ROLE OF THE SUBTHALAMIC NUCLEUS IN THE CIRCUITRY MEDIATING FOOD- AND COCAINE-SEEKING BEHAVIOR

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ABSTRACT

The subthalamic nucleus (STN) is part of the basal ganglia, which play a crucial role in motor control and in processing information from motor cortical areas. Although the STN is classically considered a motor structure, recent studies suggest that it may also be involved in the motivation for natural and drug reward. The STN may differentially modulate natural and drug reward via circuitry that includes the nucleus accumbens (NAcc), a structure belonging to the mesocorticolimbic circuit which has been identified as the neural substrate of the reinforcing effects of reward. Here, we assess the effects of bilateral STN lesions on the self-administration (SA) and subsequent reinstatement of sucrose- and cocaine-seeking behavior. Bilateral STN lesions block reinstatement of cocaine-seeking behavior, but not the reinstatement of food-seeking behavior. Neuronal correlates in the NAcc are also investigated. NAcc neurons respond to cocaine or sucrose and the conditioned stimulus (CS) during SA and the CS during reinstatement. Moreover, STN lesions have profound effects on these responses. Additionally, we assess the effects of STN lesions on operant responding for reward under a progressive ratio (PR) schedule of reinforcement, a schedule thought to measure the reinforcing efficacy of rewards. Bilateral STN lesions enhance responding for sucrose reward, but attenuate responding for cocaine reward. Furthermore, STN lesions differentially modulate NAcc neuronal activity associated with operant responding for either sucrose or cocaine reward under a PR schedule of reinforcement. Collectively, these results provide additional evidence for the role of the STN in food- and cocaine-seeking behavior and further support the NAcc in food- and cocaine-seeking behavior. In conclusion, these

experiments demonstrate that the STN, classically considered a motor nucleus, differentially modulates the motivation, or craving, for natural and drug reward.

Table of Contents

List of Abbreviations

Basolateral amygdala	BLA
Conditioned stimulus	CS
Deep brain stimulation	DBS
Dopamine	DA
Fixed ratio	FR
Gamma-aminobutyric acid	GABA
Globus pallidus	GP
Globus pallidus external segment	GPe
Globus pallidus internal segment	GPi
N-methly-d-aspartate	NMDA
Nucleus accumbens	NAcc
Parkinson's disease	PD
Perievent histogram	PEH
Prefrontal cortex	PFC
Progressive ratio	PR
Self-administration	SA
Substantia nigra	SN
Substantia nigra reticulata	SNr
Subthalamic nucleus	STN
Ventral pallidum	VP
Ventral tegmental area	VTA

Background

Neural Substrate Underlying Reward

The mesocorticolimbic circuit has been identified as the neural substrate underlying the reinforcing effects of reward [Koob, 1992; Wise, 1996]. This circuit originates from dopamine (DA) neurons in the ventral tegmental area (VTA) and includes regions that receive DAergic input, such as the nucleus accumbens (NAcc) and prefrontal cortex (PFC). In particular, the DAergic projection from the VTA to the NAcc appears to be critical in mediating the rewarding properties of both natural [Wise, 1998; Pfaus et al., 1990; Richardson & Gratton, 1996] and drug [Everitt & Wolf, 2002; Ito et al, 2004] reward. Numerous studies have focused on the importance of the NAcc in maintaining reinforced behaviors. The NAcc receives projections from limbic structures including the VTA, the basolateral amygdala (BLA), subiculum, and PFC [Zahm & Brog, 1992] and sends projections to structures involved in motor processing, such as the ventral pallidum (VP) [Zahm & Heimer, 1993]. This anatomical arrangement allows the NAcc to integrate limbic information related to motivation, memory, and the associated motor activity [Everitt & Robbins, 1992; Morgenson, 1987].

Further, the NAcc is a heterogeneous structure that can be divided into two distinct subregions, the core and shell. Different regions of the hippocampus and PFC [Brog et al., 1993] and different subcompartments of the amygdala [Wright et al., 1996] send projections to distinct subregions within the core and shell. These subregions also differ in efferents. Specifically, the core projects to conventional basal ganglia circuitry, VP, globus pallidus (GP), and substantia nigra (SN); while the shell projects to limbic

structures, lateral hypothalamus and VTA [Zahm & Brog, 1992]. Based on these anatomical differences, it has been proposed that the core is more involved with motor functions; while the shell is more involved in motivational mechanisms [Heimer et al., 1991; Zahm & Brog, 1992].

Nucleus Accumbens and Food Reward

Evidence indicates that the NAcc is involved in mediating the rewarding properties of food reward. For example, microinfusion of non-NMDA glutamate receptor antagonists or GABA agonists into the shell induces feeding behavior in rats [Kelley & Swanson, 1997; Stratford et al., 1998]. Depletion of NAcc DA [Cousins et al., 1993] or microinfusion of D_1 or D_2 antagonists into NAcc [Koch et al., 2000] attenuate lever pressing for food on a fixed-ratio (FR) schedule. Further, blockade of D_1 or D_2 receptors in core or shell decreases lever pressing for food reinforcers [Nowend et al., 2001].

Results from microdialysis and voltammetry studies provide further support for the involvement of the NAcc. Extracellular concentrations of DA and its metabolites increase in the NAcc during the initiation and maintenance of feeding in food-deprived rats [McCollough & Salamone, 1992] and during water consumption [Young et al., 1992]. In addition, DA transmission in the NAcc increases prior to lever pressing in rats responding for food [Richardson & Gratton, 1996; Kiyatkin & Gratton, 1994]. Furthermore, cues associated with the opportunity to respond for sucrose evoke DA release in the NAcc in rats where the cues have been previously paired with sucrose

[Roitman et al., 2004]. Lastly, stimuli associated with food elicit an increase in DA levels selectively in the NAcc core [Bassereo & DiChiara, 1999].

Increasing evidence from electrophysiological studies also support a role of the NAcc in goal-directed behaviors for food reinforcers. For instance, neurons in the NAcc exhibit increases and/or decreases in firing rate relative to operant responding for juice in monkeys [Bowman et al., 1996; Schultz, 1998] and water or food reinforcement in rats [Carelli & Deadwyler, 1994; Carelli et al, 2000; Miyazaki et al., 2004]. Additionally, some NAcc neurons exhibit increases in firing rate within seconds prior to the operant response for sucrose reinforcement; while others show increases or decreases within seconds following the reinforced response [Roop et al., 2002]. Furthermore, the reinforced response is closely synchronized to NAcc cell firing, occurring 3 sec before to 2 sec after peak cell firing [Carelli & Deadwyler, 1997]. Collectively, these results suggest that the NAcc mediates behaviors associated with natural rewards.

Nucleus Accumbens and Cocaine Reward

The NAcc is also involved in mediating behaviors reinforced by cocaine, a DA reuptake inhibitor [Boja & Kuhar, 1989]. For example, lesions of the NAcc attenuate cocaine self-administration (SA) in rats [Zito et al., 1985]. Evidence from microdialysis [Hinson & Poulos, 1981] and voltammetry [Kiyatkin, 1994] studies shows that DA in the NAcc increases during repeated cocaine injections. Furthermore, DA in the NAcc fluctuates during cocaine SA and reaches its peak at the time of the operant response in rats [Kiyatkin & Stein, 1995] or when cocaine delivery is contingent on the behavior of the rat [Hemby et al., 1997]. Microinfusion of low doses of D_1 antagonists, but not D_2

antagonists, reduces cocaine SA [Caine & Koob, 1994]. Moreover, microinfusion of D_1 or D_2 antagonists into the core or shell decreases responding for cocaine on a progressive ratio (PR) schedule of reinforcement; while infusion of these antagonists into the core, but not the shell, decreases food SA [Bari & Pierce, 2005]. This result suggests that DA receptors in the shell may modulate the reinforcing effects of cocaine, while DA receptors in the core may modulate more general reinforced behaviors.

Electrophysiological recordings have also provided support for a role of the NAcc. Several electrophysiological experiments have shown that NAcc neurons exhibit responses associated with operant responding for cocaine. Specifically, NAcc neurons respond within seconds of the operant response for intravenous cocaine [Carelli, 2002], within seconds following the response [Carelli & Ijames, 2001], or exhibit a phasic firing pattern during the interinfusion interval [Peoples et al., 1997]. Finally, response-related activity is not exhibited during acquisition, but develops gradually over days after the rat acquires stable operant responding [Chang et al., 1994].

Nucleus Accumbens and Cocaine Reinstatement

After chronic cocaine use, there is a high incidence of relapse that can occur after years of abstinence [Jaffe, 1990]. Relapse to cocaine-seeking behavior can be triggered by stress [Sanchez & Sorg, 2001], a drug-associated cue [Childress et al., 1999], or re-exposure to cocaine [Jaffe et al., 1989]. Increasing evidence indicates that the NAcc is critical in both cue-induced and cocaine-primed reinstatement. For instance, presentations of cocaine-associated cues selectively increase DA release in the core, but not the shell, of the accumbens [Ito et al., 2000]. Furthermore, cue-induced reinstatement

is blocked following the infusion of a glutamate antagonist into the accumbens core, and not into the shell [Di Ciano & Everitt, 2001]. This is consistent with the effect of inactivation of the BLA, which preferentially innervates the core over the shell [Groenewegen et al., 1990], on cue-induced reinstatement [Kantak et al., 2002]. Therefore, glutamatergic input from the BLA to the core seems to be critical for cue-induced reinstatement.

Both subregions of the NAcc appear to be involved in cocaine-primed reinstatement. Although blockage of DA receptors in the core does not block cocaine-primed reinstatement, inactivation of the core using GABA agonists does [McFarland & Kalivas, 2001]. Moreover, glutamate release increases in the core during cocaine-primed reinstatement [McFarland et al., 2003]. Evidence from electrophysiological recordings shows that NAcc neurons that respond to the operant event during cocaine SA maintain the response during SA recovery following a priming infusion of cocaine in a within session reinstatement task [Carelli & Ijames, 2000]. The shell also appears to be involved in cocaine-primed reinstatement. For example, blockade of D_1 receptors in the shell abolishes cocaine-primed reinstatement [Anderson et al., 2003]. More recently, it has been shown that the cooperative activation of D_1 and D_2 receptors in the shell is necessary to reinstate cocaine-seeking behavior [Schmidt & Pierce, 2006]. Collectively, these results suggest that cocaine-primed reinstatement may be mediated by glutamate transmission in the core and DA transmission in the shell.

The Subthalamic Nucleus

The subthalamic nucleus (STN) is a small, densely populated structure located ventral to the zona incerta and rostral to the substantia nigra reticulata (SNr) [Paxinos & Watson, 1998]. The volume of the STN is approximately 0.8 mm^3 in rats [Hamani et al., 2004] and the rat STN is comprised of about 25,000 cells [Hardman et al., 2002]. The soma of STN projection neurons ranges from 25 to 50 μm in diameter [Chang et al., 1983] with long axons and sparsely spined dendrites extending more than 750 μm [Rafols & Fox, 1976]. There is no consensus on the presence of interneurons in the STN [Yelnik & Percheron, 1979]. At rest, STN neurons firing rates range from 5 – 90 Hz with a mean around 20 Hz [Cheruel et al., 1996]. Also, there is evidence for oscillatory behavior in STN neurons [Plenz & Kitai, 1999].

The STN is part of the basal ganglia, which play a crucial role in motor control and in processing information from motor cortical areas. As shown in the schematic ("motor circuit") in Figure 1, the STN receives direct projections from motor, premotor, and prefrontal areas of the cortex [Monakow et al., 1978] and indirect input from the cortex through the striatum and the external segment of the globus pallidus (GPe) [Smith et al., 1998]. The STN sends glutamatergic projections to the GPe, the internal segment of the globus pallidus (GPi) [Kita & Kitai, 1987] and the SNr [Parent & Hazrati, 1995]. The STN, via its glutamatergic projections, supplies excitatory input to the GABergic neurons in the SNr and GPi; therefore, reinforcing the inhibitory influence of the basal ganglia on motor output [Alexander & Crutcher, 1990].

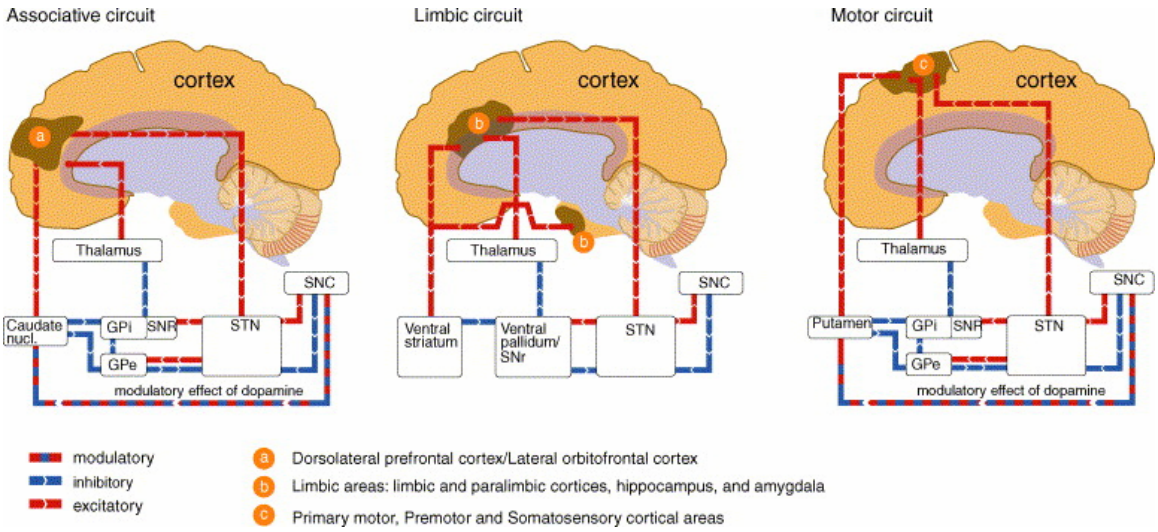

Figure 1. Schematic illustration of the basal ganglia-thalamocortical limbic and motor circuits [Temel et al., 2005]. The STN has a central location in both of these circuits. Limbic circuit: projections from the hippocampus, amygdala, limbic, and paralimbic cortices are sent to ventral striatum (NAcc). In turn the NAcc projects to the VP. From here the circuit is directed to the thalamus and is closed by projections back to cortex. The STN has reciprocal connections with the VP, a structure considered to be the major limbic circuit output region. Within this circuit, the STN has a pivotal role as it is directly connected with the output of the limbic circuit. Motor circuit: the cortical input to the motor circuit originates from the primary motor, premotor, and somatosensory areas. This input is directed to the putamen, which projects to the GPe, GPi, and SNr. From the GPe, projections are sent to the STN. The STN in turn projects to the GPi and SNr, which serve as the output nuclei of the basal ganglia.

Traditionally, the STN has been thought of as a motor nucleus. Electrophysiological data show that STN neurons are involved in the preparation and initiation of movement [Cheruel et al., 1996]. Furthermore, in restrained primates performing joystick manipulations, STN neurons increase firing rate preceding the onset of movement [Georgopoulos et al., 1983]. Hyperactivity of the STN has been linked to some of the motor deficits observed in Parkinson's disease (PD), a debilitating disease characterized by tremor, muscular rigidity, and dyskinesia [Parkinson, 1817]. Therefore, the STN has become a promising target for PD treatment. For instance, lesions or high frequency stimulation of the STN in PD patients [Limousin et al., 1995] and in animal models of PD [Bergman et al., 1990] improve motor symptoms.

Behavioral side effects following STN deep brain stimulation (DBS), which is thought to mimic STN lesions by inhibiting neuronal activity [Benazzouz et al., 2000], in PD patients provided the first indication that the STN plays an important role in cognitive and limbic functions. For example, despite improvements in motor performance, STN stimulation PD patients often experience impairments in executive functioning, attention, working memory, and visual and verbal learning [Trepanier et al., 2000]. Furthermore, STN DBS in PD patients has been associated with hypersexuality [Romito et al., 2002], uncontrollable laughter [Krack et al., 2001], pathological gambling [Smeding et al., 2007], and increased appetite [Moro et al., 1999]. Further evidence has been provided from lesion studies in rats. Specifically, bilateral STN lesions increase anticipatory responding in a reaction time task [Baunez et al., 1995]. This effect can also be achieved via pharmacological inactivation of the STN [Baunez & Robbins, 1999]. Moreover, STN

lesions affect visual attentional performance [Baunez & Robbins, 1999] and response selection and working memory [Baunez et al., 2001].

Anatomical data support a role of the STN in cognitive and limbic functions as shown in the schematic ("limbic circuit") in Figure 1. In the rat, projections from limbic areas (infralimbic, ventral prelimbic, and ventral agranular insular areas) are sent to the NAcc [Berendse et al., 1992; Brog et al., 1993]. Projections from the NAcc are then sent to the VP and relayed on to the thalamus [Heimer et al., 1995]. The circuit is then closed via projections directed back to the cortical areas [Groenewegen et al., 1990]. The STN has reciprocal connections with the VP [Nauta & Cole, 1978; Haber et al., 1985], a structure considered to be the major limbic circuit output. In fact, the majority of VP neurons, both NMDA and non-NMDA expressing neurons, are directly influenced by STN activation [Turner et al., 2001]. Thus, via connectivity with the VP, the STN may modulate cognitive and limbic functions.

The Role of the Subthalamic Nucleus in Food and Cocaine-seeking Behavior

Evidence from electrophysiological studies examining STN neuronal responses to DA, the neurotransmitter associated with reward [Wise, 2005], provided the first indication that the STN may be involved in reward processes. For instance, firing rates of STN neurons are increased by stimulation of D_1, but not D_2, receptors in anesthetized rats [Kreiss et al., 1997]. In freely moving rats, systemic administration of amphetamine, a DA agonist, increases STN neuronal firing rate [Olds et al., 1999]. The same phenomenon is observed following iontophoretic application of DA or a D_1 receptor agonist in anesthetized rats [Ni et al., 2001].

Despite the increasing evidence linking the STN to cognitive and limbic functions, only recently has the STN been implicated in the modulation of behaviors reinforced by both natural and drug reward. Bilateral STN lesions enhance locomotor activity conditioned to food presentation, increase responding for food-related conditioned reinforcers, increase the breaking point for sucrose pellets, and increase food reward pellet consumption [Baunez et al., 2002]. Similarly, reversible inactivation of the STN by GABA agonists increases the breaking point for food on a progressive ratio (PR) schedule [Baunez & Robbins, 1999]. In the monkey, STN neurons show increases or decreases in firing rate just before or after the delivery of sucrose that are not directly related to mouth movements [Darbaky et al., 2005]. Previously reported data from our own lab show STN neuronal responses to instructive cues, discriminative nose-pokes, and reinforcement in rats performing a nose-poke for sucrose task [Teagarden & Rebec, 2007]. Finally, we have observed similar STN neuronal responses in rats performing a lever press for sucrose task on a FR-5 schedule of reinforcement [Baunez et al., 2006]. Taken together, these studies clearly implicate the STN in the modulation of behaviors reinforced by natural reward.

Interestingly, there are conflicting findings from experiments investigating STN involvement in the modulation of behaviors reinforced by drug reward. In addition to the induction of *c-fos* in the STN following amphetamine and cocaine treatment [Uslaner et al., 2001], it has been reported that bilateral STN lesions increase the psychomotor effects of cocaine, the rate at which cocaine SA is acquired, and the breaking point using a PR schedule [Uslaner et al., 2005]. Another group has reported the opposite: bilateral STN lesions block cocaine conditioned place preference and decrease the breaking point for

cocaine [Baunez et al., 2005]. Methodological differences between these experiments, the dose of cocaine and the concentration of ibotenic acid, for instance, may account for the discrepancy. We have reported that STN neurons mainly exhibit motor related activity in rats working for cocaine, but are responsive to reward and a CS that has been associated with reward in rats working for sucrose [Baunez et al., 2006]. These electrophysiological data show differential coding in the STN depending on reward type and support a dissociation between natural and drug reward in the STN, similar to what is observed in the NAcc [Carelli et al., 2000; Carelli, 2002].

The STN and NAcc are part of the limbic circuitry which also includes the PFC and VP (Figure 1) [Maurice et al., 1998]. Specifically, the NAcc core sends GABAergic projections to the medial part of the STN via the VP; while the STN sends reciprocal glutamatergic projections to the VP [Groenewegen & Berendse, 1990]. It is through this circuit that the STN controls limbic information outflow [Turner et al., 2001] and may also be the circuitry through which the STN differentially modulates natural and drug rewards. Therefore, since both the STN and NAcc participate in this limbic circuit, it is not surprising that both STN and NAcc neurons show differential coding of natural and drug rewards and that STN lesions have a differential effect on natural and drug rewards.

Rationale

Although the STN is classically considered a motor nucleus, recent evidence from behavioral [Baunez et al., 2002; Baunez et al., 2005; Uslaner et al., 2005] and electrophysiological [Darbaky et al., 2005; Baunez et al., 2006; Teagarden & Rebec, 2007] studies suggests that it may also be involved in the motivation for natural and drug

reward. In fact, it has been suggested that the STN differentially modulates motivation for natural and drug rewards [Baunez et al., 2005]. One objective of these experiments is to determine the role of the STN in the reinstatement of food- and drug-seeking behavior. Therefore, our working hypothesis is that the STN differentially modulates the reinstatement of food- and cocaine-seeking behavior.

Much emphasis has been placed on the mesocorticolimbic circuit as the neural substrate underlying the reinforcing effects of reward [Koob et al., 1992; Wise, 1996]. It is this circuitry, particularly the NAcc, that appears to be critical in both cue-induced [Ito et al., 2000; Di Ciano & Everitt, 2001] and cocaine-primed [McFarland & Kalivas, 2001; McFarland et al., 2003; Schmidt & Pierce, 2006] reinstatement of cocaine-seeking behavior. Few studies have assessed the electrophysiological correlates in the NAcc during the reinstatement of reward-seeking behaviors. In fact, these correlates have only been investigated in a within session reinstatement task [Carelli & Ijames, 2000]. Thus, our second objective is to investigate electrophysiological correlates in a between session reinstatement task, which serves as a model for drug craving and relapse in humans.

Through its connectivity in the limbic circuitry including the NAcc, PFC, and VP [Groenewegen & Berendse, 1990; Maurice et al., 1998], it is thought that the STN modulates cognitive and limbic functions. Given: 1) connectivity between the NAcc and STN, 2) the NAcc is critical for cue-induced and reward-primed reinstatement and, 3) our hypothesis that the STN will differentially modulate reinstatement behavior; it seems likely that electrophysiological correlates in the NAcc will differ between sham controls and STN-lesioned animals. Thus, our third objective is to investigate these potential differences.

Finally, in light of recent conflicting evidence [Uslaner et al., 2005] the effects of STN lesions on operant responding on a PR schedule of reinforcement are not clear. Therefore, our fourth objective is to help clarify the effects of STN lesions in this paradigm. Additionally, electrophysiological correlates in the NAcc will be investigated during a PR schedule of reinforcement for either natural or drug reward in intact and STN-lesioned animals.

To test our hypotheses, we recorded NAcc core and shell neuronal activity in intact and STN-lesioned animals engaged in food- or cocaine-seeking behavior. Specifically, we examined the effects of bilateral STN lesions on the reinstatement of food- and cocaine-seeking behavior and the motivation for food and cocaine using a PR schedule of reinforcement. In each of these experiments, neuronal activity in the core and shell was monitored to assess the effects of STN lesions on limbic circuitry. These experiments provide much needed behavioral and electrophysiological data which, in addition to characterizing neuronal behavior in the limbic circuit, support a role of the STN in reward-seeking behavior. Moreover, these experiments lend further support for the STN as a potential target for developing treatments for drug abuse.

Materials and Methods

Subjects

Male, Sprague-Dawley rats (250 – 400 g) were used in all experiments. Rats were allowed *ad libitum* access to water and food prior to operant training. Rats were

housed individually and maintained on a 12 h light/dark cycle. All experimental protocols were approved by the Indiana University Animal Care and Use Committee.

Apparatus

Training and electrophysiological recording occurred in a plexiglass operant chamber (30 x 30 x 40 cm) inside a sound-attenuating cubicle equipped with a computer-controlled houselight. On one wall, a magazine (5 cm above the floor) was connected to a pump-operated syringe (Med Associates Inc., St. Albans, VT, USA) via polyethylene tubing. Just above the magazine, a lever was accessible 12 cm above the floor. A tone generator with loudspeakers was attached to the outside of the chamber just above the lever. A computer operating customized software provided automated control of the operant chamber such as turning on appropriate stimuli and the pump-operated syringe, recording lever presses, and sending appropriate event marks to a second computer operating software (SortClient, Plexon Inc., Dallas, TX, USA) that synchronized these behavioral data with electrophysiological activity. A video camera was mounted at the ceiling of the cubicle and connected to a video screen to allow recording and direct monitoring of the animal's behavior. A photograph of the operant chamber is presented in Figure 2.

Figure 2. Photograph of the operant chamber.

STN/Sham Lesion Surgery

STN/sham lesion surgery was performed under general anesthesia. A preanesthetic dose of atropine sulfate (0.05 mg/kg, s.c.) was administered to facilitate breathing. Rats were anesthetized with ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg) (i.m.). A corneal lubricant (Moisture Eyes PM, Bausch and Lomb) was applied to prevent corneal drying during surgery and the ear bars were coated with antibiotic ointment to minimize the risk of infection due to accidental rupture to the eardrum. After the animal was fixed into a stereotaxic apparatus the skull was exposed and leveled. Holes were drilled bilaterally over the STN. STN coordinates were calculated using the average of coordinates from bregma (-3.8 mm AP, 2.4 mm ML, -8.35 mm DV) and the interaural line (5.2 mm AP, 2.4 mm ML, 1.65 mm DV) [Paxinos & Watson, 1998]. A stainless steel injector cannula (33 gauge) (Plastics One, Roanoke, VA, USA) was lowered into the STN and a dose of ibotenic acid (9.4 µg/µl) (Tocris, Ellisville, MO, USA) or vehicle solution (phosphate buffer, 0.1 M) was injected. The volume injected was 0.5 µl infused over 3 min with a 10-µl Hamilton microsyringe (Hamilton Company, Reno, NV, USA), fixed on a micropump (World Precision Instruments, Sarasota, FL, USA) connected by polyethylene tubing to the injector cannula. The injector cannula was left in place for 5 min to allow diffusion after which it was raised out of the brain and lowered into the contralateral STN for the second infusion. The holes in the skull were filled with sterile gelfoam (Pharmacia & Upjohn, Inc., Kalamazoo, MI, USA), the animal's head was sutured, and antibiotic ointment was applied to the wound. Following surgery, each animal received 10 ml of lactated ringer's solution (s.c.) for rehydration. STN-lesioned rats exhibit a short-lasting self-biting

behavior that disappears when they wake up [Baunez et al., 1995]. Therefore, protection of the paws was provided by bandaging and removed after the rats had recovered from anesthesia.

Operant Training

After 2-3 weeks of recovery, animals were placed on a restricted diet (~85% free feeding weight that was adjusted for growth) for the remainder of the experiment. Rats were trained to lever press in order to receive a 10% sucrose solution reward. During training, no CS was present and animals began on a fixed ratio 1 (FR-1) schedule of reinforcement. Specifically, each lever press resulted in 4 sec of sucrose delivery followed by a 6 sec time-out period indicated by the illumination of the houselight. Lever presses had no programmed consequences during the time-out period. After criteria were met, 60 trials completed within 30 min for two consecutive sessions, rats were reinforced on an FR-3 schedule and, finally, on an FR-5 schedule. Training took 10-12 days to complete, after which animals underwent a second surgery.

Jugular Vein Catheter / Bundle Surgery

Animals were anesthetized and prepared for surgery as in the lesion surgery (see above). For the cocaine SA groups, a catheter constructed from PE10 and PE50 tubing (Fisher Scientific, Pittsburgh, PA) was inserted into the right jugular vein as described elsewhere [Caine & Koob, 1994]. The PE50 end was inserted over metal tubing of a guide cannula (22 gauge; Plastics One, Roanoke, VA, USA), which was bent into a right angle. The guide cannula was threaded under the skin and exited at the scapula of the

skull. After catheterization, rats were fixed in a stereotaxic apparatus. One hole was drilled over the NAcc core (1.70 mm AP, 1.20 mm ML) and another was drilled over the contralateral NAcc shell (1.70 mm AP, 0.80 mm ML) [Paxinos & Watson, 1998]. Four supplementary holes were drilled for placement of stainless steel screws to provide structural support. Microwire bundle electrodes were lowered 6.50 – 7.00 mm and 6.50 mm into core and shell, respectively, at a rate of 100 μm per 30 sec. After both bundles were lowered into place, they were fixed to the skull with dental acrylic. Throughout surgery, ketamine supplements were given (i.p.) periodically to maintain anesthesia. Following surgery, each animal received 10 ml of lactated Ringer's solution (s.c.) for rehydration.

Microwire Bundle Electrodes

Each bundle consisted of eight microwires [25 μm diameter, stainless steel, formvar insulated (California Fine Wire, Grover Beach, CA)], threaded through a cannula (27 gauge) that served as ground. The microwires and cannula were soldered to an 8-pin connector (Omnetics, Minneapolis, MN). Microwires were trimmed so that they protruded 1 -2 mm past the end of the cannula. Electrode impedance was typically ~1 MΩ, although this was not quantified systematically.

Electrophysiology

On recording days (see below), animals were connected to a multichannel electric swivel (Plastics One, Roanoke, VA) via a lightweight flexible cable, allowing them complete freedom of movement. Electrophysiological signals were transmitted via the

electric swivel to a preamplifier, and then to data acquisition hardware (MNAP, Plexon Inc., Dallas, TX). A multineuron acquisition program (Sort Client, Plexon Inc., Dallas, TX) was used to isolate single-unit activity between and within channels. Criteria such as a consistent waveform and amplitude, a signal-to-noise ratio of at least 2.5:1, and a trough in the autocorrelation analysis at $t<10$ [Kosobud et al., 1994] were used to identify single units. Any recordings not meeting any of the above criteria were excluded from subsequent analysis.

Following 6 – 7 days of recovery, STN-lesioned animals and sham controls with multiwire bundle electrodes chronically implanted into core and shell were distributed to the following four experiments.

Experiment 1: Effects of STN lesions on NAcc electrophysiology during food-seeking behavior.

Animals underwent 3 - 4 weeks of daily experimental sessions during which single units were isolated and recorded (see above). The first 14 sessions consisted of operant responding for sucrose. Each session was comprised of 60 trials with rats receiving a 10% sucrose solution reward on an FR-5 schedule of reinforcement. Every fifth lever press was rewarded with sucrose accompanied by a CS [tone **(**2.4 kHz**)** and two stimulus lights] for 4 sec followed by a 6 sec time–out signaled by illumination of the houselight. During CS presentations and time–outs, lever presses were recorded but had no programmed consequences. In order to determine which events elicited neuronal responses, either the CS or sucrose randomly did not occur on 25% of the trials during the 13^{th} session. The 14^{th} session was identical to sessions 1 – 12.

Following these 14 sessions, responding was extinguished to ~20% of the level observed during operant responding for sucrose. During each 60 min extinction session, responding was recording, but had no programmed consequences. Extinction training lasted 3 – 5 days. Following extinction, cue-induced reinstatement was tested using a CS conditioned reinstatement paradigm. During this 30 min session responding was reinforced by the CS alone, on an FR-5 schedule, after a noncontingent CS presentation at the beginning of the session. Once again operant responding was extinguished to ~20% over 1 – 2 sessions. Finally, animals were tested in a food-primed reinstatement paradigm. Specifically, this 30 min session began with a noncontingent delivery of sucrose solution and responding had no programmed consequences. Cue-induced and food-primed reinstatement sessions were counterbalanced.

Experiment 2: Effects of STN lesions on NAcc electrophysiology during cocaine-seeking behavior.

Animals underwent 3 – 4 weeks of daily experimental sessions during which single units were isolated and recorded (see above). The first 14 sessions, each 2 hr in duration, consisted of cocaine SA on a modified FR-5 schedule of reinforcement. Cocaine infusions were delivered into the jugular vein catheter by a fluid pump located outside of the chamber. Specifically, the first lever press resulted in an infusion of 0.25 mg of cocaine in a volume of 0.05 ml accompanied by a CS [tone (1.0 kHz) and two stimulus lights] lasting 4 sec followed by a 16 sec time-out signaled by illumination of the houselight. After the first infusion, cocaine delivery and CS presentation was contingent on an FR-5 schedule. During cocaine delivery and time-outs, lever presses

were recorded but had no programmed consequences. In order to determine which events elicited neuronal responses, either cocaine or the CS did not occur on 25% of the trials during the 13th session. The 14th session was identical to sessions 1 – 12.

Following these 14 sessions, responding was extinguished to ~20% of the level observed in cocaine SA sessions. During each 60 min extinction session, responding was recording but had no programmed consequences. Extinction training lasted 3 – 5 days. Following extinction, cue-induced reinstatement was tested using a CS conditioned reinstatement paradigm. During this 30 min session responding was reinforced by the CS alone, on an FR-5 schedule, after a noncontingent CS presentation at the beginning of the session. Once again operant responding was extinguished to ~20% over 1 – 2 sessions. Finally, animals were tested in a cocaine-primed reinstatement paradigm. Cocaine-primed reinstatement sessions began immediately following an i.p. injection of cocaine (10 mg/kg) and lasted for 60 min. Lever presses were recorded but had no programmed consequences during this session. Locomotor activity was recorded on video tape during the cocaine-primed reinstatement session in order to rule out the possibility of a motor effect of cocaine on the performance of the animals. Cue-induced and cocaine-primed reinstatement sessions were counterbalanced.

Experiment 3: Effects of STN lesions on NAcc electrophysiology during food-seeking behavior on a progressive ratio schedule of reinforcement

Animals underwent 2 weeks of daily experimental sessions during which single units were isolated and recorded (see above). The first 10 sessions, each 60 trials in duration, consisted of operant responding for 10% sucrose solution on an FR-5 schedule

of reinforcement. Specifically, every fifth lever press was rewarded with sucrose accompanied by a CS [tone **(**2.4 kHz**)** and two stimulus lights] for 4 sec followed by a 6 sec time–out signaled by illumination of the houselight. During CS presentations and time–outs, lever presses were recorded but had no programmed consequences. Following these 10 sessions, motivation for food reward was tested using a progressive ratio schedule of reinforcement for 3 sessions. During these daily sessions, sucrose solution was delivered after increasing ratios of lever presses. In order to accurately replicate the protocol used in Baunez et al. [2005], the ratios followed the modified equation of Depoortere et al., [1993] (number of lever presses required: 1, 3, 6, 10, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118). Each sucrose solution delivery was accompanied by a CS [tone **(**2.4 kHz**)** and two stimulus lights] lasting 4 sec followed by a 6 sec time-out signaled by illumination of the houselight. During CS presentations and time–outs, lever presses were recorded but had no programmed consequences. The session ended when the animal failed to complete a ratio within an hour after the previous sucrose solution delivery.

Experiment 4: Effects of STN lesions on NAcc electrophysiology during cocaine-seeking behavior on a progressive ratio schedule of reinforcement

Animals underwent 2 weeks of daily experimental sessions during which single units were isolated and recorded (see above). The first 10 sessions, each 2 hours in duration, consisted of operant responding for cocaine, 0.25 mg in a volume of 0.05 ml, on a modified FR-5 schedule of reinforcement. Cocaine was infused as described in Experiment 2. Specifically, the first lever press resulted in an infusion of cocaine

accompanied by a CS [tone (1.0 kHz) and two stimulus lights] lasting 4 sec followed by a 16 sec time-out signaled by illumination of the houselight. After the first infusion, cocaine delivery and CS presentation was contingent on an FR-5 schedule. During cocaine delivery and time-outs, lever presses were recorded but had no programmed consequences. Following these 10 sessions, motivation for cocaine was tested using a progressive ratio schedule of reinforcement for 3 sessions. During these daily sessions, cocaine was delivered after increasing ratios of lever presses as in Experiment 3. Each cocaine infusion was accompanied by a CS [tone (1.0 kHz) and two stimulus lights] lasting 4 sec followed by a 16 sec time-out signaled by illumination of the houselight. During CS presentations and time–outs, lever presses were recorded but had no programmed consequences. The session ended when the animal failed to complete a ratio within an hour after the previous cocaine infusion.

Histology

After the experiments, animals were deeply anesthetized with urethane (0.50 g/ml in saline delivered i.p. in a volume of 0.50 ml per 100 g of body weight). A current (30 μA for 5 sec) was passed through the electrodes to produce a marking lesion. Animals were transcardially perfused with saline followed by 10% neutral buffered formalin. The brains were removed and prepared for sectioning by soaking in a 30% sucrose / 10% formaldehyde solution for several days. The NAcc was sectioned at 60 μm thickness and stained with creslyecht violet in order to determine microwire bundle placement in core and shell.

The STN was sectioned at 40 μm thickness and stained with creslyecht violet and lesions were quantified via cell counting similar to that described by Isgor & Sengelaub [1998]. Specifically, cross-sectional areas of the STN were traced for all sections through the rostrocaudal axis using a digitizing tablet and computer-based morphometry system (Sigmascan, Jandal Scientific, San Rafael, CA). Area measurements were then used to estimate volume using the Cavelieri estimator [Rosen & Harry, 1990]. In addition to overall structure volume, cell number was also quantified. Counts were made using an unbiased counting frame of 75 X 75 X 40 μm (neuronal somata touching the left and bottom edges of the frame were excluded from counts) at 60X. Neurons were counted as they first appeared in focus while focusing through the z axis, and neurons in the first focal plane ("tops") were not counted. For each animal, counts were taken from 5 sections per hemisphere. Within each section, 2 sampling areas were counted, one medial and one lateral area. STN neuron counts were then expressed as a density (average neuron number per unit area multiplied by the section thickness). Estimates of the total number of neurons were then obtained by multiplying the volumetric densities by the STN volume.

Drugs

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Bethesda, MD). Cocaine was dissolved in physiological saline at a concentration of 5 mg/ml.

Data Analysis

Histology – Cell Counting

In each experiment, volume and cell number were quantified for STNs in both hemispheres in sham control and STN-lesioned animals. For each measurement, a Two-Way ANOVA (sham/lesion X hemisphere) was used for data analysis. The group means were then compared with Bonferroni post hoc test.

Experiments 1 & 2

Operant Behavior

Responding was recorded during SA, extinction, and reinstatement sessions. Response rates were calculated as responses per min for food SA, extinction, CS-, and food-induced reinstatement and as responses per 30 min for cocaine SA, extinction, CS-, and cocaine-induced reinstatement. For both food and cocaine groups, a repeated Two-Way ANOVA (sham/lesion X sessions) was used for data analysis. The group means were then compared with Bonferroni post hoc test. Locomotion was scored during cocaine-induced reinstatement using event-recording software (BEST Collection, Educational Consulting Inc., Las Vegas, NV) in order to rule out the possibility of a motor effect of cocaine on the performance of the animals. Behavior was scored during a 5 min period occurring approximately 15 min after i.p. injection of cocaine and locomotion was defined as forward movement involving all four paws. Data were expressed as time (sec) spent locomoting. Group means were then compared using an unpaired t-test.

Electrophysiology

Operant Responding for Sucrose or Cocaine

The neuronal recordings we collected were not the result of random sampling. Since we recorded from each animal over several days of sucrose or cocaine SA and the microwire bundles were chronically implanted, we were repeatedly sampling neurons from the same subregion. Thus, it was possible we were recording the same neuron over several days. The typical neuronal yield for each animal was 5 – 10 neurons per recording session. We treated each neuron, however, as a different neuron since each animal's experience was different every session due to learning the association between the CS and reward.

Neural activity was analyzed utilizing the method described in Carelli & Deadwyler [1994]. Specifically, neural activity was characterized using raster plots and perievent histograms (PEHs) showing the activity of each neuron during a 20 sec interval that included the sucrose- or cocaine-reinforced lever press. Mean firing rates for each neuron were calculated for 3 time epochs, baseline, response, and reinforcement. Baseline was defined as the time period 10 – 7.5 sec before the initiation of the reinforced lever press. For both sucrose and cocaine groups, a Two-Way ANOVA (sham/lesion X NAcc subregion) was used to analyze baseline firing rates. Group means were then compared with Bonferroni post hoc test. Response was defined as the time period 2.5 – 0 sec before and during the execution of the reinforced response. Reinforcement was defined as the time period 0 – 2.5 sec after the reinforced response.

As described previously [Carelli & Deadwyler, 1994], neurons were classified into 4 types depending on the pattern of phasic activation. A neuron was classified as a

RESPe neuron if it exhibited a >40% increase in firing rate during the response epoch compared to its respective baseline. If a neuron showed a >40% decrease in firing rate during the response epoch compared to its respective baseline, it was classified as a RESPi neuron. A <40% increase or decrease in firing rate during the reinforcement epoch compared to the respective baseline was classified as a REINe or REINi neuron, respectively. A Chi Square analysis assessed the effects of STN lesions on neuronal responsiveness by comparing proportions observed in STN-lesioned animals with the expected proportions observed in sham controls.

Population histograms of normalized firing were generated for all phasically active neurons during a 15 sec interval that included the reinforced response. Thus, for each neuron, the firing rate during this interval was divided by it's respectively baseline. Composite PEHs of normalized firing were then constructed for each neuron type allowing for the comparison of changes in the activity of populations of neurons regardless of differences in overall firing rate between individual neurons. Unpaired t-tests were then used to determine differences in normalized firing rates for each epoch between neurons from sham and lesioned animals.

Extinction, Cue-induced and Food/Cocaine-primed Reinstatement

Neural activity was characterized using raster plots and PEHs showing the activity of each neuron during a 20 sec interval that included the lever press. Mean firing rates for each neuron were calculated for 2 time epochs, baseline and response. Baseline was calculated and analyzed as previously described. Response was defined as the time period 2.5 sec before to 2.5 sec after the lever press. Neurons were classified into 2 types, RESPe and RESPi neurons and Chi Square tests were conducted as described

previously. Composite PEHs of normalized firing were then constructed and analyzed as previously described.

Experiments 3 & 4

Operant Behavior

Response rates were calculated as the last ratio reached in the PR schedule of reinforcement, or breaking point. For both food and cocaine groups, an unpaired t-test (sham versus lesion) was used for data analysis.

Electrophysiology

Neuronal recordings were analyzed as in Experiment 1 and 2. Briefly, mean firing rates were calculated for 3 time epochs, baseline, response, and reinforcement. Neurons were classified into 4 types (RESPe, RESPi, REINe, and REINi) depending on the pattern of phasic activation. Chi Square tests were used to assess the effects of STN lesions on neuronal responsiveness by comparing proportions observed in STN-lesioned animals with the expected proportions observed in sham controls. Composite PEHs of normalized firing were constructed and analyzed using unpaired t-tests.

Results

Histology – STN Lesions

Only animals with a bilateral lesion of the STN were included in the data analysis for the STN-lesioned groups. Animals with lesions outside of the STN were excluded from behavioral and electrophysiological analyses. The behavioral performance of the

excluded animals was similar to that of sham controls. Therefore, behavioral effects were specifically a result of STN lesions. A representative photomicrograph from a sham control (panel A) and a STN-lesioned animal (panel B) is shown in Figure 3. As shown in Figure 4, a Two-Way ANOVA (sham/lesion X hemisphere) revealed animals that received bilateral STN lesions had a significantly smaller STN volume in each hemisphere compared to sham controls in each experiment (Bonferroni post hoc test). Not surprisingly, we observed the same result when estimated STN neuron numbers were analyzed. These data are graphed in Figure 5. A Two-Way ANOVA (sham/lesion X hemisphere) revealed animals that received bilateral STN lesions had a significantly smaller estimated STN neuron number in each hemisphere compared to sham controls in each experiment (Bonferroni post hoc test).

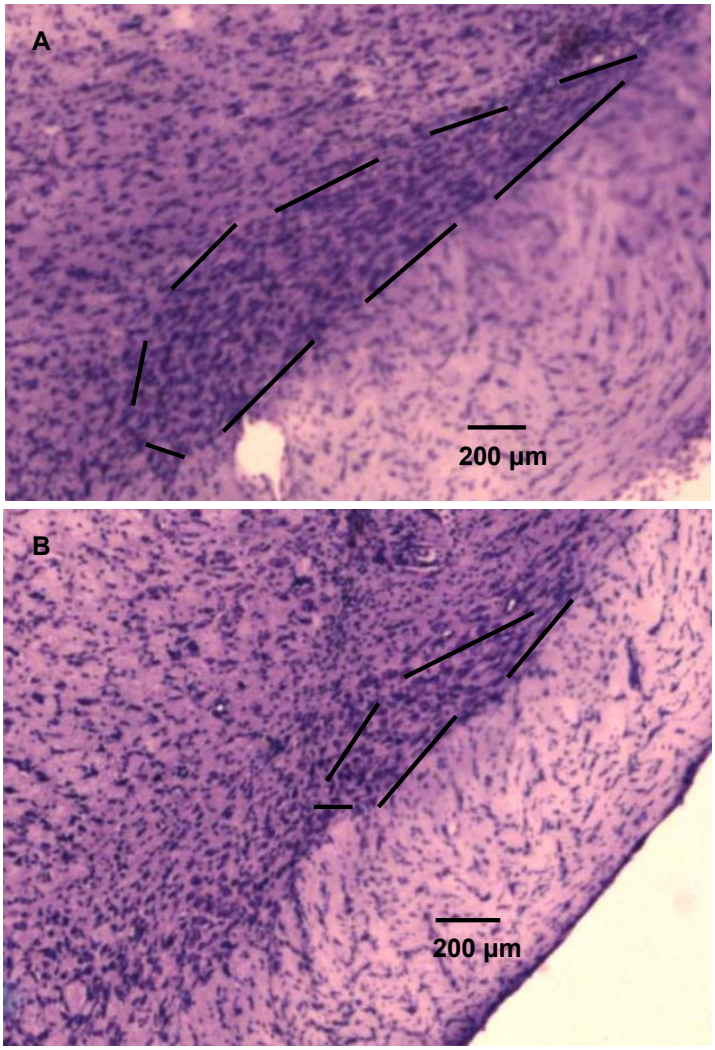

Figure 3. Photomicrographs of coronal sections at the level of the STN stained with creslyecht violet. Dashed lines outline the STN in a sham control animal (A) and an STN-lesioned animal (B).

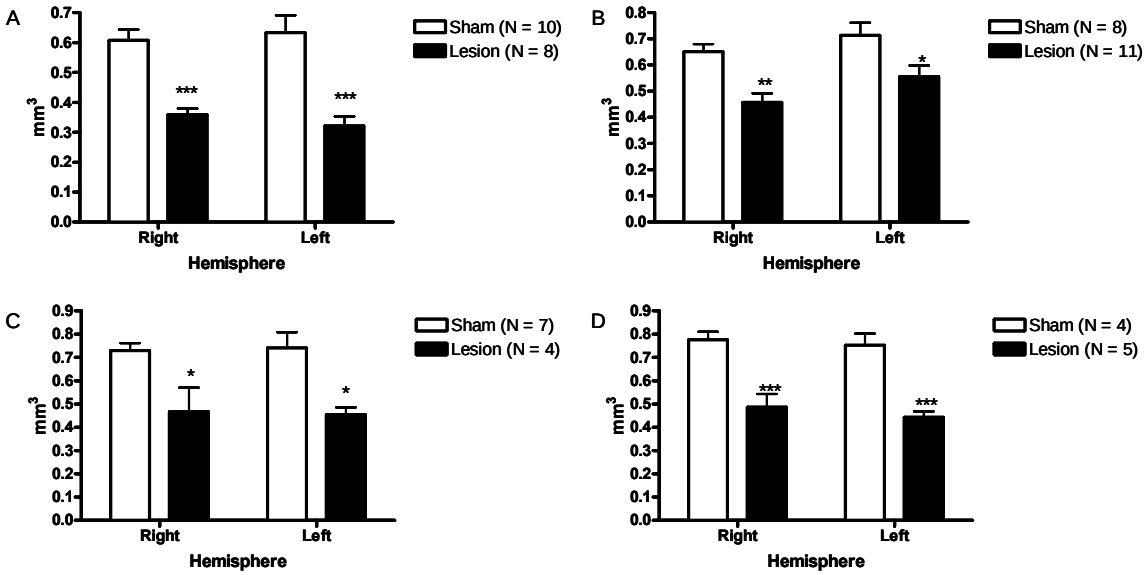

Figure 4. Mean STN volumes for sham controls and STN-lesioned animals used in Experiment 1 (A), Experiment 2 (B), Experiment 3 (C), and Experiment 4 (D). For all experiments, a Two-Way ANOVA (sham/lesion X hemisphere) revealed STN volumes in lesioned animals were significantly smaller compared to sham controls. There were no differences in volume between hemisphere in either sham controls or lesioned animals. (Bonferroni post hoc test; * $p<0.05$, ** $p<0.01$, *** $p<0.001$)

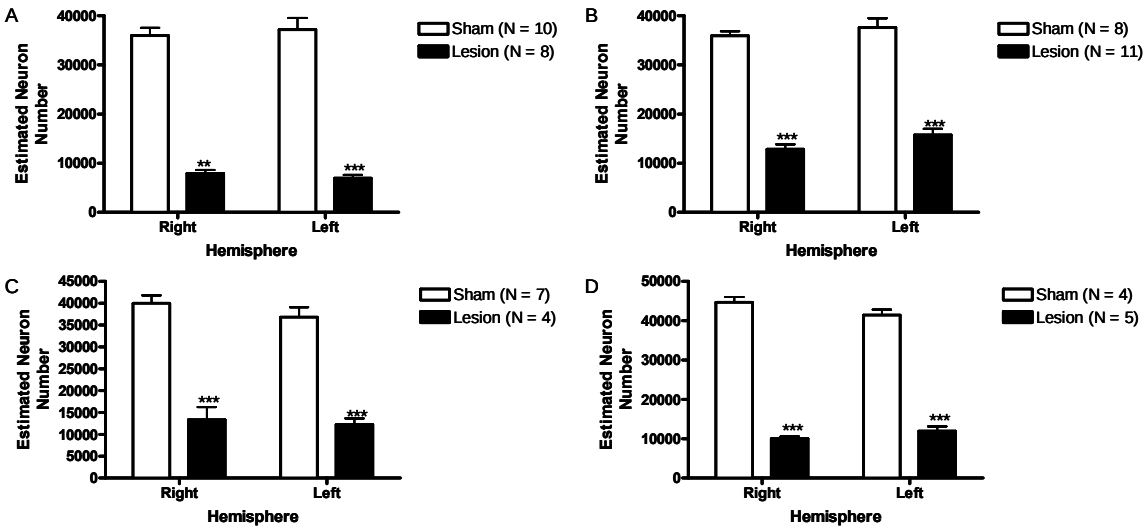

Figure 5. Mean estimated STN neuron numbers for sham controls and STN-lesioned animals used in Experiment 1 (A), Experiment 2 (B), Experiment 3 (C), and Experiment 4 (D). For all experiments, a Two-Way ANOVA (sham/lesion X hemisphere) revealed estimated STN neuron numbers in lesioned animals were significantly smaller compared to sham controls. There were no differences in estimated neuron numbers between hemisphere in either sham controls or lesioned animals. (Bonferroni post hoc test; *** $p<0.001$)

Experiment 1: Effects of STN lesions on NAcc electrophysiology during food-seeking behavior.

Operant Behavior

Using a between–subjects design, we assessed the effects of bilateral STN lesions on operant responding for sucrose and subsequent cue–induced and food–primed reinstatement. As shown in Table 1, there was no significant difference in responding for sucrose between sham and lesioned animals. After extinction training, cue–induced and food–primed reinstatement tests were conducted. These results are illustrated in Figure 6. There was no significant difference in responding between sham and lesioned animals in either reinstatement test. Note that cue–induced and food–reinstated responding in both groups was significantly higher than in the extinction sessions (Bonferroni post hoc test; $p<0.001$).

Table 1. Effects of STN lesions on food-reinforced responding

Treatment	Responding (responses/min)
Sham (n=10)	19.67 ± 3.02
Lesion (n=8)	23.84 ± 4.37

Data are mean ± SEM. Data for food-reinforced responding were from the food SA session before the extinction sessions. STN lesions did not significantly alter food-reinforced responding compared with control (Bonferroni post hoc test; $p>0.05$).

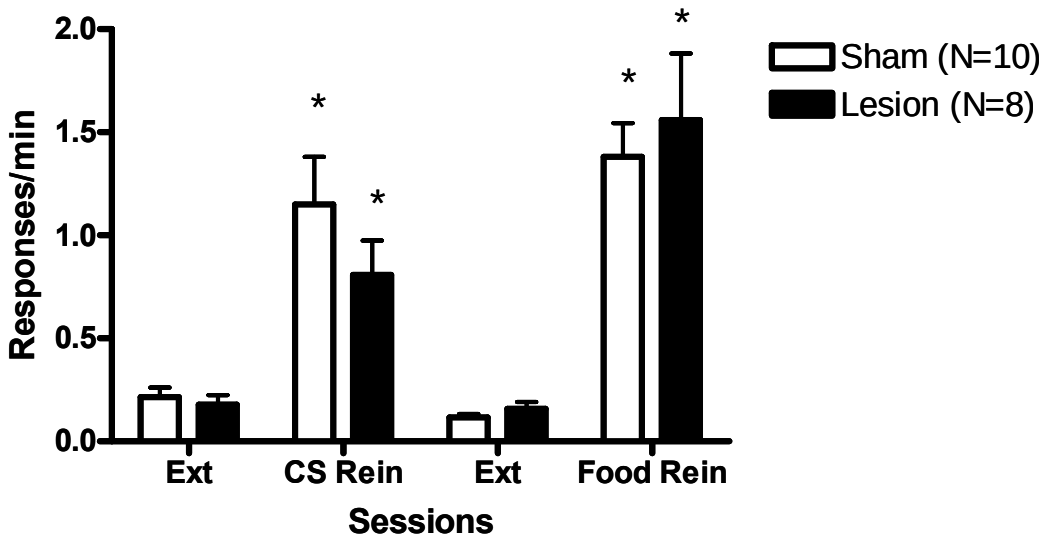

Figure 6. Effects of STN lesions on cue–induced and food–primed reinstatement. There was no significant difference between sham and lesioned animals on any session, but responding during cue–induced and food–primed reinstatement was significantly higher than during extinction in both groups (Bonferroni post hoc test; $p<0.001$).

Electrophysiology

Baseline

Microwire bundle placements for all the rats used for single-unit recording in this experiment are depicted in Figure 7. All of the microwire bundles were histologically verified to be in either the NAcc core or shell.

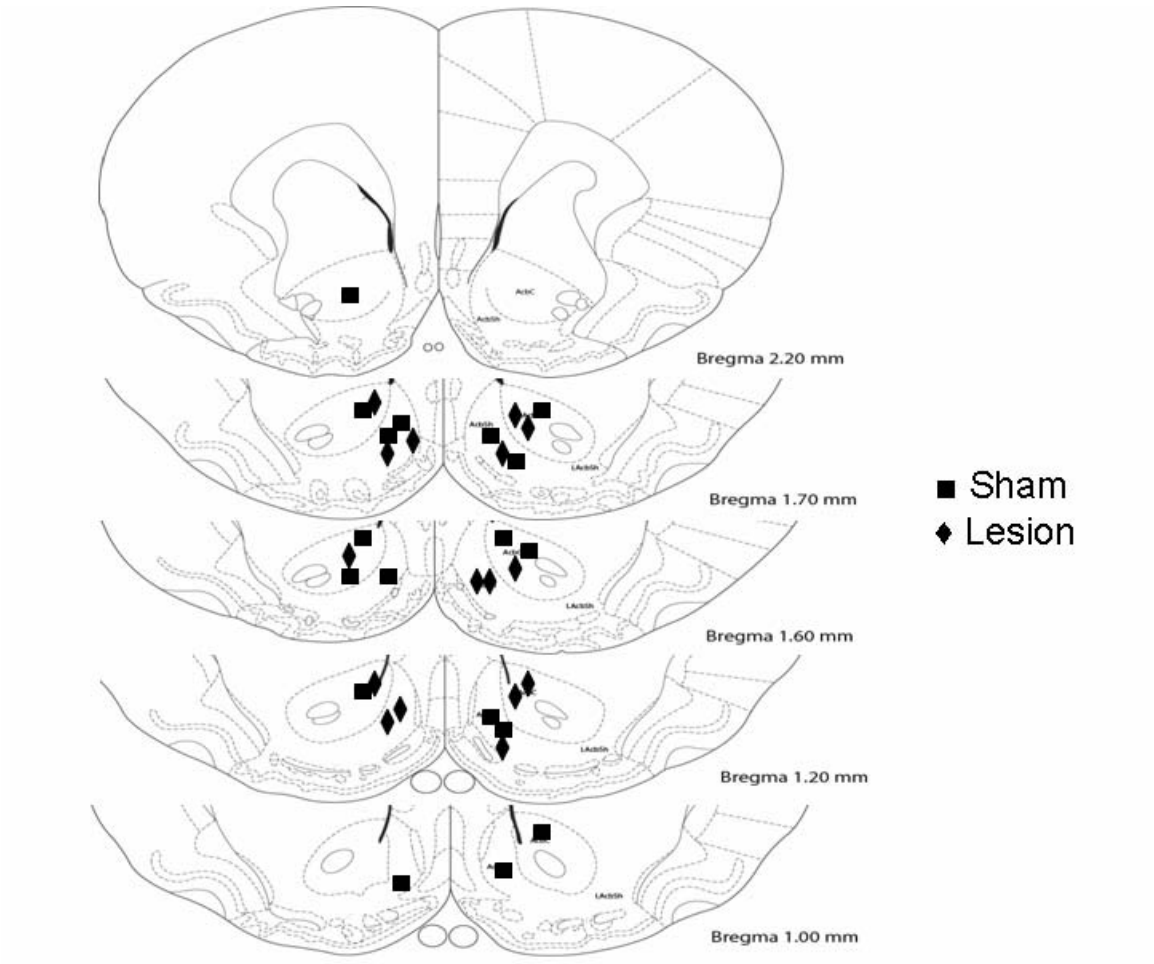

Figure 7. Anatomical location of microwire bundles in coronal sections of rat NAcc. Symbols represent the termination of microwire bundles for both groups. All bundles were located in either NAcc core or shell. Numbers indicate the distance anterior to bregma in mm.

A total of 192 core neurons and 405 shell neurons were recorded from 10 sham controls and a total of 249 core neurons and 386 shell neurons were recorded from 8 STN-lesioned animals. Table 2 contains mean baseline firing rates of core and shell neurons recorded in sham controls and STN-lesioned animals. A Two-Way ANOVA

(sham/lesion X NAcc subregion) revealed that shell neurons recorded from STN-lesioned animals exhibited significantly higher firing rates compared to core neurons recorded from STN-lesioned animals and core and shell neurons recorded from sham controls (Bonferroni post hoc test; $p<0.0001$). Action potential waveforms were typically biphasic with short durations (<2 ms) and amplitudes ranging from 300 to 500 µV. Signal-to-noise ratios were typically 3:1 to 5:1. Example core and shell waveforms are depicted in Figure 8.

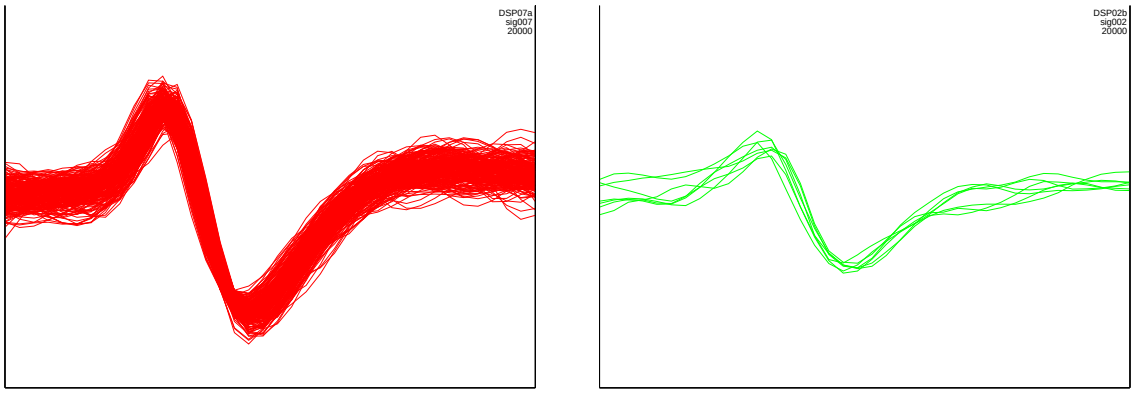

Figure 8. Examples of NAcc (core-left, shell-right) neuron waveforms from a sham animal. Length of each box is equivalent to 0.80ms. Height of each box is equivalent to 300 µV.

Table 2. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	192	405	249	386
Mean	2.72	3.36	3.58	5.16 *
SEM	0.16	0.18	0.20	0.31

Means are measured in spikes/s. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that shell neurons recorded from STN-lesioned animals exhibited significantly higher firing rates compared to the other neuron samples. (Bonferroni post hoc test; * $p<0.0001$)

Operant Responding for Food

From sham controls, a total of 127 core and 214 shell neurons were recorded during sessions 1 – 12. During sessions 1 – 12, core neurons had a mean baseline firing rate of 2.85 ± 0.19 spikes/s, while shell neurons had a mean baseline firing rate of 3.33 ± 0.25 spikes/s. A total of 148 core and 215 shell neurons were recorded from STN-lesioned animals during sessions 1 – 12. During sessions 1 -12, core neurons exhibited a mean baseline firing rate of 3.39 ± 0.27 spikes/s, while shell neurons had a mean baseline firing rate of 5.01 ± 0.48 spikes/s. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that shell neurons from STN-lesioned animals had significantly higher baseline firing rates than shell neurons from sham controls ($p<0.01$) and core

neurons from sham controls ($p<0.001$) and STN-lesioned ($p<0.01$) animals (Bonferroni post hoc test).

Neurons were divided into early (sessions 1 – 4), middle (sessions 5 – 8), and late (sessions 9 – 12) for further analysis. A phasically active neuron was defined as previously described or as illustrated in Figure 9. Briefly, an increase in firing rate immediately before the reinforced lever press was defined as an excitatory response (RESPe) neuron; while a decrease was defined as an inhibitory response (RESPi) neuron. An increase or decrease in firing rate immediately after the reinforced response was defined as an excitatory reinforcement (REINe) or inhibitory reinforcement (REINi) neuron, respectively. The results of this classification are shown in Table 3. In sham controls, 20 out of 34 (59%) core neurons recorded during the early sessions were classified as phasically active. Twenty-five out of 46 (54%) and 22 out of 47 (47%) core neurons were phasically active during the middle and late sessions, respectively. In STN-lesioned animals, 23 out of 47 (49%) core neurons recorded during the early sessions, 21 out of 52 (40%) recorded during the middle sessions, and 17 out of 49 (35%) recorded during the late sessions were classified as phasically active.

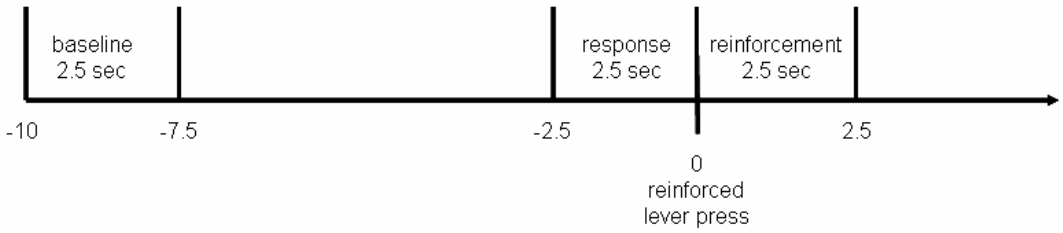

Figure 9. Timeline representing the 3 time epochs used to analyze electrophysiological data. Mean firing rates for each neuron were calculated for 3 time epochs, baseline, response, and reinforcement. Baseline was defined as the time period 10 – 7.5 sec before the initiation of the reinforced lever press. Response was defined as the time period 2.5 – 0 sec before and during the execution of the reinforced response. Reinforcement was defined as the time period 0 – 2.5 sec after the reinforced response. A neuron was classified as a RESPe neuron if it exhibited a >40% increase in firing rate during the response epoch compared to its respective baseline. If a neuron showed a >40% decrease in firing rate during the response epoch compared to its respective baseline, it was classified as a RESPi neuron. A <40% increase or decrease in firing rate during the reinforcement epoch compared to the respective baseline was classified as a REINe or REINi neuron, respectively.

Table 3. Percent of neuron type observed in the NAcc core of sham controls and STN-lesioned animals during operant responding for food.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
Sessions 1 - 4	26% (9/34)	18% (6/34)	12% (4/34)	24% (8/34)	4% (2/47)	26% (12/47)	17% (8/47)	21% (10/47)
Sessions 5 - 8	30% (14/36)	22% (10/36)	28% (10/36)	14% (5/36)	2% (1/52)	21% (11/52)	6% (3/52)	25% (13/52)
Sessions 9 - 12	23% (11/47)	15% (7/47)	23% (11/47)	4% (2/47)	4% (2/49)	22% (11/49)	14% (7/49)	2% (1/49)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As shown in Table 3, in sham controls, there was a similar distribution of RESPe (early = 9/34; middle = 14/36; late = 11/47) and RESPi (early = 6/34; middle = 10/36; late = 7/47) core neurons; while there was a much higher proportion of RESPi (early =

12/47; middle = 11/52; late = 11/49) core neurons compared to RESPe (early = 2/47; middle = 1/52; late = 2/49) core neurons in STN-lesioned animals. Composite PEHs of normalized firing of all RESPe and RESPi neurons from sham controls and STN-lesioned animals are illustrated in Figure 10, while individual examples are depicted in Figure 11. As shown in Figure 10 (panels A and B), the normalized firing during the response epoch of RESPe core neurons was significantly higher in sham controls compared to that of STN-lesioned animals (t-test; $p<0.0001$). Furthermore, the normalized firing rate during the response epoch of RESPi core neurons was significantly lower in STN-lesioned animals compared to sham controls (t-test; $p<0.001$) (Figure 10; panels C and D).

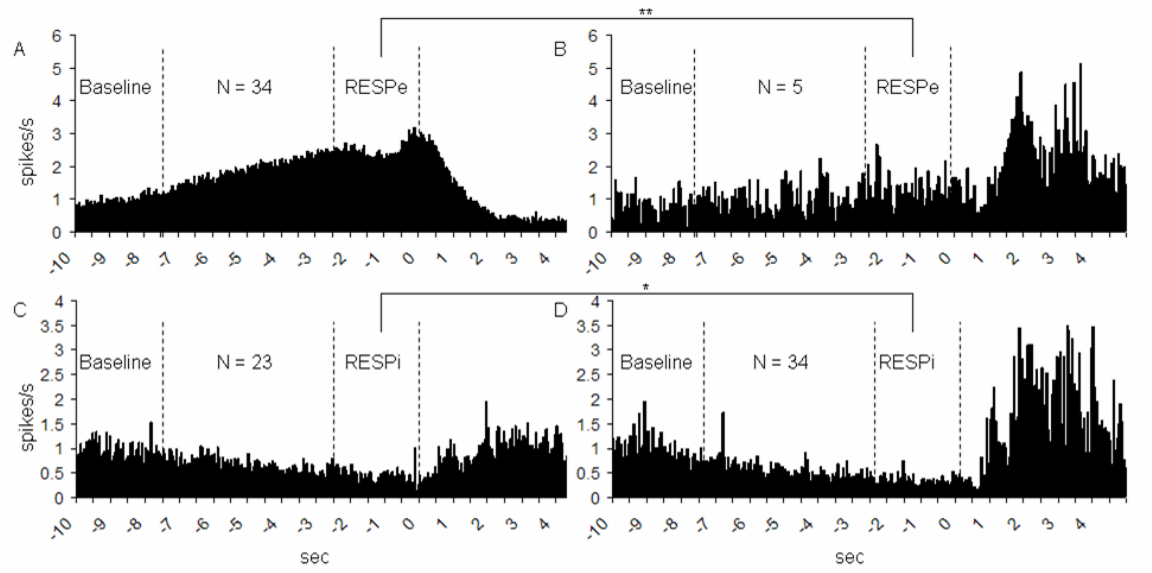

Figure 10. Composite PEHs of normalized firing of all RESPe neurons from the NAcc core of sham controls (A) and STN-lesioned (B) animals and RESPi neurons from the NAcc core of sham controls (C) and STN-lesioned (D) animals. Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing during the response epoch of RESPe core neurons was significantly higher in sham controls (A) compared to that of STN-lesioned animals (B). Furthermore, the normalized firing rate during the response epoch of RESPi core neurons was significantly lower in STN-lesioned animals (D) compared to sham controls (C). ** t-test $p<0.001$; * t-test $p<0.0001$

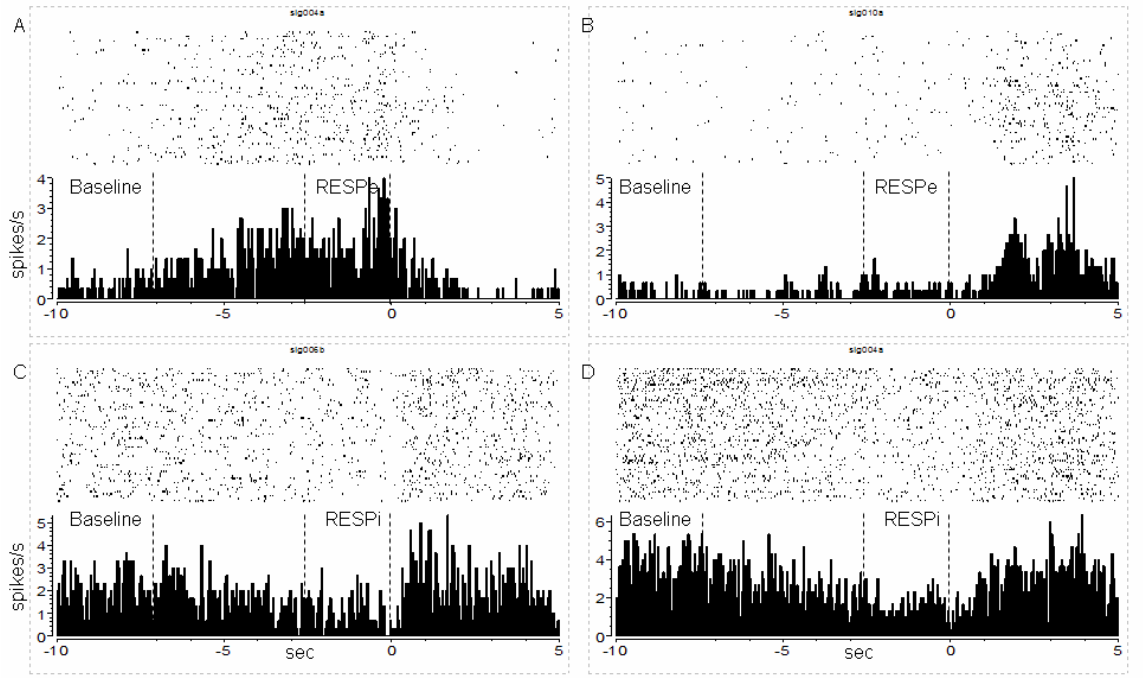

Figure 11. Example PEH of a RESPe core neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a RESPi core neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

The proportion of REINe and REINi core neurons observed in sham controls and STN-lesioned animals is shown in Table 3. In sham controls, the proportion of REINe core neurons recorded during the late sessions (11/47) was nearly twice that of those recorded during the early sessions (4/34). The proportion of REINi core neurons, however, dramatically declined from the early (8/34) to the late (2/47) sessions. In STN-lesioned animals, the proportion of REINe core neurons recorded during the early sessions (8/47) was similar to the proportion recorded during the late sessions (7/49). Similar to what was observed in sham controls, the proportion of REINi core neurons dramatically declined from the early (10/47) to the late (1/49) sessions. Interestingly, we observed a significantly higher proportion of excitatory core neurons (RESPe and REINe) in sham controls (71/117) compared to in STN-lesioned animals (23/148) (Chi

Square; p<0.001). Composite PEHS of normalized firing of all REINe and REINi neurons from sham controls and STN-lesioned animals are shown in Figure 12. Individual examples are illustrated in Figure 13. As shown in Figure 12 (panel A and B), the normalized firing during the reinforcement epoch of REINe core neurons was significantly higher in STN-lesioned animals compared to sham controls (t-test; p<0.001). Moreover, the normalized firing rate during the reinforcement epoch of REINi core neurons was significantly lower in STN-lesioned animals compared to sham controls (t-test; p<0.05) (Figure 12, panels C and D).

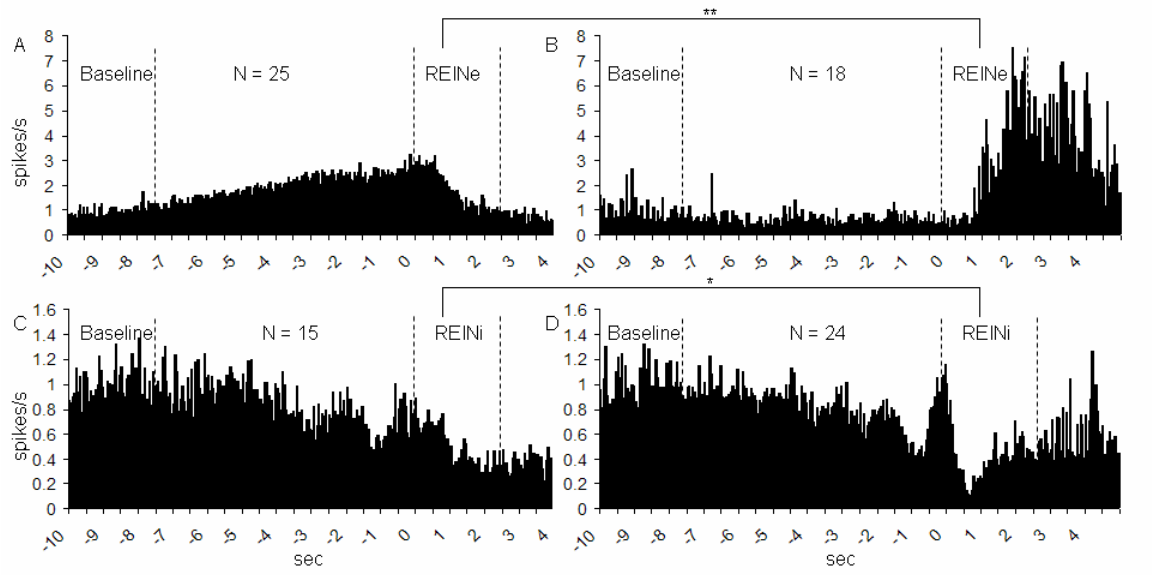

Figure 12. Composite PEHs of normalized firing of all REINe neurons from the NAcc core of sham controls (A) and STN-lesioned (B) animals and REINi neurons from the NAcc core of sham controls (C) and STN-lesioned (D) animals. Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing during the response epoch of REINe core neurons was significantly higher in STN-lesioned animals (B) compared to that of sham controls (A). Furthermore, the normalized firing rate during the response epoch of REINi core neurons was significantly lower in STN-lesioned animals (D) compared to sham controls (C). ** t-test p<0.001; * t-test p<0.05

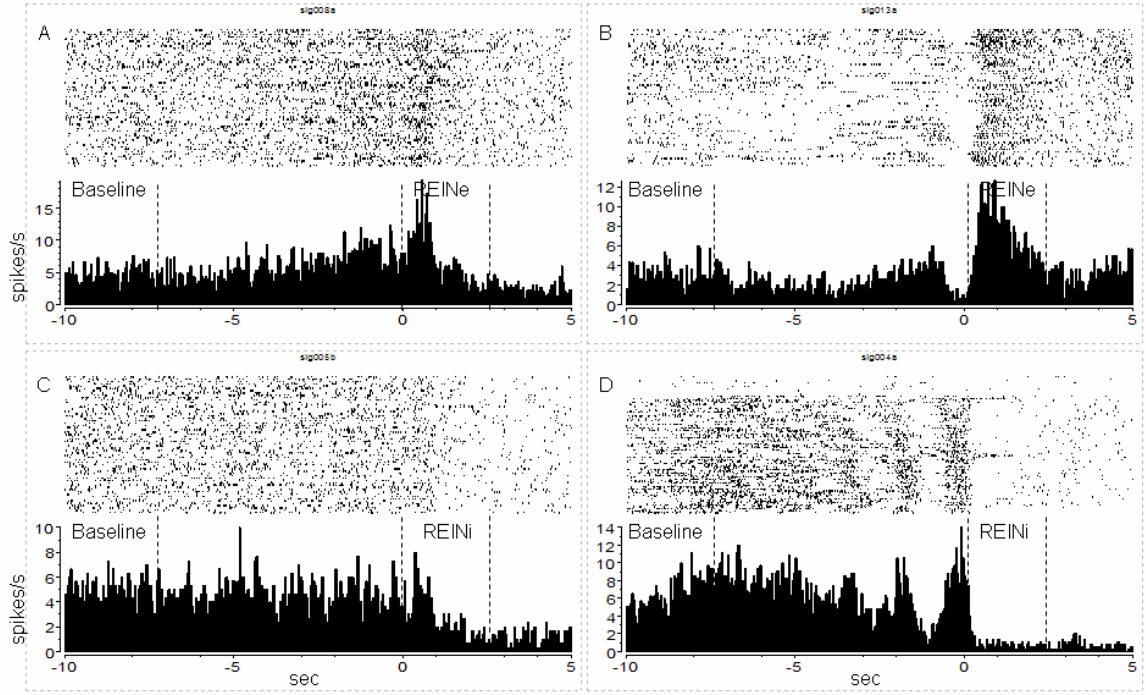

Figure 13. Example PEH of a REINe core neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a REINi core neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

In both groups of animals, there were a number of core neurons that exhibited a response in both epochs. This was the case for 30 out of the 127 neurons (24%) recorded in sham controls and 22 out of 214 (10%) in STN-lesioned animals. Furthermore, the type of response (excitation or inhibition) was the same in both epochs across groups and neuron type except for a subpopulation of 8 RESPi neurons in STN-lesioned animals. Some examples of these neurons are shown in Figure 14.

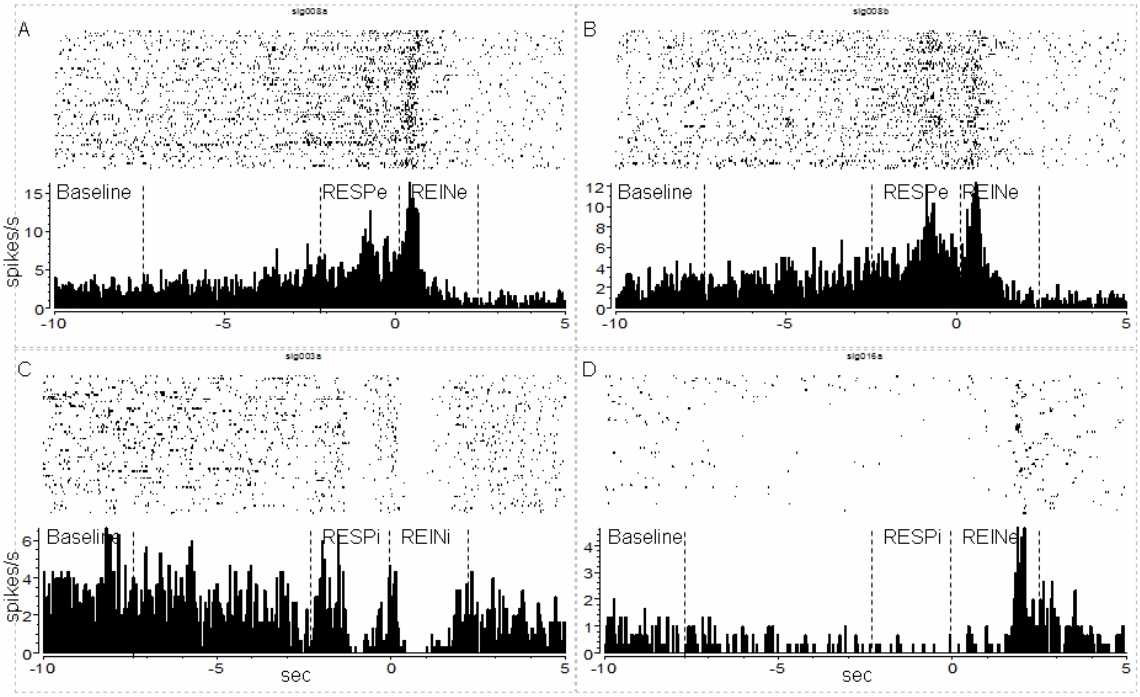

Figure 14. Example PEHs of core neurons exhibiting a response in both epochs. Neuron from a sham-lesioned animal responding with a excitation in both the response and reinforcement epoch (A and B). Neuron from a STN-lesioned animal responding with an inhibition in both epochs (C). Neuron from a STN-lesioned animal responding with an inhibition during the response epoch and an excitation during the reinforcement epoch (D). Each raster display shows the activity of the neuron across all trials of the session.

To address the issue of whether phasic activation was related to the CS or the motor act of pressing the lever, the CS was omitted on a random 25% of the trials in session 13 for a sample of the animals. A change in phasic activation on these trials would rule out a role for lever pressing. Omitting the CS altered the phasic activation of 38% (5/13) of core neurons in sham controls and 21% (3/14) in STN-lesioned animals. To assess the possibility that the sucrose reward was responsible for the phasic activation of core neurons, the sucrose reward was omitted on a random 25% of the trials in session 13 for another sample of the animals. A change in phasic activation on these trials would

rule out a role for sucrose reward and consumption. Omitting the sucrose reward altered the phasic activation of 38% (3/8) and 57% (4/7) of core neurons in sham controls and STN-lesioned animals, respectively. The effect of CS or sucrose reward omission is illustrated in Figure 15.

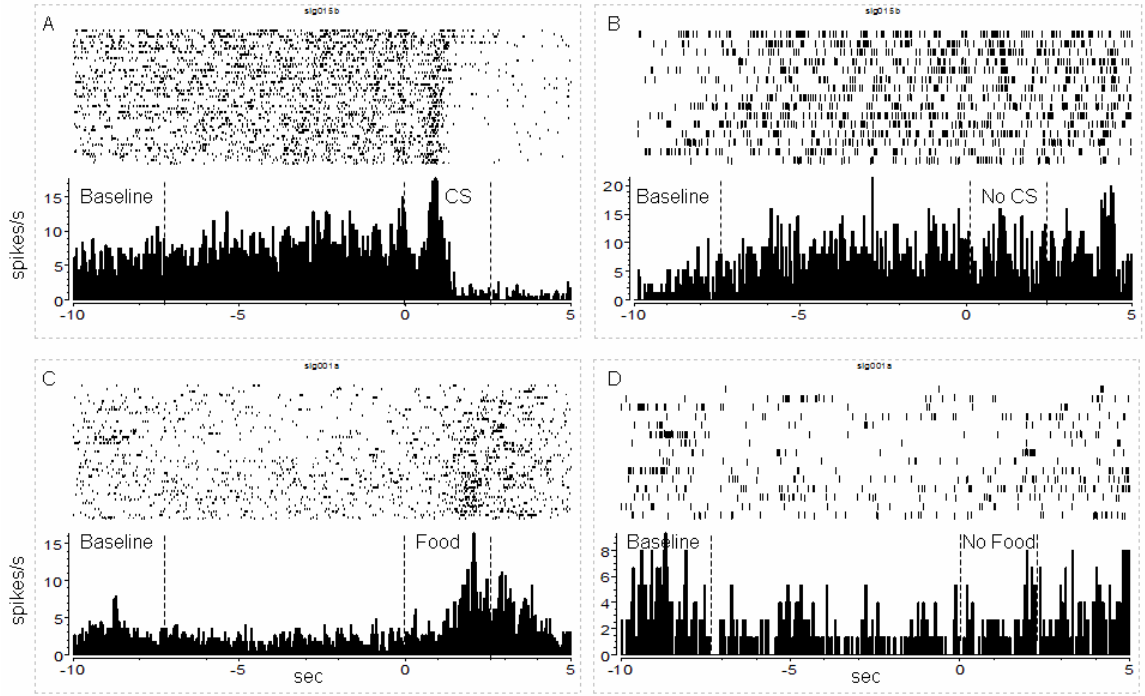

Figure 15. Example PEH of a core neuron from a STN-lesioned animal recorded during operant responding for food when the CS was present (A) and when the CS was omitted on a random 25% of the trials (B). Example PEH of a core neuron from a sham control recorded during operant responding for sucrose when sucrose was present (C) and when sucrose was omitted on a random 25% of the trials (D). For each neuron, note the difference in phasic activation when the CS or sucrose is present (A and C) compared to when the CS or sucrose is omitted (B and D). Each raster display shows the activity of the neuron across all trials of the session.

In sham controls, 21 out of 59 (36%) shell neurons recorded during the early sessions were classified as phasically active. Twenty-three out of 72 (32%) and 23 out of 83 (28%) shell neurons were phasically active during the middle and late sessions, respectively. In STN-lesioned animals, 22 out of 68 (32%) shell neurons recorded during the early sessions, 28 out of 73 (38%) recorded during the middle sessions, and 36 out of

74 (49%) recorded during the late sessions were classified as phasically active. The results of further classification are shown in Table 4. In both sham controls and STN-lesioned animals, we observed a significantly greater proportion of phasically active neurons in the core than in the shell (Chi Square; $p<0.001$).

Table 4. Percent of neuron type observed in the NAcc shell of sham controls and STN-lesioned animals during operant responding for food.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
Sessions 1 - 4	14% (8/59)	14% (8/59)	19% (11/59)	8% (5/59)	7% (5/68)	9% (6/68)	24% (16/68)	6% (4/68)
Sessions 5 - 8	4% (3/72)	17% (12/72)	13% (9/72)	4% (3/72)	12% (9/73)	7% (5/73)	19% (14/73)	9% (5/73)
Sessions 9 - 12	10% (8/83)	6% (5/83)	14% (12/83)	6% (5/83)	18% (13/74)	15% 11/74)	8% (6/74)	23% (17/74)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As Table 4 illustrates, in sham controls, there was a similar distribution of RESPe (early = 8/59; middle = 3/72; late = 8/83) and RESPi (early = 8/59; middle = 12/72; late = 5/83) shell neurons. This was also the case for RESPe (early = 5/68; middle = 9/73; late = 13/74) and RESPi (early = 6/68; middle = 5/73; late = 11/74) shell neuron recorded from STN-lesioned animals. There was no difference in the normalized firing during the response epoch of RESPe or RESPi shell neurons in sham controls versus STN-lesioned animals (data not shown). Individual examples are shown in Figure 16.

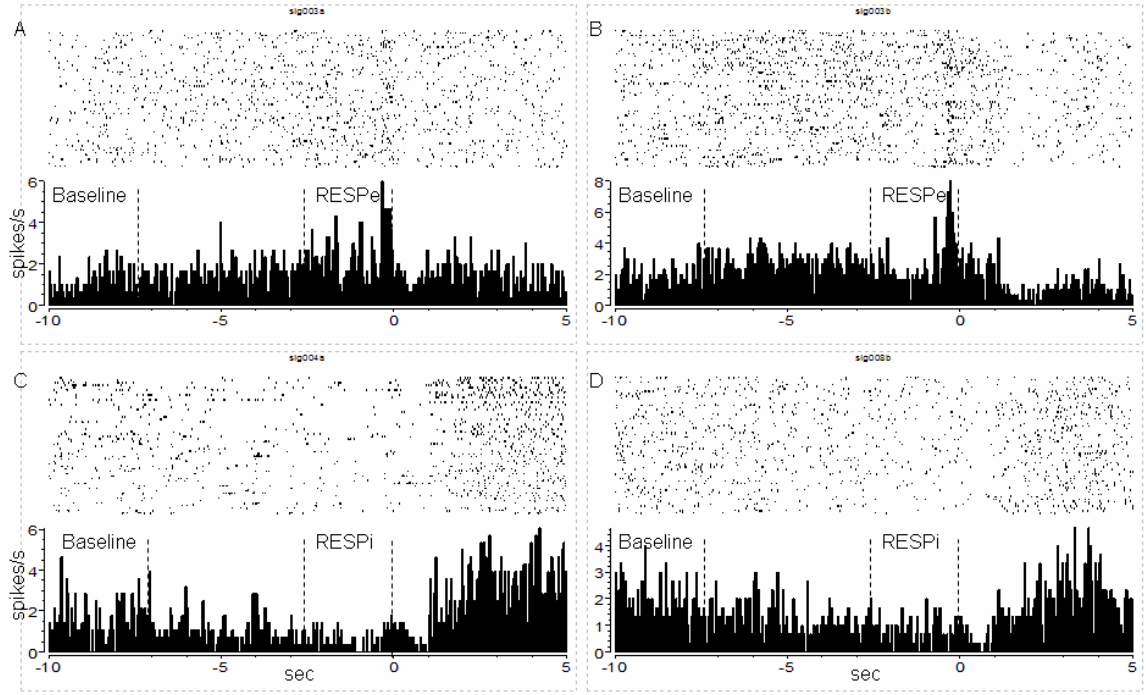

Figure 16. Example PEH of a RESPe shell neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a RESPi shell neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

The proportion of REINe and REINi shell neurons observed in sham controls and STN-lesioned animals is shown in Table 4. In sham controls, there was a similar distribution of REINe (early = 11/59; middle = 9/72; late = 12/83) and REINi (early = 5/59; middle = 3/72; late = 5/83) shell neurons across session groups. In STN-lesioned animals, the distribution of REINe shell neurons was greater than the distribution of REINi neurons in the early (REINe = 16/68; REINi = 4/68) and middle sessions (REINe = 14/73; REINi = 5/73). In the late sessions, the distribution of REINi shell neurons (17/74) was greater than the distribution of REINe neurons (6/74). Composite PEHs of

normalized firing of all REINi shell neurons from sham controls and STN-lesioned animals are illustrated in Figure 17. As shown in Figure 17, the normalized firing during the reinforcement epoch of REINi shell neurons was significantly lower in sham controls compared to STN-lesioned animals (t-test; $p<0.0001$). There was no difference in the normalized firing during the reinforcement epoch of REINe shell neurons between sham controls and STN-lesioned animals (data not shown). Figure 18 contains representative examples.

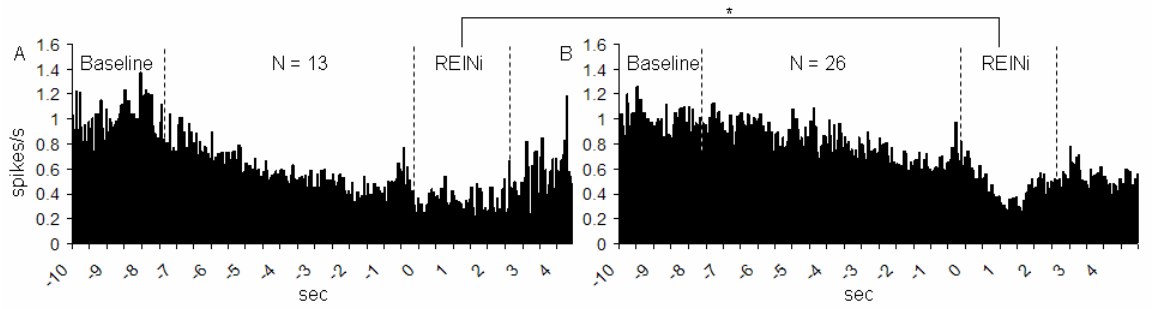

Figure 17. Composite PEHs of normalized firing of all REINi neurons from the NAcc shell of sham control (A) and STN-lesioned (B) animals. Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing rate during the reinforcement epoch of REINi shell neurons was significantly lower in sham controls (A) compared to STN-lesioned (B) animals. *t-test; $p<0.0001$

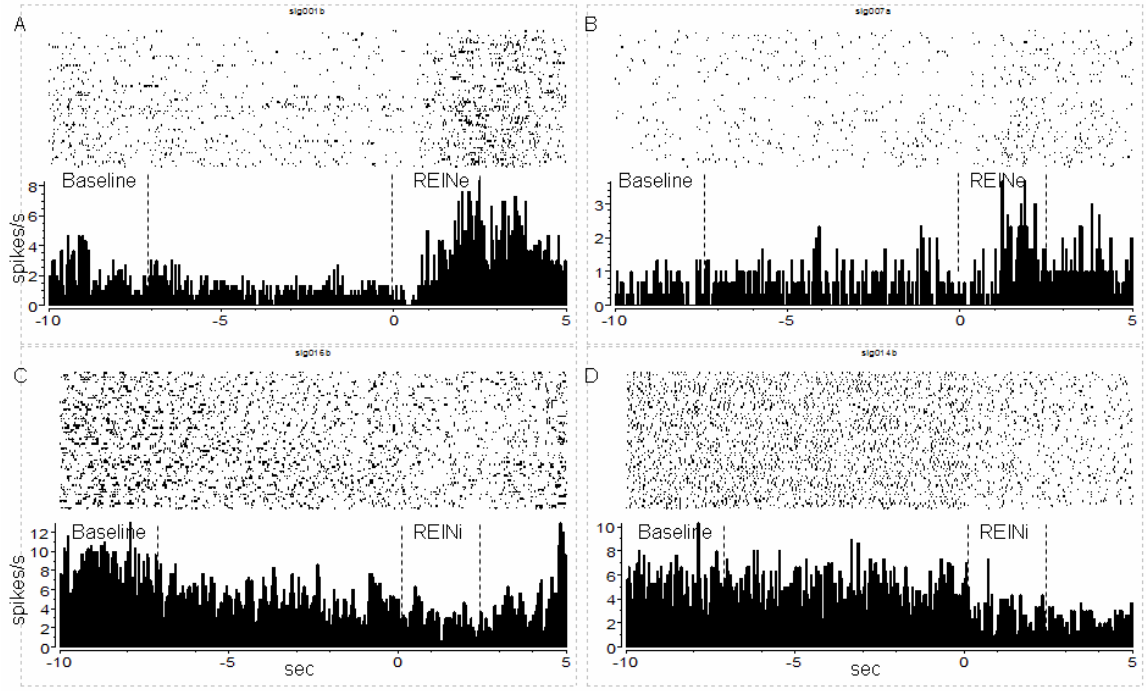

Figure 18. Example PEH of a REINe shell neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a REINi shell neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

In both groups of animals, there were a number of shell neurons that exhibited a response in both epochs. In sham controls, 24 out of 214 neurons (11%) were responsive in both epochs; while in STN-lesioned animals, 24 out of 215 neurons (11%) were responsive in both epochs. The type of response (excitation or inhibition) was the same in both epochs across group and neuron type. Examples of some of these neurons are illustrated in Figure 19.

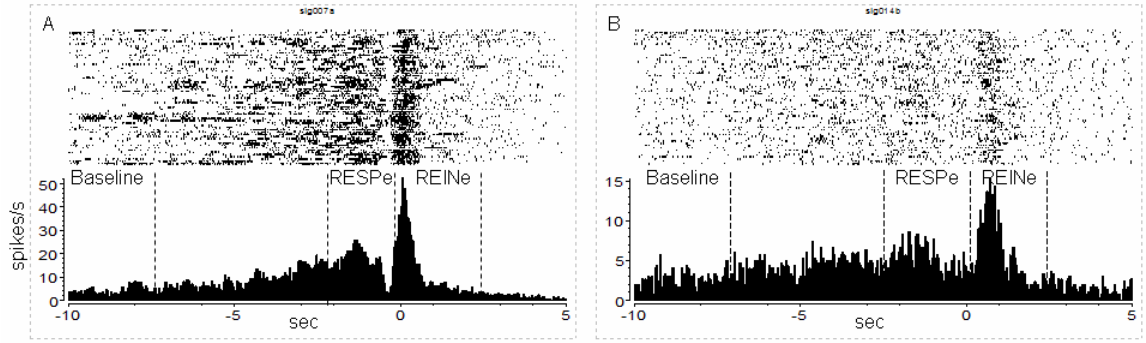

Figure 19. Example PEHs of shell neurons showing a response in both epochs. Neuron from a sham control (A) and STN-lesioned (B) animal responding with an excitation in both the response and reinforcement epoch. Each raster display shows the activity of the neuron across all trials of the session.

The CS was omitted on a random 25% of the trials in session 13 for a sample of the animals in order to address the issue of whether phasic activation was related to the CS or the motor act of pressing the lever. A change in phasic activation on these trials would rule out a role for lever pressing. Omitting the CS altered the phasic activation of 14% (3/22) of shell neurons in sham controls and 35% (6/17) in STN-lesioned animals. The sucrose reward was omitted on a random 25% of the trials in session 13 for another sample of animals in order to assess the possibility that the sucrose reward was responsible for the phasic activation of shell neurons. A change in phasic activation on these trials would rule out a role for sucrose reward and consumption. Omitting the sucrose reward changed the phasic activation of 47% (8/17) and 53% (9/17) of shell neurons in sham controls and STN-lesioned animals, respectively. The effect of CS or sucrose reward omission on shell neurons is illustrated in Figure 20.

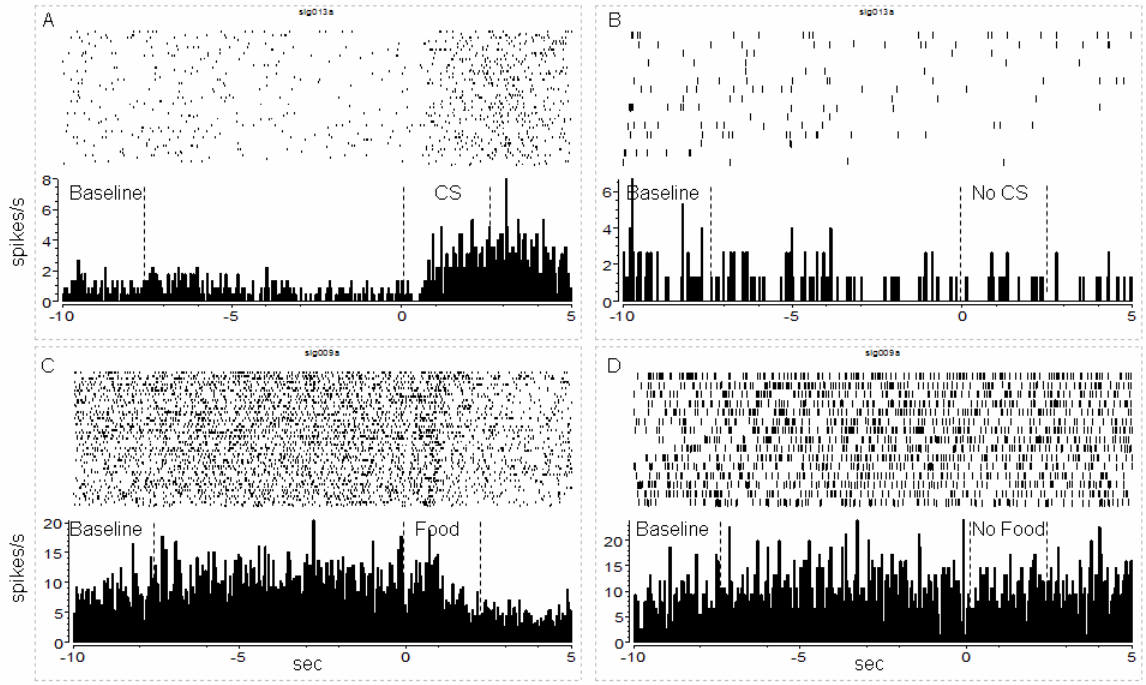

Figure 20. Example PEH of a shell neuron from a sham control animal recorded during operant responding for food when the CS was present (A) and when the CS was omitted on a random 25% of the trials (B). Example PEH of a shell neuron from a STN-lesioned animal recorded during operant responding for sucrose when sucrose was present (C) and when sucrose was omitted on a random 25% of the trials (D). For each neuron, note the difference in phasic activation when the CS or sucrose is present (A and C) compared to when the CS or sucrose is omitted (B and D). Each raster display shows the activity of the neuron across all trials of the session.

Operant Responding for Food – Summary

In sham controls, there were a significantly higher proportion of phasically active neurons in the core compared to in the shell. The same result was observed in STN-lesioned animals; therefore, STN lesions had no effect on the distribution of responses in core and shell. STN lesions, however, did affect normalized firing rate, or magnitude. Magnitudes were significantly higher in sham controls in response to the operant behavior; but, magnitudes were greater in STN-lesioned animals in response to sucrose reward. Thus, STN lesions differentially affect neuronal activity associated with obtaining sucrose and sucrose consumption.

Extinction

From sham controls, a total of 26 core and 86 shell neurons were recorded; while a total of 51 core and 83 shell neurons were recorded from STN-lesioned animals during extinction. Table 5 contains the mean baseline firing rate of core and shell neurons recorded during extinction. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that shell neurons from STN-lesioned animals exhibited higher baseline firing rates than shell neurons from sham controls (Bonferroni post hoc test; $p<0.05$).

Table 5. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	26	86	51	83
Mean	2.86	3.37	4.01	4.97 *
SEM	0.52	0.42	0.50	0.40

Means are measured in spikes/s. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that shell neurons recorded from STN-lesioned animals exhibited significantly higher firing rates compared to shell neurons from sham controls. (Bonferroni post hoc test; * $p<0.05$)

In sham controls, 42% (11/26) of core and 41% (35/86) of shell neurons were classified as phasically active in response to the lever press. Of the 11 core neurons, 10 exhibited excitations and one exhibited an inhibition. Of the 35 shell neurons, 16 exhibited excitations and 19 exhibited inhibitions. In STN-lesioned animals, 20% (10/51) of core and 27% (22/83) of shell neurons were classified as phasically active in response to the lever press. Of the 10 core neurons, 5 responded with excitations and 5

responded with inhibitions. Of the 22 shell neurons, 16 responded with excitations and 6 responded with inhibitions. Therefore, there were a higher proportion of phasically active neurons in both the core and shell of sham controls compared to in STN-lesioned animals.

Cue–induced Reinstatement

A total of 9 core and 30 shell neurons were recorded in sham controls, while a total of 17 core and 30 shell neurons were recorded in STN-lesioned animals during CS-induced reinstatement. Mean baseline firing rates of core and shell neurons recorded during CS-induced reinstatement are shown in Table 6. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no significant differences in mean baseline firing rate between NAcc subregion and group.

Table 6. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals recorded during CS-induced reinstatement.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	9	30	17	30
Mean	1.98	4.01	3.59	4.69
SEM	0.83	0.73	0.75	0.52

Means are measured in spikes/s.

In sham controls, 67% (6/9) of core and 30% (9/30) of shell neurons were classified as phasically active in response to the CS. Of the 6 phasically active core neurons, 3 responded with an excitation and 3 with an inhibition. Of the 9 shell neurons, 4 responded with an excitation and 5 with an inhibition. In STN-lesioned animals, 47% (8/17) of core and 30% (9/30) of shell neurons were classified as phasically active in response to the CS. A Chi Square analysis revealed a significantly greater proportion of phasically active core neurons in sham controls than in STN-lesioned animals ($p<0.05$). In the core, 6 of the phasically active neurons responded with an excitation and 2 responded with an inhibition. Of the 9 shell neurons, 7 responded with an excitation and 2 with an inhibition. There was no difference in the normalized firing during the response epoch of phasically active core or shell neurons between sham controls and STN-lesioned animals (data not shown). Examples of these neurons are shown in Figure 21.

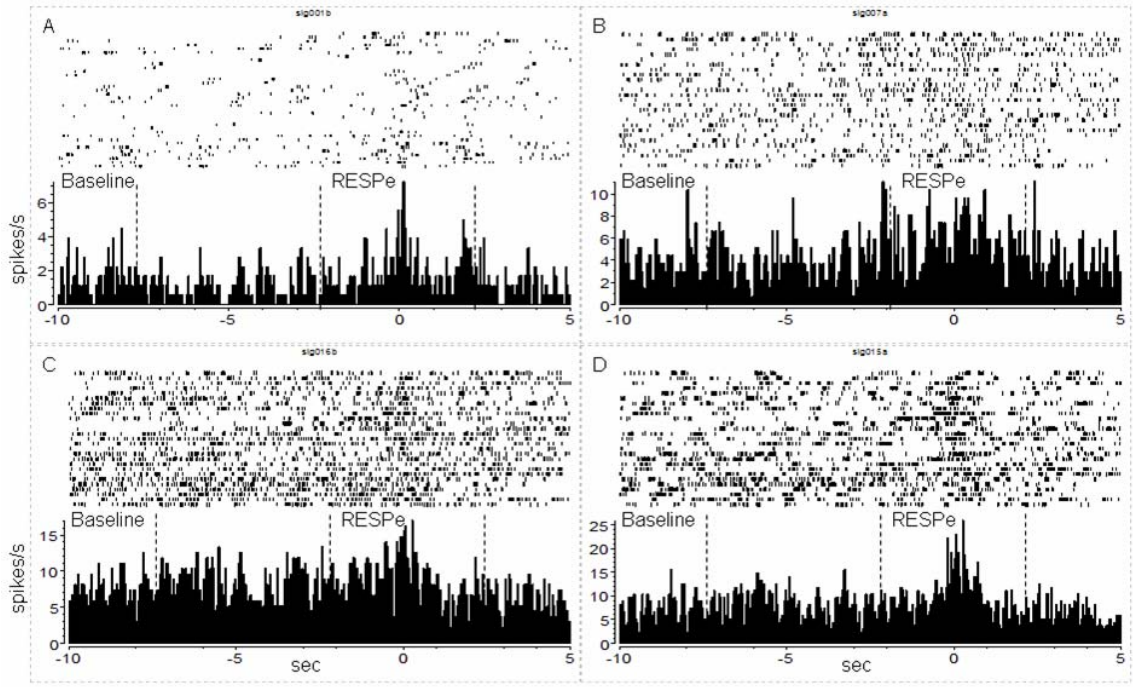

Figure 21. Example PEH of a RESPe core neuron recorded from a sham control (A) and a STN-lesioned (B) animal during CS-induced reinstatement. Example PEH of a RESPe shell neuron recorded from a sham control (C) and a STN-lesioned (D) animal during CS-induced reinstatement. The 0 point on the x-axis refers to the onset of the CS. Each raster display shows the activity of the neuron across all trials of the session.

Food-primed Reinstatement

A total of 9 core and 36 shell neurons were recorded in sham controls; while, from STN-lesioned animals, a total of 12 core and 24 shell neurons were recorded during food-primed reinstatement. Table 7 shows the mean baseline firing rates of core and shell neurons recorded during food-primed reinstatement. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that shell neurons from STN-lesioned animals exhibited a significantly higher baseline firing rate compared to core ($p<0.05$) and shell ($p<0.01$) neurons recorded from sham controls (Bonferroni post hoc test).

Table 7. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals recorded during food-primed reinstatement.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	9	36	12	24
Mean	2.23	3.98	4.31	8.41
SEM	0.44	0.72	0.61	1.46

Means are measured in spikes/s. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that shell neurons from STN-lesioned animals exhibited a significantly higher baseline firing rate compared to core (* $p<0.05$) and shell (* $p<0.01$) neurons recorded from sham controls. (Bonferroni post hoc test)

We observed no phasically active core neurons in either group during food primed reinstatement. Nineteen percent (7/36) of shell neurons in sham controls and 13% (3/24) of shell neurons in STN-lesioned animals were classified as phasically active in response to the lever press. There was a significantly higher proportion of phasically active shell neurons in sham controls compared to in STN-lesioned animals (Chi Square; $p<0.001$). All of the phasically active shell neurons in both groups responded with an excitation. Furthermore, as illustrated in Figure 22, the normalized firing rate during the response epoch was significantly higher in sham controls compared to STN-lesioned animals (t-test; $p<0.01$). Figure 23 contains individual examples of phasically active shell neurons.

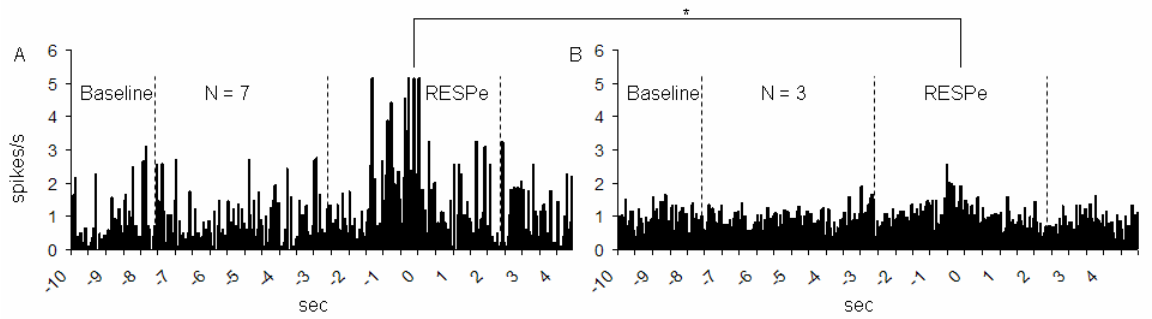

Figure 22. Composite PEHs of normalized firing of all RESPe neurons from the shell of sham controls (A) and STN-lesioned (B) animals. Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing rate during the response epoch of RESPe shell neurons from sham controls (A) was significantly higher compared to STN-lesioned animals (B). *t-test; $p<0.01$

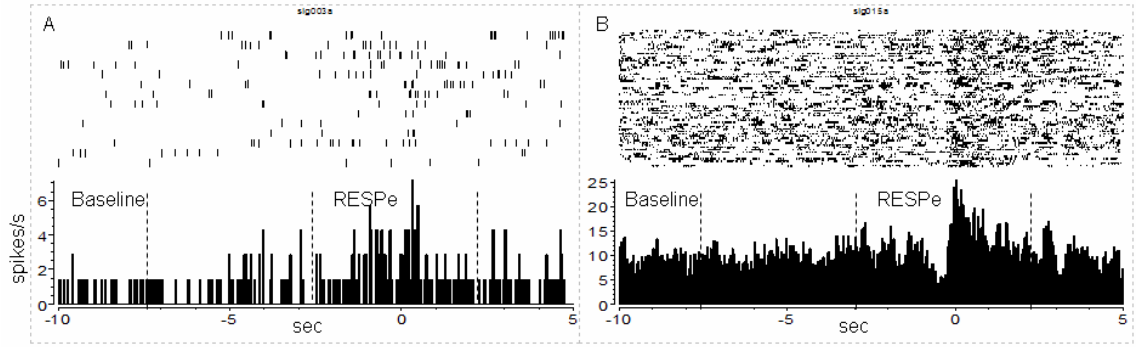

Figure 23. Example PEH of a RESPe shell neuron recorded from a sham control (A) and a STN-lesioned (B) animal during food-primed reinstatement. The 0 point on the x-axis refers to the lever press. Each raster display shows the activity of the neuron across all trials of the session.

Experiment 1 – Electrophysiology Summary

When rats were operant responding for sucrose, we observed a significantly greater proportion of phasically active neurons in the core compared to in the shell in both groups of animals. Furthermore, in addition to differences in response magnitudes in core neurons between groups, there was a significantly higher proportion of excitatory core neurons in sham controls compared to in STN-lesioned animals. Similarly, during

cue-induced reinstatement, we observed a significantly higher proportion of phasically active core neurons in sham controls compared to in STN-lesioned animals. During food-primed reinstatement, we observed a significantly higher proportion of phasically active shell neurons in sham controls compared to in STN-lesioned animals. Moreover, the response magnitude of shell neurons was significantly higher in sham controls.

Experiment 2: Effects of STN lesions on NAcc electrophysiology during cocaine-seeking behavior.

Operant Behavior

Using a between-subject design, we assessed the effects of bilateral STN lesions on operant responding for cocaine and subsequent cue-induced and cocaine-primed reinstatement. As shown in Table 8, there was no significant difference in responding between sham and lesioned animals during cocaine SA. Following extinction training, cue-induced and cocaine-primed reinstatement tests were conducted. These results are illustrated in Figure 24. Bilateral STN-lesions blocked cue-induced reinstatement (Bonferroni post hoc test; $p<0.001$), but had no effect on cocaine-primed reinstatement. Cue-induced responding in the sham-lesioned group and cocaine-reinstated responding in both groups was significantly higher than in the extinction sessions (Bonferroni post hoc test; $p<0.001$). In order to rule out the possibility of a motor effect of cocaine on the performance of the animals, locomotion was scored for a 5 min period occurring approximately 15 min following i.p. injection of cocaine in the cocaine-primed reinstatement test. There was no difference in time spent locomoting between sham (20.83 ± 3.73 sec) versus STN-lesioned (24.29 ± 6.29 sec) animals.

Table 8. Effects of STN lesions on cocaine SA

Treatment	Responding (responses/30 min)
Sham (n=8)	21.63 ± 1.94
Lesion (n=11)	24.84 ± 5.39

Data are mean ± SEM. Data for cocaine SA were from the cocaine SA session before the extinction sessions. STN lesions did not significantly alter cocaine SA compared with control (Bonferroni post hoc test; p>0.05).

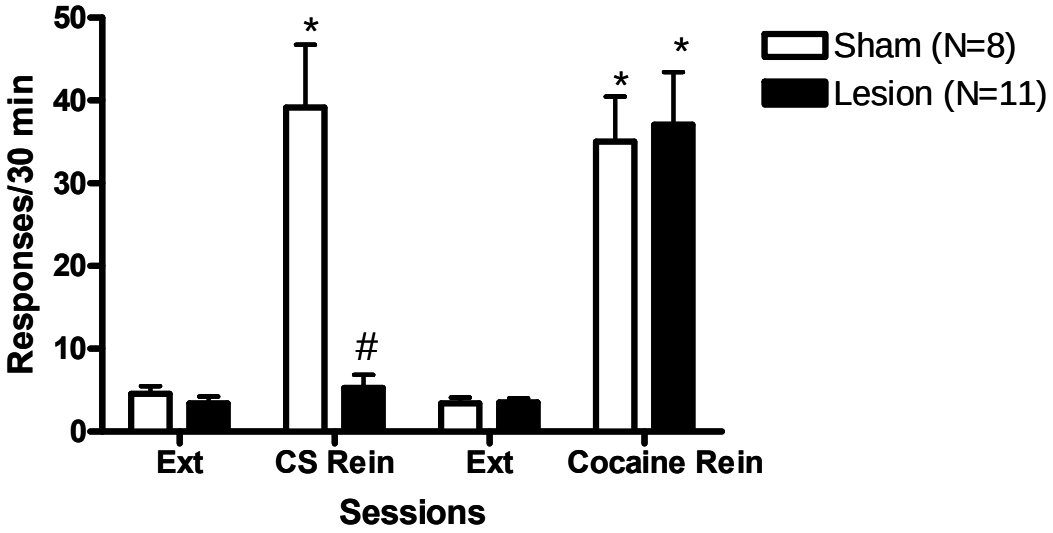

Figure 24. Effects of STN lesions on cue-induced and cocaine-primed reinstatement. STN lesions blocked cue-induced reinstatement, but had no effect on cocaine-primed reinstatement. (# Bonferroni post hoc test; p<0.001). Cue-induced reinstatement in the sham group and cocaine-reinstated responding in both groups was significantly higher than during extinction (* Bonferroni post hoc test; p<0.001).

Electrophysiology

Baseline

A schematic of microwire bundle placements for all of the rats used for single-unit recording in this experiment is shown in Figure 25. All of the microwire bundles were histologically verified to be in either the NAcc core or shell.

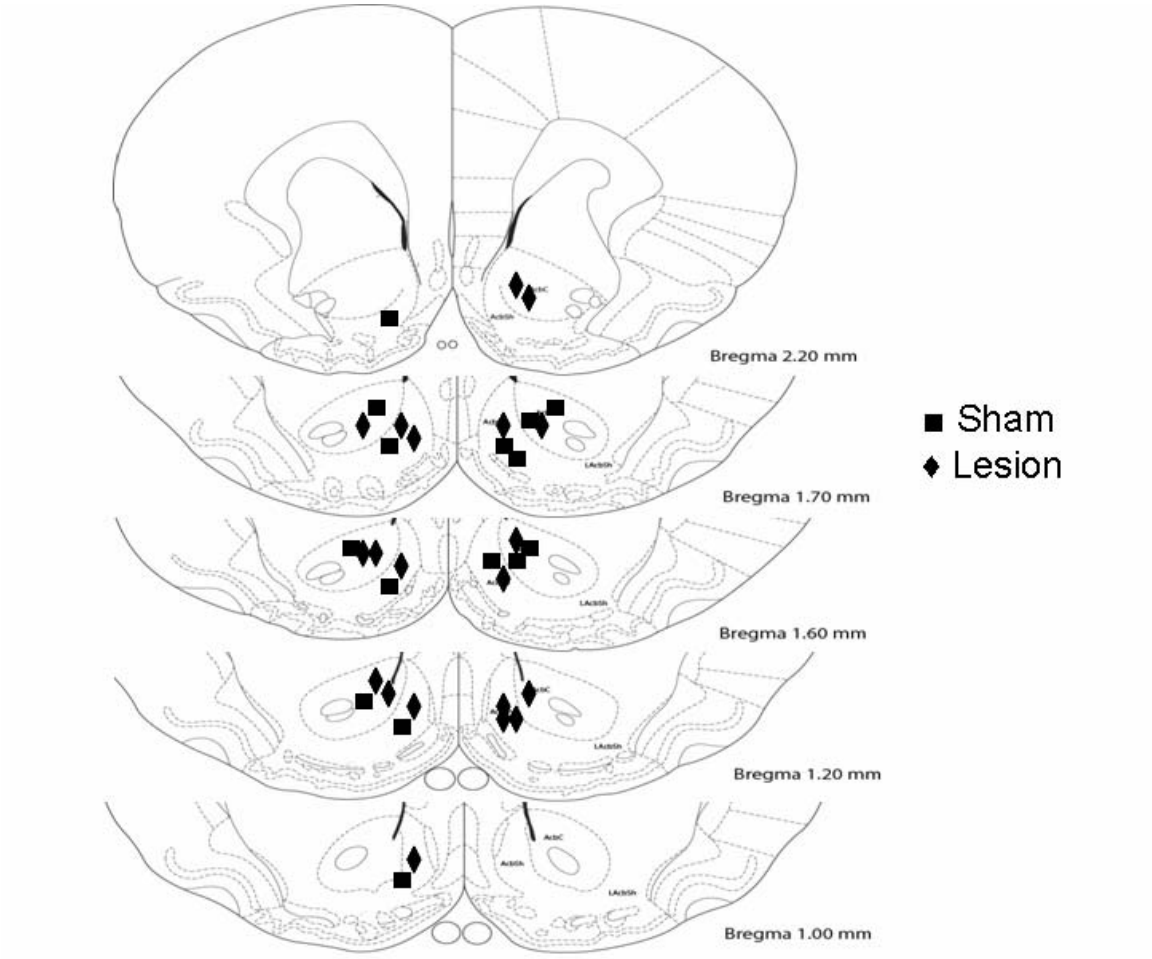

Figure 25. Anatomical location of microwire bundles in coronal sections of rat NAcc. Symbols represent the termination of microwire bundles for both groups. All bundles were located in either NAcc core or shell. Numbers indicate the distance anterior to bregma in mm.

A total of 265 core neurons and 346 shell neurons were recorded from 8 sham controls and a total of 240 core neurons and 231 shell neurons were recorded from 11 STN-lesioned animals. Table 9 contains mean baseline firing rates for all the neurons recorded in Experiment 2. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no differences in mean baseline firing rate.

Table 9. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals in Experiment 2.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	265	346	240	231
Mean	2.74	2.67	2.13	2.75
SEM	0.21	0.19	0.15	0.21

Means are measured in spikes/s.

Cocaine SA

During cocaine SA sessions 1 – 12, a total of 132 core and 209 shell neurons were recorded from sham controls. During these sessions, core neurons had a mean baseline firing rate of 3.18 ± 0.35 spikes/s; while shell neurons had a mean baseline firing rate of 2.69 ± 0.24 spikes/s. From STN-lesioned animals, a total of 137 core and 127 shell neurons were recorded during cocaine SA sessions 1 - 12. During these sessions, core neurons exhibited a baseline firing rate of 2.36 ± 0.21 spikes/s and shell neurons had a

mean baseline firing rate of 2.38 ± 0.26 spikes/s. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no significant differences in baseline firing rate.

Neurons were divided into early (sessions 1 – 4), middle (sessions 5 – 8), and late (sessions 9 – 12) for further analysis. A phasically active neuron was defined as in Experiment 1. In sham controls, 24 out of 34 (71%) core neurons recorded during the early sessions were classified as phasically active. Thirty out of 49 (61%) and 24 out of 49 (49%) core neurons were classified as phasically active during the middle and late sessions, respectively. In STN-lesioned animals, 21 out of 46 (46%) core neurons recorded during the early sessions, 27 out of 42 (64%) recorded during the middle sessions, and 21 out of 43 (49%) recorded during the late sessions were classified as phasically active. The results of further classification are shown in Table 10.

Table 10. Percent of neuron type observed in the NAcc core of sham controls and STN-lesioned animals during cocaine SA.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
Sessions 1 - 4	15% (5/34)	24% (8/34)	38% (13/34)	29% (10/34)	13% (6/46)	13% (6/46)	26% (12/46)	9% (4/46)
Sessions 5 - 8	18% (9/49)	14% (7/49)	35% (17/49)	16% (8/49)	19% (8/42)	24% (10/42)	31% (13/42)	29% (12/42)
Sessions 9 - 12	10% (5/49)	10% (5/49)	29% (14/49)	16% (8/49)	16% (7/43)	12% (5/43)	28% (12/43)	16% (7/43)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As shown in Table 10, in sham controls, there was a similar distribution of RESPe (early = 5/34; middle = 9/49; late = 5/49) and RESPi (early = 8/34; middle = 7/49; late =

5/49) core neurons across session blocks. This was also the case for RESPe (early = 6/46; middle = 8/42; late = 7/43) and RESPi (early = 6/46; middle = 10/42; late = 5/43) core neurons in STN-lesioned animals. There was no difference in the normalized firing during the response epoch of RESPe or RESPi core neurons between sham controls versus STN-lesioned animals. Representative examples are shown in Figure 26.

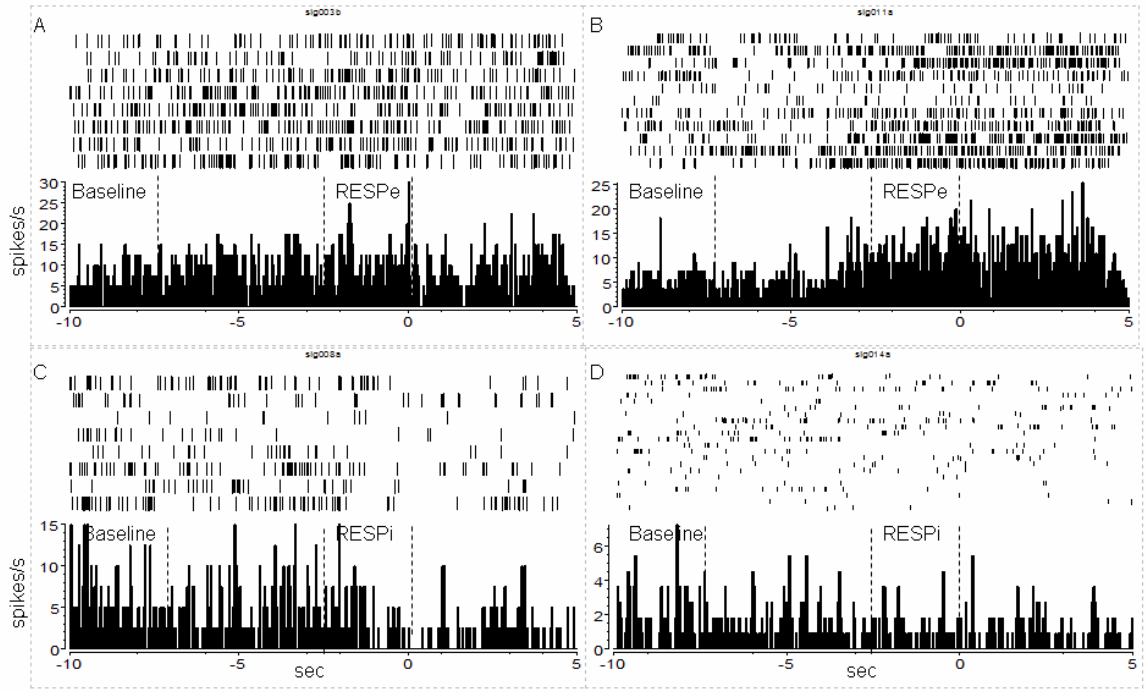

Figure 26. Example PEH of a RESPe core neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a RESPi core neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

As depicted in Table 10, the distribution of REINe core neurons recorded during the early sessions (13/34) was greater than the distribution recorded during the late sessions (14/49) in sham controls. The distribution of REINi core neurons followed the same trend (early = 10/34; late = 8/49). In STN-lesioned animals, there was a similar

distribution of REINe (early = 12/46; middle = 13/42; late = 12/43) core neurons across session blocks. The proportion of REINi core neurons, however, increased from the early (4/46) to middle (12/42) sessions, then decreased in the late (7/43) sessions. Unlike in Experiment 1, we observed no difference in the proportion of excitatory core neurons (RESPe and REINe) between sham controls (63/132) and STN-lesioned animals (58/131) (Chi Square). Composite PEHs of normalized firing of all REINe core neurons from sham controls and STN-lesioned animals are illustrated in Figure 27. As shown in Figure 27, the normalized firing during the reinforcement epoch of REINe core neurons was significantly higher in STN-lesioned animals (panel B) compared to sham controls (panel A) (t-test; $p<0.0001$). There was no difference in normalized firing during the reinforcement epoch of REINi core neurons in sham controls compared to STN-lesioned animals. Individual examples are shown in Figure 28.

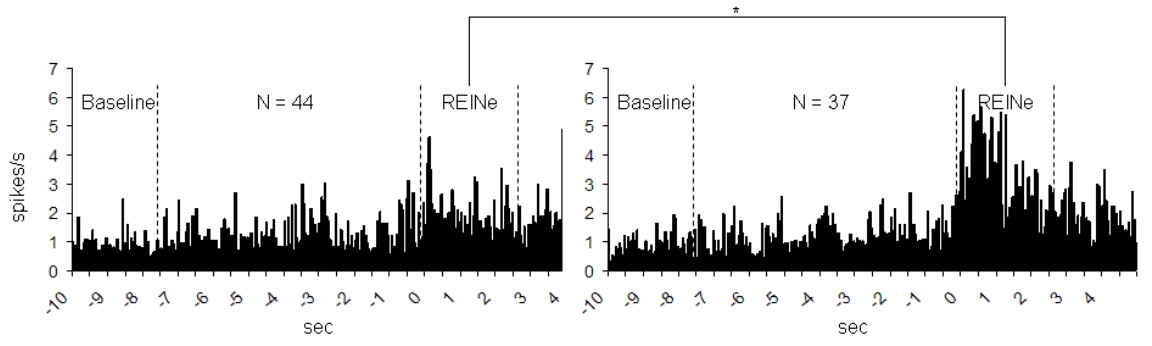

Figure 27. Composite PEHs of normalized firing of all REINe neurons from the NAcc core of sham controls (A) and STN-lesioned (B) animals. Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing rate during the reinforcement epoch of REINe core neurons was significantly higher in STN-lesioned animals (B) compared to that of sham controls (A). *t-test, $p<0.0001$

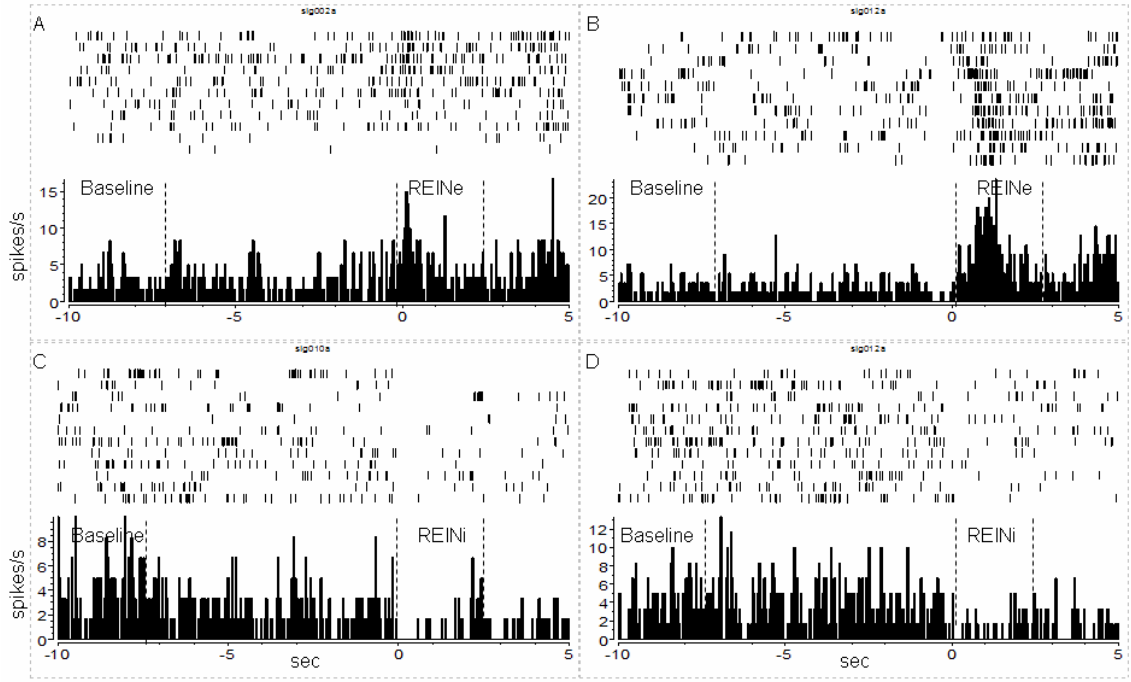

Figure 28. Example PEH of a REINe core neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a REINi core neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

In both groups of animals, there were a number of core neurons that exhibited a response in both epochs. This was the case for 30 out of the 132 neurons (23%) recorded in sham controls and 33 out of 137 (24%) in STN-lesioned animals. Furthermore, the type of response (excitation or inhibition) was the same in both epochs across group and neuron type. Example PEHs for some of these neurons are shown in Figure 29.

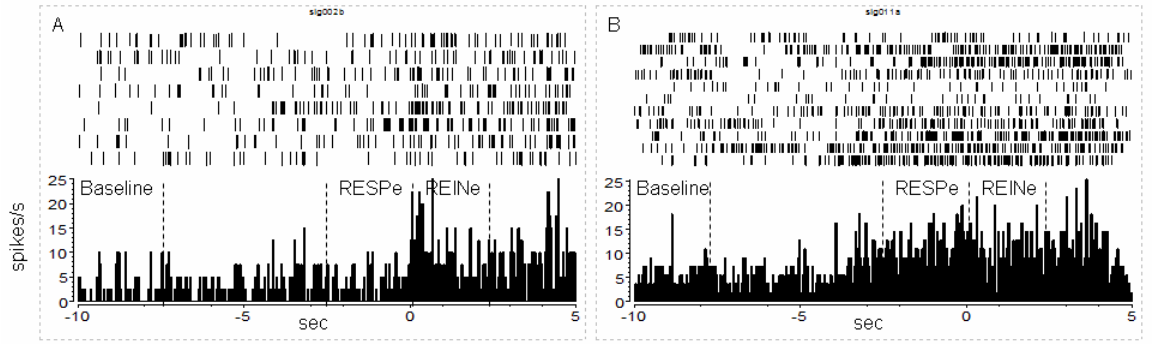

Figure 29. Example PEHs of core neurons showing a response in both epochs. Neuron from a sham control (A) and STN-lesioned (B) animal responding with an excitation in both the response and reinforcement epoch. Each raster display shows the activity of the neuron across all trials of the session.

The CS was omitted on a random 25% of the trials in session 13 for a sample of animals in order to address the issue of whether phasic activation was related to the CS or the motor act of pressing the lever. A change in phasic activation on these trials would rule out a role for lever pressing. Omitting the CS altered the phasic activation of 70% (7/10) of core neurons in sham controls and 80% (8/10) in STN-lesioned animals. Cocaine was omitted on a random 25% of the trials in session 13 for another sample of animals to assess the possibility that cocaine was responsible for the phasic activation of core neurons. A change in phasic activation on these trials would rule out a role for the motor activation associated with cocaine infusions. Cocaine omission altered the phasic activation of 37% (5/14) and 44% (8/18) of core neurons in sham controls and STN-lesioned animals, respectively. Figure 30 contains representative PEHs of individual neurons illustrating the effect of CS or cocaine omission.

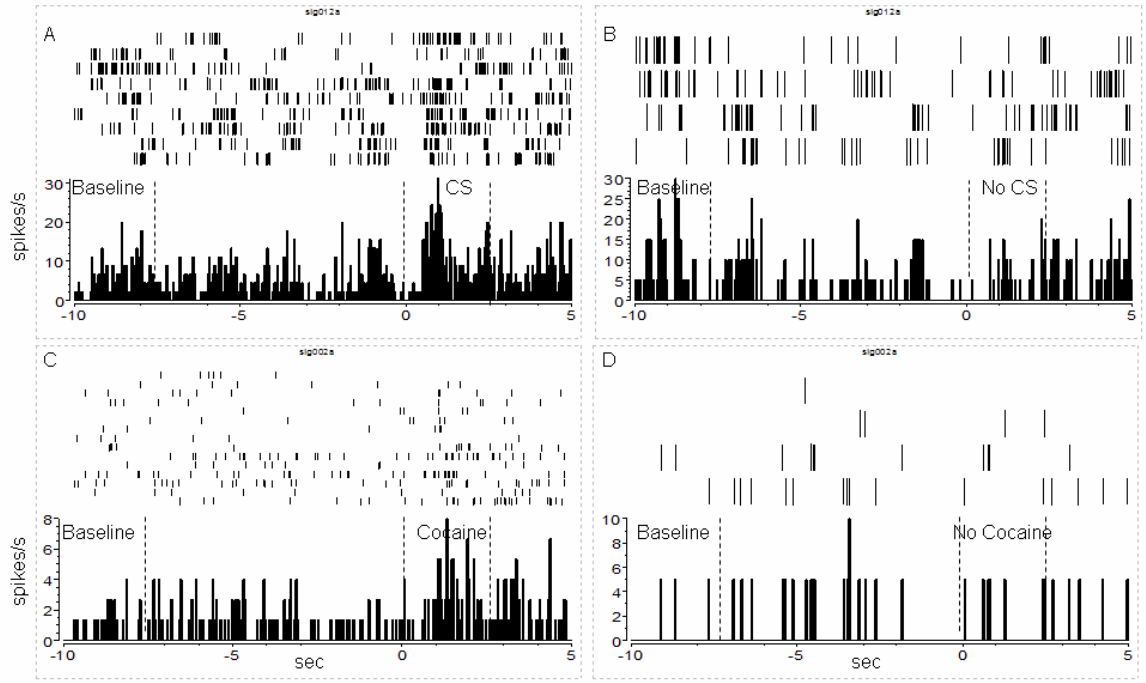

Figure 30. Example PEH of a core neuron from a STN-lesioned animal recorded during cocaine SA when the CS was present (A) and when the CS was omitted on a random 25% of the trials (B). Example PEH of a core neuron from a STN-lesioned animal recorded during cocaine SA when cocaine was present (C) and when cocaine was omitted on a random 25% of the trials (D). For each neuron, note the difference in phasic activation when the CS or cocaine is present (A and C) compared to when the CS or cocaine is omitted (B and D). Each raster display shows the activity of the neuron across all trials of the session.

In sham controls, 37 out of 60 (62%) shell neurons recorded during the early sessions were classified as phasically active. Forty-two out of 84 (50%) and 28 out of 65 (43%) shell neurons were phasically active during the middle and late sessions, respectively. In STN-lesioned animals, 13 out of 42 (31%) shell neurons recorded during the early sessions, 23 out of 42 (55%) recorded during the middle sessions, and 22 out of 43 (51%) recorded during the late sessions were classified as phasically active. In sham controls, there was a significantly higher proportion of phasically active neurons in the core compared to in the shell (Chi Square; $p<0.001$). There was no difference in STN-lesioned animals. Results of further classification are shown in Table 11.

Table 11. Percent of neuron type observed in the NAcc shell of sham controls and STN-lesioned animals during cocaine SA.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
Sessions 1 - 4	28% (17/60)	12% (7/60)	32% (19/60)	20% (12/60)	12% (5/42)	5% (2/42)	10% (4/42)	17% (7/42)
Sessions 5 - 8	15% (13/84)	4% (3/84)	38% (32/84)	10% (8/84)	17% (7/42)	12% (5/42)	33% (14/42)	12% (5/42)
Sessions 9 - 12	20% (13/65)	14% (9/65)	22% (14/65)	12% (8/65)	16% (7/43)	19% (8/43)	35% (15/43)	9% (4/43)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

In sham controls, as shown in Table 11, the distribution of RESPe shell neurons decreased from the early sessions (17/60) to the middles sessions (13/84), then increased in the late sessions (13/65). The distribution of RESPi shell neurons followed a similar pattern (early = 7/60; middle = 3/84; late = 9/65). There was a similar distribution of RESPe shell neurons across session groups in STN-lesioned animals (early = 5/42; middle = 7/42; late = 7/43). The distribution of RESPi shell neurons, however, increased from the early to the late sessions (early = 2/42; middle = 5/42; late = 8/43). There was no difference in the normalized firing rate during the response epoch of RESPe or RESPi shell neurons between sham controls versus STN-lesioned animals. Figure 31 illustrates representative individual PEHs.

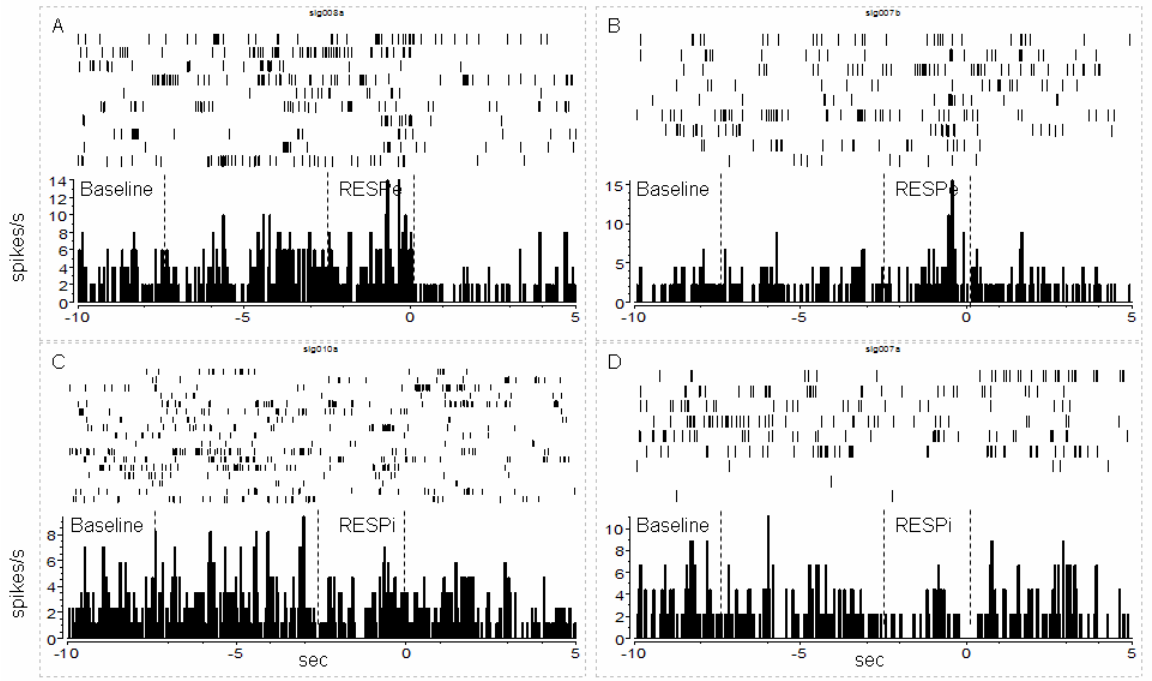

Figure 31. Example PEH of a RESPe shell neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a RESPi shell neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

The distribution of REINe and REINi shell neurons is shown in Table 11. The distribution of REINe shell neurons in sham controls decreased from the early sessions to the late sessions (early = 19/60; middle = 32/84; late = 14/65). The distribution of REINi shell neurons followed a similar pattern (early = 12/60; middle = 8/84; late = 8/65). In STN-lesioned animals, however, the distribution of REINe shell neurons increased from the early to the late sessions (early = 4/42; middle = 14/42; late = 15/43). Conversely, the distribution of REINi shell neurons decreased from the early to the late sessions (early = 7/42; middle = 5/42; late = 4/43). There was no difference in the normalized firing rate during the reinforcement epoch of REINe or REINi shell neurons between sham controls and STN-lesioned animals. Individual examples are shown in Figure 32.

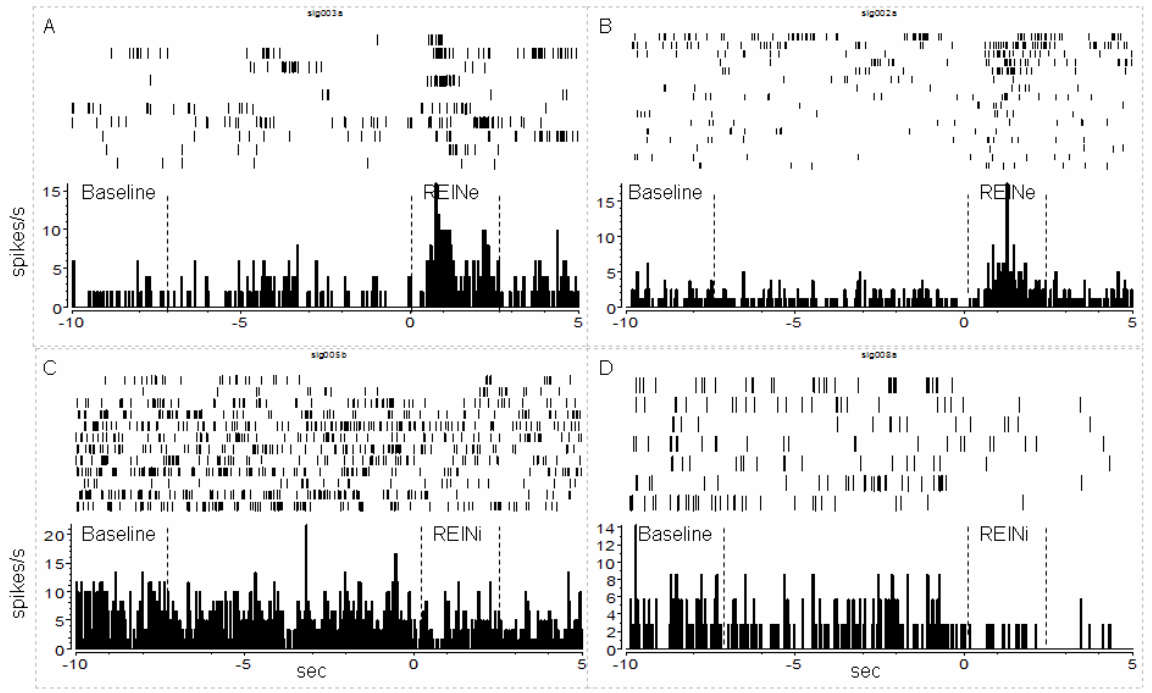

Figure 32. Example PEH of a REINe shell neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Example PEH of a REINi shell neuron recorded from a sham control (C) and a STN-lesioned (D) animal. Each raster display shows the activity of the neuron across all trials of the session.

In both sham controls and STN-lesioned animals, there were a number of shell neurons that exhibited a response in both epochs. In sham controls, 39 out of 209 neurons (19%) were responsive in both epochs; while in STN-lesioned animals, 25 out of 127 neurons (20%) were responsive in both epochs. The type of response (excitation or inhibition was the same in both epochs across group and neuron type. Examples of some of these neurons are shown in Figure 33.

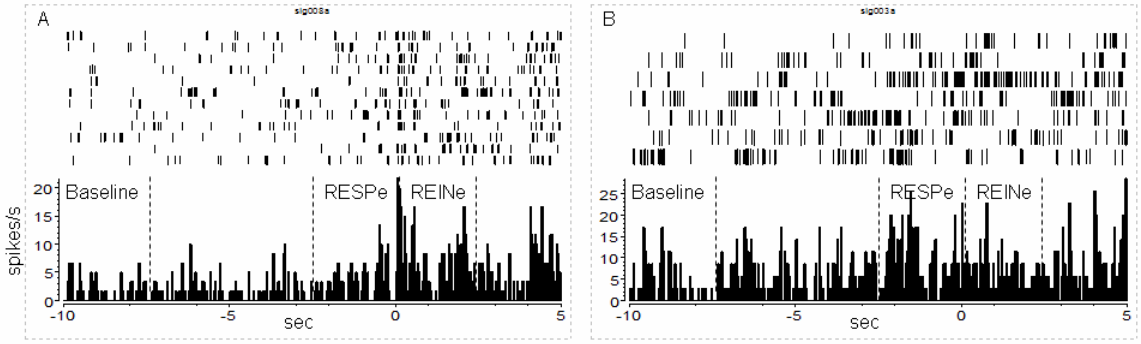

Figure 33. Example PEHs of shell neurons showing a response in both epochs. Neuron from a sham control (A) and STN-lesioned (B) animal responding with an excitation in both the response and reinforcement epoch. Each raster display shows the activity of the neuron across all trials of the session.

To address the issue of whether phasic activation was related to the CS or the motor act of pressing the lever, the CS was omitted on a random 25% of the trials in session 13 for a sample of the animals. A change in phasic activation on these trials would rule out a role for lever pressing. Omitting the CS altered the phasic activation of 59% (10/17) of shell neurons in sham controls and 60% (12/20) in STN-lesioned animals. To assess the possibility that cocaine was responsible for the phasic activation of shell neurons, cocaine was omitted on a random 25% of the trials in session 13 for another sample of animals. A change in phasic activation on these trials would rule out a role for the motor activation associated with the infusion of cocaine. Cocaine omission changes the phasic activation of 64% (9/14) and 33% (3/9) of shell neurons in sham controls and STN-lesioned animals, respectively. The effect of CS or cocaine omission is illustrated in Figure 34.

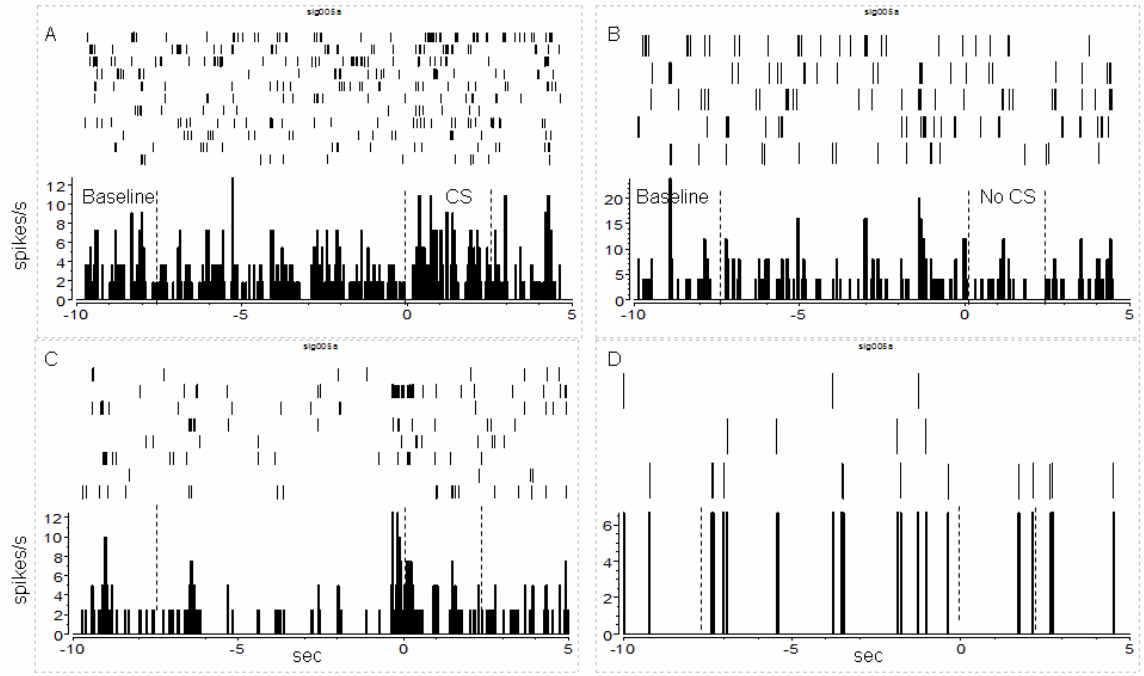

Figure 34. Example PEH of a shell neuron from a STN-lesioned animal recorded during cocaine SA when the CS was present (A) and when the CS was omitted on a random 25% of the trials (B). Example PEH of a shell neuron from a sham control animal recorded during cocaine SA when cocaine was present (C) and when cocaine was omitted on a random 25% of the trials (D). For each neuron, note the difference in phasic activation when the CS or cocaine is present (A and C) compared to when the CS or cocaine is omitted (B and D). Each raster display shows the activity of the neuron across all trials of the session.

Cocaine SA – Summary

In sham controls, there were a higher proportion of phasically active neurons in the core compared to in the shell. In STN-lesioned animals, there was no difference in the distribution of phasically active neurons between the core and shell. Thus, STN lesions had an effect on the response distribution between core and shell. Furthermore, core neurons recorded from STN-lesioned animals had higher normalized firing rates, or magnitudes, in response to cocaine infusion compared to core neuron recorded from sham controls.

Extinction

From sham controls, a total of 69 core and 71 shell neurons were recorded during extinction sessions and a total of 45 core and 45 shell neurons were recorded from STN-lesioned animals. Mean baseline firing rates are shown in Table 12. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no differences in mean baseline firing rates.

Table 12. Baseline firing rates of core and shell neurons in sham control and STN-lesioned animals recorded during extinction.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	69	71	45	45
Mean	2.29	3.20	2.15	3.36
SEM	0.27	0.48	0.31	0.41

Means are measured in spikes/s.

In sham controls, 33% (23/69) of core and 34% (24/71) of shell neurons were classified as phasically active in response to the lever press. Of the 23 core neurons, 10 responded with an excitation and 13 responded with an inhibition. Of the 24 shell neurons, 15 responded with an excitation and 9 responded with an inhibition. Forty-two percent (19/45) of core and 31% (14/45) of shell neurons in STN-lesioned animals were classified as phasically active in response to the lever press. Six core neurons responded with an excitation; while 13 responded with an inhibition. Of the 14 phasically active

shell neurons, 9 and 5 neurons responded with an excitation an inhibition, respectively. Thus, there were similar proportions of phasically active core and shell neurons between sham controls and STN-lesioned animals. Furthermore, these samples of phasically active neurons were comprised of similar numbers of excitatory and inhibitory responses.

Cue-induced Reinstatement

A total of 22 core and 16 shell neurons were recorded during CS-induced reinstatement in sham controls. From STN-lesioned animals, a total of 16 core and 18 shell neurons were recorded during CS-induced reinstatement. Table 13 illustrates the mean baseline firing rates of these neurons. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no significant differences in mean baseline firing rate.

Table 13. Baseline firing rates of core and shell neurons in sham control and STN-lesioned animals recorded during CS-induced reinstatement.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	22	16	16	18
Mean	2.20	3.59	1.61	3.01
SEM	0.47	1.08	0.48	0.83

Means are measured in spikes/s.

In sham controls, 45% (10/22) of core and 31% (5/16) of shell neurons were classified as phasically active in response to the CS. Of the 10 phasically active core

neurons, 7 responded with an excitation and 3 responded with an inhibition. Of the 5 phasically active shell neurons, 2 and 3 responded with an excitation and inhibition, respectively. In STN-lesioned animals, 75% (12/16) of core and 56% (10/18) of shell neurons were classified as phasically active in response to the CS. Of the 12 phasically active core neurons, half responded with an excitation while the other half responded with an inhibition. Of the 10 phasically active shell neurons, 7 responded to the CS with an excitation while the remaining 3 responded with an inhibition. There was no difference in normalized firing during the response epoch of phasically active core or shell neurons in sham controls and STN-lesioned animals (data not shown). Further, there was no difference in the proportion of phasically active neurons in either the core or shell in sham controls compared to STN-lesioned animals (Chi Square). Representative examples of these neurons are shown in Figure 35.

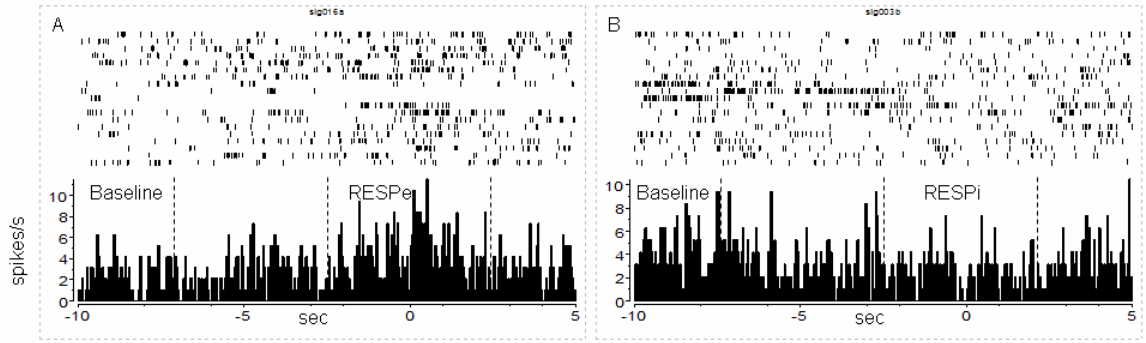

Figure 35. Example PEH of a RESPe core neuron (A) and a RESPi shell neuron (B) recorded from a sham animal during CS-induced reinstatement. The 0 point on the x-axis refers to the onset of the CS. Each raster display shows the activity of the neuron across all trials of the session.

Cocaine-primed Reinstatement

A total of 18 core and 19 shell neurons were recorded during cocaine-primed reinstatement in sham controls; while, in STN-lesioned animals, a total of 15 core and 12 shell neurons were recorded. Mean baseline firing rates are shown in Table 14. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no significant differences in mean baseline firing rate.

Table 14. Baseline firing rates of core and shell neurons in sham control and STN-lesioned animals recorded during cocaine-primed reinstatement.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	18	19	15	12
Mean	2.06	1.64	1.12	2.05
SEM	0.52	0.42	0.26	0.49

Means are measured in spikes/s.

In sham controls, 28% (5/18) of core and 32% (6/19) of shell neurons were classified as phasically active in response to the lever press during cocaine-primed reinstatement. Of the 5 phasically active core neurons, 4 responded with an excitation and 1 responded with an inhibition. Of the 6 phasically active shell neurons, 3 responded with an excitation and 3 responded with an inhibition. In STN-lesioned animals, 27% (4/15) of core and 25% (3/12) of shell neurons were classified as phasically active in response to the lever press. Of the 4 phasically active core neurons, 2 responded with an

excitation and 2 responded with an inhibition. All 3 of the phasically active shell neurons responded to the lever press with an excitation. A Chi Square test revealed a significantly higher proportion of phasically active shell neurons in sham controls compared to in STN-lesioned animals ($p<0.05$), but no difference in the proportion of phasically active core neurons. Figure 36 contains individual examples of phasically active neurons.

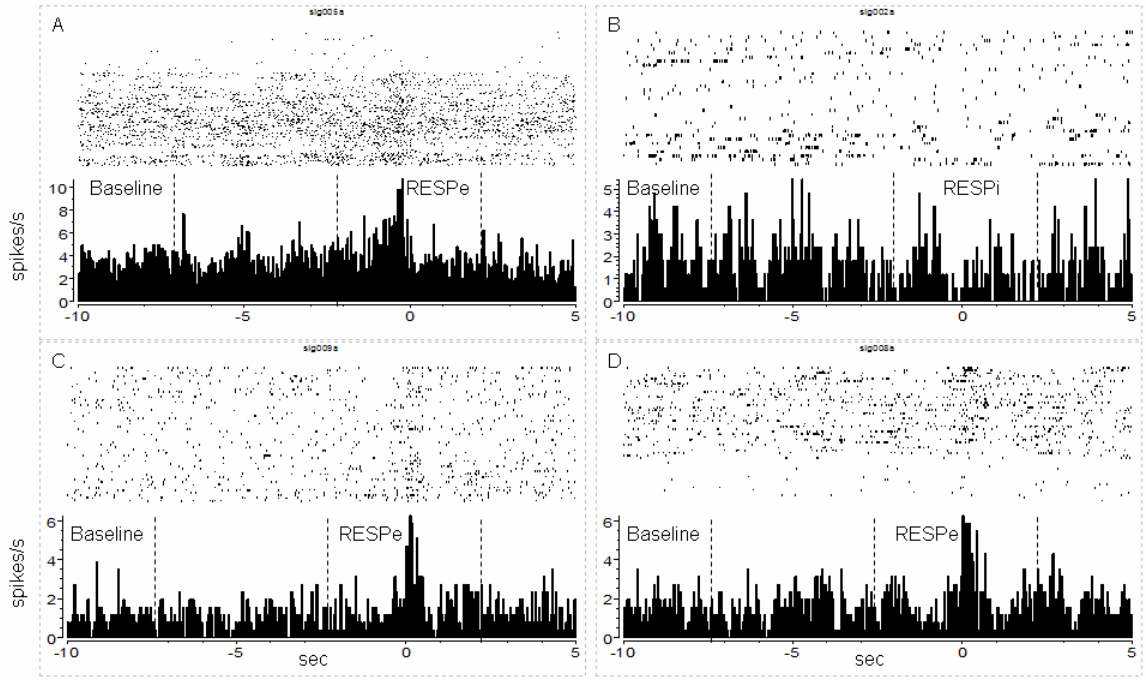

Figure 36. Example PEH of a RESPe core neuron (A) and a RESPi shell neuron (B) recorded from a sham animal during food-primed reinstatement. Example PEH of a RESP core neuron (C) and a RESPe shell Neuron (D) recorded from a STN-lesioned animal. The 0 point on the x-axis refers to the lever press. Each raster display shows the activity of the neuron across all trials of the session.

Experiment 2 – Electrophysiology Summary

When self-administering cocaine, we observed a significantly greater proportion of phasically active neurons in the core compared to in the shell of sham controls. We observed no difference in response distribution in STN-lesioned animals. During cue-

induced reinstatement, we observed a trend towards a greater proportion of phasically active core and shell neurons in STN-lesioned animals compared to in sham controls. Finally, during cocaine-primed reinstatement, we observed a significantly greater proportion of phasically active shell neurons in sham controls compared to in STN-lesioned animals.

When comparing operant responding for sucrose and cocaine SA, there were 3 main findings. First, during the SA sessions, we observed differences in core/shell response distributions. Specifically, during operant responding for sucrose, STN lesions had no effect on core/shell response distribution. However, STN lesions did affect response distribution during cocaine SA. Second, during cue-induced reinstatement, we observed differences in core responsiveness. In animals that had been responding for sucrose, we observed a greater proportion of phasically active core neurons in sham controls; while in animals self-administering cocaine, we observed a greater proportion of phasically active core neurons in STN-lesioned animals. Finally, during reward-primed reinstatement, STN lesions had no effect on shell responsiveness. Specifically, we observed a greater proportion of phasically active shell neurons in sham controls for both sucrose and cocaine.

Experiment 3: Effects of bilateral STN lesions on NAcc electrophysiology during food-seeking behavior on a progressive-ratio schedule of reinforcement.

Operant Behavior

Using a between–subjects design, we assessed the effects of bilateral STN lesions on operant responding for sucrose on a PR schedule of reinforcement. As shown in

Figure 37, STN-lesioned rats reached a significantly higher breaking point, and therefore, obtained significantly more reinforcers compared to sham controls (unpaired t-test; $p<0.05$).

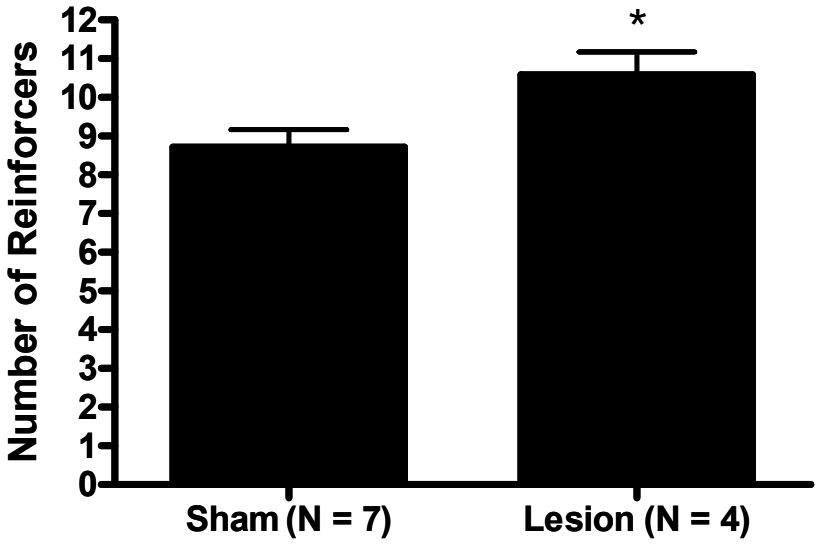

Figure 37. Mean number of sucrose reinforcers, or breaking point, reached on a PR schedule of reinforcement. STN-lesioned rats reached a significantly higher breaking point compared to sham controls (unpaired t-test; *$p<0.05$).

Electrophysiology

Baseline

Figure 38 shows a schematic of microwire bundle placements for all of the rats used for single-unit recording in this experiment. All of the microwire bundles were histologically verified to be in either the NAcc core or shell.

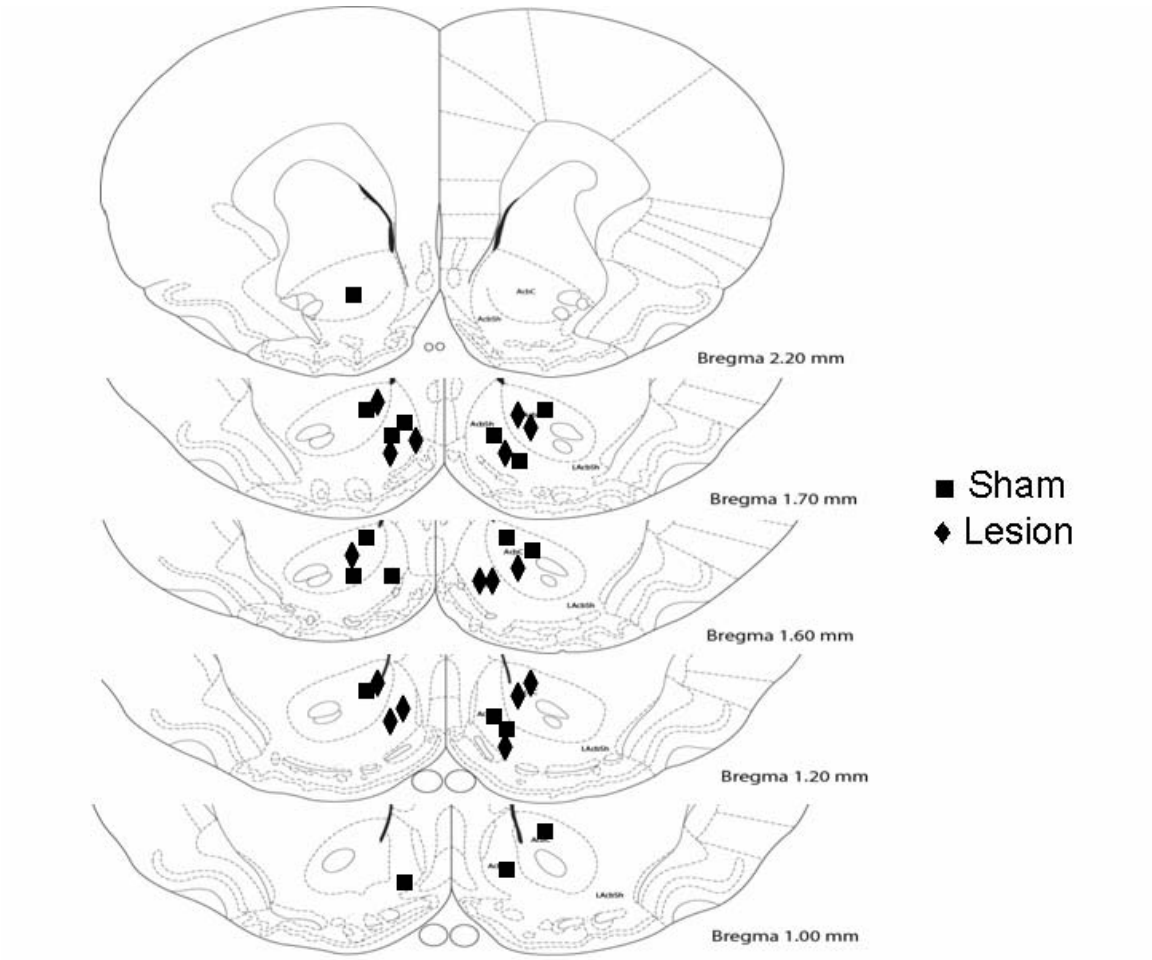

Figure 38. Anatomical location of microwire bundles in coronal sections of rat NAcc. Symbols represent the termination of microwire bundles for both groups. All bundles were located in either NAcc core or shell. Numbers indicate the distance anterior to bregma in mm.

A total of 25 core neurons and 24 shell neurons were recorded from 7 sham controls and a total of 21 core neurons and 23 shell neurons were recorded from 4 STN-lesioned animals. Table 15 contains mean baseline firing rates of core and shell neurons

recorded from sham controls and STN-lesioned animals. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed no differences in mean baseline firing rate.

Table 15. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals recorded during operant responding for food on a PR schedule of reinforcement.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	25	24	21	23
Mean	3.85	2.24	2.03	1.62
SEM	1.13	0.48	0.26	0.41

Means are measured in spikes/s.

Operant Responding for Food on a PR Schedule of Reinforcement

A phasically active neuron was defined as previously described. In sham controls, 12 out of 25 (48%) core neurons were classified as phasically active. In STN-lesioned animals, 12 out of 21 (57%) core neurons were classified as phasically active. A Chi Square analysis revealed no difference in the proportion of phasically active core neurons in sham controls versus STN-lesioned animals.

Table 16. Percent of neuron type observed in the NAcc core of sham controls and STN-lesioned animals during operant responding for food on a PR schedule of reinforcement.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
	16% (4/25)	12% (3/25)	32% (8/25)	4% (1/25)	19% (4/21)	19% (4/21)	14% (3/21)	19% (4/21)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As shown in Table 16, in sham controls, there was a similar distribution of RESPe (4/25) and RESPi (3/25) core neurons. We observed a similar distribution in STN-lesioned animals (RESPe = 4/21; RESPi = 4/21). A Chi Square analysis revealed no difference in proportion of RESPe or RESPi core neurons in sham controls versus STN-lesioned animals. Moreover, there was no difference in the normalized firing rate of RESPe or RESPi core neurons in sham controls versus STN-lesioned animals. Individual PEHs are depicted in Figure 39.

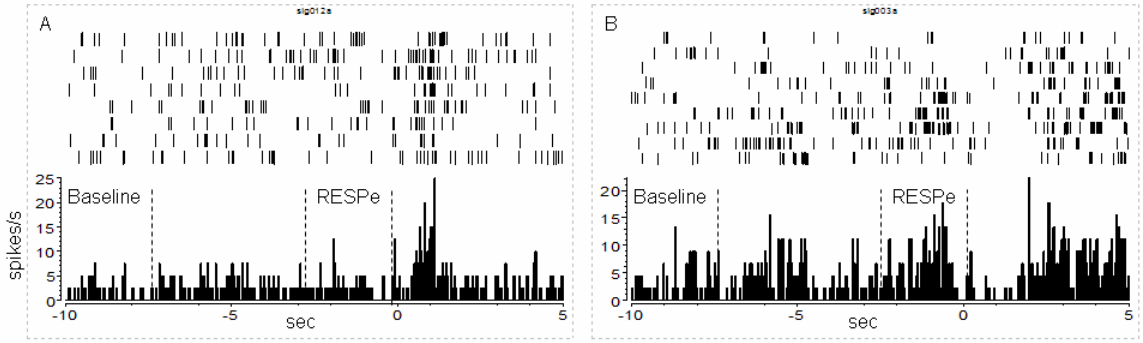

Figure 39. Example PEH of a RESPe core neuron recorded from a sham control (A) and a STN-lesioned animal (B). Each raster display shows the activity of the neuron across all trials of the session.

The proportion of REINe and REINi core neurons observed in sham controls and STN-lesioned animals is shown in Table 16. In sham controls, there was greater proportion of REINe (8/25) than REINi (1/25) core neurons. In STN-lesioned animals, we observed a similar proportion of REINe (3/21) and REINi (4/21) core neurons. Furthermore, a Chi Square test revealed no difference in the proportion of REINe core neurons in sham controls versus STN-lesioned animals, however, there was a significantly greater proportion of REINi core neurons in STN-lesioned animals compared to in sham controls (Chi Square; $p<0.01$). As shown in Figure 40, the normalized firing rate during the reinforcement epoch was significantly higher in REINe core neurons in sham controls compared to STN-lesioned animals (t-test; $p<0.05$). Individual examples are shown in Figure 41.

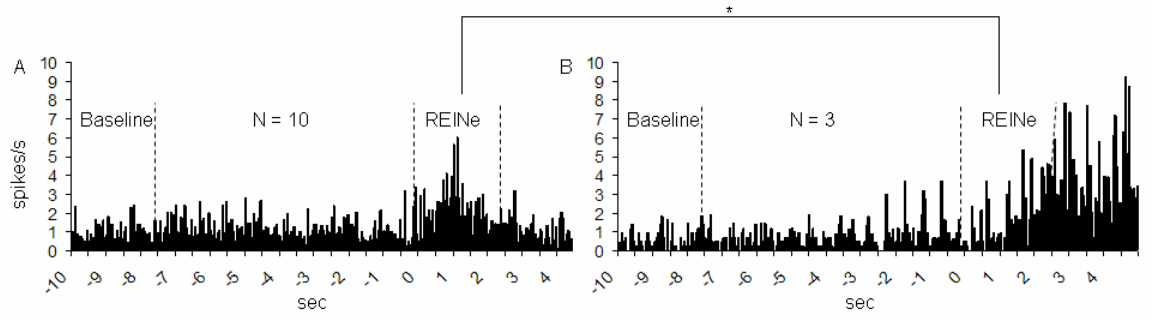

Figure 40. Composite PEHs of normalized firing of all REINe neurons from the NAcc core of sham controls (A) and STN-lesioned animals (B). Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing rate during the reinforcement epoch of REINe core neurons was significantly higher in sham controls (A) compared to that of STN-lesioned animals (B). *t-test; $p<0.05$

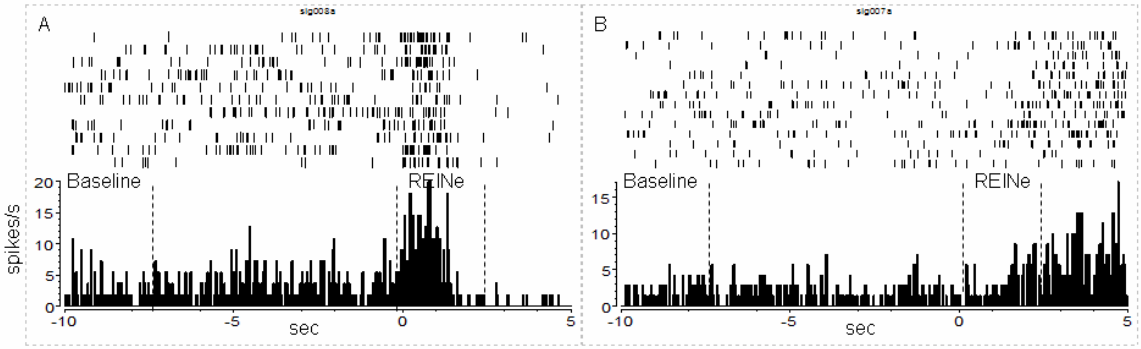

Figure 41. Example PEH of a REINe core neuron recorded from a sham control (A) and a STN-lesioned (B) animal. Each raster display shows the activity of the neuron across all trials of the session.

In sham controls, 14 out 24 (58%) shell neurons were classified as phasically active. Thirteen out of 23 (57%) shell neurons in STN-lesioned animals were classified as phasically active. A Chi Square test revealed no difference in the proportion of phasically active shell neurons in sham controls versus STN-lesioned animals.

Table 17. Percent of neuron type observed in the NAcc shell of sham controls and STN-lesioned animals during operant responding for food on a PR schedule of reinforcement.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
	8% (2/24)	25% (6/24)	29% (7/24)	8% (2/24)	17% (4/23)	13% (3/23)	48% (11/23)	0% (0/23)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As shown in Table 17, there was a greater proportion of RESPi (6/24) compared to RESPe (2/24) shell neurons in sham controls. In STN-lesioned animals, the proportion of RESPe (4/23) shell neurons was similar to the distribution of RESPi (3/23) shell neurons. A Chi Square analysis revealed no difference in the proportion of RESPe or RESPi core neurons in sham controls versus STN-lesioned animals. Furthermore, there was no difference in the normalized firing rate of RESPe or RESPi core neurons in sham controls versus STN-lesioned animals. Individual PEHs are depicted in Figure 42.

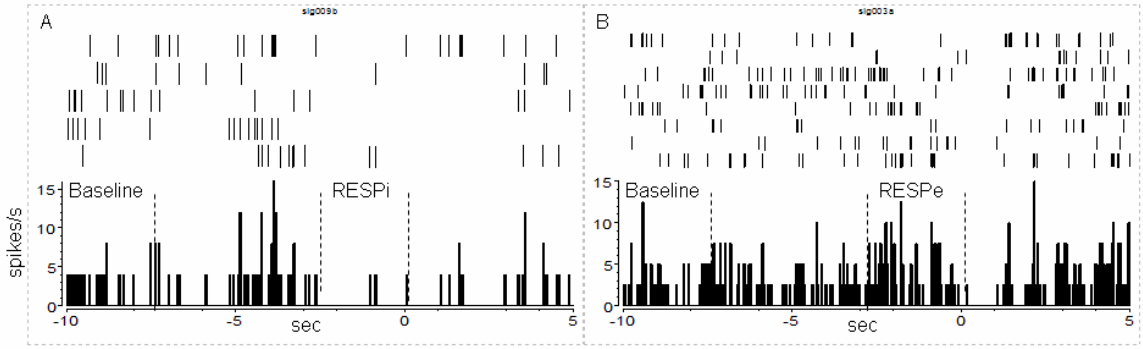

Figure 42. Example PEH of a RESPi shell neuron recorded from a sham control (A) and an example PEH of a RESPe shell neuron recorded from a STN-lesioned animal (B). Each raster display shows the activity of the neuron across all trials of the session.

The proportion of REINe and REINi shell neurons observed in sham controls and STN-lesioned animals is shown in Table 17. In sham controls, there was a greater proportion of REINe (7/24) than REINi (2/24) shell neurons. The same trend was observed in STN-lesioned animals (REINe = 11/23; REINi = 0/23). A Chi Square analysis revealed no difference in the proportion of REINe or REINi shell neurons in sham controls versus STN-lesioned animals. There was no difference in the normalized

firing rate of REINe shell neurons in sham controls versus STN-lesioned animals. Figure 43 contains individual PEHs.

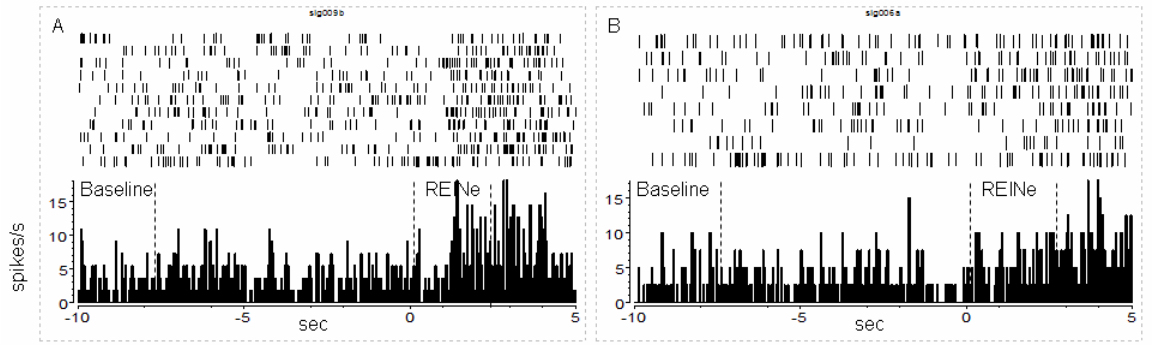

Figure 43. Example PEH of a REINe shell neuron recorded from a sham control (A) and a STN-lesioned animal (B). Each raster display shows the activity of the neuron across all trials of the session.

Experiment 4: Effects of STN lesions on NAcc electrophysiology during cocaine-seeking behavior on a progressive ratio schedule of reinforcement

Operant Behavior

Using a between–subjects design, we assessed the effects of bilateral STN lesions on operant responding for cocaine on a PR schedule of reinforcement. As shown in Figure 44, STN-lesioned rats reached a significantly lower breaking point, and therefore, obtained significantly fewer cocaine infusions compared to sham controls (unpaired t-test; $p<0.05$).

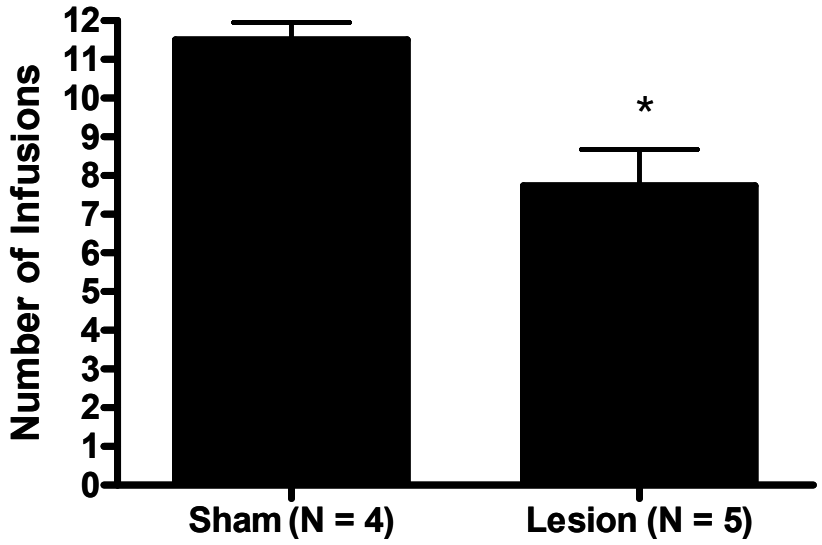

Figure 44. Mean number of cocaine infusions, or breaking point, reached on a PR schedule of reinforcement. STN-lesioned rats reached a significantly lower breaking point compared to sham controls (unpaired t-test; *p<0.05).

Electrophysiology

Baseline

Figure 45 shows a schematic of microwire bundle placements for all of the rats used for single-unit recording in this experiment. All of the microwire bundles were histologically verified to be in either the NAcc core or shell.

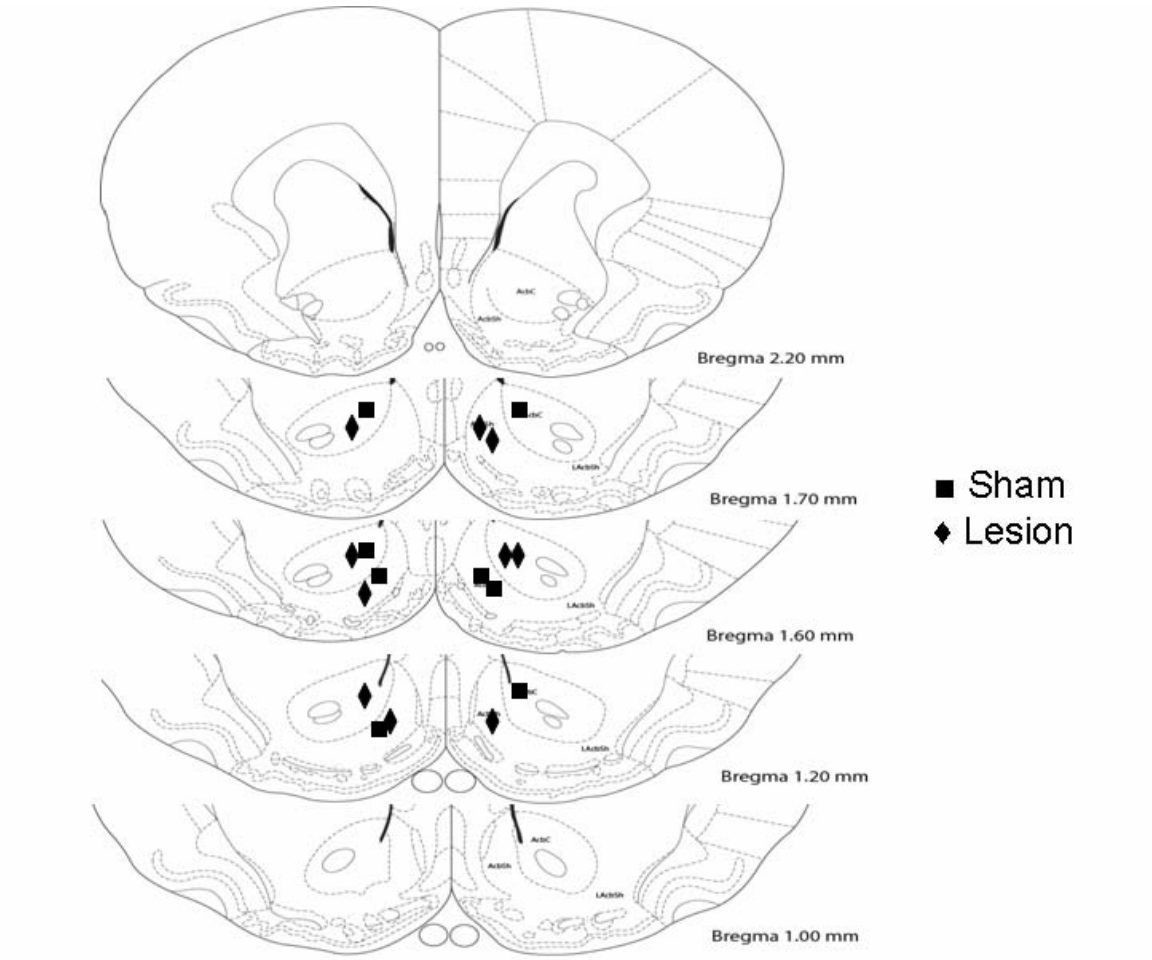

Figure 45. Anatomical location of microwire bundles in coronal sections of rat NAcc. Symbols represent the termination of microwire bundles for both groups. All bundles were located in either NAcc core or shell. Numbers indicate the distance anterior to bregma in mm.

A total of 19 core neurons and 30 shell neurons were recorded from 4 sham controls and a total of 33 core neurons and 49 shell neurons were recorded from 5 STN-lesioned animals. Table 18 contains mean baseline firing rates of core and shell neurons recorded from sham controls and STN-lesioned animals. A Two-Way ANOVA

(sham/lesion X NAcc subregion) revealed that, in STN-lesioned animals, shell neurons exhibited significantly higher firing rates compared to core neurons (Bonferroni post hoc test; $p<0.05$).

Table 18. Baseline firing rates of core and shell neurons in sham controls and STN-lesioned animals recorded during cocaine SA on a PR schedule of reinforcement.

	Sham		Lesion	
	Core	Shell	Core	Shell
N	19	30	33	49
Mean	3.06	2.57	1.72	3.58*
SEM	0.45	0.43	0.20	0.52

Means are measured in spikes/s. A Two-Way ANOVA (sham/lesion X NAcc subregion) revealed that, in STN-lesioned animals, shell neurons exhibited significantly higher firing rates compared to core neurons. (Bonferroni post hoc test; *$p<0.05$)

Operant Responding for Cocaine on a PR Schedule of Reinforcement

A phasically active neuron was defined as previously described. In sham controls, 7 out of 19 (37%) core neurons were classified as phasically active. In STN-lesioned animals, 16 out of 33 (48%) core neurons were classified as phasically active. A Chi Square analysis revealed a significantly greater proportion of phasically active core neurons in STN-lesioned animals compared to in sham controls ($p<0.001$).

Table 19. Percent of neuron type observed in the NAcc core of sham controls and STN-lesioned animals during cocaine SA on a PR schedule of reinforcement.

	Sham				Lesion			
	RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
	11% (2/19)	5% (1/19)	5% (1/19)	21% (4/19)	15% (5/33)	6% (2/33)	27% (9/33)	12% (4/33)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As shown in Table 19, we observed very few RESPe and RESPi core neurons in both sham controls (RESPe = 2/19; RESPi = 1/19) and STN-lesioned animals (RESPe = 5/33); RESPi = 2/33). There was no difference in the proportion of RESPe or RESPi core neurons in sham controls versus STN-lesioned animals. There were not enough RESPe or RESPi neurons to analyze the normalized firing rate. Individual example PEHs are illustrated in Figure 46.

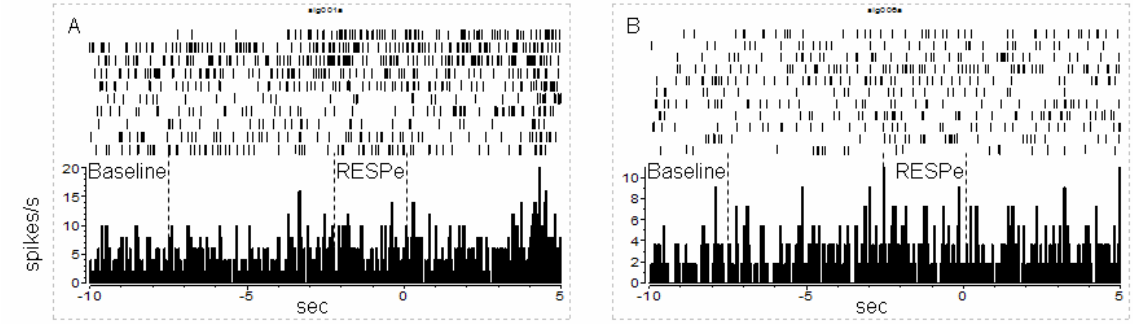

Figure 46. Example PEH of a RESPe core neuron recorded from a sham control (A) and a STN-lesioned animal (B). Each raster display shows the activity of the neuron across all trials of the session.

The proportion of REINi (4/19) was higher than the proportion of REINe (1/19) core neurons in sham controls (Table 19). In STN-lesioned animals, we observed the opposite trend (REINe = 9/33; REINi = 4/33). Results from a Chi Square test revealed a significantly higher proportion of REINe core neurons in STN-lesioned animals compared to sham controls ($p<0.001$) and a significantly lower proportion of REINi core neurons in STN-lesioned animals compared to sham controls ($p<0.05$). There was no difference in the normalized firing rate during the reinforcement epoch of REINi core neurons between sham controls and STN-lesioned animals. There were not enough REINe core neurons in sham controls to analyze the normalized firing rate of REINe core neurons. Figure 47 contains individual PEHs from sham controls and STN-lesioned animals.

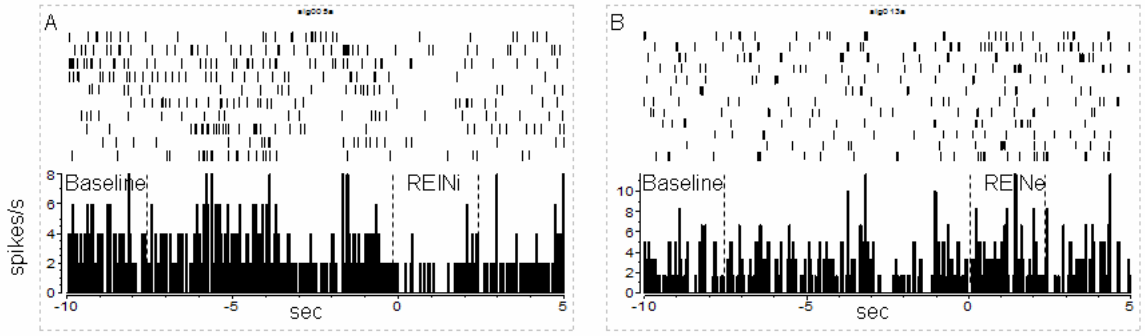

Figure 47. Example PEH of a REINi core neuron recorded from a sham control (A) and a REINe core neuron recorded from a STN-lesioned animal (B). Each raster display shows the activity of the neuron across all trials of the session.

In sham controls, 18 out of 30 (60%) shell neurons were classified as phasically active; while 23 out of 49 (47%) shell neurons were classified as phasically active in STN-lesioned animals. In sham controls, there was a significantly higher proportion of

phasically active neurons is the shell compared to in the core (Chi Square; $p<0.001$). Moreover, a Chi Square test resulted in a significantly greater proportion of phasically active neurons in sham controls compared to in STN-lesioned animals ($p<0.01$).

Table 20. Percent of neuron type observed in the NAcc shell of sham controls and STN-lesioned animals during cocaine SA on a PR schedule of reinforcement.

Sham				Lesion			
RESPe	RESPi	REINe	REINi	RESPe	RESPi	REINe	REINi
3% (1/30)	10% (3/30)	37% (11/30)	23% (7/30)	27% (13/49)	8% (4/49)	31% (15/49)	6% (3/49)

RESPe = 40% increase in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
RESPi = 40% decrease in mean firing rate 2.5 sec before the reinforced lever press compared to baseline
REINe = 40% increase in mean firing rate 2.5 sec after the reinforced lever press compared to baseline
REINi = 40% decrease in mean firing rate 2.5 sec after the reinforced lever press compared to baseline

As shown in Table 20, in sham controls, we observed a very small proportion of both RESPe (1/30) and RESPi (3/30) shell neurons. In STN-lesioned animals, we observed a greater proportion of RESPe (13/49) shell neurons than RESPi (4/49) shell neurons. There was a significantly higher proportion of RESPe shell neurons in STN-lesioned animals compared to in sham controls (Chi Square; $p<0.001$). There was no difference in the proportion of RESPi shell neurons. There was no difference in the normalized firing rate during the response epoch of RESPi shell neurons between sham controls and STN-lesioned animals. Furthermore, there were not enough RESPe shell neurons observed in sham controls to analyze the normalized firing rate of RESPe shell neurons. Individual PEHs are illustrated in Figure 48.

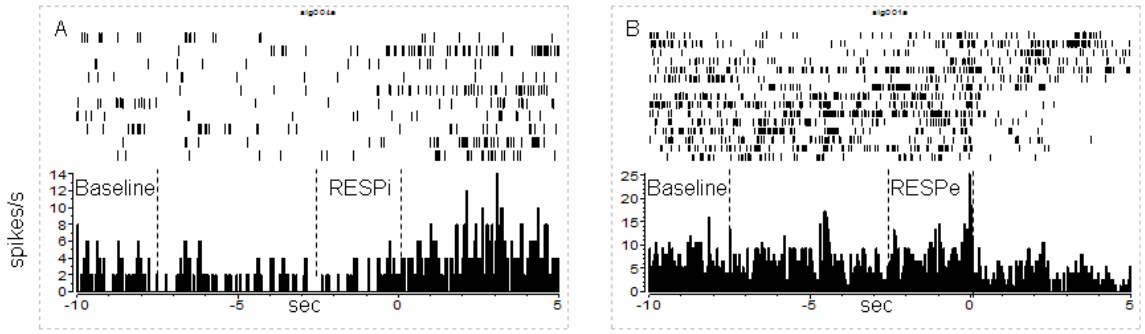

Figure 48. Example PEH of a RESPi shell neuron recorded from a sham control (A) and an example PEH of a RESPe shell neuron recorded from a STN-lesioned animal. Each raster display shows the activity of the neuron across all trials of the session.

In both sham controls and STN-lesioned animals, there was a higher proportion of REINe shell neurons (sham controls = 11/30; STN-lesioned animals = 15/49) than REINi shell neurons (sham controls = 7/30; STN-lesioned animals = 3/49). There was a significantly higher proportion of both REINe and REINi shell neurons observed in sham controls compared to in STN-lesioned animals (Chi Square; $p<0.001$). Furthermore, as shown in Figure 49, the normalized firing rate during the reinforcement epoch in REINe shell neurons in sham controls was significantly higher compared to in STN-lesioned animals (unpaired t-test; $p<0.0001$). There was no difference in the normalized firing during the reinforcement epoch of REINi shell neurons. Individual PEHs are illustrated in Figure 50.

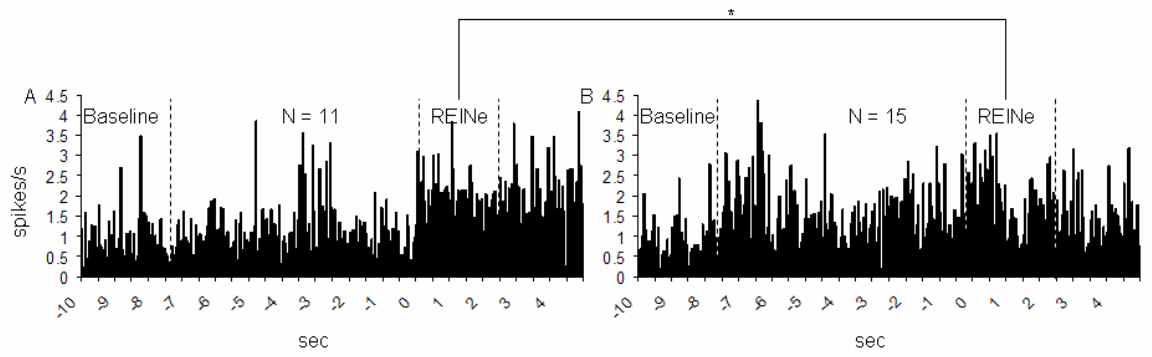

Figure 49. Composite PEHs of normalized firing of all REINe neurons from the NAcc shell of sham controls (A) and STN-lesioned animals (B). Neural activity was normalized relative to the respective baseline firing rate of each cell; therefore, these PEHs reflect relative changes in firing rate. The normalized firing rate during the reinforcement epoch of REINe shell neurons was significantly higher in sham controls (A) compared to that of STN-lesioned animals (B). *t-test; p<0.0001

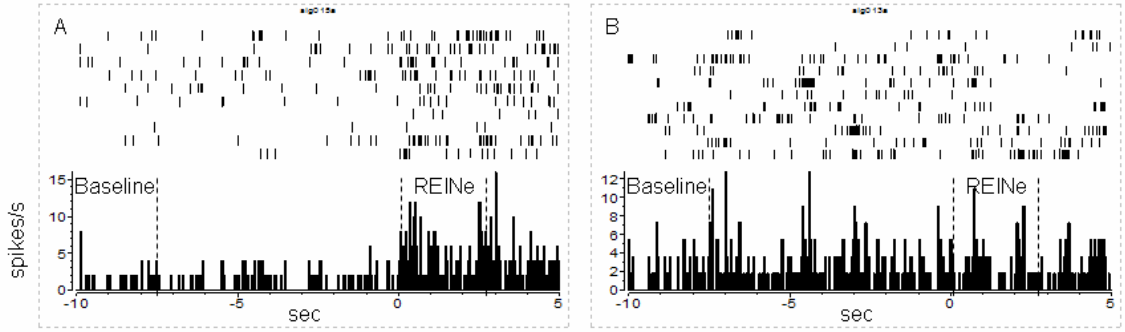

Figure 50. Example PEH of a REINe shell neuron recorded from a sham control (A) and an example PEH of a REINe shell neuron recorded from a STN-lesioned animal (B). Each raster display shows the activity of the neuron across all trials of the session.

Experiments 3 & 4 – Electrophysiology Summary

When comparing sucrose and cocaine reward, there were 3 effects of STN lesions. First, we observed differences in inhibitory core neurons. Specifically, during sucrose reinforcement, we observed a significantly greater proportion of inhibitory core neurons in STN-lesioned animals; while during cocaine reinforcement, we observed a significantly greater proportion in sham controls. Second, there was no difference in the

response magnitude of excitatory core neurons. Thus, the response magnitude of excitatory core neurons was significantly higher in sham controls for both reinforcers. Finally, we observed differences in phasically active shell neurons. During sucrose reinforcement there was an equal number of phasically active shell neurons in both sham controls and STN-lesioned animals. During cocaine reinforcement, however, there was a significantly greater proportion of phasically active shell neurons in sham controls compared to in STN-lesioned animals.

Discussion

Our primary goal in performing these experiments was to investigate the role of the STN in both food- and cocaine-seeking behavior. These experiments were designed so that we could assess electrophysiological correlates in the NAcc while animals were engaged in food- or cocaine-seeking behavior. Specifically, we examined the effects of bilateral STN lesions on the reinstatement of food- and cocaine-seeking behavior and the motivation for food and cocaine using a PR schedule of reinforcement. In each of these paradigms, we simultaneously monitored neural activity in the NAcc, an area of brain that integrates limbic information related to motivation, memory, and the associated motor activity [Everitt & Robbins, 1992; Morgenson, 1987], in an attempt to assess effects of STN lesions on electrophysiological correlates in the NAcc.

Reinstatement of Food- and Cocaine-seeking Behavior

Although several studies have investigated STN involvement in the motivation for food and cocaine using a PR schedule of reinforcement [Baunez & Robbins, 1999;

Baunez et al., 2002; Baunez et al., 2005; Uslaner et al., 2005], the experiments reported here are the first to use food and cocaine reinstatement paradigms. Here, we have shown that bilateral lesions of the STN block cue-induced reinstatement to cocaine-seeking behavior; while leaving cue-induced reinstatement to food-seeking behavior and both food- and cocaine-primed reinstatement intact. Additionally, STN lesions had no effect on operant responding for food or cocaine on a FR-5 schedule of reinforcement. It has been reported that STN lesions have no effect on operant responding on a FR-1 schedule [Baunez et al., 2005]; therefore, this result was expected.

The finding that STN lesions blocked CS-induced reinstatement of cocaine-seeking behavior is consistent with the findings that STN lesions block cocaine conditioned place preference and decrease the breaking point for cocaine [Baunez et al., 2005]; thus, extending previous evidence showing that the STN is involved in motivational processes. Further, the finding that CS-induced reinstatement of food-seeking behavior was unaffected following STN lesions supports the dissociation between natural and drug reinforcement that has been previously reported [Baunez et al., 2005]. This dissociation has been demonstrated in the NAcc, which along with the STN, PFC, and VP, is part of the limbic circuitry [Maurice et al., 1998]. Specifically, as Carelli and colleagues have shown [2000, 2002], NAcc neurons in rats respond differently to natural versus cocaine reinforcement. The same result has been found in monkeys performing a reaction-time task for juice and cocaine reward [Bowman et al., 1996]. This dissociation suggests that the limbic circuitry responds differently to natural versus cocaine reward. The NAcc core sends GABAergic projections to the medial part of the STN via the VP; while the STN sends reciprocal glutamatergic projections to the VP

[Groenewegen & Berendse, 1990]. Through this circuit, the STN influences the output of limbic information [Turner et al., 2001] and, therefore, may be the circuitry through which the STN differentially modulates natural and drug rewards.

Interestingly, we found that STN lesions block cue-induced reinstatement of cocaine-seeking behavior; but have no effect on cocaine-primed reinstatement. In the NAcc, inactivation of the core, but not the shell, via glutamate antagonist blocks cue-induced reinstatement of cocaine-seeking behavior [Di Ciano & Everitt, 2001] indicating that the core is critical for cue-induced reinstatement. Evidence from several studies [McFarland & Kalivas, 2001; McFarland et al., 2003; Anderson et al., 2003; Schmidt & Pierce, 2006] suggests that cocaine-primed reinstatement is mediated by both core and shell. Given the anatomical connectivity between the STN and NAcc core [Groenewegen & Berendse, 1990]; STN lesions would have the same effect as lesions of the core. In fact, lesions of the NAcc increase the breaking point for food reinforcement [Bowman & Brown, 1998], analogous to the effects of STN lesions [Baunez et al., 2002]. Therefore, our results following STN lesions are not surprising. Specifically, cue-induced reinstatement is blocked because it is dependent on the core; while cocaine-primed reinstatement is spared because it is dependent on both the core and shell.

Our results argue against the possibility that STN lesions disrupt a stimulus-reward association since CS-induced reinstatement of food-seeking behavior remains intact. Furthermore, STN lesions do not interfere with the association between a CS and food reward [Baunez et al., 2002] or food conditioned place preference [Baunez et al., 2005]. Moreover, our results cannot be explained by a motor impairment produced by STN lesions. To illustrate, STN lesions did not affect food or cocaine SA on an FR-5

schedule of reinforcement or locomotion following i.p. cocaine administration during cocaine-primed reinstatement. In addition, Baunez et al. report no motor disinhibition [2002] or changes in cocaine-induced locomotion [2005] following STN lesions. In fact, STN lesions typically produce a hyperkinetic effect instead of a motor depression [Whittier, 1947; Phillips & Brown, 1999]. Therefore, an increase in lever pressing during cocaine-primed reinstatement of cocaine-seeking behavior would be predicted rather than the lack of effect we observed. In addition, we found no difference in the number of lever presses during "time-out" periods between groups, arguing against an effect of STN lesions on motor behavior.

Electrophysiological Correlates in NAcc during the Reinstatement of Food-seeking Behavior

Similar to previous studies [Carelli & Deadwyler, 1994; Bowman et al., 1996; Carelli & Deadwyler, 1997; Carelli et al., 2000; Roop et al., 2002], we observed changes in the firing rate of NAcc neurons relative to operant responding for sucrose reward. Our study differs, however, because we investigated electrophysiological correlates in both subregions of the NAcc. Although we observed neurons in both the core and shell that were responsive to the operant response and sucrose, we found a greater proportion of responsive neurons in the core. Similar response properties between core and shell have observed in approach to novelty in rats [Wood & Rebec, 2004]. This difference in responsiveness may result from glutamatergic input from PFC preferentially innervating the core over the shell [Berendse et al., 1992]. In fact, the PFC is part of the circuitry implicated in the translation of motivation into action [Kalivas et al., 1999].

Similar to in sham controls, we observed a greater proportion of phasically active neurons in the core compared to shell in STN-lesioned animals. Thus, STN lesions had no effect on the distribution of responses in core and shell. However, there were differences in the normalized firing rate, or magnitude, between core neurons recorded from sham controls and STN-lesioned animals. Magnitudes were greater in sham controls in response to the operant behavior; but, magnitudes were greater in STN-lesioned animals in response to sucrose reinforcement. This indicates that the STN may differentially modulate behaviors associated with obtaining reward and reward consumption. The increase in response magnitude associated with sucrose reinforcement in STN-lesioned animals correlates with the increase in motivation for food reinforcement observed following STN inactivation via lesions [Baunez et al., 2002] or infusion of GABA agonists [Baunez & Robbins, 1999].

It is important to address the potential confound that the changes in NAcc neuronal activity reported in these experiments may be associated with the motor activity, such as locomotion and limb movement, required for an operant response. We observed a dissociation of neuronal activity when comparing firing rates within each neuron during operant responses that did not result in reward to those that did elicit reinforcement (data not shown). Other studies have yielded similar findings. For instance, the same dissociation has been found in NAcc neurons during operant responding for drug [Carelli et al., 1993; Chang et al., 1994] or natural [Schultz et al., 1992] reward.

During cue-induced reinstatement of food-seeking behavior, we observed a greater distribution of phasically active core neurons in sham controls than in STN-lesioned animals; however, there was no difference observed in the shell. This difference

in responsiveness in the core may be influenced by the glutamatergic input received from BLA [Groenewegen et al., 1990], a brain region known to be involved in cue-induced reinstatement [Kantak et al., 2002; Yun & Fields, 2003; Fuchs et al., 2006]. Additionally, STN lesions may decrease the glutamatergic input to the VP; therefore, decreasing the responsiveness of the core via an inhibitory feedback circuit [Maurice et al., 1998]. The convergence of input from the BLA and from the inhibitory feedback circuit may account for the decrease in responsiveness in the core observed in STN-lesioned animals. Another possible explanation is that STN lesions may disrupt the association of the CS and sucrose, resulting in less activation of core neurons. While it has been shown that STN lesions disrupt the association of CS and unconditioned stimuli [Winstanley et al., 2005], we found that CS-induced reinstatement of food-seeking behavior is left intact indicating that STN-lesioned animals were able to associate the CS with sucrose reinforcement.

During food-primed reinstatement, there was a similar effect in the shell. Specifically, there was a greater distribution of phasically active shell neurons in sham controls than in STN-lesioned animals. Moreover, in sham controls, shell neurons exhibited a significantly higher normalized firing rate, or response magnitude. The shell subregion of the NAcc has been associated with the modulation of the salience and reinforcing effects of natural reward [Cardinal et al., 2002; Di Chiara, 2002]. In fact, functional magnetic resonance imaging (*f*MRI) in humans indicates that the STN and NAcc are involved in immediate reward prediction [Tanaka et al., 2004]. Further, electrophysiological recordings in monkeys [Darbaky et al., 2005] and in rats [Baunez et al., 2006; Teagarden & Rebec, 2007] show STN neurons responsive to reward.

Therefore, it is possible, via connections with the NAcc, that the STN has an effect on reward salience and prediction.

At first glance it may appear contradictory that we observed differences in the electrophysiological correlates, but not in the behavior, of food-seeking behavior between sham controls and STN-lesioned animals. It is likely that the FR-5 schedule of reinforcement we used was not very demanding for the animal. A PR schedule of reinforcement would require much more effort and, therefore, expose differences in food-seeking behavior. In fact, this has been previously demonstrated [Baunez et al., 2002] and is the reason why we used a PR schedule of reinforcement in subsequent experiments reported here. Additionally, given that STN lesions increase the motivation for natural reward [Baunez et al., 2002; Baunez et al., 2005], one might predict an increase in cue-induced and food-primed reinstatement in STN-lesioned animals. A possible explanation why we did not find an increase is that the reinstatement tests we used were not sensitive enough. It is possible that we would have seen an increase in the reinstatement of food-seeking behavior in STN-lesioned animals if the latency to extinguish responding was measured, rather than the response rate. Specifically, STN-lesioned animals may have taken longer to extinguish responding during the reinstatement tests compared to sham controls.

Electrophysiological Correlates in NAcc during the Reinstatement of Cocaine-seeking Behavior

In both the core and shell of sham controls, we sampled neurons that exhibited changes in firing rate relative to the operant responding for cocaine reward. Specifically,

the firing rate of core and shell neurons increased and/or decreased relative to the lever press to obtain cocaine, the CS associated with cocaine, or the infusion of cocaine. This result is consistent with previous electrophysiological recordings obtained from the NAcc [Peoples et al., 1997; Carelli & Ijames, 2001; Carelli, 2002] and provides additional evidence for a role of the NAcc in cocaine-seeking behavior. Although we observed phasically active neurons in both the core and shell, there were a greater proportion of these neurons in the core. In addition to core neurons exhibiting a greater change in response magnitude, similar response distributions have been found between core and shell during cocaine SA [Ghitza et al., 2004]. The difference in response distribution correlates with differences in connectivity between core and shell. The core is thought to be part of the circuitry, along with the PFC and VP [Brog et al., 1993], involved in the execution of the cocaine-seeking response [McFarland & Kalivas, 2001; McFarland et al., 2003]. The shell, which is similar in connectivity to the extended amygdala [Brog et al., 1993], may help in the processing of learned information regarding the salience of stimuli associated with reward [Ghitza et al., 2003]. In fact, we observed a greater proportion of neurons exhibiting an excitation relative to the operant response in the core compared to in the shell.

Although we found phasically active neurons in both the core and shell of STN-lesioned animals, there was no difference in response distributions between core and shell. Therefore, when compare to the difference in response distribution observed in sham controls, STN-lesions had an effect on the response distribution between core and shell. This finding indicates that the STN may influence NAcc electrophysiological correlates of cocaine-seeking behavior. Indirect connectivity with the NAcc, particularly

the core [Maurice et al., 1998], may allow the STN to modulate accumbal neuronal activity. Indeed, we did find fewer phasically active core neurons in STN-lesioned animals compared to in sham controls. Furthermore, core neurons recorded from STN-lesioned animals exhibited a higher magnitude during reinforcement compared to core neurons recorded from sham controls.

Interestingly, during operant responding for sucrose, we observed a significantly smaller proportion of excitatory core neurons in STN-lesioned animals compared to in sham controls. During cocaine SA, however, this effect was absent. These results imply that in the drug-free state, STN lesions decrease excitatory neuronal responses in the NAcc core. As shown in the schematic ("limbic circuit") in Figure 1, STN lesions would increase excitatory feedback to cortex. It is likely that this would result in an increase in the excitatory input to the NAcc core; therefore, increasing the baseline activity of core neurons. In fact, we did observe a trend towards a higher baseline firing rate of core neurons in STN-lesioned animals. An increase in baseline activity would make the occurrence of excitatory responses less frequent.

During cue-induced reinstatement of cocaine-seeking behavior, there was a trend towards a greater proportion of phasically active neurons in both the core and shell of STN-lesioned animals compared to in sham controls. In light of the anatomical relationship between the STN and core [Maurice et al., 1998], an increase in phasically active neurons selectively in the core might be expected. It is possible that we observed a similar increase in the shell because, while the core is believed to be critical in cue-induced reinstatement [Di Ciano & Everitt, 2001], recent evidence indicates that the shell may play an important role in context-induced reinstatement [Bossert et al., 2006]. In our

experiments, it is possible that, in addition to a cue that was previously paired with cocaine, context may have played a role in the reinstatement of cocaine-seeking behavior. Despite this possibility, these data, along with the attenuation of cue-induced reinstatement following STN lesions, indicate STN involvement in both cocaine-seeking behavior and the electrophysiological correlates associated with this behavior. In fact, as mentioned above, both the STN and NAcc are involved in reward prediction and evaluation [Tanaka et al., 2004].

It is important to bear in mind that the electrophysiological recordings collected from STN-lesioned animals during cue-induced reinstatement consisted of only a couple trials. Since cue-induced reinstatement was attenuated in these animals, we were only able to obtain 1 – 2 trials of CS presentation. A larger number of CS presentations would have allowed us to record neuronal activity over several trials; therefore, differences in response properties may have been more evident. Regardless, we still observed a trend towards a greater proportion of phasically active neurons in both the core and shell of STN-lesioned animals compared to in sham controls during cue-induced reinstatement.

We observed a higher proportion of phasically active shell neurons in STN-lesioned animals compared to in sham controls; however, no difference was found in the proportion of phasically active core neurons during cocaine-primed reinstatement. Interestingly, we observed the opposite effect during food-primed reinstatement. Specifically, there were a greater proportion of phasically active shell neurons in sham controls compared to in STN-lesioned animals. Collectively, these data indicate that the STN may differentially modulate the salience of natural and cocaine reward via connections with the NAcc. Several studies indicate that the shell is involved in the

modulation of the salience and reinforcing effects of both natural and drug reward [Pontieri et al., 1995; Cardinal et al., 2002; Di Chiara, 2002].

It is interesting to note that STN lesions did not affect cocaine-primed reinstatement of cocaine-seeking behavior even though there was an effect on electrophysiological correlates in the shell. One possible explanation is that the dose we used enhanced the psychomotor activating effects of cocaine in STN-lesioned animals; therefore, causing these animals to be more behaviorally active than the sham controls. Our results argue against this explanation, as there was no difference in locomotion during cocaine-primed reinstatement between STN-lesioned animals and sham controls. Alternatively, STN modulation of cocaine-seeking behavior may be dose-dependent. In other words, it is possible that using a different dose of cocaine for the priming injection would have produced an effect, since STN lesions have been shown to have differential effects on cocaine SA depending on the dose of the cocaine infusions [Uslaner et al., 2005]. Therefore, it would be interesting to test a range of cocaine doses in a cocaine-primed reinstatement test in STN-lesioned animals.

Effect of STN Lesions on Operant Responding for Food or Cocaine on a PR Schedule of Reinforcement

The finding that STN lesions increase operant responding for sucrose on a PR schedule of reinforcement, but attenuate operant responding for cocaine is consistent with previous reports [Baunez et al, 2002; Baunez et al., 2005]. The same result has been produced via reversible inactivation of the STN by infusion of GABA receptor agonists [Baunez et al., 2005]. Similarly, STN lesions enhance the preference for food-associated

environment while decreasing the preference for a cocaine-associated environment [Baunez et al., 2005]. Along with the results presented earlier, these results confirm involvement of the STN in motivational processes.

Our findings are at odds with those of Uslaner et al. [2005]; who report STN lesions enhance the psychomotor-activating effect of cocaine, the rate at which cocaine SA is acquired, and the motivation for cocaine under a PR schedule of reinforcement. Several methodological differences may account for this discrepancy. First of all, there is a difference in the concentration of ibotenic acid used to lesion the STN. Uslaner et al. [2005] used a higher concentration than the experiments reported here and those of Baunez et al. [2002, 2005]. It is possible that a higher concentration damaged the surrounding areas in addition to the STN. Thus, the discrepancy in results may be due to differences in STN lesion size or damage to surrounding areas. Neither Baunez at al. [2002, 2005] nor Uslaner et al. [2005] quantify the extent of STN lesions. In fact, the experiments reported here are the first to quantify the extent of STN lesions following ibotenic acid administration. It would be interesting to quantify STN damage following administration of a higher concentration of ibotenic acid and compare the results to those we report here. This issue will need to be investigated in future studies. Secondly, there are differences in the PR task. For instance, the progression of lever presses we used required more responding than the progression used by Uslaner et al. [2005]. Third, the dose of cocaine reinforcement differed between studies. We used a dose that has been previously demonstrated to maintain SA behavior [for example, Sun & Rebec, 2003] while Uslaner et al. [2005] used a range of doses that differentially affected SA behavior. Finally, our animals were tested in the light period of the light/dark cycle, whereas

Uslaner et al. [2005] tested animals during the dark period. This difference may be important because cocaine SA can be dramatically influenced by context [Caprioli et al., 2007].

Electrophysiological Correlates in NAcc during Operant Responding for Food on a PR Schedule of Reinforcement

Similar to the findings reported here obtained from animals operant responding for sucrose on an FR-5 schedule of reinforcement, we observed changes in neuronal activity of core and shell neurons relative to operant responding for sucrose on a PR schedule of reinforcement. These findings are consistent with previous electrophysiological recordings of NAcc neurons in animals performing similar tasks [Carelli & Deadwyler, 1994; Bowman et al., Carelli & Deadwyler, 1997; Carelli et al., 2000; Roop et al., 2002]. In Experiment 1, we discovered differences in response properties between core and shell in animals responding on an FR-5 schedule of reinforcement; however, no such differences were found in animals responding on a PR schedule of reinforcement. There are a couple of possible explanations for this lack of effect. First of all, the number of neurons sampled from animals responding on the PR schedule was substantially smaller than the number sampled in Experiment 1; therefore our results must be interpreted with caution. Thus, differences in response properties may have surfaced if a larger sample of neurons were recorded. Secondly, there are inherent differences between an FR-5 and PR schedule of reinforcement. To illustrate, under an FR-5 schedule of reinforcement, an animal is only required to produce 5 responses in order to receive a reward; but under a PR schedule of reinforcement, an

animal is required to produce a number of responses that increases for each subsequent reward. Therefore, an FR-5 schedule is though to measure rate of reward intake; while a PR schedule is though to measure the reinforcing efficacy of a reward [Arnold & Roberts, 1997]. In light of this difference, it may be more appropriate to analyze neuronal activity on a trial-by-trial basis when using a PR schedule of reinforcement rather than analyzing all of the trials collectively, as we have done here.

As in sham controls, there were no differences in the distribution of phasically active neurons between core and shell in STN-lesioned animals. Thus, STN lesions had no effect on the distribution of responses in core and shell. However, we did observe differences in response properties of NAcc neurons between sham controls and STN-lesioned animals. The first difference was a significantly higher proportion of core neurons that exhibited an inhibition to sucrose reinforcement in STN-lesioned animals compared to in sham controls. Earlier electrophysiological recordings in intact animals have shown a majority of NAcc neurons responding to natural reward with an inhibition [Carelli et al., 2000]. Therefore, an increase in inhibited core neurons in STN-lesioned animals could be interpreted as an in increase in the reinforcing efficacy of sucrose. This interpretation is consistent with our behavioral data showing an augmented breaking point for sucrose reinforcement in STN-lesioned animals.

A second difference was the lower normalized firing rate of excitatory core neurons during reinforcement observed in STN-lesioned animals compared to in sham controls. Although it is difficult to reconcile this result with the finding of an increase in inhibited core neurons in STN-lesioned animals, it may still reflect a difference in the coding of the reinforcing efficacy of sucrose. An alternative explanation for these results

is an effect of STN lesions on the neuronal coding of the CS that occurred simultaneously with sucrose reinforcement. The NAcc core is necessary for the motivational effects of a reward-paired CS [Di Ciano and Everitt, 2001; Hotsenpiller et al., 2001]. Further, as we have shown here, NAcc core neurons are responsive to a CS that is paired with reward and to the CS during cue-induced reinstatement of reward-seeking behavior. Thus, via its connectivity with the core [Groenewegen & Berendse, 1990], the STN may play a role in the modulation of the motivational effects of a reward-paired CS.

Electrophysiological Correlates in NAcc during Cocaine SA on a PR Schedule of Reinforcement

Similar to the findings obtained from animals self-administering cocaine on an FR-5 schedule of reinforcement discussed above, both core and shell neurons exhibited changes in firing rate associated with operant responding for cocaine on a PR schedule of reinforcement. Several other studies have demonstrated the same phenomenon in NAcc neurons [Chang et al., 1994; Peoples et al., 1997; Carelli & Ijames, 2001; Carelli et al., 2002]. In this experiment, we observed a higher proportion of phasically active neurons in the shell compared to in the core, whereas we found the opposite distribution in animals self administering cocaine on an FR-5 schedule of reinforcement (Experiment 2). The difference in core and shell response distributions between these two experiments likely reflects differences in the schedules of reinforcement. As mentioned above, an FR schedule is believed to measure reward intake; while a PR schedule is thought to be a measurement of the reinforcing efficacy of a reward [Arnold & Roberts, 1997]. The core may be more critical for cocaine SA on an FR-5 schedule. In fact, the core, along with

the PFC and VP [Brog et al., 1993], is involved in the execution of cocaine-seeking responses [McFarland & Kalivas, 2001; McFarland et al., 2003]. On the other hand, the shell, which is similar in connectivity to the extended amygdala [Brog et al., 1993], is involved in the modulation of the reinforcing effects of cocaine [Bari & Pierce, 2005] and the processing of reward salience [Ghitza et al., 2003].

In STN-lesioned animals we found a higher proportion of phasically active core neurons compared to in sham controls. This result indicates that the STN may modulate core neuronal activity associated with the execution of cocaine-seeking responses. Alternatively, core neuronal activity associated with the pairing of a cue with reward may be modulated by the STN. This explanation is plausible because of: 1) the core is critical for cue-induced reinstatement of cocaine-seeking behavior [Di Ciano & Everitt, 2001], 2) the input the core receives from the BLA [Groenewegen et al., 1990], another region critical in cue-induced reinstatement [Kantak et al., 2005], and 3) the connectivity between the core and the STN [Groenewegen & Berendse, 1990]. Although STN lesions had an effect on response properties in the core, this may not account for decreased breaking point for cocaine reinforcement observed in STN-lesioned animals.

When analyzing the response properties of shell neurons, we found the opposite effect of STN lesions. Specifically, in STN-lesioned animals there was a higher proportion of phasically active shell neurons compared to in sham controls. Through connections within the limbic circuitry [Nauta & Cole, 1978; Haber et al., 1985], the STN is in position to play a role in modulating the reinforcing effects of reward. Given that the shell is involved in the modulation of the reinforcing effects of cocaine [Bari & Pierce, 2005] and reward salience [Ghitza et al., 2003], it is not surprising that the STN

lesions have an effect on the response properties of shell neurons. In fact, the normalized firing rate, or magnitude, of shell neurons during cocaine infusions was lower in STN-lesioned animals compared to in sham controls. Collectively, these data implicate a role of the STN, via its position in the limbic circuitry, in the coding of cocaine salience and; therefore accounting for the attenuated breaking point for cocaine observed in STN-lesioned animals.

Summary

The first aim of these experiments was to investigate the effects of STN lesions on the reinstatement of food- and cocaine-seeking behavior. We demonstrated that bilateral STN lesions differentially affect the reinstatement of food- and cocaine-seeking behavior. Specifically, bilateral STN lesions attenuated cue-induced reinstatement of cocaine-seeking behavior; however, cue-induced reinstatement of food-seeking behavior and both food- and cocaine-primed reinstatement were unaffected. This dissociation is consistent with findings from previous STN lesion work [Baunez et al., 2002; Baunez et al., 2005]. Baunez and colleagues [2005] posit that the STN "exerts opposite control on cocaine and 'natural' rewards". Our findings suggest that STN may not exert opposite control over reward type; instead the STN may differentially modulate reward type.

Much emphasis has been placed on the mesocorticolimbic circuit, particularly the NAcc, as the neural substrate underlying the reinforcing effects of reward. Not much work has been done investigating the electrophysiological correlates of the reinstatement of reward-seeking behavior. In fact, there is only one study investigating NAcc neuronal correlates during a reinstatement test [Carelli & Ijames, 2000]. Carelli & Ijames [2000]

assessed NAcc correlates in a within session reinstatement test; therefore, there are no studies investigating electrophysiological correlates in a between session reinstatement task, which serves as a model for drug craving and relapse in humans. The second objective of these experiments was to investigate NAcc electrophysiological correlates in a between session reinstatement task. During both food- and cocaine- seeking reinstatement tests, we demonstrated the presence of neuronal correlates in both NAcc subregions. Furthermore, we found differences in neuronal correlates between the reinstatement of food-seeking and cocaine-seeking behavior. Similar differences in NAcc response properties have been reported between food and cocaine reinforcement [Carelli et al., 2000; Carelli, 2002].

Through its connectivity in the limbic system [Groenewegen & Berendse, 1990; Maurice et al., 1998], the STN is in a position to modulate cognitive and limbic functions. Given that the NAcc is critical for cue-induced and reward-primed reinstatement [Di Ciano & Everitt, 2001] and that STN lesions differentially affect the reinstatement of food- and cocaine-seeking, the third aim of these experiments was to investigate the effects of STN lesions on NAcc neuronal activity during reinstatement. We demonstrated that STN lesions modulate NAcc neuronal activity in both subregions during the reinstatement of food- and cocaine-seeking behavior. Therefore, we have provided additional evidence for a role of the STN in reinstatement behavior.

Finally, in light of recent experiments [Uslaner et al., 2005], there is conflicting evidence on the effects of STN lesions on operant responding for food or cocaine on a PR schedule of reinforcement. Thus, the fourth aim of these experiments was to clarify the effects of STN lesions in this paradigm in addition to investigating the effects on NAcc

neuronal correlates. We have shown that, similar to the effects on the reinstatement of food- and cocaine-seeking behavior, STN lesions differentially effect operant responding for food and cocaine on a PR schedule of reinforcement. This finding suggests that the STN differentially modulates the reinforcing efficacy of food and cocaine reward. Furthermore, we have shown that STN lesions affect NAcc neuronal activity associated with the operant responding and subsequent reinforcement under a PR schedule of reinforcement. STN modulation of neuronal activity was especially evident in the NAcc shell, a region known to mediate reward salience [Ghitza et al., 2003].

In conclusion, these experiments have demonstrated that the STN, classically considered a motor nucleus, differentially modulates the motivation, or craving, for natural and drug reward. Not only is this difference evident in behavior, but it is also manifested in the electrophysiological correlates underlying the reinforcing effects of reward. Treatment of drug addiction is often unsuccessful, as a result of the high rate of relapse following drug treatment [O'Brien & McLellan, 1996]. The experiments reported here may present new insights into the development of successful treatments for drug abuse and addiction. Thus, in addition to increasing our knowledge of food- and drug-seeking behavior and relapse, this work provides support for the STN as a potential target for developing treatments for drug addiction and relapse.

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Curriculum Vitae

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2007 **Ph.D.** Indiana University, Bloomington, IN
Major I: **Neural Science**
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1999 **B.S.** Indiana University, Bloomington, IN
Major: **Psychology**
Concentration: **Biology**

Professional Experience:

2003-2007 Research and Teaching Assistant, Department of Psychology, Indiana University, Bloomington, IN

2001-2003 Research Assistant, Training Grant in Sensorimotor Neuroplasticity, Program in Neuroscience, Indiana University, Bloomington, IN

2000-2001 Research and Teaching Assistant, Department of Psychology, Indiana University, Bloomington, IN

Awards:

Nov 2005 **Program in Neuroscience Travel Award,** Indiana University

2001-2003 **Training Grant in Sensorimotor Neuroplasticity,** Indiana University

Research:

Areas of Specialization

2004-2007 Electrophysiological analysis of nucleus accumbens in rats during cocaine or food self-administration and subsequent reinstatement following

bilateral lesions of the subthalamic nucleus, Indiana University, Principle Investigator: George Rebec, Ph.D.

2004 Electrophysiological analysis of subthalamic nucleus in rats during cocaine of food self-administration, Indiana University, Principle Investigator: George Rebec, Ph.D.

2002-2004 Electrophysiological analysis of nucleus accumbens in high alcohol drinking rats during operant responding for ethanol, sucrose, or a mixed solution, Indiana University, Principle Investigator: George Rebec, Ph.D.

2000-2002 Electrophysiological analysis of dorsal striatum in rats following various doses of ascorbate, Indiana University, Principle Investigator: George Rebec, Ph.D.

Technical Skills

Physiological: Extracellular, single-unit electrophysiology and slow-scan voltammetry in awake, behaving rats.

Surgical: Rodent stereotaxic surgery including electrode and cannulae placement and intercranial microinfusions and jugular vein catheterization for drug self-administration.

Behavioral: Operant drug self-administration procedures and behavioral analysis methods in rats.

Anatomical: Transcardial perfusions, brain sectioning, and stereology.

Professional Organizations:

Society for Neuroscience

Educational Activities:

Independent Teaching

Fall, 2002 Instructor, **Research Methodology** (P151 laboratory), Indiana University (student evaluations available upon request)

2001-2007 **Trainer and supervisor** of 8 undergraduate research assistants enrolled in Supervised Research I and II (P493/P494) or Honors Thesis Research (P499), Indiana University

Assistant Teaching

Fall, 2006 Associate Instructor, **Cognitive Psychology** (P335), Indiana University

Fall, 2006 Associate Instructor, **Developmental Psychobiology** (P410/P444), Indiana University

Spring, 2006 Associate Instructor, **Integrated Freshman Learning Experience II** (H112), Indiana University

Fall, 2005 Associate instructor, **Neuropsychology of Language** (P457/P657), Indiana University

Fall, 2005 Associate Instructor, **Human Neuropsychology** (P423), Indiana University

Spring, 2005 Associate Instructor, **Integrated Freshman Learning Experience II** (H112), Indiana University

Fall, 2004 Associate Instructor, **Behavioral Neuroscience** (P326), Indiana University

Fall, 2004 Associate Instructor, **Psychology of Learning** (P325), Indiana University

Spring, 2004 Associate Instructor, **Introductory Psychology I** (P101), Indiana University

Fall, 2003 Associate Instructor, **Statistical Techniques** (K300), Indiana University

Spring, 2001 Associate Instructor, **Behavioral Neuroscience** (P326), Indiana University

Papers Presented at Professional Meetings:

1. Society for Neuroscience, 36th Annual Meeting, Atlanta, GA (October 2006)
   J.J. Cortright, G.V. Rebec Electrophysiological recording in nucleus accumbens during cocaine-seeking behavior in subthalamic nucleus-lesioned rats.

2. Society for Neuroscience, 36th Annual Meeting, Atlanta, GA (October 2006)
   C. Baunez, **J.J. Cortright,** G.V. Rebec Coding of various types of reward within the rat's subthalamic nucleus.

3. Federation of European Neuroscience Societies, Vienna, Austria (July 2006)
   C. Baunez, **J.J. Cortright,** G.V. Rebec Electrophysiological activity of subthalamic nucleus neurons in rats working for sucrose or cocaine reward.

4. Gill Center Symposium and Award, Bloomington, IN (May 2006)
   Cortright, J.J., Rebec, G.V., Baunez, C. Electrophysiological recording in subthalamic nucleus during cocaine-seeking behavior in rats.

5. Society for Neuroscience, 35th Annual Meeting, Washington, DC (November 2005)
   Cortright, J.J., Rebec, G.V., Baunez, C. Electrophysiological recording in subthalamic nucleus during cocaine-seeking behavior in rats. Soc. Neurosci. Abstr., Prog. 541.11, 2005.

6. Society for Neuroscience, Indianapolis Chapter Annual Meeting, Indianapolis, IN (May, 2005)
   Cortright, J.J., Kosobud, A.E.K., Rebec, G.V. Neuronal activity in nucleus accumbens core and shell of high alcohol drinking rats during operant responding for sucrose, ethanol, or a mixed solution.

7. Indiana University Animal Behavior Conference, 12th Annual Meeting, Bloomington, IN (April, 2005)
   Cortright, J.J., Kosobud, A.E.K., Rebec, G.V. Neuronal activity in nucleus accumbens core and shell of high alcohol drinking rats during operant responding for sucrose, ethanol, or a mixed solution.

8. Society for Neuroscience, 34th Annual Meeting, San Diego, CA (October, 2004)
   Cortright, J. J., Kosobud, A. E. K., and Rebec, G. V. Electrophysiological recordings in nucleus accumbens core and shell of high alcohol drinking rats during operant responding for either sucrose, ethanol, or a mixed solution. Soc. Neurosci. Abstr., Prog. 437.7, 2004.

9. Society for Neuroscience, 33rd Annual Meeting, New Orleans, LA (November, 2003)
   Cortright, J. J., Kosobud, A. E. K., Rebec, G. V. Single-unit recording in nucleus accumbens core and shell in high alcohol drinking rats during operant responding for either sucrose or ethanol. Soc. Neurosci. Abstr., Prog. 292.8, 2003.

10. Society for Neuroscience, 32nd Annual Meeting, Orlando, FL (November, 2002)
    Cortright, J. J., Rebec, G. V., Single-unit recording in striatum in response to sensorimotor stimulation and under various doses of ascorbate in freely moving rats. Soc. Neurosci. Abstr., Vol. 28, Program No. 461.6, 2002.

11. Society for Neuroscience, 31st Annual Meeting, San Diego, CA (November, 2001)
    Cortright, J. J., Rebec, G. V. Single unit recording in striatum under low, moderate, and high doses of ascorbate in freely moving rats. Soc. Neurosci. Abstr., Vol. 27, Program No. 292.1, 2001.

Publications:

Original Research Articles

Cortright J. J., Rebec G. V. (2006) Ascorbate modulation of sensorimotor processing in striatum of freely moving rats. Brain Res. 1092: 108-116.

Baunez C., **Cortright J. J.**, Rebec G. V. Differential coding for natural and cocaine reward in the subthalamic nucleus of rats. *In preparation.*

Cortright J. J., Kosobud A. E. K., Rebec G. V. Neuronal activity in nucleus accumbens core and shell of high alcohol drinking rats during operant responding for sucrose, ethanol, or a mixed solution. *In preparation.*

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