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Angel J. Billingsley Date

Ventromedial Thalamic Lesions Alter Cognitive Performance in Rats

by

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An abstract of
A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

The Mind the quintessential quality that defines us (humans), and the one that truly sets us apart from other animals. It is therefore interesting to consider that the true nature of the mind still escapes full comprehension. Despite the current general lack of knowledge surrounding the neural substrates of cognition, one must simply take a deeper, sucbcortical look inside the brain to begin to see the primitive beginnings of higher thought. One such paleomammalian brain structure attracts attention due to its extensive projections throughout the six layers of the neocortex: the thalamus. Here we show that regiospecific lesions of the Ventromedial Thalamic Nucleus in Sprague-Dawley rats produce deficits on the 5-Choice Serial Reaction Time Task, a widely accepted measure of cognitive function. The results of this experiment suggest a role alternative to the current motor-specific view of the VMT, providing evidence for a whole-brain cognitive motivational center.

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The road to the production of this paper has been tumultuous, taking me emotionally from a fear of failure, to utter confidence in my findings. I cannot begin to express how much Darryl Neill, PhD has come to mean to me over the course of my apprenticeship, but it is he whom I must acknowledge first. Dr. Neill, in my eyes you've grown from that nutty Drugs and Behavior professor, to a man I will love and respect for the rest of my life. I sincerely thank you for the opportunities you've afforded me; from selecting me for your lab to being instrumental in the production of my senior honors thesis. Secondly I must acknowledge both Cora MacBeth, PhD and Michael Crutcher PhD, for going above and beyond the roles of an instructor, and bestowing me the favor of joining this committee at a time that may not have been convenient for them. I want both of you to know that I appreciate this integral role you play in my successful matriculation. To Keith Easterling, Elizabeth Fricker, Kristen Frenzel and Nadia Brown: I appreciate the support and helpful stimulation towards the completion of this project. And finally, to my mother, Edna Billingsley, PhD: Mom, I am forever indebted to you for my life, your love, and (most especially), for this wonderful brain.

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INTRODUCTION

The thalamus, (from the greek word meaning inner chamber), is situated at the center of the mammalian brain, and has several distinct nuclei with varying purposes. At present, the functions of the thalamus are characterized as either "specific", referring to the motor and sensory functions of the thalamus, or "nonspecific", referring to neuromodulatory functions. (Herkenham, 1979). By acting as a sensory relay, it is widely accepted that the thalamus receives sensory signals such as sound, pain, and sight from the peripheral sensory organs, and forwards the information to the cortex, ultimately serving to activate the cortex by release intrinsic cortical dynamics. As a reciprocal loop, it is believed that the cortex also returns these projections to the thalamus, allowing for a feedback system. (Ogden, 1960)

On the motor side, the thalamus receives information from the cortex and the basal ganglia, a group of structures integral in the understanding of thalamic motor function. The basal ganglia are a group of densely connected nuclei located at the nadir of the forebrain, in front of, and lateral to the thalamus. The basal ganglia consist of the striatum, subthalamic nucleus (STN), substantia nigra (SN), and finally the globus pallidus (GP). Historically, many experiments have shown that the basal ganglia play a central role in the voluntary control of motor functions. For example, arousal in the striatum has been related to the anticipation (Apicella, Scarnati, Ljungberg, & Schultz, 1992; W. Schultz, et al., 1992; Vink, M., Kahn, R. S., Raemaekers, M., van den Heuvel, M., Boersma, M., & Ramsey, N. F., 2005), initiation (Lebedev & Nelson, 1999) and finally to the inhibition (Vink, et al., 2005) of locomotion. Experiments have shown that disease related damage to human STN

(Lee & Marsden, 1994) or experimental ablation of the STN in monkeys cause violent motor restlessness in half of the body,(a condition known as hemiballism.) Studies involving lesions or temporary inhibition of the SN in monkeys showed that such manipulations of the SN lead to profound motoric deficits (Burns, R. S., Chiueh, C. C., Markey, S. P., Ebert, M. H., Jacobowitz, D. M., & Kopin, I. J., 1983; Sakai & Gash, 1994). (Whittier, 1947;Carpenter et al., 1950; Crossman, 1987). Ablations of the internal segment of the GP (GPi) yield a motoric deceleration of ambulation that is contrary to standard posture (Wenger, Musch, & Mink, 1999). Clinically, 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. With the aforementioned claims in mind, one may consider that the thalamus is believed to be the culprit for the processing of basal ganglia motor output.

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.

Each of the aforementioned thalamic capabilities is dispersed functionally between the numerous thalamic nuclei, with particular nuclei performing specific or modulatory functions. The ventromedial nucleus of the thalamus (VMT), part of the modulatory/nonspecific system, is situated ventral to the ventroanterior nucleus in the rat, and receives GABAergic afferents from the substantia nigra pars reticulata

(SNPR), the GP, and the entopeduncular nucleus (EPN -a rodent homologue of the middle segment of the GP in primates) (Carter & Fibiger, 1978; Kha, H. T., Finkelstein, D. I., Tomas, D., Drago, J., Pow, D. V., & Horne, M. K,2001).

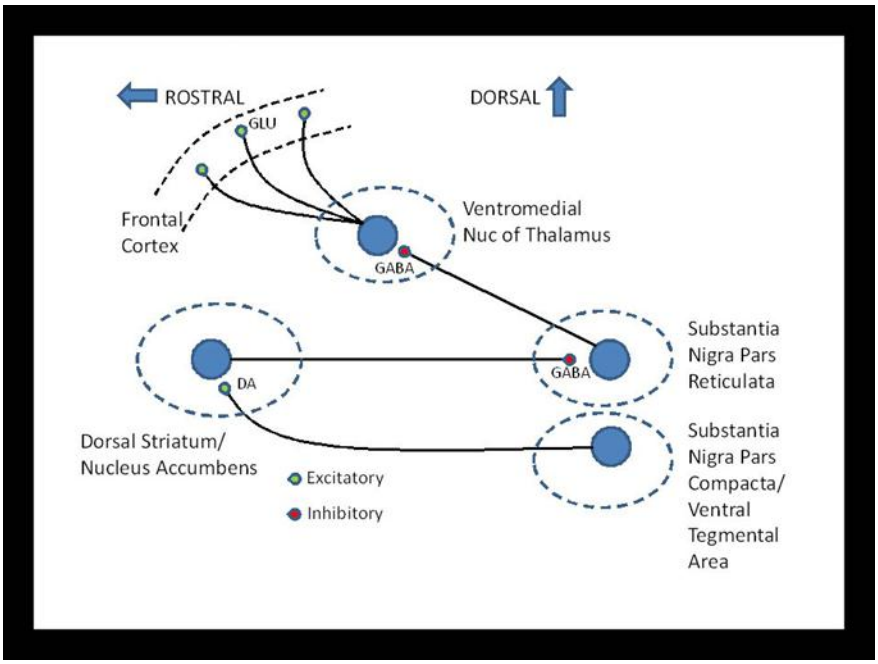


Figure 1. Afferents and Efferents of the Ventromedial Thalamus. This figure illustrates the synaptic inputs, and the neurotransmitters therein, converging upon the VMT, as well as the VMT projection to the frontal lobes.

Although there is no evidence of a definitive VMT in the primate brain, the primate ventroanterior (VA) nucleus receives dense innervation from the SNPR, and therefore the VA, more specifically the ventral-most portion, may be deemed homologous to the rodent VMT. The SNPR is preferentially important in posture, circling behavior, and general locomotion (Starr & Summerhayes, 1983). Because the SNPR densely projects to the VMT, much of the published research concerning the VMT is primarily focused on elucidating the pathways of those specific gross motor behaviors. Herkenham (1979), however, showed that the VMT possesses an output unlike any other thalamic nucleus, with projections that ‘cover almost the entire

cerebral mantle, and are directed almost exclusively at the superficial portion of layer I throughout the cortex.'(Herkenham, 1979).

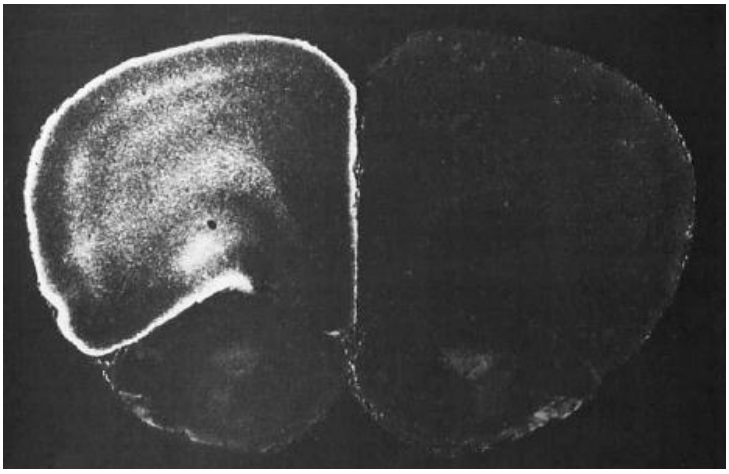


Figure 2. Darkfield Stain Photograph of Cortex. This figure illustrates where anterograde radioactive tracers, (that label black on a stain), terminate after injection into the Ventromedial Thalamus. (Herkenham, *The Journal of Comparative Neurology*, 1979)

This in turn 'suggests that VM plays a unique role in thalamocortical mechanisms which stands in contrast to that of the other nonspecific (corticomodulatory) thalamic nuclei' (Herkenham, 1979).

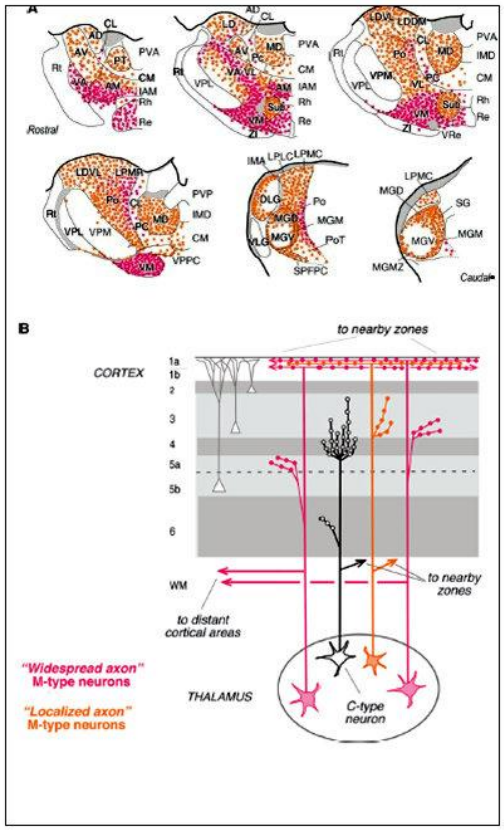


Figure 3. Visual Representation of Unique Axon Types in the Thalamus. This figure illustrates the unique axonal projection of neurons found primarily in the Ventromedial Thalamus. M = "matrix" neurons (nonspecific/modulatory). (Rubio-Garrido et al.,*Cerebral Cortex*, 2009)

In spite of the aforementioned anatomical evidence suggesting a unique modulatory capability of the VMT, few published studies exist examining the behavioral effects of manipulations of the structure. Most studies have been intended to elucidate the VMT's role as a major output center for the basal ganglia, hoping that lesions and drug manipulations thereof would give insight into the various motoric deficits produced by basal ganglia dysfunction. When unilateral, one such deficit causes animals to initiate uncontrollable circumambulation, and therefore the Jenner group intended to see whether VMT lesions would initiate the same behavior. The group ultimately showed that, when paired with a unilateral 6-Hydroxy Dopamine (6-

OHDA) lesion of the dopaminergic nigrostriatal bundle, ipsilateral electrolytic VMT lesions reduced the circumambulation produced by the 6-OHDA lesion, though unilateral lesions of the VMT alone did not alter motor behavior. (Jenner et al., 1979)

In a subsequent experiment, the Starr lab "set out to compare the effects of acute and chronic (VMT) lesions, of both the electrolytic and chemically-induced type, on the various elements of circling behavior provoked by pharmacologic manipulation of the striatonigral system in the rat", and ultimately, "found it quite remarkable that there was very little about the (motoric) behavior of a chronically VM electrolesioned rat that distinguishes it from an intact animal", though the group did show that the lesions augmented the circling behaviors produced by basal ganglia over activation. Additionally, large doses of the GABA agonist muscimol in the VMT immediately caused rats to become cataleptic, though this effect was transient, and rats returned to normal behavior within a day. (Starr & Summerhayes, 1983)

The above papers show that most VMT behavioral studies have concentrated on motor function. Published and unpublished studies conducted in the Neill laboratory, however, suggest much broader and possibly non-motor alterations in behavior following electrolytic lesions of the VMT.

The Neill studies found VMT lesions did not have significant effects on 24 hr intake of food or water or locomotor activity (Neill & Kaufman, 1977). However, in unpublished studies test subjects showed marked impairments in learning, using rewarding (food, water) and aversive (footshock) stimuli, and across response requirements (lever press, straight-alley running). On the other hand, if the lesions were made in rats that had learned the tasks, they had little to no effect. That is, the lesions

seemed to selectively impair learning, not performance. Subsequent work in the Neill laboratory in the dissertation studies of Butler (1983) found electrolytic lesions of the VMT impaired working memory performance in the 8-arm maze memory task.

The selective effects of VMT lesions on task learning, and the effect on working memory, suggest that VMT lesions alter more than motoric ability.

Most recently, studies by Jennifer McGee in the Neill laboratory have examined the effect of VMT manipulations on performance in the most commonly used test of attention in rats, the 5-choice serial reaction time (5-CSRTT) task. In this task, rats must monitor a bank of holes in a chamber wall and nose-poke within 5 sec in a hole which has just been illuminated. There are three kinds of error in the 5-CSRTT: accuracy errors (responding in the wrong hole), errors of omission (not responding in any hole), and premature responding (responding during the waiting period before light onset). McGee's results showed that electrolytic lesions of the VMT specifically resulted in an increase in errors of omission. Premature responding decreased, and accuracy increased.

Electrolytic lesions remove not only the neuronal cell bodies at the lesion site, but also any axons passing through the site ("axons of passage"). When McGee transiently deactivated the VMT via local injection of the GABA agonist muscimol, the results were very different from the lesion: premature responding increased, and errors of omission were not affected. These results suggest that the lesions affect something passing through the VMT which gives rise to the lesion-induced rise in errors of omission.

The above results were for muscimol injections in the center of the VMT. In

some cases, the injection sites were inadvertently shifted laterally, so that the injection was in the medial VMT in one hemisphere and the lateral VMT in the other. Injections into these sites resulting in increased errors of omission, mimicking the lesions. These results suggested that selective impairment of the medial or lateral VMT can produce errors of omission.

The following project was designed to test the effect of lesions targeting the medial versus the lateral VMT, in the hope of elucidating a functional difference between Medial Ventromedial Thalamus (MVMT) and Lateral Ventromedial Thalamus (LVMT). Due to anatomical evidence "there is some topographical order in the projection, with medial and dorsal areas well represented in medial cortex while lateral parts of ventromedial nucleus are more directly related to the cortical area that receives the ventrolateral thalamic (VLT) nucleus projection" (Arbuthnott & Wright, 1990), and due to behavioral evidence that links VLT to motor function (Jeljeli, Strazille Caston and Lalonde, 2003), we hypothesized that lesions of the LVMT would produce alterations in motor behavior, and perhaps increased errors of omission, while lesions of the MVMT would produce premature responding behavior.

METHODS

Animals

All subjects were adult male Sprague-Dawley rats (from Harlan Sprague Dawley in Indianapolis), 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 8 months of age and weighed approximately 500 grams at surgery. 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. A total of nineteen rats were initially trained. Of the initial rats used, one rat was eliminated from the data because his lesion was found to be off mark.

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, located in a room separate from the programming and recording equipment. On one side of the box, five evenly spaced square apertures (2.5cm square and 4cm deep), each containing a single LED light, are set 2cm 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 was a trough type pellet receptacle (2" x 2" square) with a LED light in the rear and infrared beam at the entrance. This was where nutritionally-balanced 14 mg food pellets (BioServe, Frenchtown, NJ) were delivered to a hopper in one wall 0.5 cm above the bottom of the chamber. The entire test chamber was illuminated with a 3W bulb, located above the pellet receptacle in a hooded houselight.

Training: FR1-FT1 Schedule

The rats used in this experiment were trained in a two-step process. All eighteen rats were first trained on the FR1-FT1 schedule to acquaint them with the chamber, the nose-poke response, and the reward. In this schedule, food pellets were automatically

delivered once a minute without a required response (FT1). In addition, if the rat responded at the single hole next to the food hopper, a pellet was also delivered (FR1); i.e the schedule was a combination (FR1-FT1). The FR1-FT1 program was set to run for 15 minutes, constituting one session. The house light was programmed to be illuminated for the duration of each session.

5CSRTT 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. The rat then had a period of time to nose- poke in the hole that was illuminated; this interval is the limited hold (LH). Responses in a non-illuminated hole (incorrect responses), failure to respond within the LH (omissions), and responses in a response hole 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. A new trial was not initiated until after the infrared beam is broken in the food receptacle. Training sessions were comprised of 100 trials or 30 minutes, whichever came first. On each trial, only one response hole was illuminated.

Rats were trained until they met the criterion of >70% accuracy, and <20% omissions for at least 4 days on stage 6. In addition, all scores for those 4 days had to

be be within 10% of each other. This constitutes the rat's baseline responding. The sequence of possible events in the 5CSRTT procedure is shown in Fig. 4.

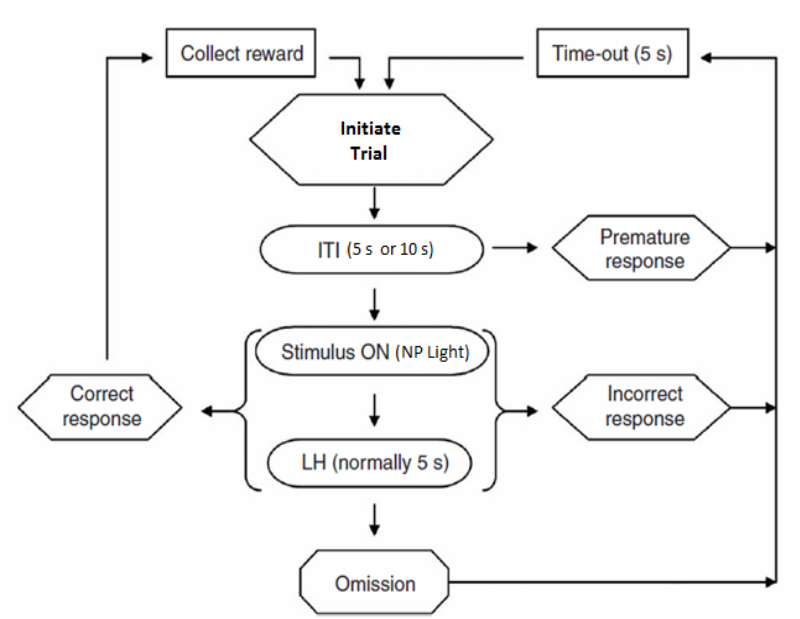


Figure 4. Flowchart Of Possible Trial Sequences in the 5CSRTT Program.

Surgical Procedure

Rats were deeply anesthetized with isoflurane (2.5-3.5% in oxygen) 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, with MVMT lesions:[anteroposterior (AP), 6.6; height (H) 2.8; lateral(L), 1.1], and LVMT lesions: [anteroposterior (AP), 6.6; height (H) 2.8; lateral(L), 2.0] 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 5 sec (cathode). Sham surgeries were performed in the same method without passing current through the brain.

5CSRTT Testing

All rats were allowed at least one week postoperative recovery before being placed on 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 light).

Performance measures

Accuracy of performance was measured as the proportion of correct responses (number of correct responses per total number of responses) expressed as a percentage. Errors of omission were the proportion of trials where no response was recorded (number of omissions per total number of trials) expressed as a percentage. Premature responses were the total number of head entries made before the trial began. The average latencies for a correct response, an incorrect response, and to collect reward were considered as a measure of motor function.

Behavioral Manipulations of the 5-CSRTT

Two behavioral manipulations of the 5-CSRTT were performed. The first involved alterations of the stimulus (light) duration and the limited hold (the time after stimulus light offset allowed for a response). The normal stimulus duration was 1.25 sec, and the normal limited hold duration was 5 sec, for a total allowed response time of 6.25 sec. In one of these tests, the stimulus duration was changed for one session to 2.5 sec with a limited hold of 3.75 sec, again for a total response time allowed of 6.25 sec. In the other test, the stimulus duration remained at 1.25 sec, but

the limited hold, normally 5 sec, was changed to 7.5 sec, for a total response time allowed of 8.75 sec. Thus, in one test the stimulus duration was doubled but the total allowable response time was unchanged from the normal, while in the other test the stimulation duration was the normal but the total time to respond was lengthened. These two altered conditions were conducted on post-operative test days 5 and 8, with approx. half the animals tested on the change in stimulus duration first and the other half on the change in limited hold first.

The second behavioral manipulation, conducted after the 10 days of post-operative testing at Stage 6, involved altering the motivation of the rats by manipulating their degree of food deprivation. The normal target for food deprivation was 90% of the rat's free-feeding weight. By adding extra food the day before a test session, weights were raised to 95% of free-feeding weight and the effects on 5-CSRTT performance examined.

Analysis of Results

After completion of all behavioral testing, the rats were humanely killed by CO_2 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 lesions, and the sections mounted on slides. The sections were subsequently stained with thionine and examined.

Performance on the first two post-operative sessions, which were at Stage 5 (stimulus duration 2.5 sec) was not analyzed; these sessions were for re-acclimation to the test procedure. In addition, although shown in the figures, data from the first

post-operative session on Stage 6 were not analyzed, because performance was unstable, even for the sham group. The statistical comparison was between the average of the last 3 preoperative sessions and each postoperative session beginning on the second day and continuing through the 4th day. This was done by Analyses of Variance for Repeated Measures.

RESULTS

Histology:

Fig. 5 shows the intended lesion targets in the medial and lateral VMT. All rats except for one lateral were on target; that rat's data were excluded from statistical analysis.

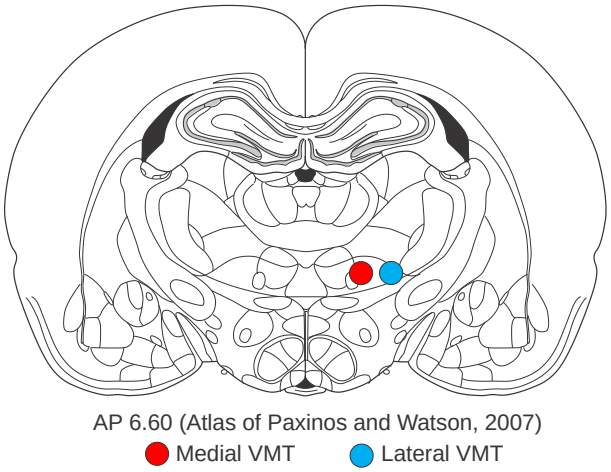
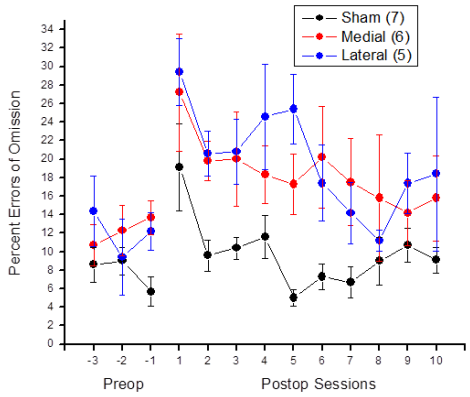


Figure 5. Intended lesion targets, and approximate size, as shown by examination of the histological material.

Errors of Omission

As shown in Fig. X, neither medial (F=1.67, df = 3/15, p = .22) nor lateral (F = 2.78, df = 3/12, p = .09) VMT lesions significantly affected omissions on the 5-CSRTT,

though there was a definite upward trend observed. Indeed, as seen in figure 7, when the data from the MVMT and LVMT groups were combined, a significant (F = 4.12, df = 3/27, p <.02) effect of lesion was found.



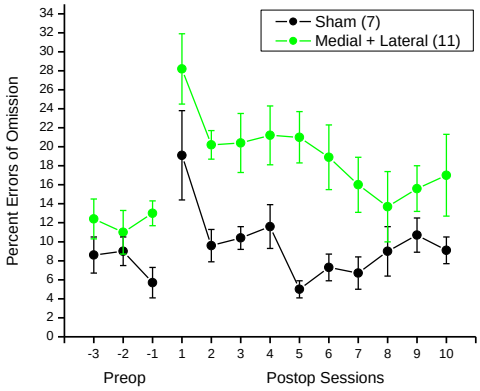


Figure 6 . Errors of omission separated by lesion group. Figure 7. Errors of omission combined.

Accuracy

As shown in Fig. 8, neither medial nor lateral VMT lesions affected accuracy on the 5-CSRTT. Although the three groups (sham, medial, lateral) had somewhat different pre-operative performance, none showed any consistent change post-operatively. Even when the data from the MVMT and LVMT groups were combined, no statistically significant (F = 0.87, df = 3/30, p > .05) effect of lesion was found.

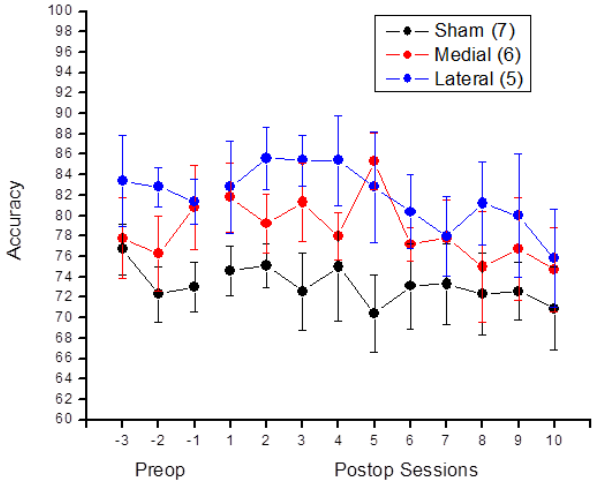


Figure 8. Accuracy, (Separated by Lesion Group).

Premature Responses

As shown in Fig. 9, neither medial nor lateral VMT lesions affected premature responding on the 5-CSRTT.

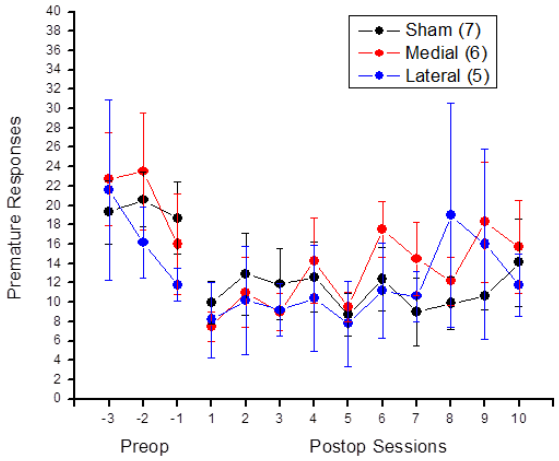


Figure 9. Premature Responses, (Separated by Lesion Group).

Latency to Correct Response

As shown in Fig. 10, neither medial nor lateral VMT lesions affected the latency to a correct response on the 5-CSRTT.

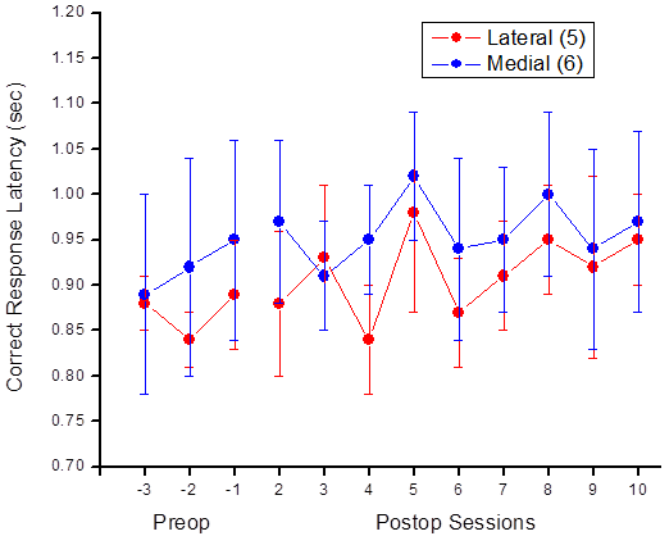


Figure 10. Latency to a Correct Response (Separated by Lesion Group).

Latency to Incorrect Response

As shown in Fig.11, neither medial nor lateral VMT lesions significantly ($F = 2.52$, $df = 3/30$, $p = .08$) affected latency to incorrect response on the 5-CSRTT, however a definite upward trend was observed.

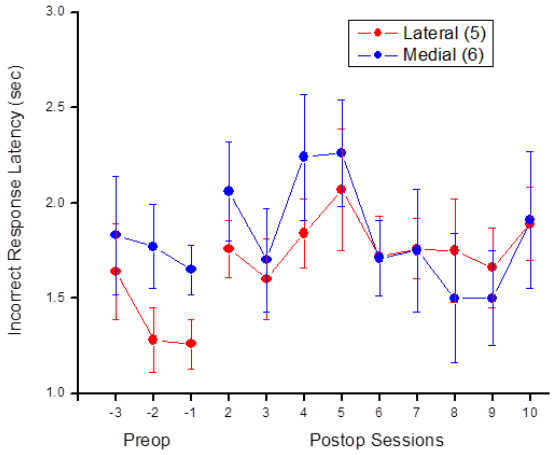


Figure 11. Latency to an Incorrect Response, (Separated by Lesion Group).

Latency to Reward

As shown in Fig. 12, neither medial nor lateral VMT lesions affected the latency to collect a reward on the 5-CSRTT.

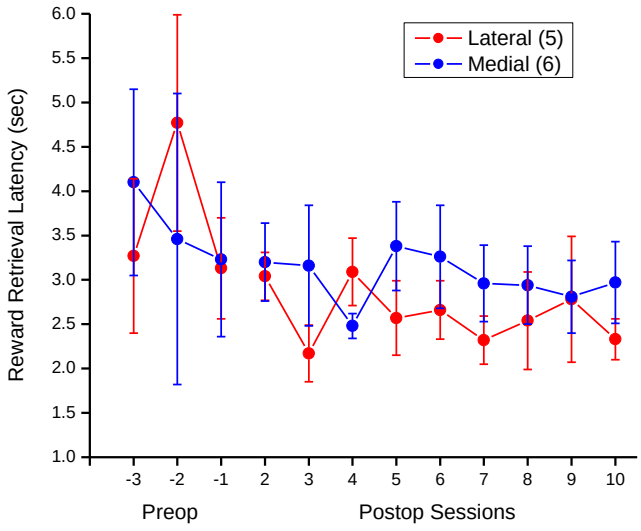


Figure 12. Latency to Collect Reward (Separated by Lesion Group).

Effect of Manipulation of Motivation to Respond

As shown in Fig. 13, decreasing motivation by increasing mean body weight

from 90% to 95% of free-feeding weight markedly increased errors of omission, while not affecting accuracy.

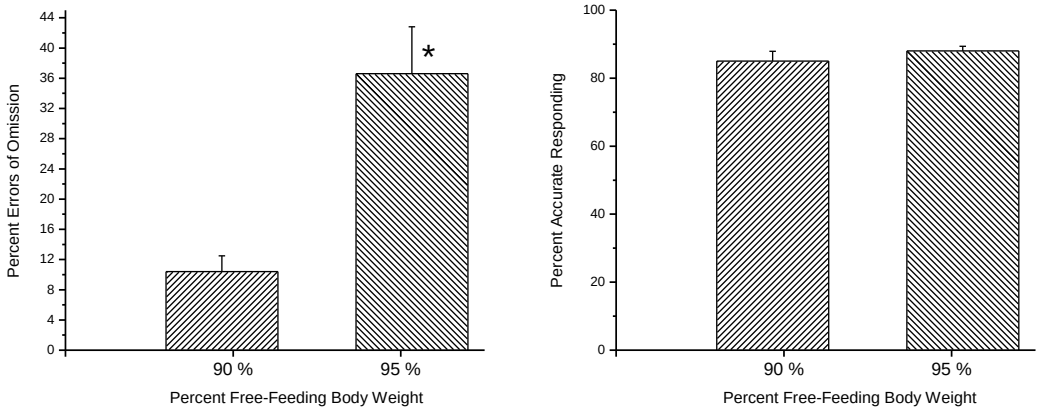


Figure 13. Increase in errors of omission, but no change in accuracy, by decreasing food motivation.

Effect of Manipulation of 5-CSRTT Stimulus and Response Parameters

Manipulation of stimulus duration and limited hold duration had interesting effects on performance. As shown in Fig. 13, neither doubling stimulus duration from 1.25 to 2.5 sec nor increasing allowable response time from 5 to 7.5 sec had any statistically significant effect on errors of omission. However, doubling stimulus duration markedly and significantly ($T = 3.63$, $df = 7$, $p=.008$) increased response accuracy; increasing the allowable response time did not significantly change accuracy, and in fact tended to decrease it.

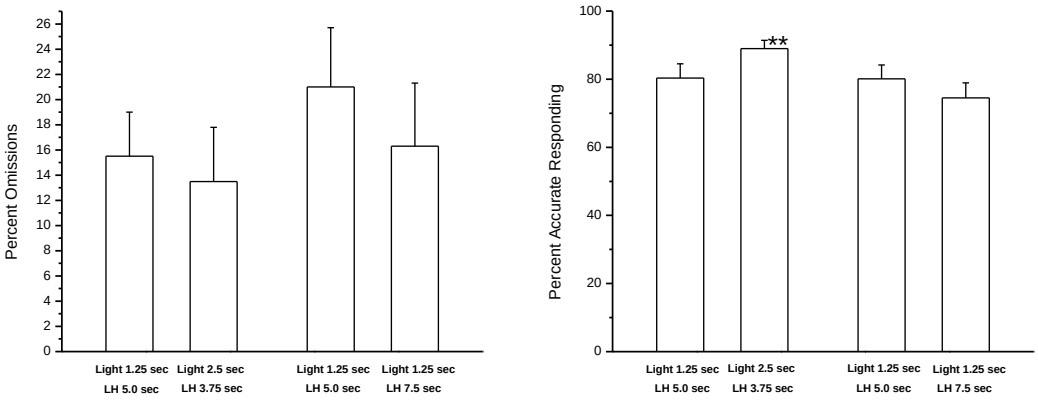


Figure 14. Errors of omission were not significantly affected by either doubling the duration of the light stimulus or increasing total time to respond by 50%. Response accuracy was, however, significantly increased by doubling the duration of the light stimulus.

DISCUSSION

Due to the hypothetical nature of cognitive processes, it is difficult to accurately use a measure, such as errors of accuracy, omissions, or premature responses, to imply an anthropomorphic deficit within a non-human experimental animal. Simply put: the cause for the productionof one behavioral deficit could be multi-faceted. For example, one might postulate that an animal would make an error of omission due to inability to perform a motor task, (particularly considering the motor functions of the VMT) or, alternatively, simply because that animal is not aware enough to perform the task (when considering the general arousal function of the VMT). Having stated this, we ultimately found that although both MVMT and LVMT lesioned animals showed an increase in errors of omission in the 5-CSRTT which alone were short of statistical significance, when data from the two groups were combined statistical significance was attained. Indeed, these combined results were similar to the data from lesions of the entire VMT.

The results of this experiment add an integral piece to the mysterious puzzle that is the role of the VMT in cognition. Jennifer McGee showed that when muscimol is injected into the VMT, (largely in what we consider here to be MVMT), rats increase errors of premature responding. One might take this to mean that the animals have lost impulse control. The same effect, however, is not shown by a MVMT-specific electrolytic lesion; rather, a different effect of increased errors of omission was observed.

Errors of omission proved to be the most important measure we assessed with this experiment. Six animals with MVMT lesions showed an increase in errors of omission that alone were not significant. This increase, though not statistically significant, provides evidence of a cognitive structure within the thalamus. This structure, the VMT, might allow the ability to multi-task rapidly, and learn new things associatively. We are left to presume, that because a muscimol induced deactivation (largely of the MVMT), produced an increase in premature responding, and our lesion, which would also destroy the aforementioned axons of passage ascending to cortex via the Inferior Thalamic Peduncle (a structure just below the VMT that receives widespread converging nonspecific input integral in cortical arousal), produced an increase in omissions, it is due to the destruction of the other nonspecific corticomodulatory inputs, combined with the VMT damage, that an increase omissions is observed.

This increase in errors of omissions is likely not due to a motor deficit, because no significant change was found in any of the most likely measures of motor performance, namely latencies for correct, and reward retrieval responses, though an upward trend nearing signifance was observed in the latency for an incorrect response. (Figs. 8 – 10).

Prior to the interpretation of our results, further investigation into the works of

(Garrett A., DeLong, M. and Strick P., 1986), revealed the discovery of parallel organized functionally segregated circuits linking the basal ganglia and cortex. In this paper, the group suggested an alternative to the dogma that the basal ganglia served, "primarily to integrate diverse inputs from the entire cerebral cortex and to "funnel" these influences, via the ventrolateral thalamus, to the motor cortex" (Garrett et al.,1986), and instead suggested that a set of five parallel circuits existed as outputs of the basal ganglia with "a 'motor' loop passing mainly through the putamen (dorsal striatum), which received inputs from sensorimotor cortex and whose influences were ultimately transmitted to certain premotor areas, (in a path similar to the proposed path of LVMT cells), and an 'association' loop passing through the caudate nucleus, which received input from the association areas and whose influence were ultimately returned to portions of the prefrontal cortex", (Garrett et al.,1986), much like the proposed path of MVMT cells. Furthermore, in a subsequent study intended to elucidate the existence of a similar parallel functional architecture within the functionally distinct motor loop, (Garrett & Crutcher) determined that it is "reasonable to view this family of circuits as having a unified role in modulating the operations of the entire frontal lobe, influencing in parallel, and byu common mechanisms, such diverse 'frontal lobe' processes such as the maintenance and switching of various behavioral sets (via the prefrontal and limbic circuits) and the planning and execution of limb and eye movements" (1990). The aforementioned data gives us lens through which to interpret our results.

One hypothesis is that the increased errors of omission in the lesioned rats reflect a deficit in attentional or motivational aspects of behavior rather than simply motor function. This is consistent with the widespread output of the VMT to the outermost layer

of cortex, particularly frontal cortex, as well as the aforementioned evidence suggesting a parallel functional architecture within basal ganglia output strucrtures. The VMT, by receiving large converging input from many different systems, and relaying them across the entire cortical mantle, reaches neurons that have the ability to affect the entire organism's function, and ultimately allows for quicker and more efficient processing of the plethora of stimuli one might encounter. An impairment of this multi-tasking system would give an animal task-dependent "tunnel vision," and decrease behavioral flexibility. A lesion destroying both this multi-tasking center, and components of another general arousal system, potentially attenuates cortical activation so much that rats lose the ability to perform the task, i.e commit errors of omission.

In the McGee muscimol experiment, low volumes of muscimol injected into the middle of the VMT produced premature response behavior, whereas high volumes produced errors of omission. Additionally, when an inadvertently misplaced cannula caused the injection sites of small volumes of muscimol to be shifted, (rather than being placed centrally in both VMTs, the cannulae were medial in one hemisphere and lateral in the other), errors of omission were observed. One interpretation of these results is that selective muscimol inhibition of the medial or lateral VMT results in errors of omission, and this was revealed by the asymmetrically located cannulae. This led to the hypothesis of the present experiment that lateral lesions would likely produce many more omissions than medial ones.

The five animals with LVMT lesions showed an increase in errors of omission that, alone, were not significant. These results contradicted the hypothesis that LVMT lesions work alone to produce omissions, however, much like the MVMT, when

considered along with other activational and motivational substrates that are destroyed by the lesion, one can see how the lateral lesion could contribute to increases in omissions. One of the aforementioned general arousal substrates are the intralaminar nuclei (ILN) of the thalamus. Lesions of the ILN lead to an increase in the latency to perform in a modified version of 5CSRTT (Burk and Mair, 2001). Though not explicitly destroyed in our experiment, significant damage to the aforementioned region, combined with a lesion of the LVMT, would lead to a decrease in the ability to decide to perform a motor task, (Burk and Mair, 2001) and perhaps an overall decrease in the ability to recall how to perform said motor task. Such deficits also could combine to produce what we observe as an increase in omissions, though not be functionally similar to the deficits observed in the MVMT lesion group.

Furthermore, the functional system described above could provide a mechanism by which rewarding stimuli, carried via the nigro-striatal dopamine system, could alter either sensory, motor, or arousal systems in the brain. The Neill lab showed that rats with a VMT lesion showed no specific locomotor deficits, but showed a marked inability to learn new tasks. This, in essence, makes sense. Operant conditioning is rooted in the idea that positive reinforcement of learned behaviors can cause such behaviors to be learned faster. Unexpected rewarding input to the Ventral Striatum or The Nucleus Accumbens Septi (NAS), activates GABAergic NAS neurons, which in turn inhibit the Substantia Nigra Pars Reticulata (SNPR), removing SNPR's inhibition on VMT. This would ultimately lead to an increased activity of the VMT, and widespread activation of the corticomodulatory system. Thus, when considering VMT's matrix-like afferents to layer I, a lesion of the VMT would elicit effects across

the entire cortical mantle, ultimately preventing the priming of all neurons with dendrites in this region. More simply, VMT lesions might cause a widespread decrease of cortical long term potentiation (LTP), which is widely believed to be the primary mechanism for learning and memory. (Neill & Kaufman, 1977). Indeed, in an aforementioned lesion study of the ventrolateral-ventromedial thalamic complex, "bilateral electrolytic lesions of the VL-VM thalamic complex impaired the acquisition but not the performance of a motor skill in cats*".* (Jeljeli et al, 2003) *This* shows that, although the Ventromedial Thalamus is largely considered to be a part of the specific motor system, it ultimately does not affect movement itself, but instead modulates the learning of all forms of positively reinforced behaviors, including motor learning.

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