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The Effects of Damage to the Central Thalamus on Learned Behaviors

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research article

The Effects of Damage to the Central Thalamus on Learned Behaviors

—**Kimberly Voorhies** (Edited by Kendra Nourie and Jennifer Lee)

During the past year I observed the behavior of rats with brain lesions in a University of New Hampshire psychology lab. I was part of a research team investigating the connections of the brain's central thalamus to motor sequence learning. Although an undergraduate, I was involved in the whole project from pre–training the rats through surgery and post–training to the present, where I am still analyzing data and running the last groups of rats through their tasks. (Fig. 1)

This hands–on research experience has made me truly understand and appreciate the many psychology lectures I have attended and textbooks I have read. I had significant responsibility in something real and felt that I was contributing to important knowledge in my field. Though data from this project is still being tabulated, new and related research studies have already resulted, including one of my own design.

Fig. 1.The author handling one of her subjects

The Brain and Motor Sequence Learning

When we learn to carry out a series of motor (movement) actions so that we do them without conscious thought or direction, we have participated in motor sequence learning. We are able to perform automatic, sequential behaviors, which have become learned routines, such as putting on a jacket, shifting gears in a car, or locking a door. The brain directs these activities for us so we can at the same time plan activities, imagine and fantasize, or think abstractly.

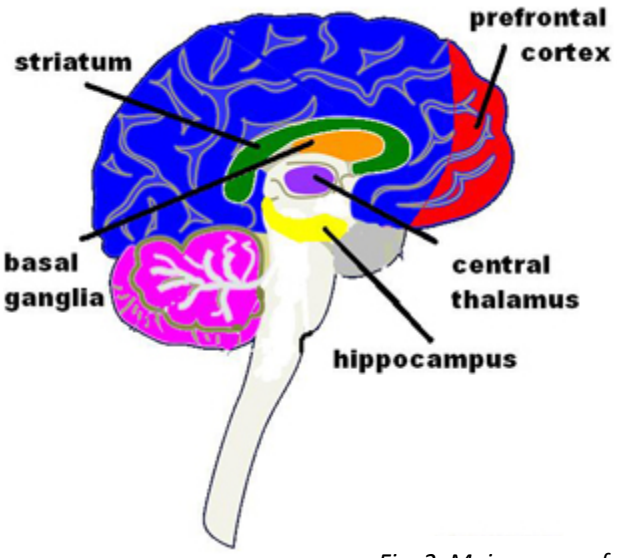
Research has identified particular areas of the brain that are significantly involved in motor sequence learning and has linked the control of these areas to the brain's central thalamus (Bailey & Mair 2006). The central thalamus transforms sensory signals into motor commands to these areas of the brain, a process which then results in automatic actions—all without our conscious direction. The brain essentially plans out the actions we are about to conduct without our awareness. Damage to the central thalamus would impede this automatic behavior, interfering with the brain's ability to plan (Bailey & Mair 2007; Burk & Mair 2001). Such damage has been connected to diseases of cognition and awareness such as amnesia, dementia, and delirium (Kobylarz & Schiff 2005).

In June 2007 a UNH Summer Undergraduate Research Fellowship gave me the opportunity to participate in a study of the central thalamus's role in motor sequence learning. The objective of this research project was to discover which parts of the central thalamus control motor sequence learning behavior. Graduate student Jackie Hembrook, in collaboration with psychology professor Dr. Robert Mair, had designed and was supervising this project for her master's thesis. I became part of her research team.

We hypothesized that specific nuclei in the central thalamus were involved in motor sequence learning and that damaging these nuclei in the brains of rats would cause them to take longer to plan learned behaviors. This would then hinder the rats' performances in sequence learning tasks. We proposed to test this hypothesis by surgically damaging selected nuclei in the central thalamus of five groups of rats, then running the rats through tasks which would test their motor sequence learning abilities. This would be a long and complex procedure, but we hoped any information gained would help identify factors causing comparable problems in humans and advance the development of solutions to these problems.

The Central Thalamus and Its Connections

The central thalamus is found in the very center of the brain. (Fig. 2) It is composed of clusters of nuclei, that is, cell bodies of a similar function and structure grouped together. These clusters are thought to communicate through circuits to the prefrontal cortex, basal ganglia, hippocampus, and striatum, allowing the organism to perform actions.



This communication and the roles of these parts of the brain are very complex and not yet fully understood. To give a brief, basic description: the prefrontal cortex has an important role in planning motor actions, something one does subconsciously before completing even the simplest sequence of movements. The basal ganglia regulate motor movements (Jones 1985). The hippocampus is largely associated with spatial and episodic memory, which are used in certain learned behaviors (Vertes, Hoover, & Di Prisco 2004). The striatum is thought to control some steps in motor actions and learning, such as working memory, sustained and divided attention, and memory for motor responses (Jones 1985).

Fig. 2. Major areas of the brain. (Adapted from CNS forum *of the Lundbeck Institute, 2007)*

The Nuclei Clusters

We were interested in three specific clusters of nuclei of the central thalamus: the rostral intralaminar nuclei (Rostral IL), the caudal intralaminar nuclei (Caudal IL), and the ventral midline group nuclei (VM). The Rostral IL nuclei communicate to parts of the prefrontal cortex and related areas in the striatum. There is strong simultaneous activity in the cortex and the striatum during automatic sequential behaviors; therefore, control of sequence learning might be related to this cluster of nuclei (Bailey & Mair 2007). The Caudal IL nuclei are significant providers of input to the striatum and the basal ganglia. Evidence from other studies indicate that these nuclei reach an optimal level of activity during sensory–guided responses, that is, they work their hardest while we are responding automatically during routine behaviors. This cluster may also have a role in the control of directing and planning these behaviors (Bailey & Mair 2007). The VM nuclei communicate

strongly with the hippocampus and somewhat less strongly with the prefrontal cortex and striatum (Vertes, Hoover, & Di Prisco 2004). By damaging these particular nuclei, we can study the relation of the central thalamus to the control of the hippocampus in sequence learning (Bailey & Mair 2007).

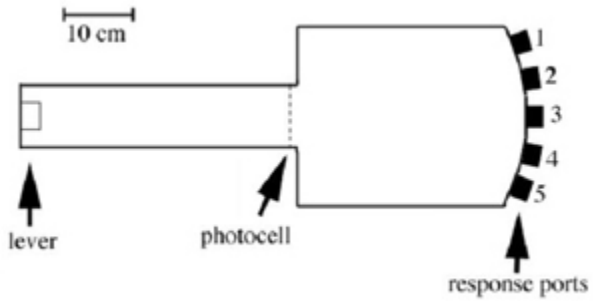
Surgery and Training

Before beginning surgery to damage systematically the nuclei clusters in the rats, we handled them one by one to let them become familiar with humans. At first, this made me as uneasy as it made them. This initial hesitation quickly left me, though, as I grew more comfortable—just in time to begin pre–surgery training.

We then ran the rats through pre–surgery training programs to accustom them to the testing apparatus. Here they learned to press a lever and to figure out the stimulus–reward system: they needed to poke their nose into a small, recessed port with a light (stimulus) and, in return, receive a small amount of water (reward). Monday through Friday, water was withheld from the rats so they would be motivated to find water by learning to poke their noses into a lighted port. At the end of each day they had thirty minutes of free access to water. We carefully monitored the rats to insure they were tolerating the water deprivation.

After the rats became familiar with the apparatus and tasks, Dr. Mair began surgery on five groups of eight rats each. He performed lesions in one of the three different nuclei clusters of the central thalamus for each of the first three groups. In a fourth group he performed lesions in all three nuclei clusters; and the fifth group was a control group with no lesions and a sham surgery. Surgery began with an injection of ketamine and zylazine to put the rats into a deep state of anesthesia, and then an incision on the top of the skull was made. For the control group the surgery stopped here, and the rats' heads were stitched up. This is called a sham surgery, which provides a similar environment for equal comparisons, each group having gone through any minor stress the surgery may cause.

During the lesion surgeries, Dr. Mair used a highly accurate instrument to mathematically pinpoint the exact location in the rat's central thalamus and inject a drug that caused cell damage to the target nuclei. This procedure could take up to an hour per rat, so surgery was split into four days over the course of a month. The rats had two weeks of recovery before post–surgery testing began.



Once the rats had recovered, we allowed them to become reacquainted with the testing apparatus, a Visual Spatial Reaction Time (VSRT) apparatus, designed and built by Med Associates, Inc. (Fig. 3) Then we began observations. The rats participated in different tasks aimed at testing their ability to perform both already learned and novel, or new, behaviors.

Fig. 3. Diagram of a Visual Spatial Reaction Time (VSRT) apparatus.

All the tasks follow the same basic pattern: When the rat presses the lever at the entrance of the runway, it retracts and a trial begins. The rat then moves down the runway leading to the larger chamber, where the action sequence learning will take place. When the rat enters the larger chamber, a signal from the entry photocell activates the lights of the particular trial. Each response port on the opposite wall consists of a recessed light (stimulus), a photocell beam across the port's entrance (to detect a poke from a rat's nose), and a well, which delivers 0.1 ml of water as a reward and reinforcement. When the rat pokes at the light with its nose, that port's photocell detects the movement and turns off the light.

The Sequence Task

The rats performed three different tasks during our research: the variable delay task, the single nose poke task, and the sequence task. My research work was focused on the sequence task in which a single nose poke represents a single action, or movement. A sequence of nose pokes, then, represents a sequence of movements, or actions. The sequence can be novel, or it can be already learned and therefore automatic. By comparing the lesioned rats' behavior during these tasks to the control group's behavior, we could see the effects of damaging the different nuclei clusters and thus the cluster's involvement in controlling automatic sequential motor action behavior.

During the sequence task one of the five lights turned on when the rat entered the large chamber. When the rat responded to the correct (lighted) port, instead of receiving water, another stimulus (light) of a different response port was activated. This procedure, causing the rat to "chase" the lights, was repeated until the rat made five correct nose pokes, thereby performing a sequence of actions. The fifth nose poke reinforced the correct responses by providing water in the well of the last (fifth) port. This completed one trial.

There were two versions of the sequence task: the repeated sequence and the random sequence. In the repeated sequence, the light sequence was fixed and did not vary between trials. This version simulated a series of actions that we perform automatically. In the second version, the random sequence, the light sequence varied for every trial the rat performed and, therefore, required novel learning for each trial. The rats followed a test cycle in which sixty trials of random alternated with 300 trials of repeated in this pattern: sixty random—300 repeated—sixty random—300 repeated—sixty random. This cycle took between three to four weeks to complete depending on the rats' abilities to respond.

The rats' performance times in each of the two sequence tasks were measured within each lesioned group to see the differences between a learned sequence, that had become automatic, and a new, unlearned sequence. The averaged performance time differences of each lesioned group were then compared with those of the control group. If there was a difference, particularly a delay, in a lesioned group's response times compared to the control group's, the area that has the lesion must be responsible for controlling the performance of learned behaviors.

Preliminary Results

Though final data are still being tabulated, preliminary results from the trials of nineteen rats indicate that rats in all four lesioned groups, when compared with the control group, had problems with planning the sequence before performing it. Using the computer programs Excel and Prism, we have depicted these findings in a graph. (Fig. 4) The negative numbers on the graph indicate a quicker response during the trials of the repeated sequence. All rats showed a quicker response on the fifth nose poke because the brain has already planned this last action in the sequence. This quicker response shows that the sequence has been learned. However, when compared to the control group, all the lesioned groups took longer to respond on the first nose poke. This indicates that it may be harder for the groups with a damaged thalamus to hold the learned sequence in their memory in order to unconsciously plan their learned nose pokes.

Although we don't yet have data on the significant statistical differences, it seems that rats with damaged caudal intraliminar nuclei clusters have the longest reaction times for the first nose poke. This suggests that these nuclei clusters may be principally responsible for planning learned motor sequences. This possibility is supported by recent studies of motor sequence learning in which particular areas of the rats' striatum or frontal cortex were damaged (Bailey and Mair, 2006; 2007).

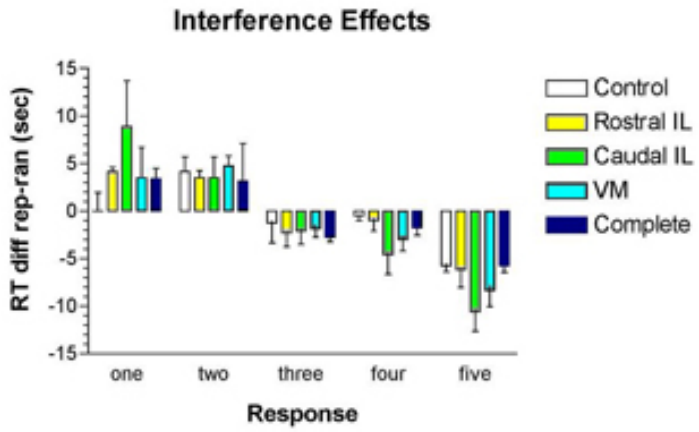


Fig. 4. Showing the relative reaction times of the four lesioned groups and the control group. The horizontal axis represents the 5 nose pokes of each trial. The vertical axis shows the response time (RT) differences in seconds, obtained by subtracting times of repeated nose pokes (in learned sequence) from times of random nose pokes (in new learning sequence.) The colors correspond to the nuclei(s) damaged.

Inspiration and Future Research

Working on this project motivated me to think about further involvement in research. In order to have another opportunity to participate in research, I applied to and was accepted into the honors program in psychology. This time, however, I would create my own project (under the guidance of Dr. Mair, of course). I decided to spin off Jackie's project by working with reversible inactivation instead of lesions on one set of nuclei in the central thalamus, the RI nuclei. In reversible inactivation a drug is injected that temporarily disables its target instead of permanently damaging it. I wanted to see if I could replicate the effects of the lesions on the sequence tasks using reversible inactivation. Temporarily rather than permanently knocking out a system is beneficial because it allows the comparisons of active and inactive systems within the same subject.

Not only was I motivated to create a new research project, but Jackie and Dr. Mair were inspired as well. After running the lesioned rats through the motor sequence learning apparatus, they decided to examine the effects of the lesions on memory using another apparatus, the radial arm maze. They are currently outlining the methods of that project.

Seeing the real life procedures of research made me realize how important research can be. We proposed a question, set up an experiment, and are getting real results, that is, possible answers to our question. I found myself discussing what I did in the lab with my friends, teachers, and parents. Research, I realized, was something I thoroughly enjoyed and wanted to continue. This opportunity has not only given me valuable experience but has also provided me with direction and options for furthering my education.

I would like to thank all the people who supported me and helped make this experience possible. Thank you to my UNH faculty mentor, Dr. Mair, and to graduate student, Jackie Hembrook, for allowing me to participate in this project with them and for all of their guidance throughout the summer. Thank you to James, Owen, Ian, and all the newcomers to Dr. Mair's lab for assisting me with my project. Also, thank you to the staff of the Hamel Center for Undergraduate Research and to the donors who made this grant available to me.

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Author Bio

One research project has led to another for ***Kimberly Voorhies****, a senior from Hudson, Massachusetts. Kim finds research very interesting and important and feels that there is no better way to learn than by doing. She says her research experience was "so satisfying, and I am so grateful to have had the opportunity. I took as much as I could out of it—academically, socially, and professionally." Kim will graduate in May with a B.A in psychology with a designation in honors from the University Honors Program. After graduation, Kim plans to either enter a doctoral program in behavioral neuroscience or continue participating in some more research assistantship programs.*

Mentor Bio

Professor ***Robert Mair*** *has been on the faculty of the University of New Hampshire since 1985; currently he is the chairperson of the Department of Psychology. He specializes in behavioral neuroscience, the study of brain function and how it relates to behavior. Of most interest to him are neurological diseases that impact memory and other aspects of cognition. Dr. Mair is no stranger to being a mentor. He typically works with one or two students on projects such as honors theses along with students carrying out independent projects. Dr. Mair believes a project like Kim's is important because it "leads us to rethink the relationship between the thalamus and systems in the brain that give rise to voluntary behavior."*