Dissociating Cortico-Striato-Thalamo-Cortical Neural Circuitry using Rodent Models of Cognitive Flexibility

Dawson C. Cooper

Submitted under the supervision of Dr. Alik Widge to the University Honors Program at the University of Minnesota-Twin Cities in partial fulfillment of the requirements for the degree of Bachelor Science, *summa cum laude* in Neuroscience.

4/12/2021

Abstract

Mental illness is the single largest cause of disability worldwide. These disorders are characterized by breakdowns in neuronal communication between and among different areas of the brain. In order to restore proper functioning, treatment strategies have increasingly focused on modulating specific neuronal circuits. Deep brain stimulation (DBS) allows for targeted circuit-based neuromodulation and has shown to be a promising treatment for mental disorders. Despite its success, the mechanisms underlying its therapeutic effects remain unclear. Further investigating cortico-striato-thalamo-cortical (CSTC) circuits, often impaired in those with major depressive (MDD) or obsessive-compulsive disorder (OCD), may provide mechanistic clues. MDD and OCD can be characterized by impairments in cognitive control—the ability to organize, plan, and schedule mental operations in different environments. Cognitive control depends on distinct subregions of the prefrontal cortex (PFC) which project into the striatum. Here we show that DBS applied to the mid-striatum in an attentional set-shifting task improves cognitive flexibility in outbred rats (n=12) by significantly decreasing reaction time ($p < 0.01$). Furthermore, we developed a novel touchscreen two-armed bandit task which may help in determining which parts of the PFC are responsible for DBS' effects on cognitive flexibility. Our results demonstrate that DBS is able to modulate the neural circuitry underlying cognitive flexibility and that Long-Evans rats can serve as a viable animal model in translating the two-armed bandit behavioral paradigm. Our future study will evaluate the effects of DBS in both set-shifting and the two-armed bandit. Behavioral paradigms with an increased dependency on more ventral parts of the PFC, involved in the two-armed bandit, are hypothesized to not benefit from mid-striatum DBS treatment. Our results may translate to human behavioral tasks and serve as a predictor for DBS' effectiveness.

Introduction

Mental health disorders are the single largest cause of disability worldwide, with nearly 50% of all Americans meeting the criteria for a mental disorder sometime throughout their life (Whiteford, 2013; Kessler et al., 2005). Mental illness can take many forms and underlies a broad range of conditions that affect mood, thinking, and behavior. Despite the heterogeneity among manifestations, mental disorders can be broadly characterized as breakdowns in neuronal communication and circuitry (Hyman, 2000). Psychiatric treatments are targeted at restoring these breakdowns.

Treatments such as medications and psychotherapy are effective for many patients with psychiatric disorders. Despite these successes, however, a significant number of patients experience an incomplete resolution of symptoms or no significant response to these traditional therapies (Holtzheimer and Mayberg, 2011). For example, 20% of patients with major depressive disorder (MDD) or obsessive-compulsive disorder (OCD) are treatment refractory (Sullivan et al., 2020). In the search for better treatments, increasing interest has been focused on neuromodulation—the alteration of neuronal activity through targeted delivery of a stimulus (e.g. electrical stimulation, Tye et al., 2020).

Deep brain stimulation in psychiatry: mechanisms and next steps

Neuromodulation has an advantage over more conventional therapies in that it can deliver timed, adjustable stimuli to a specific neuronal circuit(s). Among these neuromodulation treatments, deep brain stimulation (DBS) has emerged as a powerful tool to treat motor disorders (e.g. Parkinson's disease, dystonia, tremor), and more recently, neuropsychiatric disorders. DBS is an invasive neurosurgical method that involves implanting one or more electrodes into the brain. These electrodes are able to deliver precisely timed electrical pulses that affect the surrounding tissue; roughly estimated as an area of 0.5-1 cm in diameter (Widge et al., 2018). DBS has an advantage over other neuromodulation therapies (e.g. transcranial magnetic stimulation, electroconvulsive therapy) as it is able to target deep brain regions such as the basal ganglia, which are involved in both psychiatric and neurologic conditions (Williams, 2016). Therefore, this treatment is advantageous in some cases due to its ability to alter neuronal

functioning beyond that of the cortical neurons and superficial brain structures targeted in other therapies (e.g. various forms of transcranial magnetic stimulation).

The exact therapeutic mechanism(s) of DBS is not well established, but multiple theories have been proposed. Prior to the implementation of DBS as a standard treatment option in motor disorders, irreversible lesion surgeries were performed (Laitinen et al., 1992). Around the same time, DBS was implemented as an alternative treatment with promising results (Chiken and Nambu, 2015). As more patients with motor disorders were enrolled in clinical studies, DBS was found to be the superior option. DBS treatment outcomes were comparable to ablative procedures, where brain tissue is scarred or destroyed, but its main advantages were its reversibility and adjustability (Benabid et al., 1991). This allowed for an individualized approach based on each patient's condition and symptoms. While DBS offered a promising alternative treatment to ablative procedures, its therapeutic mechanism was largely unknown.

Due to the similarity in outcomes between the two therapies, this led to the early idea that DBS acted in the same manner as a brain lesion—inhibiting local neuronal elements, which was termed the "inhibition hypothesis" (Dostrovsky et al., 2000). This hypothesis was strengthened by physiological investigation among the neuronal elements close in proximity to the electrode. Studies examining DBS of the subthalamic nucleus (STN) and internal globus pallidus (GPi) found an overall suppression of neuronal firing near the electrode (Filali et al., 2004; Welter et al., 2004). Additionally, a subset of STN neurons showed a complete cessation of firing during high frequency stimulation (Tai et al., 2003). These findings are in agreement with the increased/abnormal neuronal firing rates exhibited in the STN and GPi of untreated Parkinson's patients (Chiken and Nambu, 2015). The inhibition hypothesis provided an early explanation of DBS' mechanism but was limited in its scope. Specifically, it failed to account for the physiological, anatomical, and electric field orientation differences found in other studies (Rattay, 1999; McIntyre et al., 2004; Florence et al., 2016). Additionally, increased brain activity has been associated with structures near the electrode in other disorders which is directly in contrast to earlier findings (Rauch

et al., 2006; Herrington et al., 2016). Together, these findings cast doubt on the inhibition hypothesis as the sole mechanism of DBS.

Others have argued that DBS acts on a broader circuit/network level, restoring dysfunctional neuronal communication between and among different brain regions (Bourne et al., 2012; Laxpati et al., 2014; Bilge et al., 2018). Networks can be defined as connectivity profiles found using advanced neuroimaging techniques, but in this paper will refer broadly to a set of brain regions acting in concert (Haber et al., 2020). Networks are formed and connected by bundles of white matter (axons), which are common targets of DBS. These axons can be tracked throughout the brain using diffusion tensor imaging (DTI) revealing specific neuronal circuits. In a study evaluating the effectiveness of DBS targeting the subcallosal cingulate, retrospective DTI analysis revealed patterns in patient outcomes that were dependent on the number of white matter bundles captured in the DBS field (Riva-Posse et al., 2014). The group found that in patients who responded to DBS treatment all three bundles of interest were captured. Conversely, non-responders lacked engagement in at least one of the bundles. Similarly, physiological changes in white matter bundles connecting the frontal lobe to the DBS target site were able to retrospectively predict patient outcomes (Coenen et al., 2019). This work, among others, has shown DBS to act on brain-wide networks.

Within neural networks, clusters of neurons may communicate via coordinated oscillations (i.e. brain waves between and among different brain regions), which can be measured by an electroencephalogram or by changes in local field potential (Herreras, 2016). Coordinated oscillations can be observed in functional neuronal assemblies, with different neurons showing different “preferences” of phase coupling (Canolty, 2010). Such activity can be determined by recording local field potentials (LFPs). LFPs are a measure of brain activity used to measure dynamic changes across the brain (Herreras, 2016). Psychiatric and neurologic conditions arise when these oscillations become uncoordinated with one another (Little et al., 2012; McNally and McCarley, 2016). For example, abnormal gamma- and beta-band (brain waves of different frequencies) activity has been observed in schizophrenia (Uhlhaas and Singer, 2010). Additionally, similar dysfunction of the circuits underlying OCD has been observed (Saxena and Rauch,

2000). In a study aimed at determining how DBS works in patients with severe OCD, the group found that DBS restored low-frequency power during a task designed to evoke disease-related symptoms (Figee et al., 2013). These findings suggest that DBS works in part by correcting pathological neural oscillations and the synchronization between and among different brain regions.

Neuronal networks underlying psychiatric disorders

The neural networks underlying higher order cognitive processes are impaired in psychiatric disorders that respond to DBS. These cognitive processes include decision making, emotional regulation, and evaluative thinking. The regions and subregions involved in these constructs become activated during behavioral tasks measuring cognitive control (Braver et al., 2003). Here, cognitive control can be defined as the set of processes that organize, plan, and schedule mental operations. These processes, specifically the ability to make flexible, goal-oriented decisions, are often disrupted in those with psychiatric disorders (Remijnse et al., 2013). The neural correlates of these processes (i.e. the brain regions and networks activated during these decision making tasks) are often targets for therapeutic intervention.

Of interest in many psychiatric disorders are the circuits of the salience network (SN, Peters et al., 2016). The SN may be activated by salient sensory stimuli, which include novel or behaviorally relevant cues (Corbetta, 2000). Within the SN are the cortico-striato-thalamo-cortical (CSTC) loops, thought to underlie cognitive control (Fig. 1a). From an anatomical viewpoint, the CSTC circuits are composed of direct and indirect pathways from specific regions of the cortex to subregions of the thalamus and striatum (Heuvel et al., 2016, Fig. 1c). The behaviors controlled by the direct and indirect pathways have been identified in motor disorders. The direct pathway functions as a self-reinforcing positive feedback loop which contributes to the initiation and continuation of behaviors. The indirect pathway modulates these functions by inhibiting behavior as well as switching between behaviors (Heuvel et al., 2016).

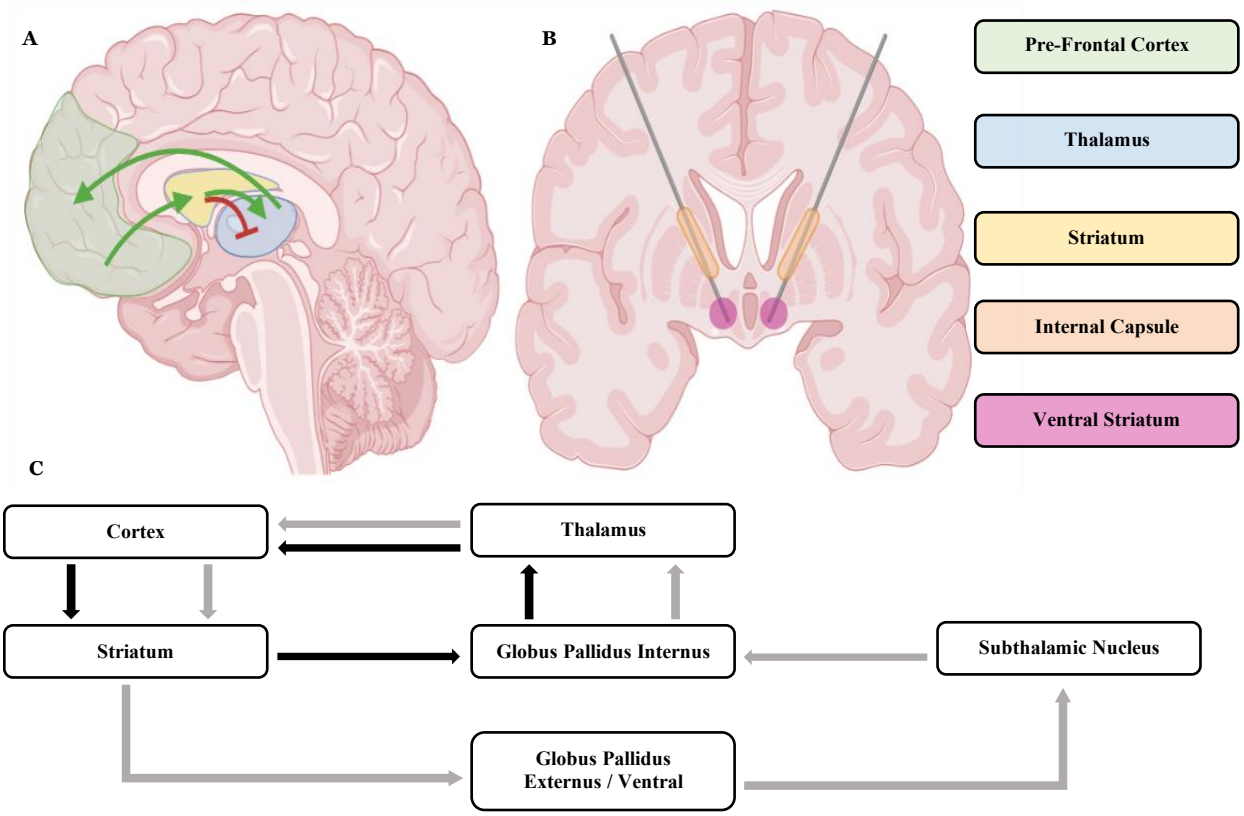

Figure 1. **Anatomical view of cortico-striato-thalamo-cortical neural circuitry (CSTC).** All brain regions are color coded. **(a) S**agittal view of the CSTC circuits. Green arrows indicate activation and red arrows indicate inhibition. **(b)** A coronal slice of the brain cut at the basal ganglia with bilateral deep brain stimulation electrodes aimed at the ventral capsule/ventral striatum. **(c)** Direct and indirect pathways of the CSTC circuits identified in motor disorders. Black and grey arrows indicate the direct and indirect pathways, respectively.

Neuronal networks underlying psychiatric disorders continued

Together, the indirect and direct pathways of the CSTC loops make up the neural network thought to underly cognitive control, thus making the brain regions involved in these circuits targets for DBS. One of the primary target areas of DBS includes the ventral internal capsule/ventral striatum (VC/VS, Hariz et al., 2013, Fig 1b). DBS of the VC/VS has shown success as a target in MDD and OCD patients (Graat et al., 2016). These disorders are often comorbid and are marked by lapses in cognitive control or the ability to make flexible, goal-oriented decisions (Remijnse et al., 2013). Cognitive control relies on many different brain regions, notably the prefrontal cortex (PFC) and its connections to the VC/VS (Egner and Hirsch, 2004).

Brain oscillations, cognitive control, and the modulation of neural circuits with DBS

Combining these concepts, Widge et al. (2019) recently showed that DBS to the VC/VS enhances cognitive control and PFC function, marked by changes in neuronal oscillations and reaction times in a behavioral task. Specifically, the group noted an improvement in patient performance in a cognitive control task which was linked to an increase in theta oscillations (brain wave of 4-8 Hz) in distinct parts of the PFC. Furthermore, this theta increase was predictive of subjects' clinical outcomes.

Despite these results, the study was limited in several ways including a relatively small sample size and the inability to measure longitudinal changes. Additionally, theta increases were observed in medial and lateral PFC (both dorsal and ventral regions), however, cognitive control may only depend on a subset of these regions (Widge et al., 2019). These anatomical and physiological shortcomings represent a significant gap in the mechanistic understanding of DBS. Rodent models may provide both large-scale behavioral/physiological recording and the ability to measure longitudinal changes—typically not feasible in humans. Further understanding these mechanisms and correlating their biomarkers to cognitive tasks in rodent models presents possible advances in both clinical neuromodulation and cognitive neuroscience.

Reverse translation of cognitive control biomarkers: animal models of decision making

The search for biomarkers of DBS has been studied extensively in animal models. Furthermore, the neural circuitry underlying cognitive control can be explored in a rodent model of DBS due to well-

known rat to human anatomic homology (Haynes and Haber, 2013; Choi et al., 2017). The rodent model, in this case rats, has the advantage of being rather straightforward to manipulate with DBS, the availability of control subjects (i.e. implanting sham electrodes), and the limited influence of confounding environmental variables (Schwabe and Krauss, 2017). Two well-studied behavioral paradigms used to study cognitive control, in both rats and humans, include the two-armed bandit (also referred to as probabilistic learning) and the attentional set-shifting task (AST, Garner et al., 2006). These tasks may be useful in dissociating CSTC neural circuitry involved in decision making and understanding which neuronal circuits are responsible for each specific type of decision making. This is in part due to the general brain areas engaged in each task being similar (due to being part of the same CSTC circuits), yet distinct enough as they employ different subregions of the cortex and striatum (Bissonette and Powell, 2011). Targeting these differences with DBS may elucidate specific circuits associated with changes in performance in each task, addressing one of the limitations in the Widge et al. (2019) study.

Attentional set-shifting: overview and neural correlates

The AST was developed to measure cognitive flexibility (Shepp and Schrier, 1969; Garner et al., 2006). The task now used in rodents was modeled after the Cambridge Neuropsychological Test Automated Battery and the Wisconsin Card Sorting task (Sahakian and Owen, 1992; Grant and Berg, 1948, Fig. 2). These tasks can be used to identify cognitive dysfunction in humans, non-human primates, and rodents. A core component of the AST is the subject's ability to learn a set of rules and subsequently modify their behavior when those rules are changed (Heisler et al., 2015). For example, a subject could start by sorting blocks according to their shape for a certain number of trials—these trials, all based on the same rule, are collectively called a set. The rule is then switched on the subject (i.e. instead of sorting based on shape, the color of the object is of interest); previous stimuli must be ignored in order to switch to the new rule. Collectively, switching from one set to another is known as set-shifting (Dajani and Uddin, 2015). Many individuals with psychiatric illness (e.g. schizophrenia, OCD, MDD) exhibit impairments not in learning the rules, but rather in shifting between sets of rules (Stuss et al., 2000). This demonstrates an impairment in cognitive flexibility. These results can also be interpreted as measures of cognitive rigidity, or the

inability to mentally adapt to new demands or information (Cohen, 2017). The regions associated with optimal performance in set-shifting have been identified through lesion and pharmacologic studies (Hamilton and Brigman, 2015). The neural correlates important to the AST in the rat include the intact medial wall structures (anterior cingulate, prelimbic and infralimbic cortex), amygdala, and dorsomedial striatum (Bissonette and Powell, 2012). Of particular interest are the structures involved and activated in the CSTC circuitry. These are the dorsomedial striatum (DMS) and pre/infralimbic (PL and IL, respectively) cortex of the rat.

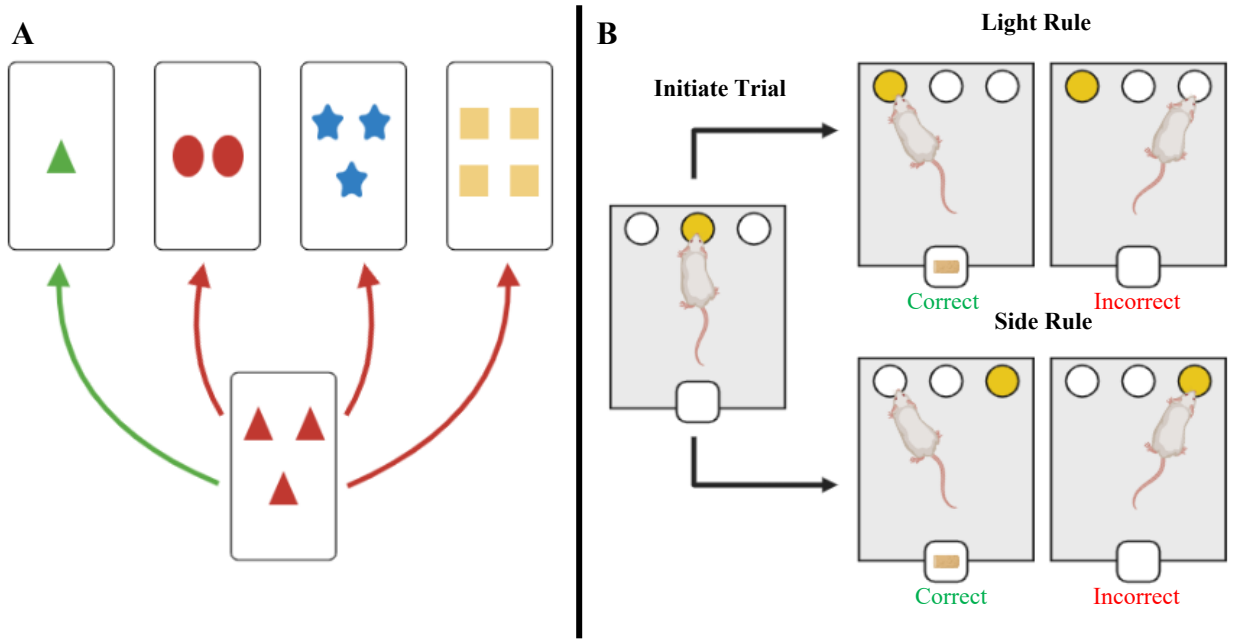

Figure 2. **Schematic of the Wisconsin Card Sorting Task and attentional set-shifting.** Both tests are often used as measures of cognitive flexibility in humans **(a)** and rodents **(b)**. **(a)** In this example, a participant is asked to sort based on shape. The green and red arrows indicate correct and incorrect responses, respectively. **(b)** Attentional set-shifting with light and side rules. During light rule blocks, the subject must first initiate a trial and then select the noseport with the light for a pre-determined number of trials. The rule then switches (i.e. from light to side) and the rodent must respond to a side (in this case left) despite being previously rewarded for responding to the light.

Two-armed bandit: overview and neural correlates

The two-armed bandit task has also been used to study cognitive flexibility in rodents (Roberts et al., 1988; Mar et al., 2013). In this behavioral paradigm, subjects are taught to discriminate between two different options, each with a varying level of reward. For example, two distinct images may be used in a touchscreen operant conditioning box, with varying reward contingencies for each image. After the initial discrimination phase, the reward contingencies are reversed (i.e. the previously rewarded stimulus becomes the non-rewarded option, Mar et al., 2013). The rate at which subjects are able to learn the new reward contingencies after the reversal can provide investigators with an index of cognitive flexibility. For example, a subject able to quickly learn the new contingencies after reversal would be deemed to have a higher level of cognitive flexibility than a slower responding subject. Deficits in reversal learning have been observed in neuropsychiatric disorders (e.g. schizophrenia), which has prompted further investigation underlying the behavioral and molecular mechanisms (Fellows and Farah, 2003; Schlagenhauf et al., 2014). Similar to studies involving set-shifting, lesion and pharmacological manipulations have revealed distinct neural correlates important to successful reversal learning (Boulougouris et al., 2007; Brigman et al, 2010). These areas include the orbital frontal cortex (OFC), ventral striatum (VS), and amygdala (Rogers et al., 2000; Nagahama et al., 2001; Cools et al., 2002; Wassum and Izquierdo, 2015). Important to this work are the structures involved in the CSTC circuitry including the OFC and VS.

Dissociating CSTC circuits

These differences in neural circuitry (Table 1.) underlying each behavioral task may be dissociated using a rodent model of DBS—taking advantage of the brain's inherent connections. The cortex and striatum are connected topographically (Haber, 2016). In other words, ventral parts of the cortex are connected to ventral parts of the striatum. Successful set-shifting relies on more dorsal and medial parts of both the striatum and PFC. Conversely, the bandit-task employs more ventral brain regions. Therefore, the neural elements responsible for enhancing cognitive control should enhance performance during set-shifting but

not during the bandit task. We hypothesize that DBS targeted at more dorsal regions of the striatum will improve cognitive control in the AST while showing no significant effects in the bandit task.

Attentional Set-Shifting Neural Correlates	Two-Armed Bandit Neural Correlates
• Dorsomedial striatum	• Ventral striatum
• Pre/Infralimbic Cortex	• Orbitofrontal cortex

Table 1. Neural correlates of attentional set-shifting and the two-armed bandit task.

Evaluating cognitive flexibility in AST and the two-armed bandit

Cognitive control, similar to what Widge et al. used, was mainly measured by changes in reaction time during the two tasks. When DBS is on during AST, we would expect the subject to perform more quickly, while not sacrificing changes in accuracy. Conversely, we would not expect to see these effects in the bandit task regardless of the stimulation conditions. To do this, Long-Evans rats (n = 12) underwent bilateral mid-striatum electrode implantation. This site was selected based on the aforementioned information regarding neural correlates and by previous work from Rodriguez-Romaguera et al. (2012) who found that electrode placement aimed at more dorsal regions of the ventral striatum facilitated faster fear extinction in rodents. Subjects were assigned to only one of the two tasks and their performance was measured using the cognitive flexibility construct described earlier. Here, we show that mid-striatum DBS improves cognitive flexibility in a rodent model of DBS. Additionally, we have developed a two-armed bandit protocol capable of testing our hypothesis. Together, both tasks may provide mechanistic clues underpinning the efficacy of DBS in psychiatry.

Materials and Methods

Subjects

Twelve male Long-Evans rats were obtained from Charles River, ranging from 276-300 grams. Rats were acclimated upon arrival for 5-7 days and singly housed under a 10:14 dark/light cycle (lights on at 07:00 h). Rats were then handled for three consecutive days for 5 minutes/day. This was done in order to familiarize each subject with the experimenter. At the end of each handling session, ~20 45 mg sucrose pellets were placed in each subject's home cage in order to familiarize the rat with the rewards given in the operant chamber during training/testing. During this time (acclimation and handling), rats had *ad libitum* access to food and water. After handling had been completed, rats were food restricted to 85-90% of their original weight, taking approximately 7-10 days. Food restriction was done in order to establish motivation for the subsequent tasks. Once target weight had been established, experimenters fed animals daily in order to keep each subject within their target weight. This consisted of 10-15 grams of rat chow per day, depending on the subject.

Surgery

Each rat (n = 12) was anesthetized with 3-4% isoflurane in an induction chamber and subsequently mounted in a stereotaxic surgical station. During surgery, rats remained under 0.5-2% isoflurane. To evaluate the effects of DBS, bipolar platinum/iridium electrodes with a ground wire (MS333/8-BIU/SPC, Plastics One, Roanoke, VA) were bilaterally implanted in the mid-striatum (AP: 1.4, ML: ± 2.0, DV: -6.0, from the surface of the brain) according to the atlas of Paxinos and Watson, 2007. The coordinates were selected based on previous work by Rodriguez-Romaguera et al., 2012. The group found that fear extinction was enhanced by DBS applied to more dorsal regions of the ventral-striatum (i.e. mid-striatum). Once the electrodes were placed, ground wires were wrapped around a nearby screw embedded in the cranium. After surgery, rats were returned to their home chambers and allowed to recover for 7-14 days prior to any behavioral experimentation. During this period, rats had *ad libitum* access to food and water.

Operant attentional set-shifting task

Set-shifting sessions took place in standard automated operant chambers (25 × 29 × 25 cm) with metal sidewalls, a transparent plexiglass rear wall and front door, and a stainless-steel rod floor (Coulbourn Instruments, Holliston, MA). The operant chamber was enclosed by a sound-attenuating chamber (Med Associates, Chicago, IL). A 10-W light bulb illuminated the chamber throughout the entirety of each session. Each behavioral chamber was equipped with three noseports on a single side of the chamber. Each noseport contained infrared sensors to detect head entries, with white LEDs that provided visual cues. A pellet dispenser was placed on the wall opposite to the noseports. Food rewards were 45 mg sucrose pellets. Software and an appropriate interface (GraphicState 4.0, Coulbourn Instruments) controlled the presentation and sequencing of stimuli. Behavior was recorded by video cameras mounted on the top of each chamber.

The set-shifting protocol was designed by Darrah et al., 2008 and modified in house by Dr. Adriano Reimer (Fig. 3). Shaping took place for a period of 5 days before training. The first day of shaping included each rat being placed in the chamber, with 10 reward pellets delivered at the beginning of the

session. This initial session lasted 20 minutes. The next day consisted of a 20-minute session, which included reward pellets being delivered in 30 second intervals. This schedule was contingent on the rat eating the pellet in the food trough prior to receiving the next reward. In other words, if the rat had not eaten the latest pellet, a new pellet would not be delivered after 30 seconds had elapsed. Days 3-5 consisted of a single session in which rats were trained in one of the two discrimination rules used during the set-shifting task, including light or side (refer to Fig. 2b). During these discrimination shapings, rats were reinforced with a single reward pellet for each correct response. Sessions terminated when the performance criteria of 10 consecutive correct responses was reached or 90 minutes had elapsed, whichever occurred first. Following shaping, rats underwent 4 days of training sessions on the full set-shifting task. These sessions included both rules (light and side)—in contrast to the shaping sessions where one rule was learned per session.

In the full set-shifting task, each trial began with the illumination of the central nosepoke hole; poking this hole caused one of the two side nosepoke holes to illuminate. A correct response, according to the current rule, was rewarded with a single food pellet. Incorrect responses were not rewarded. A 7-second inter-trail interval followed each response regardless of reward. The rule was switched once the subject reached a performance criterion of 5 consecutive correct responses, thus requiring the rat to switch its behavior to receive a reward (e.g. shifting from a side to light rule). Each training day consisted of the rats reaching the performance criteria a total of 8 times (7 set-shifts total) in a single session. After training, each rat was submitted to six sessions to establish a reliable baseline prior to testing sessions. Testing sessions followed the same protocol as the training sessions. Stimulation and sham treatments were alternated over 5-day intervals (i.e. sham, stimulation, sham, etc). In order to control for any confounding variables, the sham sessions consisted of the same components as the stimulation treatment—subjects were connected to the stimulation cable and equipment despite not receiving any stimulation. A total of 16 testing sessions were conducted (8 sham and 8 stimulation sessions).

Electrical stimulation to the mid-striatum during set-shifting

To stimulate the mid-striatum, bipolar platinum/iridium electrodes were used. Chronic biphasic stimulation (300μA, 0.1 ms pulse width, 130 Hz) was delivered continuously to the mid-striatum one hour prior to and during set-shifting in order to evaluate the effects of DBS (Fig. 4). The stimulation protocol from Rodriguez-Romaguera et al., 2012 was modified due to in-house findings that one versus three hours of stimulation prior to set-shifting produced similar behavioral effects.

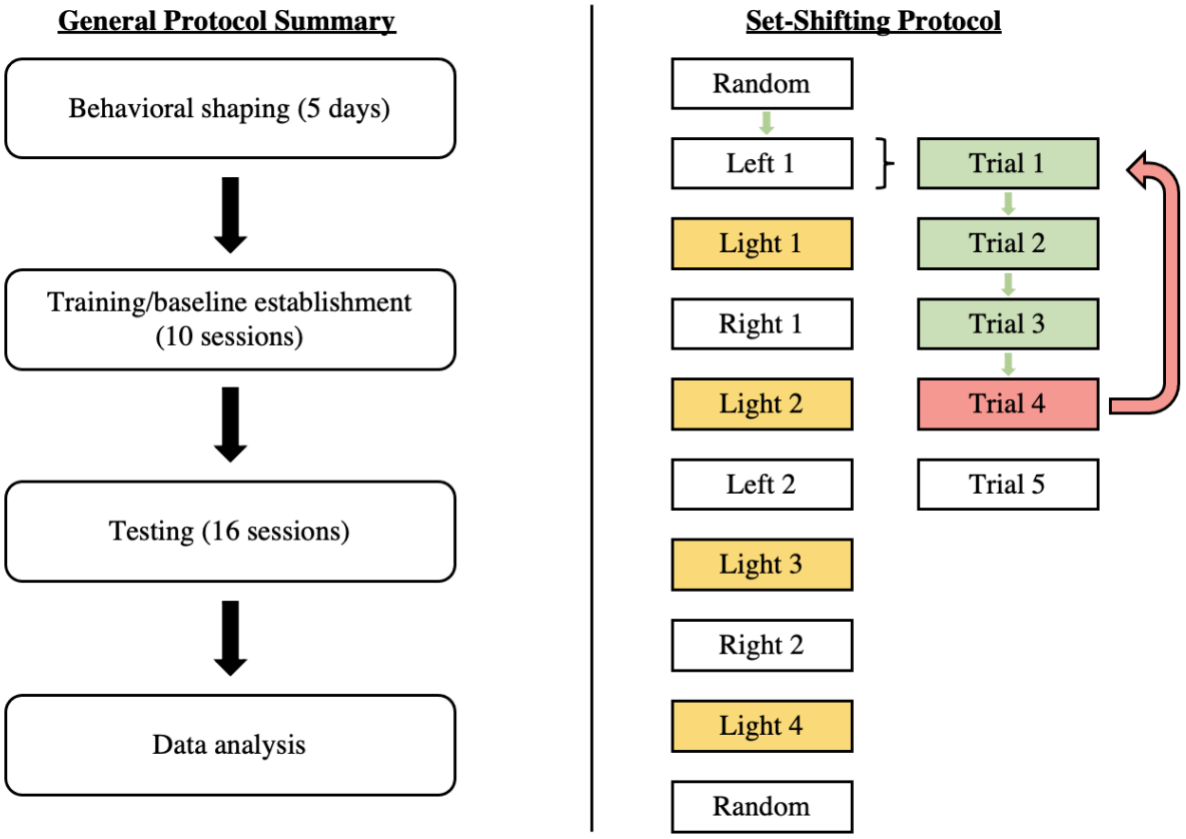

Figure 3. **Attentional set-shifting protocol summary and single session example**. The left panel displays a brief chronological overview of set-shifting experiments. The right panel displays an example protocol in which a subject has entered the "left 1" rule but failed to move onto "light 1". Side rules were referred to as right or left for the purposes of this figure. Each protocol follows the same general pattern (e.g. side rule followed by light rule) with random trial blocks at the beginning and end of each session. Green and red arrows indicate correct and incorrect trials, respectively.

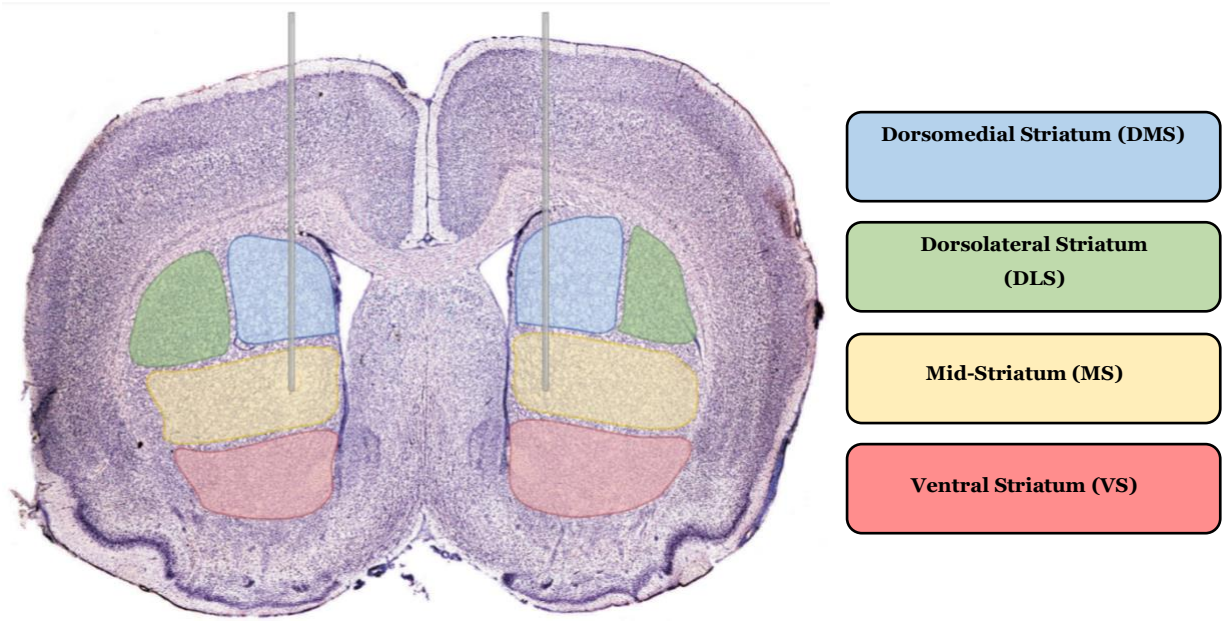

Figure 4. **Coronal view of the rat striatum and distinct subregions.** DBS electrodes were aimed at the mid-striatum shown in yellow (AP: 1.4, ML: ± 2.0, DV: -6.0, from the surface of the brain) according to the atlas of Paxinos and Watson, 2007.

Two-Armed Bandit Task

Behavioral sessions took place in standard automated touchscreen operant conditioning chamber (30.5 × 24.1 × 21 cm) with a metal backwall, two transparent plexiglass side walls, a touchscreen, and a stainless-steel rod floor (Lafayette Instruments. IN). The operant chamber was enclosed by a sound attenuating chamber (Med Associates, Chicago, IL). The chamber was equipped with a 10-W light bulb, used to establish association with an incorrect response. On one wall, a food magazine functioned as both a noseport and a food dispenser. Food rewards were 45 mg sucrose pellets. This magazine contained an infrared sensor to detect head entries, with white LEDs that provided visual cues. Opposite to the food magazine was the touchscreen. A black plastic mask was placed over the screen, which only allowed the rat to touch the screen where images were displayed. Software and interface developed in house controlled the presentation and sequencing of stimuli. Behavior was recorded by video cameras mounted on the top of the chamber.

The two-armed bandit protocol was designed by Mar et al., and modified by Chen et al., 2021. Behavioral shaping took place for a period of approximately nine days prior to training. Similar to the set-shifting protocol, the first day of shaping began with the experimenter placing 10 sucrose pellets into the food magazine prior to the session starting. The session concluded after the subject ate all the pellets or 20 minutes elapsed, whichever occurred first. The next day consisted of additional food magazine shaping with the addition of a light cue. Each subject placed its nose into the illuminated magazine which extinguished the light cue, resulting in the delivery of a pellet. Sessions were terminated after completion of 10 trials (each trial had a 10 second inter-trial interval) or after 20 minutes, whichever occurred first. This step was repeated two consecutive days for most animals or continued until the performance criteria was reached, defined as finishing 10 trials in under 20 minutes for two consecutive sessions. Following magazine shaping, touch screen shaping took place. This consisted of the subject initiating a trial by nose poking the illuminated food magazine. Once a trial had been initiated, the food magazine light cue was extinguished and a single white box appeared on the touch screen (opposite the food magazine) in one of two locations outlined by the plastic mask. The rat then had two image choices, either a black (no reward)

or a white box (rewarded). The rat had 120 seconds to nosepoke the screen after the trial was initiated. If the rat failed to touch the screen, the reward was omitted, and the trial was followed by a 10 second inter-trial interval. Additionally, the house light was activated in order to establish an aversive association cue for the incorrect response. Sessions terminated when the rat had completed 100 trials or 60 minutes had elapsed, whichever occurred first. Performance criteria to move onto the training stage was defined as a single session of 80%≥ of trials correct, with a minimum of 60 rewards.

Two-armed bandit training took place in order to train subjects to discriminate between two images. Image pairs were selected based on previous work by Chen et al., 2021. During training, images were assigned 100:0 reward probabilities and displayed on the touchscreen according to a random walk. However, an image could only be displayed up to three times on the same side in order to reduce the development of a side bias. That is, image 'A' and 'B' could not be displayed in the same positions (e.g. image 'A' on the left and image 'B' on the right) on the screen more than three trials in a row. Correction trials were also implemented, as described by Horner et al., 2013. Sessions terminated after completing 200 trials or 60 minutes had elapsed, whichever occurred first. Each subject completed these sessions until the reversal criteria was reached, defined as 80%≥ correct responses in a single session. The image reward contingencies were then reversed. Sessions were then conducted until the aforementioned performance criteria was reached with the new reward contingencies. This training phase was considered complete after the subject had completed both acquisition and reversal phases. Subjects then moved on to the final stage of training, which consisted of intraday reversals.

During intraday reversal sessions, images were assigned 80:20 reward probabilities. The more highly rewarding image (e.g. image 'A') would reward a subject an average of 80% of the time when selected; image 'B' would reward a subject 20% of the time when selected. Therefore, a subject could select the more highly rewarding image ('A' in this example) but was not rewarded during some trials. In order to determine when reversals would occur, correct responses were defined as those made to the most highly rewarding image, while touches to the other image were labeled as incorrect—regardless of a reward

being delivered during that trial. Reversal criteria outlined by Groman et al., 2018 was adapted for this protocol. The criteria was refined over the course of the experiment in order to maximize efficiency (see results, Fig 8) Once the performance criteria was met (70% of the last 30 responses were of the image associated with the highest probability of reinforcement), the image contingencies were reversed. A session concluded when the subject had completed 250 trials or 75 minutes had elapsed, whichever occurred first. Figure 5 displays the protocol summary and task.

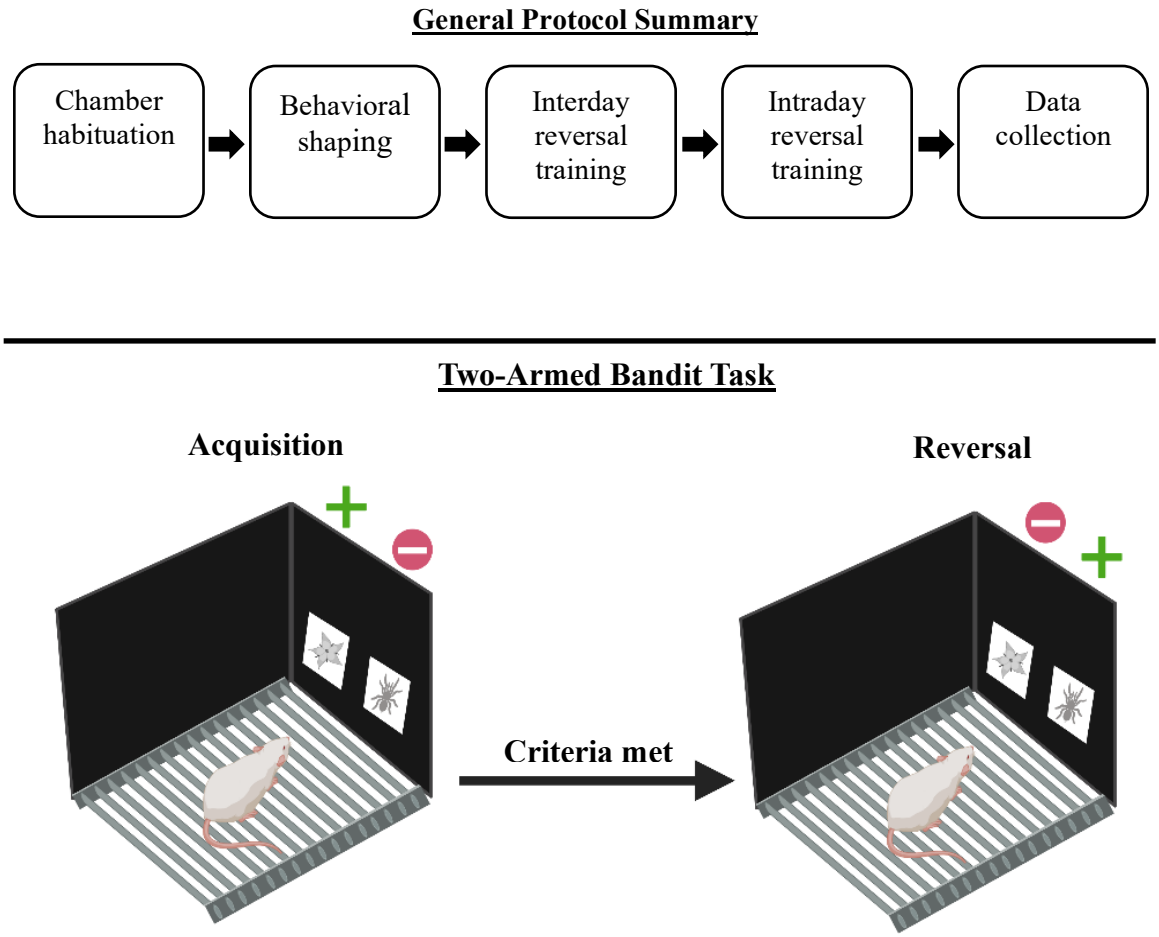

Figure 5. **Visually cued two-armed bandit protocol summary and task.** The top panel displays a chronological summary of the protocol. The bottom panel displays the two-armed bandit task, with both acquisition and reversal phases. In the acquisition phase, the image on the left is more highly rewarding. After the performance criteria is met, reward contingencies are reversed. Note: images are displayed according to a random walk throughout the entirety of the session.

Results

Effects of DBS on Attentional Set-Shifting

Fourteen male Long-Evans rats were submitted to an attentional set-shifting task for a total of 16 sessions to assess DBS' effects on cognitive flexibility. Due to surgical errors, two rats were eliminated from all data analysis which left a total of 12 subjects. We recorded behavioral data from each subject during set-shifting with DBS on or off (26,558 trials). Because reaction times (RTs) were not normally distributed (Fig. 6a), we analyzed data in a generalized mixed model (gamma distribution, link function: identity). On average, subjects were 57 milliseconds faster in responding per trial when DBS was on ($\beta = -0.057$, $z = -3.01$, $p = 0.003$, Fig. 6b). This improvement in RT was not due to a speed-accuracy tradeoff, as we found no significant differences in error rate between sessions with DBS on vs. off ($p > 0.05$, Fig. 6c).

In order to further characterize which aspects of cognitive flexibility DBS had modulated, we investigated RTs and error rates between side and light rule trials. We found that the reduction in reaction time was independent of rule type (i.e. reaction times did not differ significantly between side and light rule trials during sham or stimulation conditions, Fig. 7). Conversely, DBS produced different effects dependent on the rule type. As shown in Figure 8, DBS decreased the number of light rule errors ($p = 0.021$) while having no significant effect on side rule errors ($p > 0.05$).

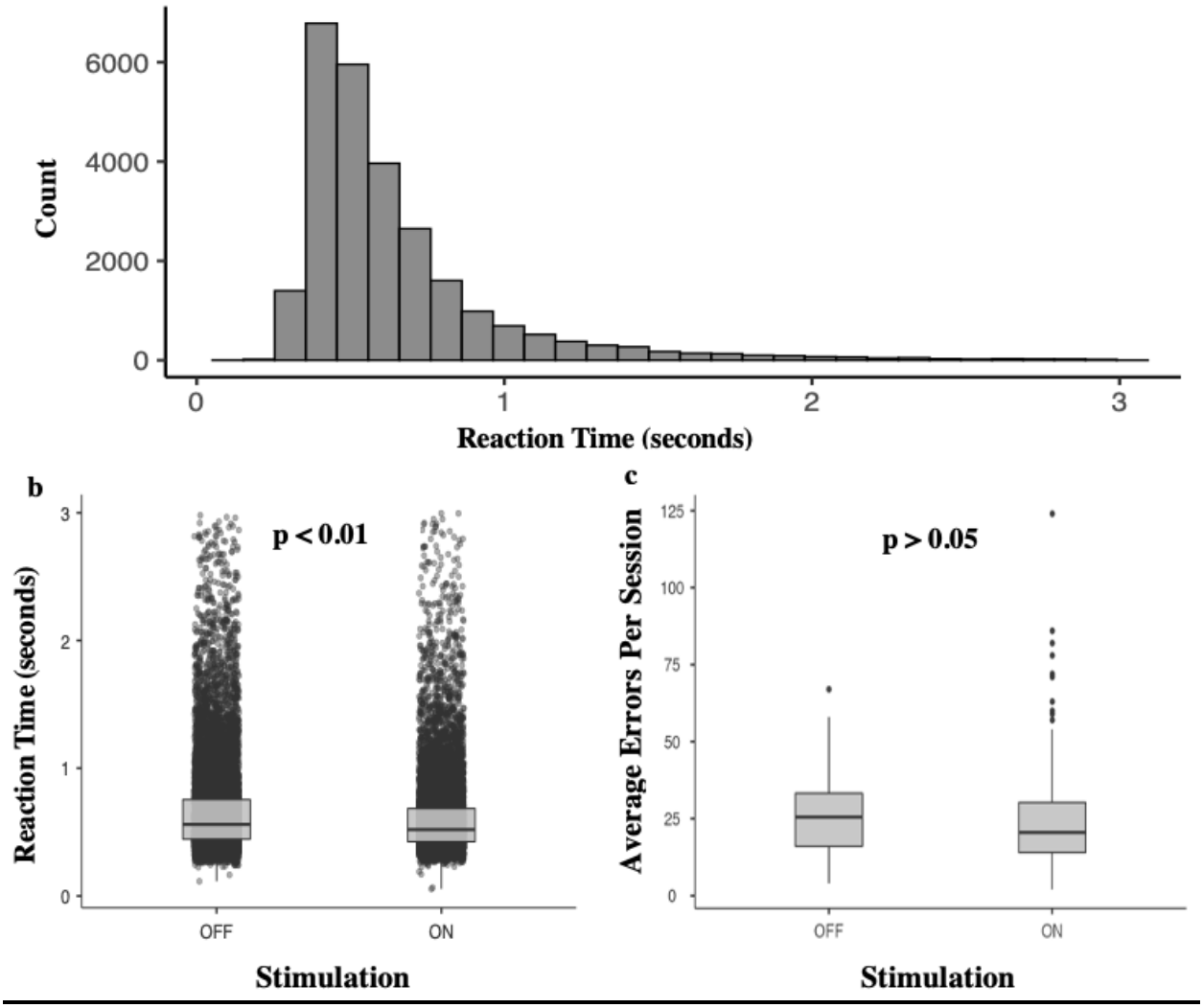

Figure 6. **Reaction time and average error rate per session during attentional set-shifting.** A total of 16 sessions (8 sessions of DBS on and off) of set-shifting were recorded for each subject (n = 12, total of 26,558 trials) to assess the effects of mid-striatum DBS. **(a)** Reaction times during all sessions were collected and plotted in a histogram. **(b)** Reaction times of mid-striatum DBS during on and off conditions. DBS significantly reduced reaction time ($p = 0.003$). **(c)** Error rate during DBS on and off conditions. No significant difference in overall error rate was found between DBS on and off conditions ($p > 0.05$).

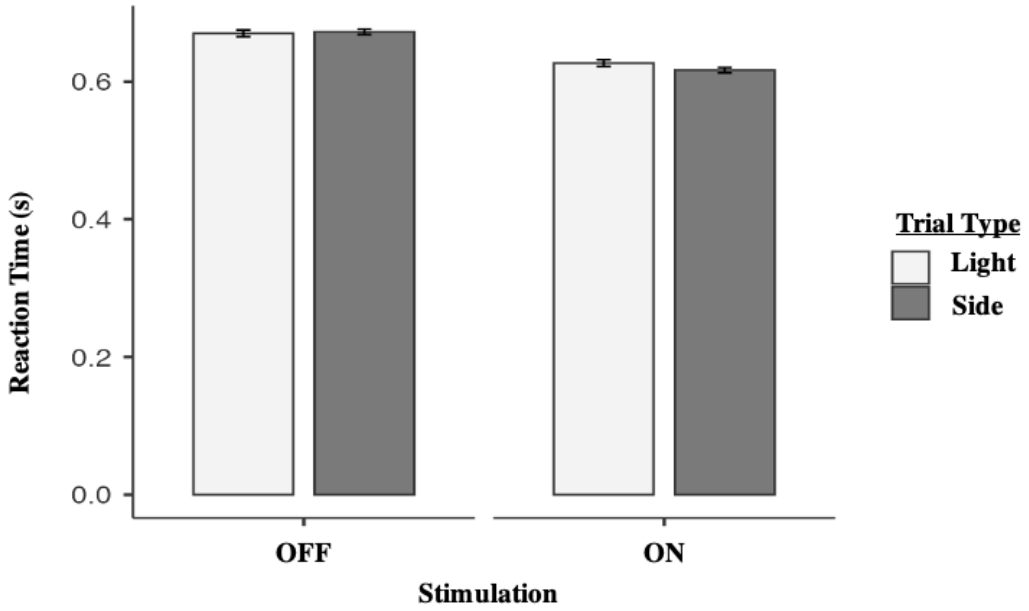

Figure 7. **DBS' effects on reaction time during light and side rule trials.** Set-shifting trials were classified as either light or side and reaction times were recorded during DBS on and off conditions. Data expressed as mean ± standard error of the mean. DBS significantly reduced reaction time ($p = 0.003$) independent of trial type ($p > 0.05$).

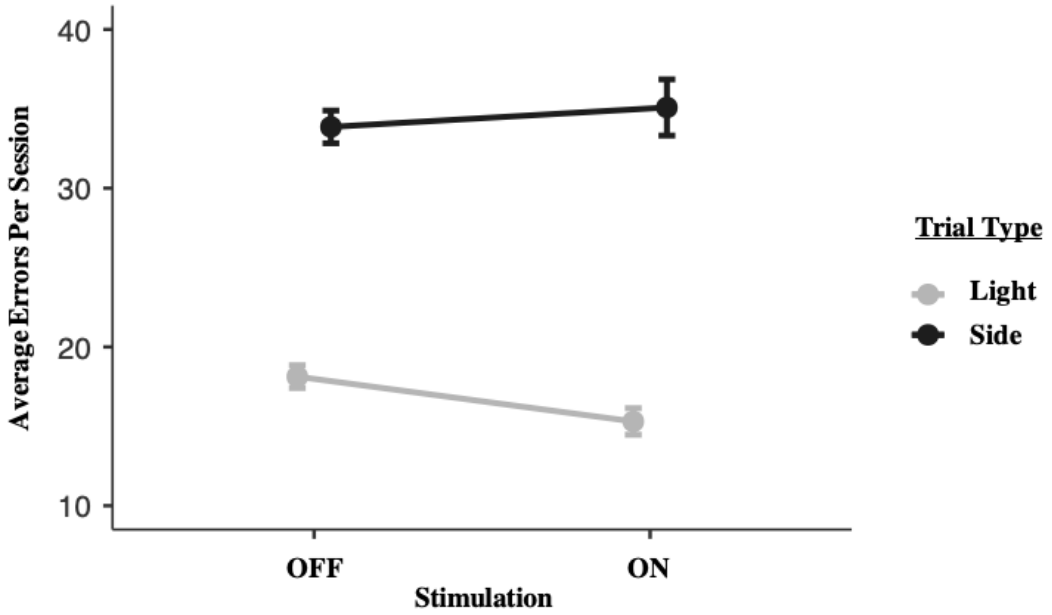

Figure 8. **Effect of DBS on side and light rule error rate during attentional set-shifting.** Error rate per session was recorded and organized according to trial type. Data expressed as mean ± standard error of the mean. DBS significantly reduced light rule error rate ($p = 0.021$), however, had no significant effect on side rule trials ($p > 0.05$).

Results Continued

Two-Armed Bandit Task

Six male Long-Evans rats were used to establish the two-armed bandit protocol. One subject was removed from the study as it was unable to fully complete touch-screen training. To optimize the protocol, two reversal criteria were analyzed. Initial performance to criterion (referred to as criteria one) was defined as ≥80% of touches made to the most highly rewarded image over the entire session. The second criteria (referred to as criteria two), modeled after work by Groman et al. (2018), was defined as ≥70% of the last 30 touches made to the most highly rewarded image. We determined that the latter reduced the amount of trials to criterion during the acquisition phase but not during the reversal phase of the task (Fig. 9).

Once criterion two had proven to be the most effective, we then characterized behavior of three subjects across all sessions of available data in order to determine response selection under varying image-reward probabilities. As shown in Fig. 10, subjects were able to select the more highly rewarding image in both the acquisition and reversal phases.

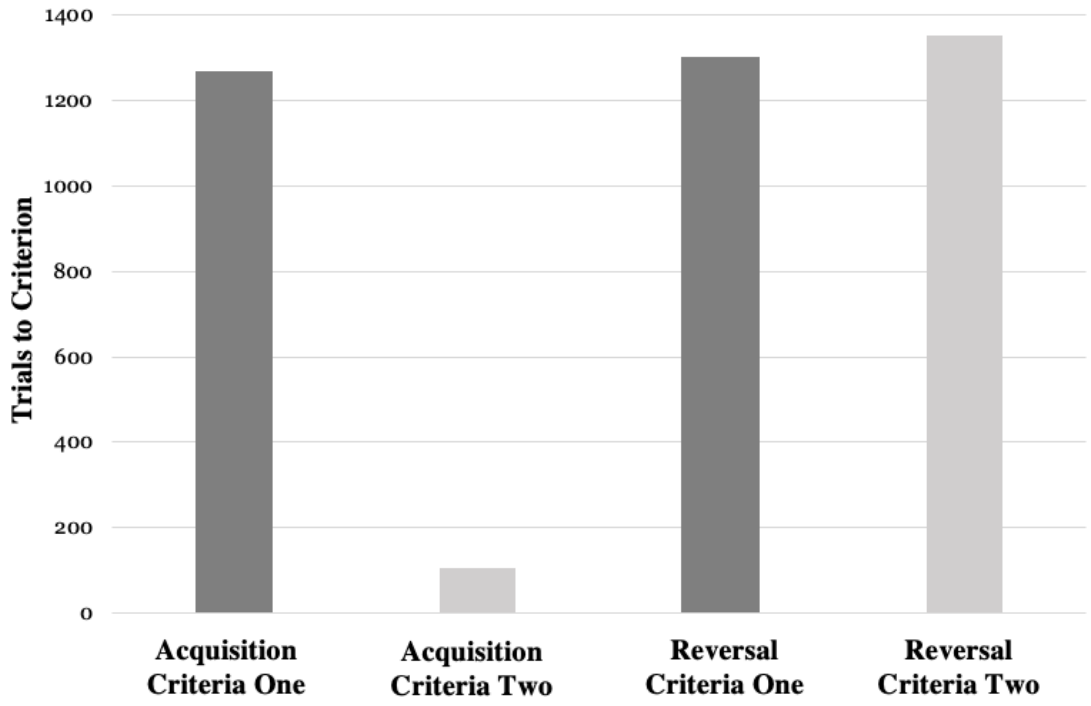

Figure 9. **Comparison of two performance criteria in the two-armed bandit task.** The performance criteria were recorded across multiple sessions of performance in order to determine which would be more effective in designing the behavioral protocol. Data are expressed as mean (n = 2 subjects). Criterion one was defined as ≥80% of touches made to the most highly rewarded image over the entire session. The second criterion was defined as ≥70% of the last 30 touches made to the most highly rewarded image. Once performance criterion had been reached, image probabilities reversed (i.e. acquisition to reversal phase). The number of trials to criterion was of interest, with fewer being more desirable. Fewer trials were required to reach criterion two during the acquisition phase, however, no difference was found between criteria one and two during the reversal phase.

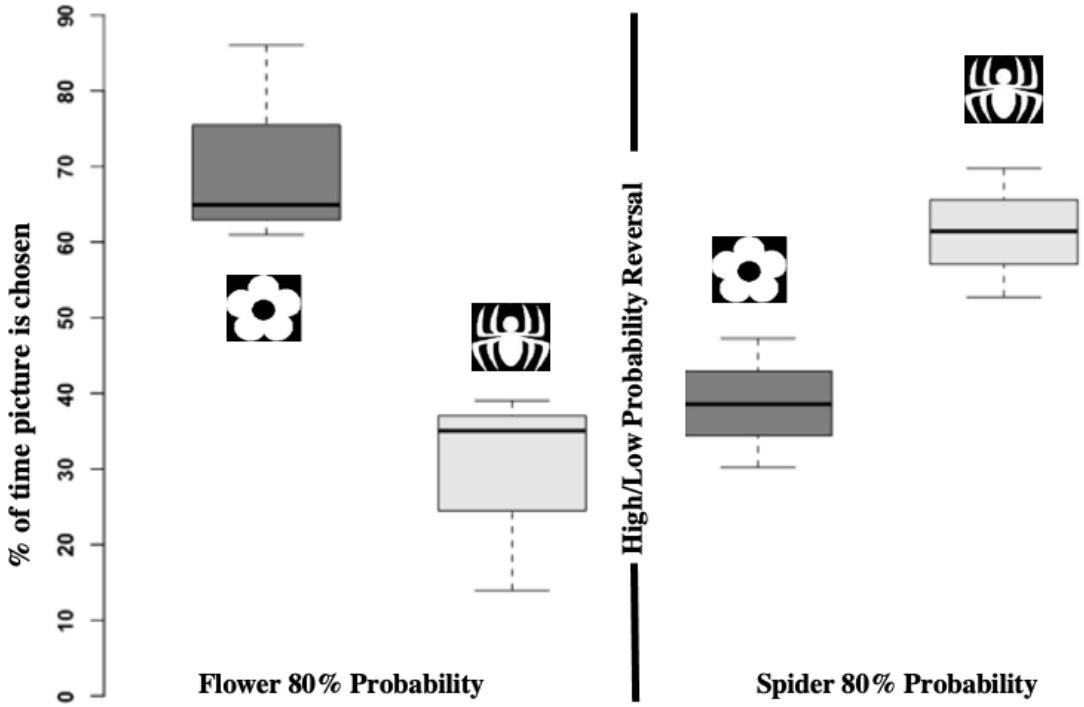

Figure 10. **Average two-armed bandit performance across a single inter-day reversal.** Behavioral data was averaged across subjects (n = 3) in the form of a boxplot in order to determine overall performance during the task. Subjects chose the high rewarding image more reliably than the low rewarding image, thus demonstrating the ability to reverse probabilities across sessions (i.e. inter-day reversals).

Discussion

We were able to reverse translate the results reported by Widge et al. (2019) in their human cohort by using a rodent model of cognitive flexibility: attentional set-shifting. DBS was applied to the mid-striatum, a striatal region homologous to human VC/VS. Cognitive flexibility was modulated as evidenced by a significant reduction in RTs that was not due to a speed-accuracy tradeoff, as we found no difference in overall error rate during stimulation versus sham conditions. DBS' effects on RT were non-specific to trial type but were specific to error rate as shown by the reduction of errors in light-, but not side-rule trials. The effects of DBS on side-rule error rate may indicate that these types of trials demand a greater level of cognitive control when compared to light rule trials, most likely due to the salience of the stimuli. Nonetheless, these findings suggest that DBS aimed at the mid-striatum improves cognitive flexibility in an attentional set-shifting task, thus partly confirming our working hypothesis. Additionally, we were able to create and refine a visually cued two-armed bandit protocol capable of accessing cognitive flexibility across and within sessions. With additional refinement, this protocol will be used to understand if the neural elements responsible for enhancing cognitive control in set-shifting are distinct from those in the bandit task.

Basu et al. (2019) found that the effects of DBS in human patients were linked to physiologic and anatomical markers. Notably, the group found that cognitive control enhancement was dependent on electrode placement—electrodes placed more dorsally (as opposed to ventrally) produced more positive effects. These ventral-dorsal axis effects have also been reported in previous work focused on modulating the neural circuitry associated with performance in a fear-conditioning paradigm (Rodriguez-Romaguera, 2012). Our study was limited in this aspect as we were unable to confirm electrode placement in all subjects at this time. Furthermore, because our work was limited to observing behavior, we cannot make conclusions regarding physiological changes caused by DBS. One method to address this may be monitoring for c-fos expression, which can be used as a valid biological marker for detecting changes in neuronal activity in our rodent models (Bullitt, 1990). Obtaining overall neuronal activation at sites near and associated with the electrode (e.g. PFC and striatum) may provide insight into how DBS modulates

neuronal networks at a cellular level. However, electrode placement and overall neuronal activation alone may not be enough to determine DBS' mechanism of action, as DBS acts on neuronal networks, thus pointing towards collecting additional electrophysiological data across brain regions.

We were also limited, at this moment in time, in our ability to record from individual neurons and gather electrophysiological data. In doing so, we could investigate previous findings of cross-regional synchrony across brain regions associated with attentional-set shifting, specifically that of the theta band (Doesburg et al., 2013). The technology needed to do this is readily available in our laboratory and is one of the next steps in further understanding how DBS modulates brain networks. Doing so may also shed light in explaining the differences in error rate between the two rule types (side vs. light) on a physiological level.

In addition to our set-shifting findings, we created a protocol for a visually cued two-armed bandit task. Our initial results are somewhat similar to those reported by other groups using variations of the same task (Groman et al., 2018; Chen et al., 2021), but there were notable differences. Interestingly, we saw a large reduction in trials to criterion during the acquisition phase but not during the reversal phase using criteria two. Groman et al. (2018) reported a significant increase in trials to criterion while switching from acquisition to reversal phases, but the magnitude of our change was much greater for criteria two. The cause of this could be attributed to switching reversal criteria multiple times while creating the protocol, causing general confusion in our subjects. Additionally, in refining the protocol, the experimenters manipulated the number of total trials per session and session length numerous times which most likely added to this confusion. However, once a criteria had been selected and the experimental conditions had been normalized (e.g. session length, number of trials, sessions per week), we were able to successfully train multiple subjects. Overall performance was similar to what has been described by Chen et al., (2021) during both the acquisition and reversal phases across sessions.

Despite these limitations, our work still provides a significant framework through which others can analyze and understand the effects of DBS on cognitive flexibility. DBS aimed at the mid-striatum reduced reaction times, thus confirming a crucial part of our hypothesis. Although we did not examine DBS' effects on the bandit task, we have established a reliable protocol that can be used to test this

question. Ultimately, future work will be aimed at implanting electrodes capable of stimulating and recording from the sites implicated in each task. In doing so, we may gain insight underpinning the mechanisms of DBS in psychiatric disorders and apply these findings to broader clinical applications in psychiatry.

References

Benabid, A.L., Pollak, P., Gervason, C., Hoffmann, D., Gao, D.M., Hommel, M., Perret, J.E., and de Rougemont, J. (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet *337*, 403–406.

Bilge, M.T., Gosai, A.K., and Widge, A.S. (2018). Deep Brain Stimulation in Psychiatry. Psychiatric Clinics of North America *41*, 373–383.

Bissonette, G.B., and Powell, E.M. (2012). Reversal learning and attentional set-shifting in mice. Neuropharmacology *62*, 1168–1174.

Boulougouris, V., Dalley, J.W., and Robbins, T.W. (2007). Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. Behavioural Brain Research *179*, 219–228.

Bourne, S.K., Eckhardt, C.A., Sheth, S.A., and Eskandar, E.N. (2012). Mechanisms of deep brain stimulation for obsessive compulsive disorder: effects upon cells and circuits. Front. Integr. Neurosci. *6*. Available at: https://www.frontiersin.org/articles/10.3389/fnint.2012.00029/full [Accessed November 3, 2020].

Braver, T.S., Reynolds, J.R., and Donaldson, D.I. (2003). Neural Mechanisms of Transient and Sustained Cognitive Control during Task Switching. Neuron *39*, 713–726.

Brigman, J.L., Mathur, P., Harvey-White, J., Izquierdo, A., Saksida, L.M., Bussey, T.J., Fox, S., Deneris, E., Murphy, D.L., and Holmes, A. (2010). Pharmacological or Genetic Inactivation of the Serotonin Transporter Improves Reversal Learning in Mice. Cereb Cortex *20*, 1955–1963.

Bullitt, E. (1990). Expression of C-fos-like protein as a marker for neuronal activity following noxious stimulation in the rat. Journal of Comparative Neurology *296*, 517–530.

Canolty, R.T., Ganguly, K., Kennerley, S.W., Cadieu, C.F., Koepsell, K., Wallis, J.D., and Carmena, J.M. (2010). Oscillatory phase coupling coordinates anatomically dispersed functional cell assemblies. Proceedings of the National Academy of Sciences *107*, 17356–17361.

Castañé, A., Theobald, D.E.H., and Robbins, T.W. (2010). Selective lesions of the dorsomedial striatum impair serial spatial reversal learning in rats. Behavioural Brain Research *210*, 74–83.

Chen, C.S., Ebitz, R.B., Bindas, S.R., Redish, A.D., Hayden, B.Y., and Grissom, N.M. (2021). Divergent Strategies for Learning in Males and Females. Current Biology *31*, 39-50.e4.

Chiken, S., and Nambu, A. (2016). Mechanism of Deep Brain Stimulation. Neuroscientist *22*, 313–322.

Choi, E.Y., Tanimura, Y., Vage, P.R., Yates, E.H., and Haber, S.N. (2017). Convergence of prefrontal and parietal anatomical projections in a connectional hub in the striatum. Neuroimage *146*, 821–832.

Coenen, V.A., Schlaepfer, T.E., Bewernick, B., Kilian, H., Kaller, C.P., Urbach, H., Li, M., and Reisert, M. (2019). Frontal white matter architecture predicts efficacy of deep brain stimulation in major depression. Translational Psychiatry *9*, 1–10.

Cohen, S.J. (2017). Cognitive Rigidity, Overgeneralization and Fanaticism. In Encyclopedia of Personality and Individual Differences, V. Zeigler-Hill and T. K. Shackelford, eds. (Cham: Springer International Publishing), pp. 1–7. Available at: https://doi.org/10.1007/978-3-319-28099-8_834-1 [Accessed November 4, 2020].

Cools, R., Clark, L., Owen, A.M., and Robbins, T.W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. J Neurosci *22*, 4563–4567.

Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., and Shulman, G.L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nature Neuroscience *3*, 292–297.

Darrah, J.M., Stefani, M.R., and Moghaddam, B. (2008). Interaction of N-methyl-D-aspartate and group 5 metabotropic glutamate receptors on behavioral flexibility using a novel operant set-shift paradigm. Behav Pharmacol *19*, 225–234.

Doesburg, S.M., Vidal, J., and Taylor, M.J. (2013). Reduced Theta Connectivity during Set-Shifting in Children with Autism. Front. Hum. Neurosci. *7*. Available at: https://www.frontiersin.org/articles/10.3389/fnhum.2013.00785/full [Accessed April 9, 2021].

Dostrovsky, J.O., Levy, R., Wu, J.P., Hutchison, W.D., Tasker, R.R., and Lozano, A.M. (2000). Microstimulation-Induced Inhibition of Neuronal Firing in Human Globus Pallidus. Journal of Neurophysiology *84*, 570–574.

Egner, T., and Hirsch, J. (2005). The neural correlates and functional integration of cognitive control in a Stroop task. NeuroImage *24*, 539–547.

Fellows, L.K., and Farah, M.J. (2003). Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. Brain *126*, 1830–1837.

Filali, M., Hutchison, W.D., Palter, V.N., Lozano, A.M., and Dostrovsky, J.O. (2004). Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. Exp Brain Res *156*, 274–281.

Florence, G., Sameshima, K., Fonoff, E.T., and Hamani, C. (2016). Deep Brain Stimulation: More Complex than the Inhibition of Cells and Excitation of Fibers. Neuroscientist *22*, 332–345.

Garner, J.P., Thogerson, C.M., Würbel, H., Murray, J.D., and Mench, J.A. (2006). Animal neuropsychology: Validation of the Intra-Dimensional Extra-Dimensional set shifting task for mice. Behavioural Brain Research *173*, 53–61.

Graat, I., Figee, M., and Denys, D. (2017). The application of deep brain stimulation in the treatment of psychiatric disorders. Int Rev Psychiatry *29*, 178–190.

Grant, D.A., and Berg, E.A. (1948). A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol *38*, 404–411.

Groman, S.M., Rich, K.M., Smith, N.J., Lee, D., and Taylor, J.R. (2018). Chronic Exposure to Methamphetamine Disrupts Reinforcement-Based Decision Making in Rats. Neuropsychopharmacol. *43*, 770–780.

Haber, S.N. (2016). Corticostriatal circuitry. Dialogues Clin Neurosci *18*, 7–21.

Hariz, M., Blomstedt, P., and Zrinzo, L. (2013). Future of brain stimulation: New targets, new indications, new technology. Movement Disorders *28*, 1784–1792.

Haynes, W.I.A., and Haber, S.N. (2013). The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for Basal Ganglia models and deep brain stimulation. J Neurosci *33*, 4804–4814.

Heisler, J.M., Morales, J., Donegan, J.J., Jett, J.D., Redus, L., and O'Connor, J.C. (2015). The Attentional Set Shifting Task: A Measure of Cognitive Flexibility in Mice. JoVE (Journal of Visualized Experiments), e51944.

Herreras, O. (2016). Local Field Potentials: Myths and Misunderstandings. Front. Neural Circuits *10*. Available at: https://www.frontiersin.org/articles/10.3389/fncir.2016.00101/full [Accessed November 3, 2020].

Herrington, T.M., Cheng, J.J., and Eskandar, E.N. (2015). Mechanisms of deep brain stimulation. Journal of Neurophysiology *115*, 19–38.

Holtzheimer, P.E., and Mayberg, H.S. (2011). Deep Brain Stimulation for Psychiatric Disorders. Annual Review of Neuroscience *34*, 289–307.

Horner, A.E., Heath, C.J., Hvoslef-Eide, M., Kent, B.A., Kim, C.H., Nilsson, S.R.O., Alsiö, J., Oomen, C.A., Holmes, A., Saksida, L.M., *et al.* (2013). The touchscreen operant platform for testing learning and memory in rats and mice. Nature Protocols *8*, 1961–1984.

Hyman, S.E. (2000). Mental Illness: Genetically Complex Disorders of Neural Circuitry and Neural Communication. Neuron *28*, 321–323.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., and Walters, E.E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry *62*, 593–602.

Laitinen, L.V., Bergenheim, A.T., and Hariz, M.I. (1992). Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. Stereotact Funct Neurosurg *58*, 14–21.

Laxpati, N.G., Kasoff, W.S., and Gross, R.E. (2014). Deep Brain Stimulation for the Treatment of Epilepsy: Circuits, Targets, and Trials. Neurotherapeutics *11*, 508–526.

Little, S., Pogosyan, A., Kuhn, A.A., and Brown, P. (2012). Beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. Exp Neurol *236*, 383–388.

Mar, A.C., Horner, A.E., Nilsson, S.R.O., Alsiö, J., Kent, B.A., Kim, C.H., Holmes, A., Saksida, L.M., and Bussey, T.J. (2013). The touchscreen operant platform for assessing executive function in rats and mice. Nat Protoc *8*, 1985–2005.

McIntyre, C.C., Grill, W.M., Sherman, D.L., and Thakor, N.V. (2004). Cellular Effects of Deep Brain Stimulation: Model-Based Analysis of Activation and Inhibition. Journal of Neurophysiology *91*, 1457–1469.

McNally, J.M., and McCarley, R.W. (2016). Gamma band oscillations: a key to understanding schizophrenia symptoms and neural circuit abnormalities. Curr Opin Psychiatry *29*, 202–210.

Nagahama, Y., Okada, T., Katsumi, Y., Hayashi, T., Yamauchi, H., Oyanagi, C., Konishi, J., Fukuyama, H., and Shibasaki, H. (2001). Dissociable Mechanisms of Attentional Control within the Human Prefrontal Cortex. Cereb Cortex *11*, 85–92.

Peters, S.K., Dunlop, K., and Downar, J. (2016). Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. Front. Syst. Neurosci. *10*. Available at: https://www.frontiersin.org/articles/10.3389/fnsys.2016.00104/full [Accessed November 4, 2020].

Rattay, F. (1999). The basic mechanism for the electrical stimulation of the nervous system. Neuroscience *89*, 335–346.

Rauch, S.L., Dougherty, D.D., Malone, D., Rezai, A., Friehs, G., Fischman, A.J., Alpert, N.M., Haber, S.N., Stypulkowski, P.H., Rise, M.T., *et al.* (2006). A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. J Neurosurg *104*, 558–565.

Remijnse, P.L., Heuvel, O.A. van den, Nielen, M.M.A., Vriend, C., Hendriks, G.-J., Hoogendijk, W.J.G., Uylings, H.B.M., and Veltman, D.J. (2013). Cognitive Inflexibility in Obsessive-Compulsive Disorder and Major Depression Is Associated with Distinct Neural Correlates. PLOS ONE *8*, e59600.

Roberts, A.C., Robbins, T.W., and Everitt, B.J. (1988). The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. The Quarterly Journal of Experimental Psychology Section B *40*, 321–341.

Rodriguez-Romaguera, J., Do Monte, F.H.M., and Quirk, G.J. (2012). Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. Proc Natl Acad Sci U S A *109*, 8764–8769.

Rogers, R.D., Andrews, T.C., Grasby, P.M., Brooks, D.J., and Robbins, T.W. (2000). Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. J Cogn Neurosci *12*, 142–162.

Sahakian, B.J., and Owen, A.M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J R Soc Med *85*, 399–402.

Saxena, S., and Rauch, S.L. (2000). FUNCTIONAL NEUROIMAGING AND THE NEUROANATOMY OF OBSESSIVE-COMPULSIVE DISORDER. Psychiatric Clinics of North America *23*, 563–586.

Schlagenhauf, F., Huys, Q.J.M., Deserno, L., Rapp, M.A., Beck, A., Heinze, H.-J., Dolan, R., and Heinz, A. (2014). Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. NeuroImage *89*, 171–180.

Schwabe, K., and Krauss, J.K. (2018). What rodent models of deep brain stimulation can teach us about the neural circuit regulation of prepulse inhibition in neuropsychiatric disorders. Schizophrenia Research *198*, 45–51.

Shepp, B.E., and Schrier, A.M. (1969). Consecutive intradimensional and extradimensional shifts in monkeys. Journal of Comparative and Physiological Psychology *67*, 199–203.

Stuss, D.T., Levine, B., Alexander, M.P., Hong, J., Palumbo, C., Hamer, L., Murphy, K.J., and Izukawa, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. Neuropsychologia *38*, 388–402.

Sullivan, C.R.P., Olsen, S., and Widge, A.S. (2021). Deep brain stimulation for psychiatric disorders: From focal brain targets to cognitive networks. NeuroImage *225*, 117515.

Telles Correia, D. (2017). The concept of validity throughout the history of psychiatry. Journal of evaluation in clinical practice *23*.

Tye, S.J., Frye, M.A., and Lee, K.H. (2009). Disrupting Disordered Neurocircuitry: Treating Refractory Psychiatric Illness With Neuromodulation. Mayo Clinic Proceedings *84*, 522–532.

Uhlhaas, P.J., and Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci *11*, 100–113.

van den Heuvel, O.A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S.R., Nakamae, T., Denys, D., Goudriaan, A.E., and Veltman, D.J. (2016). Brain circuitry of compulsivity. European Neuropsychopharmacology *26*, 810–827.

Wassum, K.M., and Izquierdo, A. (2015). The basolateral amygdala in reward learning and addiction. Neurosci Biobehav Rev *57*, 271–283.

Welter, M.-L., Houeto, J.-L., Bonnet, A.-M., Bejjani, P.-B., Mesnage, V., Dormont, D., Navarro, S., Cornu, P., Agid, Y., and Pidoux, B. (2004). Effects of High-Frequency Stimulation on Subthalamic Neuronal Activity in Parkinsonian Patients. Arch Neurol *61*, 89.

Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., *et al.* (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. The Lancet *382*, 1575–1586.

Widge, A.S., Zorowitz, S., Basu, I., Paulk, A.C., Cash, S.S., Eskandar, E.N., Deckersbach, T., Miller, E.K., and Dougherty, D.D. (2019). Deep brain stimulation of the internal capsule enhances human cognitive control and prefrontal cortex function. Nature Communications *10*, 1536.

Widge, A.S., Malone, D.A.J., and Dougherty, D.D. (2018). Closing the Loop on Deep Brain Stimulation for Treatment-Resistant Depression. Front. Neurosci. *12*. Available at: https://www.frontiersin.org/articles/10.3389/fnins.2018.00175/full#B65 [Accessed November 3, 2020].

Williams, L.M. (2017). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depression and Anxiety *34*, 9–24.