, while the NAcS may fulfill a dual role, inhibiting inappropriate responses while also aiding in the production of active behaviors (Ambroggi et al., 2011; Blaiss and Janak, 2009; Floresco, 2015; Floresco et al., 2008; Ghazizadeh et al., 2012; Ghods-Sharifi and Floresco, 2010; Piantadosi et al., 2017). For example, neurophysiological studies have shown that neurons in both the NAcC and NAcS encode a discriminative stimulus that signals reward availability, yet a higher proportion of neurons in the NAcS (as compared to NAcC) also encode a neutral stimulus that signals reward unavailability (Ambroggi et al., 2011). Inactivation of the NAcC preferentially affects behavior elicited by reward-predictive stimuli, while inactivation of NAcS unmasks irrelevant behaviors, such as lever-pressing and Pavlovian approach during non-rewarded task periods (Ambroggi et al., 2011; Blaiss and Janak, 2009). The NAcS (but not NAcC) has also been suggested to actively suppress extinguished and non-reinforced instrumental behavior during the reinstatement of food (Floresco et al., 2008), alcohol (Millan et al., 2010), or cocaine seeking (Peters et al., 2008). These data imply that each subnucleus facilitates reward-seeking in distinct ways, with the NAcS enforcing response-inhibition to focus and constrain behavioral output, and the NAcC promoting approach towards relevant stimuli.

Although the NAc is typically viewed as a part of the brain's "reward" circuitry, it is important to note that neurons within this region are also responsive to primary and conditioned aversive stimuli (Delgado et al., 2008; Jensen et al., 2003; Roitman et al., 2005; Schoenbaum and Setlow, 2003; Setlow et al., 2003). For example, on a mixed valence Go/No-Go task, largely separate populations of NAc neurons develop phasic responses to cues that predict appetitive or aversive outcomes (Setlow et al., 2003). These responses may facilitate behavioral flexibility in both appetitive and aversive contexts, allowing for active responses to be elicited to obtain rewards, while also enabling the response-suppression necessary to avoid aversive outcomes. Interestingly, NAc neurons track the behavioral response necessitated by a Go or No-Go cue, in keeping with a role for this nucleus in action selection (Roitman and Loriaux, 2014). Consistent with this idea, we have recently shown that subregions of the NAc are differentially responsible for the promotion and inhibition of reward-seeking during instrumental punishment. Inactivation of the NAcS disinhibited punished reward-seeking, whereas similar inactivation of the NAcC induced a general suppression of instrumental responding for reward (Piantadosi et al., 2017). Yet, it remains unclear how the NAcS and NAcC may regulate the expression of defensive actions versus reactions in response to discrete cues that predict aversive outcomes.

Previous work has separately examined the NAc contribution to these two types of defensive behaviors. With respect to defensive actions, the NAc and its dopaminergic input are integral for the learning and expression of "Go"-like actions such as active avoidance (Fernando et al., 2013; Gentry et al., 2016; Ilango et al., 2014; Lichtenberg et al., 2014; Oleson et al., 2012; Ramirez et al., 2015; Salamone, 1994). In particular, inactivation of NAcS, or disconnection of amygdalar inputs to this nucleus impairs the expression of active avoidance (Fernando et al., 2013; Ramirez et al., 2015). DA release in the NAcC increases during the presentation of an active avoidance cue, suggesting that transmission in this region may be relevant for the execution of this behavior (Gentry et al., 2016; Oleson et al., 2012). Thus, both subnuclei of the accumbens may contribute to initiating behaviors to avoid negative consequences.

In comparison to its role in active avoidance, neurotransmission in the NAc has been shown to be necessary for the acquisition, but not expression, of defensive reactions such as passive avoidance, as measured by latency on one-trial step-through tasks (Bracs et al., 1984; De Leonibus et al., 2003; Lorenzini et al., 1995; Martínez et al., 2002; Shirayama et al., 2015). Perturbations of NAc functioning prior to learning cause rats to approach a context previously associated with foot-shock more rapidly than control rats, although these effects are typically absent when conducted prior to expression. Unlike active avoidance, this mnemonic test is acute and not amenable to repeated testing. In addition, the difficulty posed by a No-Go trial during Go/No-Go performance is enhanced by the necessity to accurately discriminate between discrete Go vs. No-Go stimuli, and then withhold a prepotent response. These crucial aspects of response inhibition are not captured by such traditional inhibitory avoidance tasks. Thus, development of a task that can adequately measure the flexibility and repetition associated with fully aversively-motivated "Go" vs. "No-Go" performance would have considerable utility for ascertaining the neural mechanisms underlying different forms of avoidance. In this regard, gerbils have been trained to perform a two-way active avoidance procedure, whereby two different auditory stimuli indicate whether an inhibitory or active avoidance response is required to avoid foot-shock (Schulz et al., 2015; Stark et al., 2004; Wetzel et al., 2008). Interestingly, coherence between the auditory cortex and ventral striatum is increased following presentation of an active avoidance stimulus, an effect which is strengthened over the course of training (Schulz et al., 2015). These latter results suggest that the NAc may similarly integrate afferent input to accurately promote or inhibit responding during complex avoidance performance.

Additional insights into accumbal contributions to active versus passive avoidance comes from functional imaging studies conducted in humans (Levita et al., 2009, 2012). Participants were trained to discriminate between two visual stimuli that instructed them to either make an active avoidance response (i.e.; press a button) or passively withhold this same response to avoid an aversive outcome. Active avoidance increased the BOLD signal within the NAc, whereas successful inhibitory avoidance was associated with a deactivation in this region (Levita et al., 2012). This pattern suggests that the NAc may function to promote active avoidance, while suppression is necessary for successful inhibitory avoidance. Unfortunately, the spatial resolution constraints imposed by fMRI did not permit a more detailed characterization of whether changes in activation within different subregions of the NAc were associated with different types of avoidance responses. Developing a preclinical analog of this task would aid in clarifying how different brain nuclei contribute to the appropriate promotion versus suppression of behavior to avoid aversive outcomes, as well as generally improving our understanding of complex avoidance behaviors.

Here we report the development of a novel operant task that required rats to use discriminative cues that informed whether a foot-shock could be avoided by either pressing a lever or withholding a press, permitting the examination of the neural basis of the active versus inhibitory poles of avoidance. Using reversible inactivation, we explored the contribution of the NAcC or NAcS to these different aspects of behavior. In addition, we probed potential monoaminergic contributions, investigating the effect of systemically administered D-amphetamine (AMPH).

2. Materials and methods

Active/Inhibitory avoidance training was adapted from previous reports conducting active avoidance in an operant setting (Fernando et al., 2013, 2015; McCullough et al., 1993; Sokolowski et al., 1994), and based on a task used in humans, as described by Levita et al. (2012).