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Jennifer Marie Juergensen McGee Date

Alterations of Performance on an Attentional Task Following Manipulations of the Ventromedial Thalamic Nucleus in the Rat

By

Jennifer Juergensen McGee
Doctor of Philosophy

Psychology

_____

Darryl B. Neill, PhD
Advisor

_____ _____

Jocelyn Bachevalier, PhD
Committee Member

Joseph Manns, PhD
Committee Member

_____ _____

Patricia Brennan, PhD
Committee Member

Hillary Rodman, PhD
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

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By

Jennifer Juergensen McGee
M.A., Emory University, 2010
B.A., George Washington University, 2007

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An abstract of
A dissertation submitted to the Faculty of the
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Abstract

Alterations of Performance on an Attentional Task Following Manipulations of the Ventromedial Thalamic Nucleus in the Rat

By Jennifer MJ McGee

It is not yet understood how an organism brings together motivational and sensorimotor information to make decisions on how to respond to contingencies in their environment. Previous research suggests a pivotal role of the basal ganglia in integrating this information yet one major output of the basal ganglia, the ventromedial nucleus of the thalamus (VMT), has been largely ignored. The goal of the present study was to determine the role of the VMT in a complex test of attention in rodents, the 5-choice serial reaction time test (5-CSRTT). Primary findings were that bilateral lesions of the VMT resulted in an increased performance (as measured by an increase of accuracy, a decrease in omissions and extraneous responding) and increased time to retrieve the food reward. Further, transient deactivation using three doses of the $GABA_A$ receptor agonist muscimol resulted in a mix of responses, in particular an increase in impulsivity (as measured by an increase in premature responding). Other manipulations failed to produce a statistically significant change in behavior. We hypothesize that the lesions may have inadvertently destroyed other axons of passage, causing either motoric or motivational aberrations. The finding that muscimol increases impulsivity adds to the existing literature that has already implicated a role of the basolateral amygdala, striatum, basal ganglia and frontal cortices; four regions that are strongly connected to the VMT.

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The ability to learn a task, attend to relevant stimuli, and move towards a goal to receive a reward is an important skill for survival. These behaviors require the activation and synchrony of many different brain structures, including the limbic system, the basal ganglia, the cortex, and the thalamus. There have been numerous publications outlining the specific contributions of the limbic system in memory and goal-directed behaviors (for reviews see Mogenson, Jones, & Yim, 1980; Phillips, Ahn, & Howland, 2003; Squire, 1992), the basal ganglia's role in voluntary movement and reward salience (for reviews see Middleton & Strick, 2000; Packard & Knowlton, 2002; Wolfram Schultz, Tremblay, & Hollerman, 2000; Sesack & Grace, 2009; Vink et al., 2005; Yin & Knowlton, 2006), and the role of the cortex in decision making and other executive functions (for reviews see Alvarez & Emory, 2006; Fuster, 2008; Miller & Cohen, 2001; Miyake et al., 2000; Smith & Jonides, 1999). There are far fewer reviews on the functional contributions of the thalamus. Further, it is not yet understood how an organism brings together motivational and sensorimotor information to make decisions on how to respond to contingencies in their environment. Previous research suggests a pivotal role of the basal ganglia in integrating this information yet one major output of the basal ganglia, the ventromedial nucleus of the thalamus (VMT), has been largely ignored.

Thalamus

The mammalian thalamus has several distinct nuclei which are characterized as either "specific", referring to the motor and sensory functions of the thalamus, or "nonspecific", referring to neuromodulatory functions (Herkenham, 1979). The

neuromodulatory or nonspecific function of the thalamus is often described as having a role in awareness, wakefulness, or general arousal (Burk & Mair, 1983). Although a tremendous amount of research has been devoted to the sensory and motor functions of the thalamus, a relatively small amount has been devoted to the neuromodulatory functions.

One nonspecific nucleus of the thalamus is the ventromedial nucleus (VMT). The VMT is a longitudinally elongated nucleus of mostly medium to large multipolar and rounded closely packed cells (Herkenham, 1979). Situated ventral to the ventroanterior nucleus in the rat, the VMT receives dense GABAergic afferents from the substantia nigra pars reticulata (SNr) (Bentivoglio, Van der Kooy, & Kuypers, 1979; G. Di Chiara, M. L. Porceddu, M. Morelli, M. L. Mulas, & G. L. Gessa, 1979; Faull & Carman, 1968), and projects to the frontal cortex (Herkenham, 1979). While there is no evidence of a separate VMT in the primate brain, the primate ventroanterior (VA) nucleus receives substantial input from the SNr and therefore the VA, particularly the ventral portion of it, might be considered a homologue of the rodent VMT. This nucleus is uniquely situated to be a major output station of the basal ganglia and thus the VMT may be a juncture for critical information to reach the frontal cortices.

Basal ganglia

The basal ganglia, a group of densely interconnected nuclei located at the base of the forebrain, consist of the striatum, the globus pallidus (GP), substantia nigra (SN), and the subthalamic nucleus (STN). Decades of experimental research have illustrated that the basal ganglia play a central role in voluntary motor control. For example, activity in

the striatum has been linked to the anticipation (Apicella, Scarnati, Ljungberg, & Schultz, 1992; Schultz, Apicella, Scarnati, & Ljungberg, 1992; Vink et al., 2005), initiation (Lebedev & Nelson, 1999), and inhibition (Vink et al., 2005) of movement. Lesions to the internal segment of the GP (GPi) result in motoric slowing when moving in opposition of standard posture (Wenger, Musch, & Mink, 1999). Lesions and transient inactivation of the SN in monkeys lead to profound motoric deficits (Burns et al., 1983; Sakai & Gash, 1994). Pathological damage to the STN in humans (Lee & Marsden, 1994) or experimental lesioning of the STN in monkeys induce hemiballism (Crossman, 1987; Whittier, 1947). Clinical evidence of the role of the basal ganglia in motor function is clearly evidenced in patients with Huntington's disease, a degenerative disease affecting the striatum, and Parkinson's disease, a degenerative disease of the SN.

Although there is substantial evidence that the basal ganglia are important in voluntary movement, some structures may contribute to non-motor functions as well. Yet, because of the dense projections of the SNr to the VMT, much of the published research concerning the VMT is primarily focused on gross motor movements supported by the SNr, such as posture, circling behavior and general locomotion (Starr & Summerhayes, 1983a, 1983b). However, bilateral lesions of the VMT did not affect posture, circling behavior, or incidences of stereotypy after pharmacological manipulations of the SNr in rats (Starr & Summerhayes, 1983b), suggesting that the VMT may be receiving non-motor information from the SNr or from other brain regions. Indeed, there is substantial evidence that the SNr contributes not only to gross motor function, but also to higher order cognitive functioning (Boehler et al., 2010; Hikosaka & Wurtz, 1983a, 1983b; Rinne, Mlic, Paljärvi, & Rinne, 1989). For example, Hikosaka and

colleagues, using single neuron recording techniques, have found cells within the SNr that do not respond to simple movement, but rather respond when movement to a previously learned location is required (Hikosaka & Wurtz, 1983a, 1983b). Parkinsonian dementia has been linked to the destruction of neurons in the medial SNr (Rinne et al., 1989) and functional MRI shows activation of the SN during tasks that require flexible cognitive control (Boehler et al., 2010). This evidence thereby suggests a possible non-motor or cognitive role for the SNr-VMT pathway.

Furthermore, as illustrated in Figure 1, the medial SNr receives dense inputs from the nucleus accumbens septi (NAS) (De Leonibus, Mele, Oliverio, & Pert, 2001), a region located in the anterior, ventromedial part of the striatum (Nauta, Smith, Faull, & Domesick, 1978). Two major sources of incoming information to the NAS come from the amygdala, a limbic structure, and the ventral tegmental area (VTA), a dopamine producing nucleus in the midbrain (Nauta et al., 1978). The importance of dopamine in the NAS has been substantially demonstrated elsewhere, (see Ikemoto & Panksepp, 1999; Salamone, Correa, Farrar, & Mingote, 2007 for reviews). Briefly, the mesoaccumbal DA system is currently thought to promote behavioral activation (Gray, 1995; Salamone & Correa, 2002), conditioning (Sellings & Clarke, 2006; Wise & Schwartz, 1981), some forms of general arousal (Robbins, 1997), attention (Pliszka, McCracken, & Maas, 1996), and reward processing (Wise, 1978) amongst other functions. Additionally, a growing body of evidence suggests that the NAS is preferentially involved in some forms of impulsivity (Basar, Sesia, Groenewegen, Steinbusch, Visser-Vandewalle, & Temel, 2010; Dalley, et al., 2007). The NAS consists of two distinct subsections: the more medial "shell" region and the more lateral "core" region. The shell and core have clear

anatomical and pharmacological distinctions (Groenewegen, Wright, Beijer, & Voorn, 1999; Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991; Jongen-Ręlo, Groenewegen, & Voorn, 1993; Voorn, Gerfen, & Groenewegen, 1989) and appear to be functionally and behaviorally distinct as well.

So, while the VMT may appear to be integral to certain motor abilities, it could be a necessary structure for translating accumbal dependent motivational information to the motor cortex as evidenced by damage to the VMT preventing locomotor stimulation induced by N-methyl-d-aspartate receptor blockade in the NAS (De Leonibus et al., 2001).

Limbic system

Another major efferent pathway to the SNr originates in the basolateral nucleus of the amygdala, an area within the limbic system. The limbic system is a set of structures that are preferentially involved in memory and emotion and have long been recognized as critical for fear learning and conditioning (Calder, Lawrence, & Young, 2001; Medina, Repa, Mauk, & LeDoux, 2002). The experience of emotion and the memory for emotionally salient stimuli are integral components of motivation. For example, the presence of a predator can motivate an animal to initiate a motor sequence to escape through motor activation (e.g. a zebra running from a lion) or through motor retardation (e.g. a rat freezing when confronted with a cat). Similarly, the memory of eating something unpalatable (e.g. a monarch butterfly) can motivate an animal to avoid potentially harmful foods in the future. Fear and disgust are, therefore, two emotions which can be active behavioral motivators and the amygdala is essential for the proper

expression of them (Davis, 1992; Meunier, Bachevalier, Murray, Málková, & Mishkin, 2008; Phillips et al., 1997; Phillips & LeDoux, 1992). While historically the amygdala has been identified behaviorally as a center for negative emotions and drives, recently more research has focused on its possible role in the ability to also attend to non-fear inducing motivationally significant stimuli (Anderson & Phelps, 2001; Arana et al., 2003; Cunningham, Van Bavel, & Johnsen, 2008). For example, people who had fasted for eight hours had an increase in amygaloid activation in response to images of food, but not to motivationally irrelevant images like tools, whereas satiated participants did not have an increase in amygdaloid activation to either visual cues (LaBar et al., 2001). Similarly, bilateral lesions of the amygdala in non-human primates resulted in the inability of the animal to change their behavior based on motivational state (Machado & Bachevalier, 2007). In addition, the BLA has also been associated with impulsivity, specifically delay aversion (Ghods-Sharifi, Onge, & Floresco, 2009; Winstanley, Theobald, Cardinal, & Robbins, 2004).

The amygdala contribution to motivation and goal-directed movement is supported by direct connections to the motor and premotor cortices as well as to the prefrontal cortex in the rat (Divac, Kosmal, Björklund, & Lindvall, 1978; Kita & Kitai, 1990; Krettek & Price, 1977; Llamas, Avendano, & Reinoso-Suarez, 1977; McDonald, 1987; Sripanidkulchai, Sripanidkulchai, & Wyss, 1984), and also from dense projections to the ventral and dorsal striatum (Kita & Kitai, 1990; Mogenson et al., 1980; Sah, Faber, Lopez De Armentia, & Power, 2003) and through modulating DA output from VTA neurons in the ventral striatum (Geisler, Derst, Veh, & Zahm, 2007; A.G. Phillips, S.

Ahn, & J.G. Howland, 2003). Therefore, the amygdala-SNr connection may affect the SNr-VMT projection as well.

Functional significance

As just described, through its connections with the amygdala and the NAS, the SNr receives information encoded for both locomotion and motivational salience (Carter & Fibiger, 1978; Deniau & Chevalier, 1985; Di Chiara, M. Porceddu, Morelli, Mulas, & Gessa, 1979; Herkenham, 1979; Kha et al., 2001; Kuramoto et al., 2011; Sakai & Bruce, 2004). But what is the functional significance of this confluence? A major destination for SNr neurons is the VMT, making it one of the final outputs of the basal ganglia and possibly a bridge connecting the basal ganglia, in both "motor" and "affective" aspects, to the cortex. The highest density of terminals emanating from the VMT innervate the prefrontal cortex (PFC) in rats (Leonard, 1969), more specifically the superficial layer 1 (L1) of the PFC (Glenn, Hada, Roy, Deschenes, & Steriade, 1982; Herkenham, 1979; Kuramoto et al., 2013). Only some of these prefrontal areas are considered "motor" cortex in the rat, suggesting additional non-motor, possibly cognitive, functions of this pathway (Kuramoto et al., 2013). The widespread superficial innervation of the cerebral cortex could indicate that this nucleus may be essential for the recruiting response (Girault, Savaki, Desban, Glowinski, & Besson, 1985; Herkenham, 1980), a general activation of the cerebral cortex thought to be important for synchronizing, amplifying, and/or filtering neural activity (Castro-Alamancos, 1997). Further, the specificity of the VMT synapsing largely on L1 is worth considering. Recently, interest in the microcircuitry within the neocortex has resulted in a number of publications indicating L1 as being important for sensory processing (Palmer et al., 2012), learning (Letzkus et

al., 2011), and playing a pivotal role in some neuropsychiatric disorders (Lewis, Hashimoto, & Volk, 2005; Marin, 2012; Ruzicka et al., 2007; Yizhar et al., 2011)

The conceptualization of the VMT as a hub for coalescing information regarding both motoric and motivational salience is further supported by its involvement with nociceptive processing. Monconduit, Bourgeais, Bernard, Le Bars, and Villanueva (1999) used single cell recording techniques to demonstrate that all cutaneous receptive cells in the lateral VMT responded only to cutaneous nociceptive stimuli (both mechanical and thermal) and did not respond to non-noxious stimulation or proprioceptive stimuli. This response of the VMT occurred no matter where on the body the stimulation originated. Additionally, the expectation of visually noxious stimuli also resulted in midline thalamic activation in humans (Herwig, Kaffenberger, Baumgartner, & Jancke, 2007; Herwig, Abler, Walter, & Erk, 2007) and lesions of the VMT impaired the learning ability of rats to avoid footshock (Neill, unpublished). The role of the VMT in identifying noxious stimuli and adapting behavior accordingly is just starting to be parsed out.

Anatomically, it would appear that the VMT is ideally positioned to contribute to the completion of motor tasks to achieve a reward or to avoid punishment. Previous unpublished research from the Neill lab showed a dramatic impairment in the ability to learn to lever-press for food or water reward, run a straight-alley for food reward, or run a straight-alley to avoid footshock after bilateral electrolytic VMT lesions (Neill, unpublished). Rats with VMT lesions showed marked impairments in learning to navigate around a series of detours for a food reward and when learning to avoid foot shock (Thompson, Huestis, Crinella, & Yu, 1987). We decided to follow up on these

findings and test the idea that recruitment of the VMT is necessary for a complex cognitive task that requires motivation, sustained attention, and a motor response.

5-CSRTT

The continuous performance test (CPT), has long been used clinically as an objective evaluation of attention in humans (Riccio, Waldrop, Reynolds, & Lowe, 2001), and has been adapted for rodents as the five-choice serial reaction time task (5-CSRTT; (Bari, Dalley, & Robbins, 2008; Carli, Robbins, Evenden, & Everitt, 1983). While originally developed to test attentional processes in animals, further research has validated its use as a measure of response disinhibition/impulsivity, cognitive flexibility/compulsivity, and processing speed (Amitai & Markou, 2010; Robbins, 2002). In this task the rat is expected to attend to 5 holes in anticipation of a light stimulus. A nose poke in the hole where a light was briefly flashed results in the delivery of a food pellet. Across a 30 min test, the rat can make errors of omission by not responding during the allotted time, errors of commission by nose-poking in the wrong hole, and premature responses between trials.

Because this test requires sustained attention to accomplish we anticipated that both permanent (electrolytic lesion) and transient (injection of the $GABA_A$ receptor agonist muscimol) VMT inactivation, by reducing cortical arousal, would cause an increase in errors of omission. Increases in omissions in the 5-CSRTT occur after disrupting other parts of the circuitry being examined. For example, rats with excitotoxic lesions of the lateral striatum showed severe disturbances in responding, including a marked increase in omissions (Rogers, Baunez, Everitt, & Robbins, 2001). Although the

striatal damaged rats showed locomotor and food consumption rates similar to controls, they failed to respond to more to than 90% of the trials (Rogers et al., 2001). Lesions of the medial striatum also showed in an increase in omissions, but the rats were able to recover to pre-surgical responding rates after a few sessions (Rogers et al., 2001). Omissions were also increased after the application of a D1 or D2 receptor antagonist to the nucleus accumbens (Pezze, Dalley, & Robbins, 2006). Selectively inactivating the subthalamic nucleus using an NMDA receptor antagonist or a $GABA_A$ agonist also increases omissions on the 5-CSRTT (Baunez & Robbins, 1999). And finally, selective destruction of the pregenual area of the frontal cortex (an area heavily innervated by the VMT) caused in increase in omissions, whereas destruction of the post-genual area did not (Passetti, Chudasama, & Robbins, 2002).

Electrolytic lesion experiments have the weakness of damaging axons passing through the target area, complicating interpretation. We conducted the lesion experiment because prior studies in the Neill laboratory found learning impairments used this method (Neill, unpublished). In addition, transient manipulations of VMT function were conducted to evaluate the role of VMT cell bodies. Intra-VMT injection of lidocaine was used to inactivate both the cell bodies and axons of passage through the VMT; the expectation was a lesion-like effect on performance. Intra-VMT injection of muscimol (a $GABA_A$ agonist) would inactivate only the cell bodies of the VMT. If VMT cell bodies play a role in the attentional abilities of rats, this should result in a decline in performance. If the axons passing through this area are the important structures for this attentional task, then the muscimol will not affect performance. Finally, the injection of picrotoxin (a $GABA_A$ antagonist) should activate the VMT cell bodies. We hypothesized

that this would improve 5-CSRTT performance, due to the glutamatergic innervation of the prefrontal cortex. If the lidocaine, but neither the muscimol nor the picrotoxin was effective, the results would be consistent with the idea that axons of passage normally facilitate the performance of this task.

Although prior research in the Neill lab (Neill, unpublished) did not find a significant alteration in motoric capabilities following electrolytic lesions, Starr and Summerhays (1983a) found that transient deactivation of VMT neurons via local injections of the GABA agonist muscimol resulted in profound catalepsy while GABA antagonists resulted in hyperactivity (Starr & Summerhayes, 1983a). Conversely, Jeljeli et al. (2003) showed that bilateral electrolytic lesions of the VL-VM thalamic complex impaired the acquisition, but not the performance of a motor skill in cats. These results suggested a more subtle effect of VMT lesions than simply a motoric deficiency. Consistent with this result, Neill (unpublished) has shown electrolytic lesions of the VMT impair rats' ability to learn a variety of operant tasks, while showing minimal effect on preoperatively learned tasks. For both the results of Jeljeli et al. and Neill, if the effect of VMT damage was simply motoric, performance of preoperatively learned tasks should have been affected. Therefore, analyzing response latencies was important in the current experiment.

Summary

The goal of the present study was to determine the role of the VMT in a complex test of attention, the 5-choice serial reaction time test (5-CSRTT). Because the VMT receives information, indirectly via the SNr, from brain regions that are essential to both focusing attention to salient stimuli and motoric activation, and then projects to the PFC,

an area preferentially important in planning and executing goal directed movement, we hypothesized that an intact VMT would be critical for successful completion of the 5-CSRTT. Furthermore, we hypothesized that activation of this area through pharmaceutical manipulation would enhance performance on the 5-CSRTT, whereas deactivation and lesion of the VMT will hinder performance. Various response latencies were recorded to gain insight into any possible motoric or motivational effects on responding.

Materials and Methods Experiment 1: VMT Lesion

Subjects

All subjects were adult male Sprague-Dawley rats (Harlan Sprague Dawley, Indianapolis), singly housed under temperature-controlled conditions and in an alternating 12 hour light/dark cycle. The rats were deprived of food and maintained at 90% of their free feeding weight throughout the experiment. All testing occurred at a regular time during the light period. Animals were approximately 7 months of age and weighed approximately 450g at surgery. Six rats were lesioned and seven rats were sham lesioned. All experimental procedures were carried out in accordance with Emory's Division of Animal Resources (DAR), approved by the Institutional Animal Care and Use Committee of Emory University, and were in compliance with National Institutes of Health guidelines for the care and use of laboratory animals.

Apparatus

The test apparatus consisted of three five-hole operant conditioning chambers (Med Associates, Vermont), each individually contained within a ventilated and sound attenuated chamber. On one side of each chamber, five evenly spaced square apertures

(2.5 cm x 2.5 cm x 4 cm deep) each containing a single LED light were set 2 cm above the floor within a curved wall. An infrared beam located at the entrance of each aperture enabled detection of nose-poke responses. Located on the opposite wall, a trough type pellet hopper (2 in x 2 in), with a LED light in the rear and infrared beam at the entrance, delivered reward pellets (45mg nutritionally balanced food pellets; BioServe, Frenchtown, NJ). A 3W incandescent overhead lamp was positioned above the pellet hoper and was illuminated to serve as a ready signal to indicate the upcoming trial.

Training

Habituation to the testing apparatus: 10 reward pellets were placed in the food hopper and 2 pellets in each of the 5 response holes for each of the three operant boxes. For the first training session the house light, the light in the food hopper, and the lights in the response holes were illuminated. Rats were placed in the box for 15 minutes to acclimate to the box and learn the positions of the holes. All rats consumed all the pellets during the first day of habituation training.

5-CSRTT training: No pellets were placed in the food hopper or in the response holes. The beginning of the session started with the delivery of a free reward pellet. Head entry into the food receptacle initiated the first trial. After an inter-trial interval (ITI) of 5 s, a light in one of the five response holes illuminated for a short period. The spatial presentation of the light varied randomly between the five response holes throughout the trial. Responses in the correct hole within the period after the light illuminated (limited hold period; LH) were recorded as correct responses. Correct responses were followed by a single food reward, dropped down the reward receptacle. Responses in a non-illuminated hole (incorrect responses), failure to respond within the

LH (omissions), and responses during the ITI (premature responding) were recorded and punished by a 5 second timeout period, during which all lights in the chamber were turned off. Repeated responding after a correct response (perseverative responding) was recorded, but not punished. After making the correct response, a single food pellet was delivered. Every new trial – after a correct response or a timeout period – was initiated by a response breaking the infrared beam in the food receptacle. On each trial, only one response hole was illuminated. The sequence of possible events in the 5CSRTT procedure is shown in Figure 2. Training sessions were comprised of 100 trials or 30 minutes, whichever came first.

There were 6 training stages (see Figure 3) that differed by the duration of the stimulus (the light in the response hole), the inter-trial-interval, the limited hold, and/or the performance criterion to move to the next stage.

Rats were trained until they met the criterion of >50 correct responses, >70% accuracy, and <20% omissions for at least four days on stage 6. This constituted the rat's baseline responding.

Surgical procedure

Previously food deprived, the rats were given free access to food and water for at least 7 days prior to surgery. The rats were then deeply anesthetized with isoflurane (99.9% / ml, Piramal Healthcare) and secured in a Kopf stereotaxic frame fitted with atraumatic earbars. The scalp was retracted to expose the skull, and craniotomies were made directly above the target region of the brain [anteroposterior (AP), 6.6; mediolateral (ML) 1.7; dorsoventral (DV), 2.8; all relative to the interaural line]. Bilateral lesions were made with a 0.25 mm dia stainless steel wire, insulated except for the cross-

sectional area of the tip through which a direct current at an intensity of 1 ma was passed between the electrode (anode) and a saline-soaked gauze square wrapped around the animal's tail for 10 sec (cathode). Sham surgeries were performed in the same method without passing current through the brain. Rats were carefully observed for 24 to 48 hours following all surgical procedures and were allowed to recover for a minimum of seven days before behavioral training. Food and water were available *ad libitum* during the recovery process.

5-CSRTT Testing

Prior to testing, all rats were placed on a restrictive food deprivation schedule to maintain 90% of their free feeding weight. When body weights were at 90% of their free feeding level, postoperative behavioral testing began. The first two 5-CSRTT postoperative sessions were Stage 5 (light duration of 2.5 sec); all subsequent sessions were at Stage 6 (1.25 sec), see Figure 3.

Performance measures

Accuracy: The proportion of responses that were correct (number of correct responses/total number of responses), expressed as a percentage. This measured errors of commission (incorrect responses) without including errors of omission.

Errors of omission: The number of trials in which no response was made during the limited hold period was recorded. This measure reflects possible failures of detection as well as motivational/motor deficits, depending on the overall pattern of effects.

Premature responding: The number of responses in the apertures during the ITI was recorded. This measure reflects deficits in inhibitory mechanisms of response preparation and is thought to be closely related to impulse control.

Time out responding: The number of responses in the apertures during a 5-s time out period (period of darkness) after an incorrect response, an omission, or a premature response. This measure reflects the efficacy of inhibitory processes of response control.

Total responding: The summation of all nose-pokes in a session. This measure reflects general locomotor activity as it does not consider the timing of nose-pokes.

Latency: Three measures of response speed were recorded. The first was the latency to respond correctly: the time between the onset of the light stimulus and the point at which the rat's nose broke the infrared beam of the illuminated hole. The second was the latency to respond incorrectly: the time between the onset of the light stimulus and the point at which the rat's nose broke the infrared beam of a non-illuminated hole, or incorrect hole. The third was the latency to collect reward: the time between performance of a correct response and the retrieval of the food pellet from the food receptacle.

Analysis of Results

After completion of all behavioral testing, the rats were euthanized by CO2 exposure in the Emory DAR facility in the Rollins Research Building. They were then intracardially perfused with isotonic saline followed by 10% formol-saline. After a few days of fixation, the brains were removed, 50 micron-thick frozen sections taken through the area of the lesion, and the sections mounted on slides. The sections were subsequently stained with thionine and examined to confirm lesioned areas.

One way multivariate analyses of variance (MANOVA) was performed on percent correct, percent omission, premature responses, time-out responses, and total responding using the mean data from the four days prior to surgery and the first four testing days after surgery. Standard, follow-up, univariate analyses of variance were then

performed to determine if there the groups differed prior to surgery and whether they differed after surgery. This approach was chosen because it allowed me to determine whether or not the control group differed from the experimental group prior to surgery, then it allowed me to compare the control group to the experimental group post-surgery while controlling for family-wise error. Furthermore, due to the nature of the hypothesis, I was unconcerned with interaction effects.

A paired Students T-test was performed on all measures of latency, comparing the speed of responding pre-surgery to post-surgery in seconds.

Materials and Methods – Experiments 2, 3 & 4

Subjects

All subjects were male Sprague-Dawley rats, singly housed under temperature-controlled conditions and in an alternating 12 hour light/dark cycle. Rats were deprived of food and maintained at 90% of their free feeding weight throughout the experiment. All testing occurred at a regular time during the light period. Animals were approximately 7 months of age and weighed approximately 450g at the start of behavioral training. All experimental procedures were carried out in accordance with Emory's Division of Animal Resources (DAR), approved by the Institutional Animal Care and Use Committee of Emory University, and were in compliance with National Institutes of Health guidelines for the care and use of laboratory animals.

Training

Training for experiments 2, 3 & 4 followed the same protocol as previously described (see Figure 3)

Surgical procedure

Previously food deprived, the rats were given free access to food and water for at least 7 days prior to surgery. Then the rats were deeply anesthetized with isoflurane (99.9% / ml, Piramal Healthcare) and secured in a Kopf stereotaxic frame fitted with atraumatic earbars. The scalp was retracted to expose the skull, and craniotomies were made directly above the target region of the brain. [anteroposterior (AP), 6.6; mediolateral (ML) 1.5; dorsoventral (DV), 4.0; all relative to the interaural line]. All rats were implanted with a 22-gauge bilateral guide cannulae assembly (Plastics One, Inc., Roanoke, VA) with flush stylets and a center-to-center distance of 3-4 mm. Guide cannulae tips were aimed to terminate 1 mm above the VMT (AP= 6.6, L= 1.5, DV= 4.0). Stereotaxic coordinates were obtained using the atlas of Paxinos and Watson (1998). The implants were secured to the skull with jeweler's screws and dental cement. The incisions were cleaned with an OTC antibiotic containing polymyxin B, bacitracin, and neomycin (CVS, Woonsocket, RI) and sutured in front and behind the cement skullcap with polyethylene sutures. Flush stylets were inserted in the cannulae and a protective dust cap (both Plastics One, Inc., Roanoke, VA) was attached to the top of the assembly to prevent debris from clogging the guide cannulae. Rats were carefully observed for 24 to 48 hours following all surgical procedures and were allowed to recover for a minimum of seven days. Food and water were available *ad libitum* during the recovery process.

5-CSRTT Testing

All rats were allowed at least one week postoperative recovery before food deprivation. When body weights were at the 90% free feeding level, postoperative behavioral testing began. The first two 5-CSRTT postoperative sessions were Stage 5 (light duration of 2.5 sec); all subsequent sessions were at Stage 6 (1.25 sec).

Drugs: Experiments 2 & 3 utilized the $GABA_A$ agonist muscimol HBr and the $GABA_A$ antagonist picrotoxin (Sigma-Aldrich Co., St. Louis, MO) dissolved in 0.9% w/v NaCI (saline). Experiment 4 utilized lidocaine (Sigma-Aldrich Co., St. Louis, MO) dissolved in 0.9% w/v NaCI (saline).

Intracerebral microinjections: Bilateral microinjections into the VMT were performed at a flow rate of 0.6 µl/min by means of a stainless steel infusion cannula (30 gauge; Plastics One, Inc., Roanoke, VA) cut to protrude 1 mm beyond the tip of the guide cannulae. The plastic stopper on the infusion cannula was permanently affixed using superglue to prevent injector shortening or lengthening over time. The infusion cannula was securely attached to PE-10 standard wall cannula tubing (Clay-Adams, Parsipanny, NJ) by first relaxing the tubing with friction. The other end of the PE-10 tubing was connected to a 10 µl Hamilton syringe (Hamilton Company, Reno, NV) and mounted on a mechanical infusion pump (Sage Instruments, Cambridge, MA). A single bilateral sham injection (no fluid) was administered to all subjects following surgical recovery to induce the initial tissue trauma from injector insertion during a non-drug trial. During drug trials, the flush stylets were removed from the guide cannulae and the injector was lowered into each guide cannula. During the infusion procedure, rats were allowed a small range of mobility in a non-bedded home cage replica.

Using a within subjects, counterbalanced, repeated measures design, three different doses of muscimol (10, 20, and 40 ng) and picrotoxin (25, 50, and 100 ng), one dose of lidocaine (40 ng), and a control vehicle injection of isotonic saline were each bilaterally injected in a constant volume of 0.5 μl/side into the VM of all rats. Injection cannulae were maintained in place for 30 seconds after injection completion to allow for diffusion of the drug/vehicle into the brain tissue. Upon completion of the injection, flush stylets were reinserted into the guide cannulae to prevent drugs from reentering the guide cannulae and rats were immediately transferred to the testing chambers.

Performance measures

All the performance measures outlined in Experiment 1, were repeated here. In addition, data regarding locomotor activity was also collected.

Locomotor activity

After completion of the 5-CSRTT testing phase, we tested the effects of the highest dose of picrotoxin (100mg/kg) and muscimol (40mg/kg) on locomotor activity with 7 non-naïve rats.

Locomotor activity of each animal was measured with the Digiscan "Micro" system consisting of four mounting frames and one analyzer (Omnitech Electronics, Columbus, OH). A mounting frame contained two parallel panels, one photocell panel with 16 infrared light beams spaced 2.54 cm apart, and one light beam detector panel. Each

rat was placed in a transparent Plexiglas cage (46 x 24 x 18 cm) within a mounting frame located in a sound-attenuated chamber, The Digiscan system detected locomotor activity by counting interruptions of consecutive light beams caused by the animal

moving from one location to another. Data were automatically recorded and processed by the analyzer. Using a semi-counter balanced repeated measures design, each rat was bilaterally injected with either picrotoxin or muscimol, immediately placed in the chamber, and individually monitored for 30 minutes.

Analysis of Results

My hypotheses for these experiments are that the various drug doses will differ from saline. A comparison across all doses is not of interest for these experiments. Therefore, it is statistically valid to consider only the F-values of planned contrasts after running an analyses of variance (ANOVA) for repeated measures (Howell, 1997; Iacobucci, 2001; O'Brian, 1983; Rosenow & Rosenthal, 1989; Rutherford, 2001). ANOVAs for repeated measures with planned contrasts were performed on percent correct, percent omission, premature responses, time-out responses, and total responding between one dose of saline and three muscimol doses as well as saline and three picrotoxin doses.

Responses to injection of 0.5 µl of lidocaine 40 ng were compared to vehicle injections using paired Student's T-tests. An ANOVA for repeated measures was conducted on all latency data, comparing saline with the three different doses of either muscimol or picrotoxin. Locomotor activity was assessed using a paired Students T-test comparing number of light beams interrupted after saline injections to the number of light beams interrupted after either muscimol or picrotoxin injections

Results

From the 30 rats at the beginning of training, 7 failed to reach criterion and were excluded from further behavioral testing. Twelve rats were randomly assigned to

experiment 1 and from those 12, 6 were randomly assigned to receive a VMT lesion and 6 received a sham surgery. The remaining 11 rats were assigned to the other experiments.

Histology

After completion of all behavioral testing, the rats were euthanized by CO2 exposure in the Emory DAR facility in the Rollins Research Building. They were then intracardially perfused with isotonic saline followed by 10% formol-saline. After a few days of fixation, the brains were removed, 50 micron-thick frozen sections taken through the area of the guide cannulae, and the sections mounted on slides. The sections were subsequently stained with thionine and examined to confirm placement of cannula.

The lesions were found to be centered in the VMT, appearing to destroy most of it. They extended about 0.5 mm in the anterior-posterior axis. The surrounding tissue collapsed inward, making it a bit difficult to determine just what of the VMT remained. See Figure 9.

As shown in Figure 10, the cannula placements in those animals which were used because they were bilaterally accurate within the center of the VMT extended over a range approximately 0.5 mm in the anterior-posterior axis. Four rats had incorrect placement of cannula and were excluded from statistical analysis.

Percent Correct

Percent correct was calculated by dividing the number of correct responses by the total number of nose poke responses (correct responses + incorrect responses) and multiplying by 100.

Effects of bilateral VMT lesions on percent correct. A one-way multivariate analysis of variance was run to determine the effect of VMT lesions on accuracy. Two measures were assessed: the average percent correct during the four day pre-surgery period and the average percent correct during the four day post-surgery period. The differences between the two groups were statistically significant, $F(2,9) = 8.51$, $p < .01$; Wilk's $\Lambda = .35$; partial $\eta^2 = .65$. Follow-up univariate ANOVAs determined that there was no statistical difference between the two groups prior to surgery (VMT: $M = 74.96$, $SD = 10.31$; sham: $M = 73.71$, $SD = 5.53$), $F(1,10) = .07$, $p > .05$; partial $\eta^2 = .007$, but post-surgery the rats with VMT lesions increased accuracy (VMT: $M = 85.13$, $SD = 5.73$; sham: $M = 73.33$, $SD = 6.81$), $F(1, 10) = 10.52$, $p < .01$; partial $\eta^2 = .51$, using a Bonferroni adjusted α level of .025. There was a statistically significant interaction between lesion group and time on percent correct, $F(1,10) = 9.77$, $p = .011$, partial $\eta 2 = .494$. See Figure 4 for a full graphical summary of the data.

Effects of local injections of muscimol on percent correct. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of muscimol compared to one dose of saline. Planned contrasts identified a statistically significant decrease in accuracy after 20ng of muscimol when compared to saline, $F(1,6) = 8.34$, $p < .05$. No other doses were significantly different than saline [saline and 10 ng, $F(1,6) = 0.19$, $p > .05$; saline and 40 ng, $F(1,6) = 2.95$, $p > .05$]. See Table 1 for means and standard deviations and Figure 5 for a graphical summary.

Effects of local injections of picrotoxin on percent correct. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of

intra-VMT injections of three doses of picrotoxin compared to one dose of saline. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 25 ng of picrotoxin [$F(1,6) = 1.53$, $p > .05$], saline and 50 ng of picrotoxin [$F(1,6) = 0.16$, $p > .05$], or saline and 100 ng of picrotoxin [$F(1,6) = 0.02$, $p > .05$]. See Table 2 for means and standard deviations.

Effects of local injections of lidocaine on percent correct. A paired Student's T-test was performed to determine the effects of intra-VMT injections of 40 ng of lidocaine ($M = 71.29$, $SD = 13.45$) as compared to injections of saline ($M = 74.57$, $SD = 9.52$) on percent correct. There was no statistically significant difference between the two groups, $t(6) = .838$, $p > .05$.

Omissions

This measured the number of trials in which the rat did not make a response in the time allowed.

Effects of bilateral VMT lesions on omissions. A one-way multivariate analysis of variance was run to determine the effect of VMT lesions on omissions. Two measures were assessed: the average number of omissions during the four day pre-surgery period and the average number of omissions during the four day post-surgery period. The differences between the two groups were statistically significant, $F(2,9) = 4.50$, $p < .05$; Wilk's $\Lambda = 0.50$; partial $\eta^2 = 0.50$. Follow-up univariate ANOVAs determined that there was no statistical difference between the two groups prior to surgery (VMT: $M = 9.13$, $SD = 4.41$; sham: $M = 8.58$, $SD = 3.56$), $F(1,10) = 0.06$, $p > .05$; partial $\eta^2 = .005$, but post-surgery rats with VMT lesions significantly increased the number of omissions compared to sham controls (VMT: $M = 24.46$, $SD = 6.69$; sham: $M = 13.75$, $SD = 4.91$),

$F(1, 10) = 9.99$, $p = .01$; partial $\eta^2 = .005$), using a Bonferroni adjusted α level of .025. There was a statistically significant interaction between lesion group and time on omissions, $F(1,10) = 6.61$, $p = .028$, partial $\eta 2 = .398$. See figure 6.

Effects of local injections of muscimol on omissions. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of muscimol compared to one dose of saline. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 10 ng of muscimol [$F(1,6) = .08$, $p > .05$], saline and 20 ng of muscimol [$F(1,6) = 0.80$, $p > .05$], or saline and 40 ng of muscimol [$F(1,6) = 0.35$, $p > .05$]. See Table 1 for means and standard deviations, see Figure 7 for a summary of significant responses for 20 ng of muscimol.

Effects of local injections of picrotoxin on omissions. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of picrotoxin compared to one dose of saline. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 25 ng of picrotoxin [$F(1,6) = .220$, $p > .05$], saline and 50 ng of picrotoxin [$F(1,6) = 2.17$, $p > .05$], or saline and 100 ng of picrotoxin [$F(1,6) = 1.06$, $p > .05$]. See Table 2 for means and standard deviations.

Effects of local injections of lidocaine on omissions. A paired Student's T-test was performed to determine the effects of intra-VMT injections of 40 ng of lidocaine ($M = 4.71$, $SD = 2.06$) as compared to injections of saline ($M = 5.86$, $SD = 5.64$) on omissions. There was no statistically significant difference between the two groups, $t(6) = .595$, $p > .05$.

Premature

A premature response is a response in the nose poke receptacle before the beginning of a trial and is considered a measure of impulsivity.

Effects of bilateral VMT lesions on premature responding. A one-way multivariate analysis of variance was run to determine the effect of VMT lesions on premature responses. Two measures were assessed: the average number of premature responses during the four day pre-surgery period and the average number of premature responses during the four day post-surgery period. The difference between the two groups were not statistically significant, $F(2,9) = 3.00$, $p > .05$; Wilk's $\Lambda = .60$; partial $\eta^2 = .40$.

Effects of local injections of muscimol on premature responding. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of muscimol compared to one dose of saline on premature responding. Planned contrasts showed an increase in responding relative to saline for every dose tested; 40 ng, $F(1,6) = 14.41$, $p < .01$; 20 ng, $F(1,6) = 10.81$, $p < .05$; and 10 ng $F(1,6) = 5.99$, $p = .05$. See Table 1 for means and standard deviations.

Effects of local injections of picrotoxin on premature responding. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of picrotoxin compared to one dose of saline on premature responding. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 25 ng of picrotoxin [$F(1,6) = .51$, $p > .05$], saline and 50 ng of picrotoxin [$F(1,6) = 0.00$, $p > .05$], or saline and 100 ng of picrotoxin [$F(1,6) = 2.53$, $p > .05$]. See Table 2 for means and standard deviations.

Effects of local injections of lidocaine on premature responding. A paired Student's T-test was performed to determine the effects of intra-VMT injections of 40 ng of lidocaine (M = 4.71, SD = 2.06) as compared to injections of saline (M = 5.86, SD = 5.64) on premature responding. There was a trend to increase premature responding with lidocaine injections compared to saline injections, $t(6) = 2.41$, $p = .053$.

Perseverative

Perseverative responses are irrelevant nose poking after a correct choice.

Effects of bilateral VMT lesions on perseverative responding. A one-way multivariate analysis of variance was run to determine the effect of VMT lesions on perseverative responses. Two measures were assessed: the average number of perseverative responses during the four day pre-surgery period and the average number of perseverative responses during the four day post-surgery period. The differences between the two groups were not statistically significant, $F(2,9) = 0.55$, $p > .05$; Wilk's $\Lambda = 0.89$; partial $\eta^2 = 0.11$. There was no statistically significant interaction between lesion group and time on perseverative responses, $F(1,10) = .034$, $p = .857$, partial $\eta 2 = .003$.

Effects of local injections of muscimol on perseverative responding. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of muscimol compared to one dose of saline on perseverative responding. Planned contrasts showed a decrease in responding relative to saline for 10 ng, $F(1,6) = 10.50$, $p < .05$, and 20 ng, $F(1,6) = 7.88$, $p < .05$, but no statistical difference between saline and 40 ng, $F(1,6) = 2.65$, $p > .05$ See Table 1 for means and standard deviations.

Effects of local injections of picrotoxin on perseverative responding. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of picrotoxin compared to one dose of saline on perseverative responding. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 25 ng of picrotoxin [$F(1,6) = 0.37$, $p > .05$], saline and 50 ng of picrotoxin [$F(1,6) = 0.51$, $p > .05$], or saline and 100 ng of picrotoxin [$F(1,6) = 0.04$, $p > .05$]. See Table 2 for means and standard deviations.

Effects of local injections of lidocaine on perseverative responding. A paired Student's T-test was performed to determine the effects of intra-VMT injections of 40 ng of lidocaine ($M = 10.14$, $SD = 7.24$) as compared to injections of saline ($M = 10.00$, $SD = 7.28$) on perseverative responding. There was no significant difference between the two groups, $t(6) = 0.67$, $p > .05$.

Time Out

Irrelevant nose poking after an incorrect response.

Effects of bilateral VMT lesions on time out responses. A one-way multivariate analysis of variance was run to determine the effect of VMT lesions on responses made during when timed-out. Two measures were assessed: the average number of nose-pokes while timed-out during the four day pre-surgery period and the average number of nose-pokes made while timed-out during the four day post-surgery period. The differences between the two groups were statistically significant, $F(2,9) = 19.46$, $p < .01$; Wilk's $\Lambda = .19$; partial $\eta^2 = .81$. Follow-up univariate ANOVAs determined that there was no statistical difference between the two groups prior to surgery (VMT: $M = 19.58$, $SD = 13.53$; sham: $M = 19.50$, $SD = 9.92$), $F(1,10) < 0.001$, $p > .05$; partial $\eta^2 < .001$, but post-

surgery rats with VMT lesions significantly decreased the number of responses while timed-out compared to sham controls (VMT: $M = 4.58$, $SD = 4.53$; sham: $M = 12.21$, $SD = 5.72$), $F(1, 10) = 6.56$, $p < .025$; partial $\eta^2 = .40$, using a Bonferroni adjusted α level of .025. There was no statistically significant interaction between lesion group and time on responses while timed-out, $F(1,10) = 3.255$, $p = .101$, partial $\eta 2 = .246$.

Effects of local injections of muscimol on time out responses. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of muscimol compared to one dose of saline on responses while timed-out. Planned contrasts identified a trend to increase responding with 20 ng of muscimol when compared to saline, $F(1,6) = 5.67$, $p = .055$. There were no statistically significant differences between saline and 10 ng of muscimol ($F(1,6) = 1.52$, $p > .05$) or saline and 40 ng of muscimol ($F(1,6) = 4.01$, $p > .05$). See Table 1 for means and standard deviations.

Effects of local injections of picrotoxin on time out responses. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of picrotoxin compared to one dose of saline on responding while timed-out. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 25 ng of picrotoxin [$F(1,6) = 0.84$, $p > .05$], saline and 50 ng of picrotoxin [$F(1,6) = 5.25$, $p > .05$], or saline and 100 ng of picrotoxin [$F(1,6) = 0.92$, $p > .05$]. See Table 2 for means and standard deviations.

Effects of local injections of lidocaine on time out responses. A paired Student's T-test was performed to determine the effects of intra-VMT injections of 40 ng of lidocaine ($M = 19.57$, $SD = 10.26$) as compared to injections of saline ($M = 19.57$, SD

= 3.88) on responding while timed-out. There was no statistically significant difference between the two groups, $t(6)= 0.68$, $p > .05$.

Total Responding

Total responding was calculated by adding all the incorrect, correct, perseverative, time out and premature responses for each session**.**

Effects of bilateral VMT lesions on total responding. A one-way multivariate analysis of variance was run to determine the effect of VMT lesions on total responding. Two measures were assessed: the average number of nose-pokes during the entire session during the four day pre-surgery period and the average number of nose-pokes during the entire session during the four day post-surgery period. The differences between the two groups were not statistically significant, $F(2,9) = 3.180$, $p > .05$; Wilk's $\Lambda = .586$; partial $\eta^2 = .414$. There was no statistically significant interaction between lesion group and time on total responses, $F(1,10) = 3.50$, $p = .091$, partial $\eta 2 = .259$.

Effects of local injections of muscimol on total responding. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of intra-VMT injections of three doses of muscimol compared to one dose of saline on total responses. Planned contrasts identified a statistically significant increase in responding with 40 ng of muscimol when compared to saline, $F(1,6) = 6.960$, $p < .05$. There were no statistically significant differences between saline and 10 ng of muscimol ($F(1,6) = 0.55$, $p > .05$) or saline and 20 ng of muscimol ($F(1,6) = .49$, $p > .05$). See Table 1 for means and standard deviations.

Effects of local injections of picrotoxin on total responding. A repeated measures ANOVA with planned contrasts was conducted to determine the effects of

intra-VMT injections of three doses of picrotoxin compared to one dose of saline total responses. Planned contrasts did not identify any statistically significant differences between any dose tested; saline and 25 ng of picrotoxin [$F(1,6) = 0.02$, $p > .05$], saline and 50 ng of picrotoxin [$F(1,6) = 2.14$, $p > .05$], or saline and 100 ng of picrotoxin [$F(1,6) = 2.10$, $p > .05$]. See Table 2 for means and standard deviations.

Effects of local injections of lidocaine on total responding. A paired Student's T-test was performed to determine the effects of intra-VMT injections of 40 ng of lidocaine ($M = 154.00$, $SD = 21.38$) as compared to injections of saline ($M = 148.71$, $SD = 17.27$) on total responding. There was no statistically significant difference between the two groups, $t(6) = 0.68$, $p > .05$.

Latency

Three different measures of latency were recorded; latency to a correct response, latency to an incorrect response, and latency to retrieve the food pellet after a correct response

Effects of bilateral VMT lesions on latency measures. To determine the effect of lesions on latency measures, a paired Students T-test was performed on the average latency for the four days prior to surgery and the four test days after surgery. We found no difference in the latency to correct response, $t(5) = .86$, $p > .05$, or latency to incorrect responses, $t(5) = .252$, $p > .05$. However, latency to retrieve the reward for a correct response increased after surgery, $t(5) = 3.22$, $p < .05$. See Table 3 for means and standard deviations and Figure 8 for a comparison of statistically significant results.

Effects of bilateral injections of muscimol on latency measures. Repeated measures ANOVA showed no difference in the average latency to a correct response

[F(3,18) = 2.33, $p > .05$], average latency to an incorrect response [F(3,18) = .883, $p > .05$], and average latency to retrieve the reward for a correct response [F(3,18) = .618, $p > .05$], across all conditions.

Effects of bilateral injections of picrotoxin on latency measures. Repeated measures ANOVA showed no difference in the average latency to a correct response [F(3,18) = .114, $p > .05$], average latency to an incorrect response [F(3,18) = 2.29, $p > .05$], and total latency to retrieve the reward for a correct response [F(3,18) = 1.29, $p > .05$], across all conditions.

Effects of bilateral injections of lidocaine on latency measures. A paired t-test was conducted to determine any difference in time to respond to the cue or to retrieve the reward. There was no significant difference between latency to correct response [$t(6) = .442$, $p > .05$], latency to incorrect responses [$t(6)= .949$, $p > .05$], or latency to collect the reward [$t(6) = .055$, $p > .05$] when comparing saline and lidocaine injections

Locomotor Activity

A paired-samples T-test was used to determine whether there was a statistically significant mean difference between locomotor activity after intra-VMT injections of 100 ng of picrotoxin or 40 ng of muscimol when compared to intra-VMT injections of saline. Compared to saline ($M = 849.86$, $SD = 193.46$), injections of picrotoxin ($M = 1398.00$, $SD = 479.938$) significantly increased locomotor activity ($t(6) = 2.875$, $p < .05$) whereas there was no statistically significant difference between injections of muscimol ($M = 1052.29$, $SD = 326.39$) and injections of saline, $t(6) = 1.163$, $p > .05$.

Discussion

The purpose of this study was to see whether the VMT contributed not only to the control of posture and motoric ability, such as locomotion, as had been previously reported, but also to an acquired and more complex goal oriented task. Considering the anatomical loop connecting the amygdala, nucleus accumbans, basal ganglia, VMT, and frontal cortex together, it was reasonable to assume that manipulations of this neural pathway would significantly alter behavior on a task that required sustained attention and selective responding for a food reward (the 5CSRTT). However, the results were, in many ways, surprising.

We originally hypothesized that due to the innervation of the whole cortex by the VMT, deactivation of the VMT via local injections of muscimol would result in decreased performance, as measured by increased omissions and decreased accuracy. Since the 5-CSRTT is particularly sensitive to measuring changes in executive functioning, such as working memory and attentional capabilities (Dalley, Cardinal, & Robbins, 2004; Floresco & Jentsch, 2010; Robbins, 2002), we assumed that decreasing cortical activity would cause cognitive disturbances that could be measured by these parameters. Furthermore, we hypothesized that activation of the VMT via local injections of picrotoxin would result in increased performance. However, our results suggest that the role of the VMT on behavior may be more complex than originally thought.

Impact of muscimol injections

For all doses tested, deactivation of the VMT by muscimol increased premature responding, which has been validated as a measure of impulsivity (Robbins, 2002) (see Figure 4 for a graphical summary of all results). The middle dose tested, 20 ng/µl, also resulted in a decrease in perseverative responding, an index of compulsivity (Dalley,

Mar, Economidou, & Robbins, 2008), and a decrease in accuracy. The lowest dose, 10 ng/µl, increased premature responding and also decreased perseverative responding. The highest dose, 40 ng/µl, increased premature responding and total responding, but did not alter locomotor activity as measured by a locomotor chamber. Surprisingly, we did not see a decrease in omissions or a change in response latencies for any dose tested.

The finding that deactivation of the VMT through application of muscimol resulted in premature responses adds to the existing literature on impulsivity. Impulsivity is often conceptualized as acting suddenly without planning or forethought and it is the hallmark symptom of several neuropsychiatric diseases including drug addiction, ADHD, and mania (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Premature responses on the 5-CSRTT are considered to be a good indicator of behavioral inhibition, which is a component, or sub-type, of impulsivity. It is well understood that impulsivity is supported by mechanisms in the striatum and prefrontal cortex (for reviews see Aron et al., 2007; Dalley et al., 2008) but the precise contributions have yet to be parsed out. Limiting $GABA_A$ synthesis in the PFC (Asinof & Paine, 2013) increased impulsivity and Paine, Slipp, and Carlezon (2011) found that deactivation of the prefrontal cortex, specifically the border of the infralimbic (IL) and prelimbic cortices (PrL), with muscimol resulted in significantly higher premature responses. Murphy (2012) also found increases in premature responding after application of muscimol to the IL cortex and lesions to the IL cortex did as well (Chudasama et al., 2003). The medial portion of the VMT projects extensively to these areas (Desbois & Villanueva, 2001), thus similar results on the 5-CSRTT are not surprising. Further, the PrL projects almost exclusively to the NAS (Vertes, 2004) and pharmaceutical manipulations of the NAS can ameliorate

the cognitive impairments on the 5-CSRTT in rats with PFC lesions (Pezze, Dalley, & Robbins, 2009), suggesting the communication between these two structures is paramount for proper impulse control.

Of particular interest is the finding that while disconnection lesions of the NAS and PFC increased premature responses on the 5-CSRTT, bilateral NAS core lesions did not (Christakou, Robbins, & Everitt, 2004). Since the NAS core projects indirectly to the medial VMT (Brog, Salyapongse, Deutch, & Zahm, 1993), which then projects directly to the IL cortex (Desbois & Villanueva, 2001), it would seem that the mechanism driving premature responses may begin with the coalescing of information in the VMT. However, others have reported increased impulsivity after NAS core lesions using other tests of impulsivity (Cardinal et al., 2001). Recently, research into the specific contributions of these areas has moved away from gross anatomical tracing to more precise signal alterations based on receptor type and neurotransmitter function. However, an understanding of the circuitry of striatal-thalamic-cortical loops is still needed to determine the functional significance of the connections.

Muscimol vs electrolytic lesions and lidocaine

We chose to compare muscimol injections to an electrolytic lesion of the VMT and hypothesized these two manipulations would result in similar impairments. They did not. VMT lesions resulted in increased omissions, an increase in accuracy, a decrease of time-out responding, increased time to retrieve the food reward, and no change in the other measures. One explanation for these results is that the lesions somehow disrupted the rats' locomotor ability considering some have described profound motor deficits after electrolytic lesions of the VMT (Klockgether, Schwarz, Turski, & Sontag, 1986; Starr &

Summerhayes, 1983). If the rats were incapable of moving as quickly or as coordinately that could explain the increase in omissions, the decreases in time out responding, and the slower food retrieval rate. It may also explain the increase in percent correct, as the rats may have limited their responding to only the two or three closest holes, reducing the attentional and motoric requirements and thereby increasing accuracy at the expense of omissions. Further research should consider collecting data on hole 'preferences' to determine if accuracy and omissions differ between holes.

However, as described previously, the anatomic connections of the VMT do not suggest that this is a purely motor nucleus and deactivation of the VMT cell bodies using muscimol did not result in a pattern of responses that indicate motoric deficits. And contrary to previous publications (Klockgether et al., 1986) we report no difference in locomotor behavior in the open field task after intracerebral injection of muscimol in the VMT. Interestingly, the same dose of muscimol (40ng) increased total responding, in particular premature responding, in the 5-CSRTT. In addition, there was no change in response latency to a correct response, an incorrect response, or when retrieving the reward after intracerebral injections of muscimol. This suggests that the increased responding is not due to a general increase in activity or locomotion, but rather to another mechanism. Because of the anatomical connection, we posit that this mechanism is decrease of thalamic glutamate in L1 of the frontal cortex, an area which has been shown to be involved in behavioral inhibition (Aron et al., 2007; Chudasama et al., 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002; Lewis, Hashimoto, & Volk, 2005; Miller & Cohen, 2001; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004; Yizhar et al., 2011).

Electrolytic lesions run the risk of damaging axons passing through the target area and thus are more susceptible to unexpected results. It is possible that our lesions damaged axons from other brain structures leading to a change in behavioral responses measured by the 5-CSRTT. One potential tract that could have been damaged is known as the anterior thalamic peduncle (Domesick, 1972; Von Cramon, Hebel, & Schuri, 1985). This tract is made up of fibers originating in the dorsomedial and anterior thalamic nuclei and terminating in the prefrontal cortex and the cingulate gyrus (Parent, 1996). The prefrontal cortex is involved in memory function (Buckner et al., 1999; Fletcher et al., 1997; Fuster, 2000) and the anterior cingulate region in task switching, error monitoring, and working memory, functions particularly related to memory retrieval (Baddeley, 2003; Muller & Knight, 2006; Rushworth et al., 2003). These connections suggest a role of this pathway in attention and memory and there is limited evidence supporting that idea (Markowitsch, von Cramon, Hofmann, Sick, & Kinzler, 1990; Tatemichi, Desmond, Cross, Gropen, & Mohr, 1992). So if this tract is supporting memory and attention, it would be reasonable to assume an increase of omissions that was not related to motor deficiencies but rather to a decrease in cognitive abilities to complete the task. However, this does not explain the increase in percent correct that we found.

Further, in our study focal injections of lidocaine, an anesthetic which deactivates both cell bodies and their processes (Tabatabai & Booth, 1990), in the VMT resulted in increased premature responses and no change to other measures. We had hypothesized that transient deactivation of both the cell bodies and nearby axons would result in behavior similar to lesions, but instead the results of the lidocaine injections looked

similar to the results found with muscimol injections. It is important to note, however, that each rat only received one lidocaine injection and that occurred at the very end of testing. This means that the lidocaine injections could have been impacted by developing scar tissue or unknown long term effects of repeated injections of muscimol, picrotoxin, and saline. This limitation could have impacted the results and further research should limit the number of injections to identify the exact effect of lidocaine on VMT neurons.

Possible incentive salience connection

An alternate explanation for the behavioral pattern seen after electrolytic lesions worth considering is a decline of motivational, or incentive, salience. Incentive salience is "a psychological process that transforms the perception of stimuli, imbuing them with salience, making them attractive, 'wanted', incentive stimuli" (Robinson & Berridge, 1993). Much of the research available points to a role of the NAS and PFC in incentive salience (Berridge & Robinson, 1998; Cardinal et al., 2001; Nicola, Yun, Wakabayashi, & Fields, 2004; Peciña & Berridge, 2013; Pujara & Koenigs, 2014; Richard & Berridge, 2013; Robinson & Berridge, 1993; Roitman, Wheeler, & Carelli, 2005; Salamone & Correa, 2002; Wise, 2004), and the VMT is one nucleus through which those two structures communicate. Of course, that would suggest that information about reward or incentive motivation is relayed by the SNr but there is very little evidence supporting such a claim.

It is possible that when the entire VMT is lesioned, the motivation to complete a task for a food reward is disrupted. Perhaps the learning deficits found by Neill (unpublished) and Thompson, et al (1987) discussed earlier, were driven by the decline in food-related motivation. Supporting evidence for this interpretation comes from our

latency data, as VMT lesioned animals were significantly slower to retrieve the food pellet from the hopper than sham operated animals, whereas no other latency increase was noted. Further research to test this possibility is suggested. This could be accomplished by using a progressive ratio schedule and comparing results after saline, picrotoxin, or muscimol infusion. Progressive ratio tasks are similar to fixed ratio operant tasks except that the required number of responses increases according to a pre-set interval at each trial. So the first trial may require only two nose-pokes to receive a food pellet, but the second trial now requires four responses, the next, six, and so on up to a predetermined ratio or the end of the session. The "break-point", the session where the animal judges the effort to be greater than the reward, can be used as a measure of motivational salience (Hodos, 1961).

Although these rats were food deprived to 90% of their free feeding weight, it is possible that by the end of the trial the motivation to work for food pellets naturally decreased. Analyzing the pattern of results from the first half of the trial separately from the second half might indicate a different behavioral profile.

Picrotoxin results

Intercerebral injections of picrotoxin into the VMT resulted in no changes of behavior measured with the 5-CSRTT. It did, however, increase locomotor activity in the open field task at the highest dose (100 ng). Picrotoxin, a $GABA_A$ receptor antagonist, was used to transiently activate the cell bodies in the VMT and we believed that would enhance performance on the 5-CSRTT. It is unclear why muscimol and picrotoxin had such different effects in this experiment. One possible explanation is that the criterion level we set for baseline responding was too strict and what resulted was a ceiling effect

whereby a significant improvement in performance was unlikely to be revealed. Future research should consider injecting picrotoxin into rats with poor baseline responding in an attempt to improve responding. It could be due to the within-subjects counter-balanced design of the experiment. Even though there were a few days between injections, it is possible that using the same rats for both conditions resulted in aberrant responding for both drugs or the sheer number of injections caused unknown damage. To parse out the relative influence of picrotoxin and muscimol, future research should limit the number of injections for each animal. Antagonizing $GABA_A$ receptors may have the desired effect of increasing cellular activity in the VMT, but it is possible that by blocking $GABA_A$ receptors it simply changes the message being transmitted. There are a number of other neurotransmitter receptors in the thalamus, including $GABA_B$ which may actually function to potentiate action potentials (Crunelli & Leresche, 1991).

Implications and future directions

The VMT may be topographically organized in terms of anatomical connections and also functionality. While the VMT does innervate layer 1 of the entire cortex, the medial and lateral areas of the VMT project to different areas of the cortex (see Figure 9). The medial VMT preferentially innervates the prefrontal cortex (Desbois & Villanueva, 2001) whereas the lateral VMT projects more to the dorsolateral frontal cortex in rats, an area of sensorimotor cortex (Monconduit, Bourgeais, Bernard, Le Bars, & Villanueva, 1999). VMT afferents may also differentiate between the medial and lateral areas, as the NAS core remains segregated through the SNr and projects exclusively to the medial area of the VMT (Groenewegen, Galis-de Graaf, & Smeets, 1999).

We noted possible functional distinctions between the medial and lateral VMT after analyzing the patterns of behavior seen in rats that were inadvertently placed with misaligned cannulae. We found that some rats had one cannula placed in the medial VMT of one hemisphere and the lateral VMT of the other and originally removed them from our analysis. Upon further investigation, it was clear that these rats showed large increases in errors of omission. Additionally, the results of a few rats with injections into the more medial VMT, at the standard volume of 0.5 μL, showed an increase in premature responding, while the same amount of drug, at the same site, increased errors of omission when administered in a volume of 1.0 μL, perhaps due to spreading over the lateral VMT. We hypothesize that the lateral VMT contributes to goal directed movement and the medial VMT contributes to general cortical recruitment necessary for proper response inhibition and completion of complex cognitive tasks that require sustained attention. However, because the ability to move freely is necessary for the execution of said cognitive tasks, any disruption of the lateral VMT will result in a behavior pattern that appears to have motoric deficits. This explains why a complete lesion of the VMT results in increased errors of omissions and some increased latency measures. It may also explain why our accidental finding that increasing the volume of muscimol but not the functional dose leads to increased omissions. It could be that the increased volume is spreading to nearby areas, namely the lateral VMT. Conversely, sparing the lateral VMT should result in our ability to manipulate the activation of the medial prefrontal cortex through the medial VMT. In primates, the ability to localize and discriminate changes in nociceptive information may depend on different thalamic neurons than those dedicated to determining our affective-motivational reaction to pain

(Besson, Guilbaud, & Ollal, 1995). Considering the anatomical inputs to the VMT it is possible that the lateral and medial VMT are processing the same information in different ways. To test this hypothesis, I propose the following experiments based on the 5-CSRTT paradigm: 1) Comparing muscimol and picrotoxin injections in the medial VMT to injections in the lateral VMT. 2) Comparing a higher volume of muscimol and picrotoxin injected into the medial and lateral VMT to the volume used here. 3) Comparing lesions of the medial VMT to lesions of the lateral VMT.

Considering the clear segregation of information from the NAS core, through the SNr, to the medial VMT, it is tempting to presume that the VMT is the primary way information from the NAS core reaches the cortex. Christakou et al. (2004), combined unilateral lesions of the medial prefrontal cortex (mPFC) and the core sub region of the nucleus accumbens in opposite hemispheres (disconnection) to determine the functional significance of these structures as measured by the 5CSRTT. Their results are similar to our muscimol data, as they also reported an increase in premature responding. Disconnecting the NAS core and the medial VMT would allow us to parse out the relative influence of the NAS-medial VMT system on behavioral disinhibition. Demonstrating the effects of this disconnection using the 5-CSRTT would be very helpful when comparing previous 5-CSRTT literature, but other paradigms could be useful in parsing out the particular influence of this system on behavioral inhibition. In particular, we recommend using similar bilateral VMT manipulations as in the current study after disconnecting the medial VMT and NAS to determine how that would affect responding during extinction (Reading et al., 1991), under progressive ratio schedules (Bowman and Brown, 1998), and in a delayed gratification procedure for the

measurement of impulsive responding (Cardinal et al., 2001). Further, we could manipulate some of the parameters of the 5-CSRTT to make impulsive or compulsive behaviors more likely. Increasing the inter-trial-interval (ITI), manipulating the stimulus duration, altering the brightness of the visual stimuli, or adding a distracting noise are all common manipulations of the procedure.

In conclusion, manipulation of the VMT by muscimol, picrotoxin, lidocaine and electrolytic lesions resulted in differing behavioral profiles as measured by the 5-CSRTT. The finding that deactivation using muscimol increases premature responding at all doses tested adds to the existing literature on impulsivity. To the best of my knowledge, no other research has implicated the VMT as part of the neural substrates contributing to impulsivity, yet it is clearly related anatomically. However, the lack of response to picrotoxin and the behavioral profile of electrolytic lesions is puzzling and indicate that more research is needed into the behavioral contributions of the VMT. In particular, more sophisticated tracing techniques and neurotransmitter binding assays are required to understand the precise afferent and efferent connections of the VMT and the relative importance of the various neurotransmitters in the nucleus. Further, we believe that the VMT can be subdivided into medial and lateral sections and thus contribute differentially to behavior. Future research should consider the two subsections independently when analyzing results.

While the dearth of behavioral research regarding the VMT prevents true consideration of the clinical implications, there exists a possibility that this nucleus of the thalamus may be important for synthesizing and translating limbic, basal ganglial, accumbal, and nociceptive information to the cortex. This could impact how animals,

and perhaps humans, judge and respond to contingencies in their environment. Human neuropsychiatric disorders such as drug addiction, ADHD, mania, conduct-disorder, schizophrenia and depression all indicate aberrations in these related brain structures and adding to the VMT literature may increasing our understanding of the etiology and treatment of these disorders.

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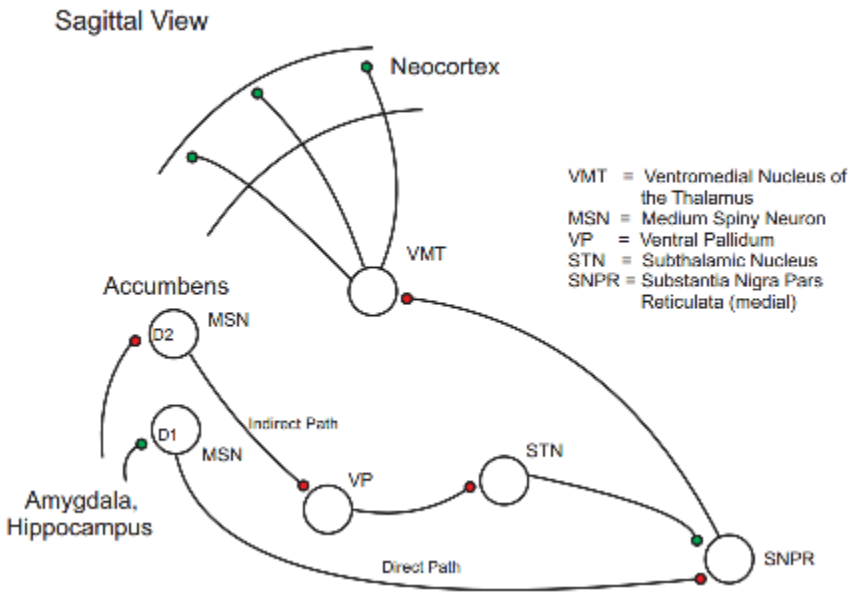

Figure 1. Afferents and efferent of the ventromedial thalamus (modified from Deniau et al., 1994).

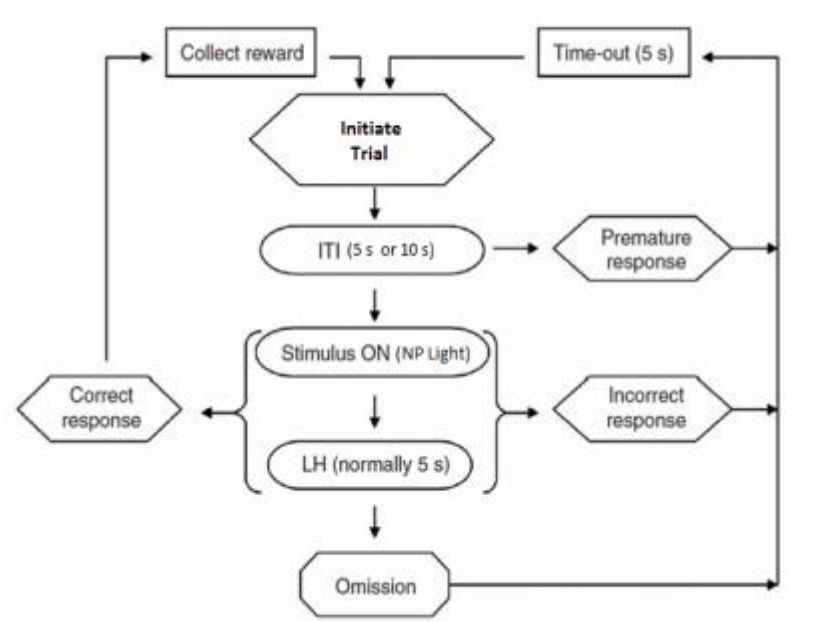

Figure 2. Flowchart of possible trial sequences in the 5-CSRTT (modified from Barry et al., 2008).

Training stage	Stimulus duration (s)	Intertrial interval (ITI) (s)	Limited hold (LH) (s)	Criterion to move to next stage
1	30	2	30	≥30 correct trials
2	20	2	20	≥30 correct trials
3	10	5	10	≥50 correct trials
4	5	5	5	≥50 correct trials >80% accuracy
5	2.5	5	5	≥50 correct trials >80% accuracy <20% omission
6	1.25	5	5	≥50 correct trials >80% accuracy <20% omission

Figure 3. 5-CSRTT training schedule (modified from Bari, et al., 2008)

	Lesion	Musc 10	Musc 20	Musc 40	Picro 25	Picro 50	Picro 100	Lido 40
% Correct	↑	—	↓	—	—	—	—	—
Omissions	↑	—	—	—	—	—	—	—
Premature	—	↑	↑	↑	—	—	—	↑
Perseverative	—	↓	↓	—	—	—	—	—
Time Out	↓	—	↑	—	—	—	—	—
Total Responding	—	—	—	↑	—	—	—	—
Latency: Correct	—	—	—	—	—	—	—	—
Latency: Incorrect	—	—	—	—	—	—	—	—
Latency: Reward	↑	—	—	—	—	—	—	—
Locomotor	X	X	X	—	X	X	↑	X

Figure 4. Graphical summary of changes in behavior relative to saline, given the stated treatments. Up-arrow indicates an increase in responding for that variable, down-arrow indicates a decrease in responding for that variable, horizontal bar indicates no difference from saline for that variable, and an 'X' indicates no data available for that combination of treatment and behavioral response.

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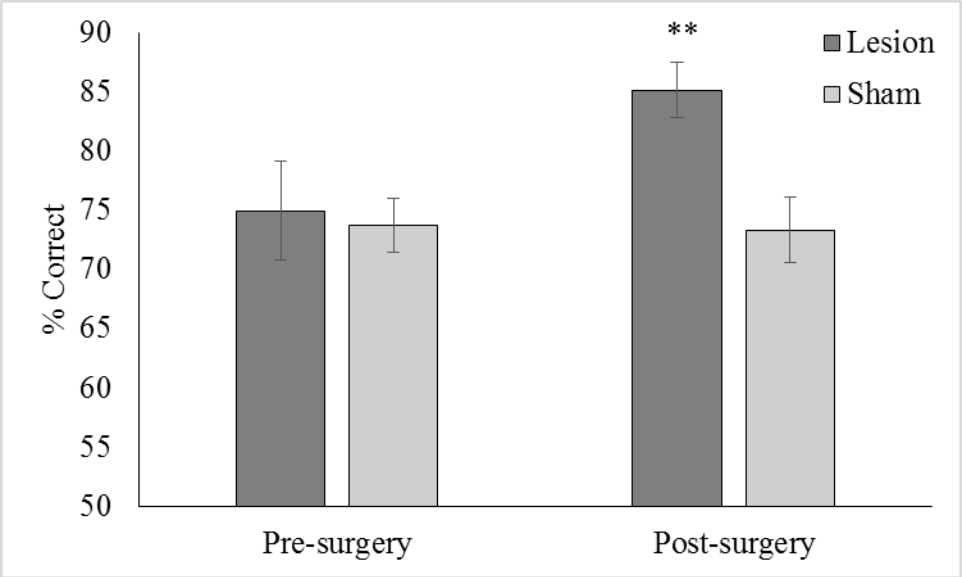

Figure 5. Percent correct before and after surgery, divided by lesion and sham groups.

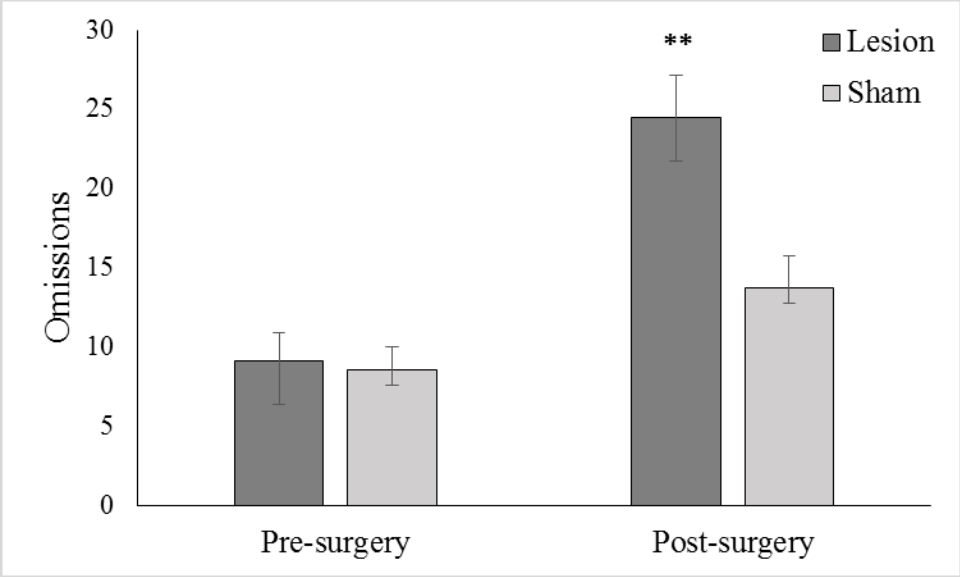

Figure 6. Errors of omission before and after surgery, divided by lesion and sham groups

Table 1

Means of Responses on Each Measure of the 5-CSRTT by Drug and Dose (Standard Deviation in Parentheses)

	Saline	Muscimol		
Measure	0.5 µl	10 ng/0.5 µl	20 ng/0.5 µl	40 ng/0.5 µl
% Correct	74.57 (9.52)	72.71 (5.43)	67.43 (7.91)	70.00 (5.54)
Omissions	5.86 (5.64)	6.71 (3.25)	10.43 (9.50)	8.71 (10.05)
Premature	15.71 (8.98)	35.57 (19.36)	30.86 (14.89)	51.57 (27.62)
Perseverative	10.00 (7.28)	2.14 (1.68)	2.43 (1.62)	5.71 (2.36)
Time Out	19.57 (10.26)	30.43 (13.91)	32.43 (11.01)	43.29 (34.19)
Total Responding	148.71 (17.27)	159.86 (31.89)	155.29 (18.41)	188.86 (46.88)

Table 2

Means of Responses on Each Measure of the 5-CSRTT by Drug and Dose (Standard Deviation in Parentheses)

	Saline	Picrotoxin		
Measure	0.5 µl	25 ng/0.5 µl	50 ng/0.5 µl	100 ng/0.5 µl
% Correct	74.71 (7.95)	77.14 (4.56)	75.71 (9.18)	74.43 (6.75)
Omissions	5.71 (5.41)	4.57 (3.15)	7.57 (6.16)	7.29 (5.31)
Premature	18.00 (8.52)	21.29 (11.71)	18.00 (6.48)	35.00 (27.95)
Perseverative	14.57 (13.11)	11.57 (8.50)	12.57 (11.21)	13.71 (9.83)
Time Out	21.86 (5.15)	19.00 (6.73)	15.29 (4.96)	31.86 (29.02)
Total Responding	148.71 (17.27)	147.29 (18.83)	138.29 (17.25)	173.29 (48.61)

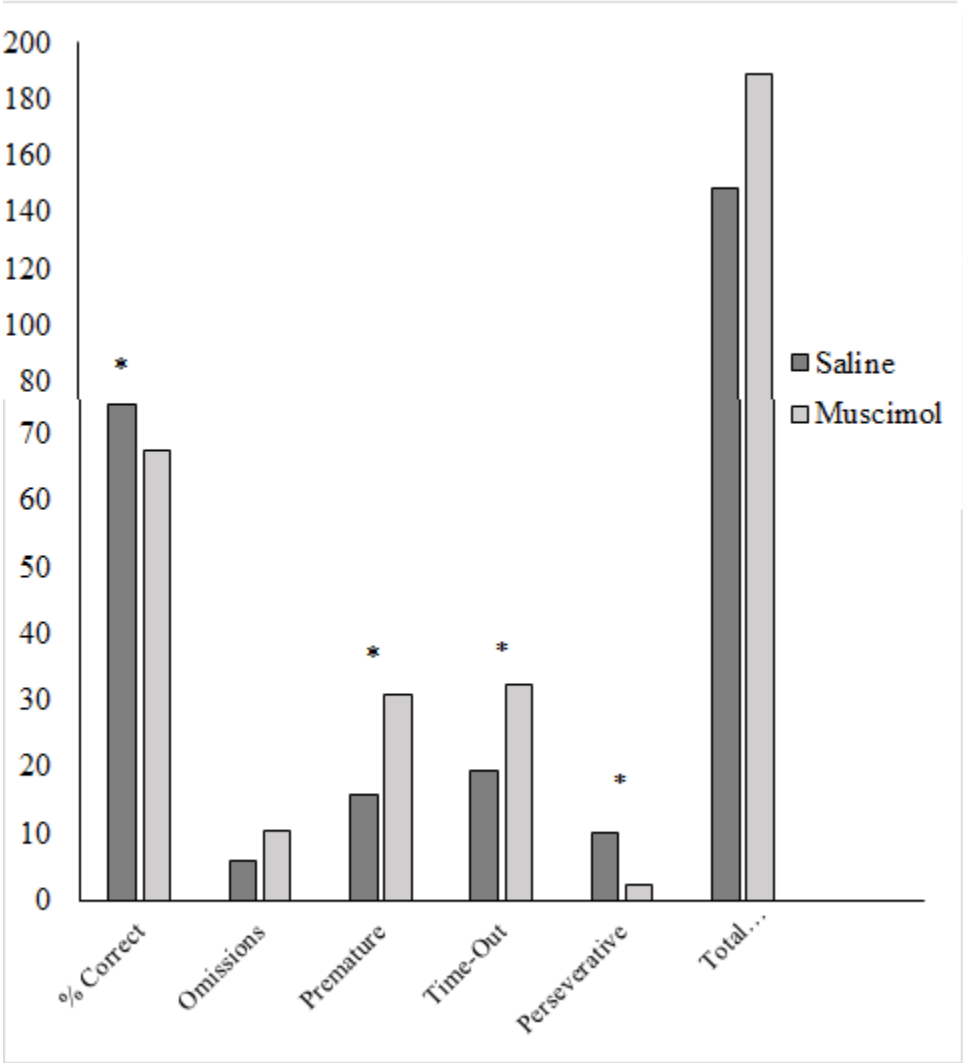

Figure 7. Results on the 5-CSRTT after 20 ng of muscimol.

Table 3

Mean Latency Data for Correct Responses, Incorrect Responses, and Time to Retrieve the Reward in Seconds for Rats with VMT Lesions, Before and After Surgery (with Standard Deviations in Parentheses)

	Latency		
Time	Correct	Incorrect	Reward
Before lesion	1.22 (1.06)	2.23 (0.53)	1.74 (0.35)
After lesion	0.87 (0.09)	2.15 (0.31)	2.83 (0.97)

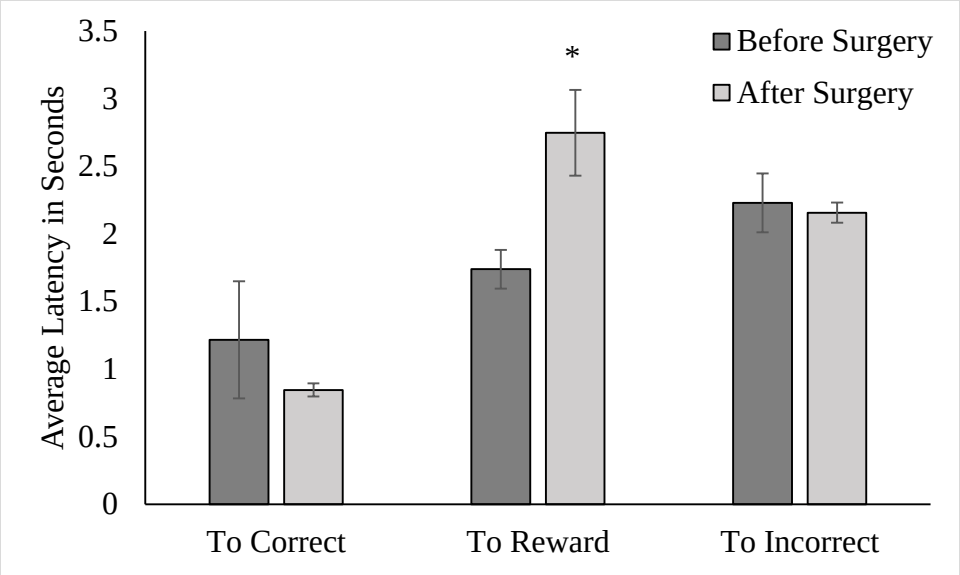

Figure 8. Average latencies to a correct response, to retrieve the food reward, and to an incorrect response, before and after surgery.

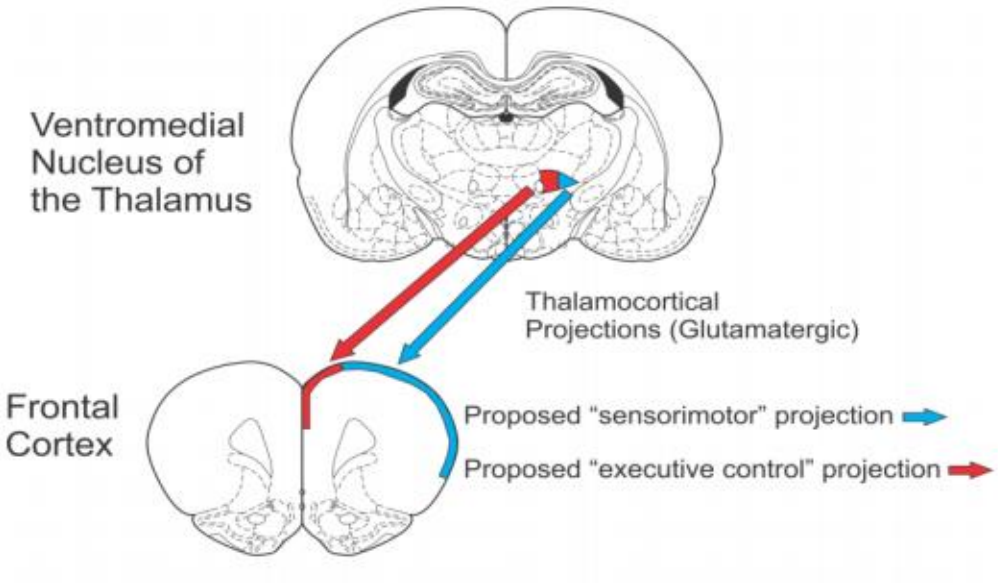

Figure 9. Cortical projections of the sub-regions of the VMT

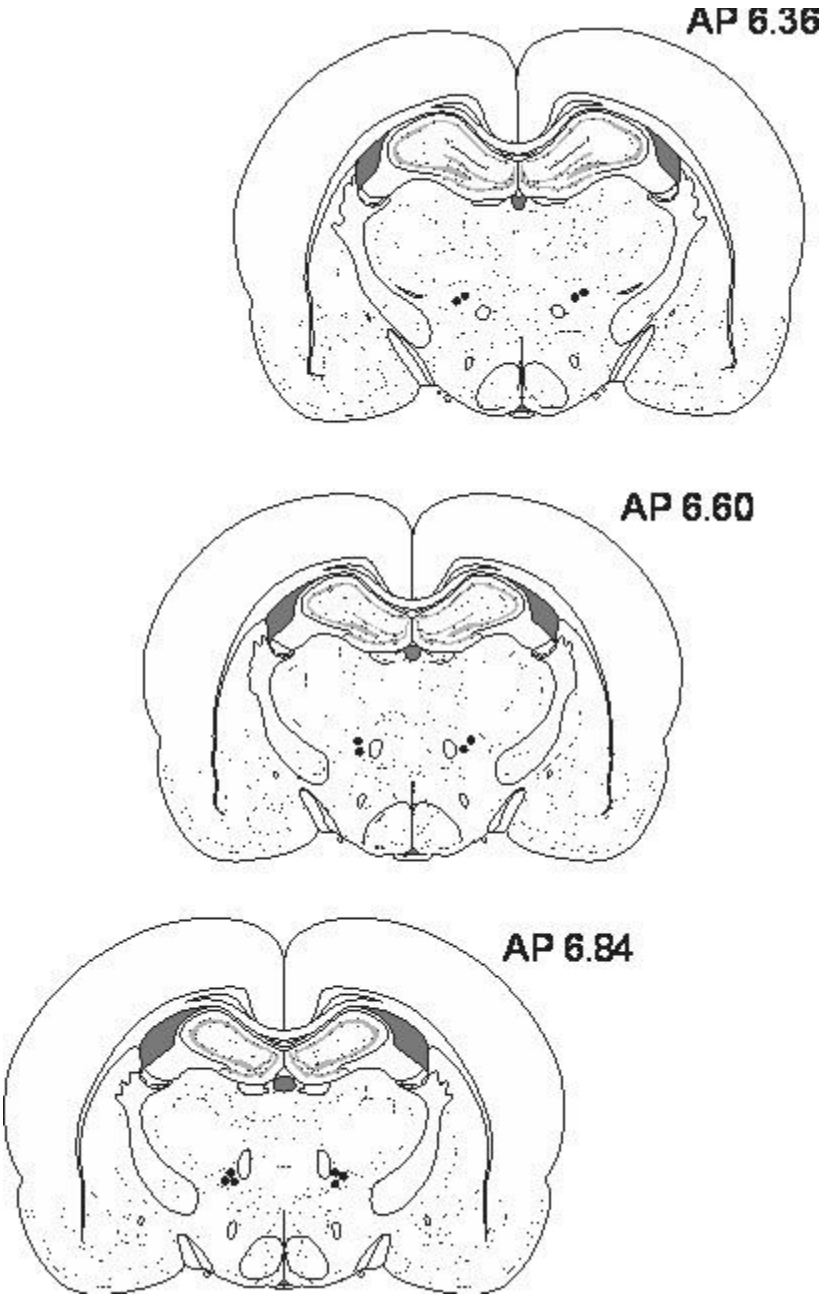

Figure 10. Placement of cannulae.

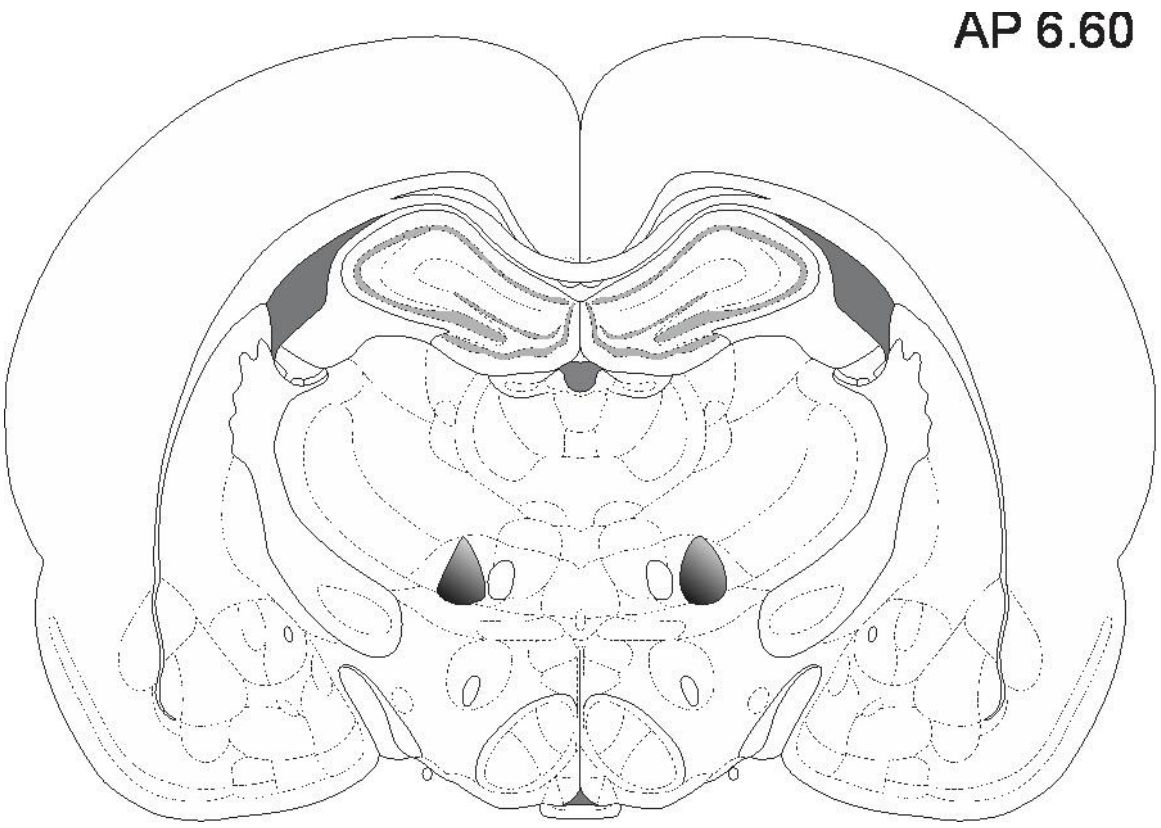

Figure 11. Location of lesions.