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The prelimbic cortex and subthalamic nucleus contribute to cue-guided behavioral switching

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ABSTRACT

Frontal cortex–basal ganglia circuitry supports behavioral switching when a change in outcome information is used to adapt response patterns. Less is known about whether specific frontal cortex–basal ganglia circuitry supports behavioral switching when cues signal that a change in response patterns should occur. The present experiments investigated whether the prelimbic cortex and subthalamic nucleus in male Long-Evans rats supports cue-guided switching in a conditional discrimination test. Rats learned in a cross-maze that a start arm cue (black or white) signaled which of two maze arms to enter for a food reward. The cue was switched every 3–6 trials. Baclofen and muscimol infused into the prelimbic cortex significantly impaired performance by increasing switch trial errors, as well as trials immediately following a switch trial (perseveration) and after initially making a correct switch (maintenance error). NMDA receptor blockade in the subthalamic nucleus significantly impaired performance by increasing switch errors and perseveration. Contralateral disconnection of these areas significantly reduced conditional discrimination performance by increasing switch and perseverative errors. These findings suggest that the prelimbic area and subthalamic nucleus support the use of cue information to facilitate an initial switch away from a previously relevant response pattern.

1. Introduction

Fundamental to daily living and survival is the ability to learn associations among stimuli, actions and outcomes, as well as switching between learned associations as environmental contingences change. These switches in behavior can be guided by changes in outcomes or by cues which predict the appropriate response pattern to be selected (Hikosaka & Isoda, 2010). The findings from several studies indicate that the rodent prefrontal cortex is involved in behavioral switching under certain conditions in which a learned response pattern is followed by a change in outcomes such that a new response pattern must be learned. In particular, infusion of local anesthetics, GABA agonists, or NMDA receptor antagonists into the prelimbic cortex impair extra-dimensional shifts when a response pattern based on particular stimulus information e.g. spatial cues, is no longer reinforced and a different pattern based on other stimulus information, e.g. odor cues, is now reinforced (Birrell & Brown, 2000; Floresco, Block, & Tse, 2008; Ng, Noblejas, Rodefer, Smith, & Poremba, 2007; Ragozzino, Kim, Hassert, Minniti, & Kiang, 2003; Ragozzino, Wilcox, Raso, & Kesner, 1999; Stefani, Groth, & Moghaddam, 2003). Several of these studies also revealed that manipulations of the prelimbic cortex impair extra-dimensional shifts, by increasing perseveration of the previously learned response pattern in the initial trials of a shift, but not after a rat chooses the new correct response (Dias & Aggleton, 2000; Ragozzino, 2002; Ragozzino, Detrick, & Kesner, 1999; Ragozzino, Wilcox, et al., 1999; Ragozzino et al., 2003). Taken together, the findings from past studies indicate that when information about outcomes must be used to enable a behavioral switch, the prelimbic cortex selectively supports extra-dimensional shifts by initially inhibiting preservation of the previously learned response pattern.

There has been significantly less examination of whether the prelimbic cortex supports behavioral switching when cues can be used to shift response patterns for an upcoming choice. Past studies found that prelimbic lesions alone or prelimbic and infralimbic lesions do not impair acquisition of a conditional discrimination task (Chudasama, Bussey, & Muir, 2001; Delatour & Gisquet-Verrier, 1999). Importantly, past conditional discriminations have pseudorandomly switched between conditions with at most 3 consecutive trials of the same contingency which may limit an establishment of a response set and any switch costs. A more recent study trained rats on a conditional discrimination task in

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which two different cues indicated making a distinct response to obtain a reward (if white noise press the left lever – if lights press the right lever). A cue was presented for 5–10 consecutive trials before a switch to presentations of the other cue occurred (Leenaars et al., 2012). This is similar to task-switching tests commonly administered to humans which cause an established choice pattern and induces a switch cost between blocks of trials (Monsell, 2003). After learning this cue-guided switch test, prelimbic inactivation with GABA agonists was found to impair performance for the switch trial, but not the fifth trial in each block (Leenaars et al., 2012). These findings suggest that the prelimbic cortex also supports behavioral switching when cue-information must be used to enable a switch from an established choice pattern in order to obtain a reward. However, while this study examined the first (switch) and fifth trial in each block, unclear is whether prelimbic inactivation also increases perseveration of the previous response pattern and/or impairs maintenance of the currently correct response pattern. Therefore, unknown is whether the prelimbic cortex supports a similar process when a change in outcomes signals a switch, e.g. inhibiting perseveration of a previously relevant response pattern, as when cues can be used to switch a response pattern.

The prefrontal cortex, including the prelimbic area, has extensive projections to basal ganglia structures and together these areas may act in a cooperative manner to facilitate behavioral switching when a change in outcomes or a change in cues guides a behavioral switch (Afsharpour, 1985; Chudasama & Robbins, 2006; Jahfari et al., 2011; Kehagia, Murray, & Robbins, 2010; Mailly, Aliane, Groenewegen, Haber, & Deniau, 2013). The subthalamic nucleus is one basal ganglia area that receives direct excitatory input from the prelimbic cortex that is mediated, at least in part, by NMDA receptors (Magill, Sharott, Bolam, & Brown, 2006; Maurice, Deniau, Glowinski, & Thierry, 1998; Nambu et al., 2000). Individual neurons in the non-human primate subthalamic nucleus show increased activity in response to a cue that signals when a switch from one response pattern to another will be rewarded (Isoda & Hikosaka, 2008). One possibility is that the rodent subthalamic nucleus also enables rapid and repeated behavioral switches when cue information can be used to proactively switch. Moreover, because the prelimbic cortex and subthalamic nucleus are interconnected and these two areas are involved in behavioral switching, both brain regions may need to be intact in order to facilitate cue-guided behavioral switching.

To determine whether the prelimbic cortex and subthalamic nucleus together are necessary to enable cue-guided behavior switching, the present experiments used a contralateral disconnection approach as in a past study (Chudasama, Baunez, & Robbins, 2003). This involved infusions of the GABA agonists, baclofen and muscimol into the prelimbic cortex (Leenaars et al., 2012) and the NMDA receptor antagonist, AP-5 into the subthalamic nucleus (Baunez & Robbins, 1999). The experiments further determined whether these pharmacological manipulations affected switch trial performance, initial perseveration of a previously relevant response pattern and/or maintenance of the currently relevant response pattern once selected.

2. Materials and methods

2.1. Subjects

Adult, male Long–Evans rats weighing between 300 and 350 g at the time of testing served as subjects ($n = 49$). Rats were individually housed in plastic cages (26.5 × 50 × 20 cm) in a temperature (22 °C) and humidity (30%) controlled environment and placed on a 12 h light/dark cycle (lights on at 7:00 A.M.). Rats were food restricted to 85–90% of their *ad libitum* body weight during the experiment, and water was available *ad libitum*. Animal care and use was in accordance with the National Institutes for Health Guide for the Care and Use of Laboratory Animals and approved by the University of Illinois at Chicago Institutional Laboratory Animal Care and Use Committee.

2.2. Apparatus

Training and testing occurred in a four arm cross maze made of black acrylic. Maze arms contained a base that was 10 cm wide × 55 cm long, two side walls that were 15 cm high by 55 cm long and a back wall that was 8 cm wide and 15 cm high. A 10 × 10 cm square base piece connected all four arms together. A circular food well (3.2 cm diameter and 1.6 cm deep) was located 3 cm away from the end of each arm. The maze was elevated 72 cm above the floor in a room with various extra-maze cues.

2.3. Surgery

Prior to behavioral training, all rats underwent stereotaxic surgery for bilateral implantation of guide cannulae aimed at both the prelimbic cortex and subthalamic nucleus. Thus, each rat had a total of 4 guide cannulae implanted. Although rats in Experiments 1 and 2 (see below) only received infusions into the either the prelimbic cortex or subthalamic nucleus, 4 guide cannulae were implanted in all rats to control for the possibility that effects observed in the contralateral disconnection study were partially due to the number of cannulae implanted. For surgery, rats received 0.2 mL atropine sulfate (250 μg/mL solution) 20 min prior to injection of sodium pentobarbital (50 mg/kg, i.p.). Twenty-two gauge stainless steel guide cannulae (Plastics One, Roanoke, VA) were implanted into the prelimbic cortex at a 15° angle. The stereotaxic coordinates were A-P +3.0; M-L ±1.8; D-V −3.0 (mm). For the subthalamic nucleus, cannulae were implanted at a 10° angle. The stereotaxic coordinates were A-P −3.6; M-L ±4.0; D-V −6.7. Cannulae were implanted at an angle because both the prelimbic cortex and subthalamic nucleus are located relatively medial allowing sufficient space for accurate placements. The coordinates were based on the stereotaxic atlas by Paxinos and Watson (1998). Four jeweler screws were positioned in the skull surrounding the cannulae and secured with dental acrylic (Stoetling, Wood Dale, IL). Stylets were placed into the guide cannulae to prevent clogging. During the surgical procedure, meloxicam (1 mg/kg) was administered to manage pain post-operatively. Rats recovered for 7 days after surgery before commencing behavioral training. For 5 days following surgery, rats were fed *ad libitum* and subsequently food restricted as described above. Following this period, subjects were handled approximately 10 min per day.

2.4. Training

One week after surgery, behavioral training commenced in the cross maze. Each arm of the maze was designated either "East", "West", "North" or "South". Each rat received a training procedure in multiple phases. In the first phase, a rat was allowed to consume a quarter piece of Froot Loops cereal (Kelloggs, Battle Creek, MI) in each food well. A rat was also picked up after consuming cereal pieces to acclimate being handled in the maze as in past studies (Baker, Thompson, Sweeney, & Ragozzino, 2011; Brown, Baker, & Ragozzino, 2010). This stage of training lasted 3–7 sessions.

In the second training phase, the "North" and "South" arms always served as the choice arms. The "East" and "West" arms were pseudorandomly alternated to serve as start arms. In this phase, a plastic block was placed in either the "East" or "West" arm giving the maze a T-shape (Fig. 1A). The stem arm served as the start arm