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Episodic Memory: The Role of the Hippocampal-Thalamic Circuit

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Introduction

In 1999, Aggleton and Brown proposed a neurological system for episodic memory that had been based upon about three decades of research. One of the intriguing features of this circuit is that it involves three different regions of the telencephalon (the frontal lobe, the temporal lobe, and parts of the limbic system), but it also includes the diencephalon (thalamus). In the late 1960s it had been known for some time that the diencephalon and the temporal lobe were involved in episodic memory (Delay & Brion, 1969). Part of the mystery, however, was that these two brain regions develop from different secondary vesicles, yet damage to one or the other of these regions results in similar forms of amnesia. This led Delay and Brion to hypothesize that the diencephalon and the temporal lobe must be a part of the same neural circuit, whereby damage to any part of it would result in a similar memory deficit.

The hippocampal-thalamic circuit includes the hippocampus, the mammillary bodies, the thalamus, and the fornix (a white matter tract that connects the mammillary bodies to the hippocampus. Using this circuit as the basis for discussion, I am going to introduce the research that has focused on these different regions, and explain their significance in episodic memory; episodic memory, as Aggleton and Brown (2006) point out, is “our conscious memory for personal events and experiences occurring at a specific time in a specific place.” I will first examine the how animals studies have explored this circuit and its role in memory, and then I will take a look at some human studies. Finally, I will explore the role of theta waves in the hippocampal-thalamic region and see how this activity is involved with memory processes.

The Hippocampus and the Fornix: Animal Studies

Delay and Brion were primarily involved with patients suffering from Korsakoff's syndrome, but many other scientists turned to animal models in order to understand the neurological systems involved in memory. Despite being unable to "declare" memories in modern day English, animal studies are still possible to explore episodic memory because of our ability to study how they memorize spatial arrangements. Episodic memory of an event can be regarded as a mental snapshot, and so by undertaking a spatial learning task the animal will have to sequence past memories in the correct order in order to re-obtain a reinforcer.

The hippocampus was implicated in spatial learning as early as 1978 by O'Keefe and Nadel, but the groundbreaking study that presented a simple but brilliant paradigm for spatial learning in the rat came from Morris et al. (1982) just a few years later. Since then, numerous studies have employed this test to study spatial memory in rats with hippocampectomies (Morris et al., 1990; Nagahara et al., 1995; Logue et al., 1997); if the hippocampus is lesioned then the rats are unable to learn and remember the location of the hidden platform. The control rats in these experiments get better and better at finding the hidden platform just beneath the surface of the milky water, meaning that they can clearly draw from past experiences and sequence them together in the correct order and arrive quickly at the platform. However, Morris et al. (1982) did find that rats with hippocampectomies can still use visual cues to arrive quickly at a visible platform, meaning that they can use visual cues to find a particular location. Clearly, the recognition of a cue that indicates a reinforcer does not require

a great deal of sequencing of past experiences and may even hint at semantic memory, i.e. the platform means to the rat that it can escape the aversive stimuli of being in the water and swimming towards the platform is simply goal-orientated movement.

The use of cues is still important in episodic memory as they provide an appropriate stimulus to facilitate memory retrieval and expedite moments of reinforcement for the organism. We know from Morris et al. (1982) that the hippocampus plays a minimal role in utilizing cues to facilitate memory retrieval, but a study by O'Keefe et al. (1975) revealed that lesions to the fornix in rats does hinder cue-orientated learning; in fact, even after training, the fornix lesioned rats could not accurately locate a correct drinking well[1] if there were no visual cues present. Remarkably, however, in the same study, O'Keefe et al. found that rats with fornix lesions were *faster* at locating correct drinking wells that were marked by cues (illuminated by spotlights) than the non-lesioned rats. This led the authors to hypothesize that during place finding, rats use the competing strategies of cue orientation and place memorization, and by lesioning the fornix there are no longer two competing strategies as the capacity for place memorization has been eliminated; this lack of competition, therefore, leads to the rat excelling in the use of the remaining strategy. As the hippocampus was still left intact, and we have seen that the hippocampus is involved in spatial learning, it appears that lesioning the fornix in the rats hindered the use of their hippocampus, but enhanced cue-oriented aspects of the episodic memory circuit. However, by contrast, Whishaw et al. (1995) found that fornix lesioned rats could still use spatial memorization in the Morris Water Maze, and even

[1] Out of many wells, a correct well was one where if the rat began to flick its tongue out in the empty well then water would be injected into it, but only if it was the right well. This behavior was trained during the pre-test.

though they could not perfom as well as the control group, they were still not as hindered as rats with hippocampectomies.

Whishaw and Maaswinkel (1998) continued with their fornix studies, and decided to look at dead-reckoning, which is the ability for an animal to leave its burrow (home) and be able to piece together cues generated by its movement to know where its burrow is in relation to its current position. Dead-reckoning, therefore, appears to be the integration of cue orientation and spatial memory in order to help an animal return home (or perhaps to another important location (such as an area rich in food). Whishaw and Maaswinkel pre-trained both fornix lesioned rats and control rats to leave a home-cage, wander out into a simulated test environment and retrieve food, and then return the food to their home-cage. They found that during training, control rats were able to return accurately to a home-cage in a novel location (with about 40% accuracy on the first attempt, and on the second attempt nearly all the rats could get back to the novel home cage), but the fornix lesioned rats had very little success returning to the novel home cage location on the first or the second attempt. We might expect this from rats with hippocampectomies rather than lesions of the fornix, but it could suggest that the hippocampus, plus the inputs and outputs of the fornix contribute to spatial memory. When Whishaw and Maaswinkel explored the ability of the rats to return to the home cage under sensory deprivation conditions (denying visual cues and disrupting olfactory signals), the fornix lesioned rats did not return successfully after retrieving their food, and were therefore unsuccessful in the use of dead-reckoning.

Mammillary Bodies and the Thalamus

Parker and Gaffan (1997) wanted to explore any potential differences in mammillary body lesions and fornix lesions in rhesus monkeys. Rats with mammillary body lesions had shown only minor spatial learning deficits compared to when their fornix was lesioned (Aggleton et al., 1995), but in primates a lesion to the mammillary bodies was just as detrimental to spatial learning as a fornix lesion (Kapur et al., 1994).[2] Parker and Gaffan used a task they had designed in 1994 to see how rhesus monkeys with a lesion to the mammillary bodies would affect the monkeys' ability to learn. The task, called an 'Object-in-place' task, tests the monkeys' ability to identify a particular section of a randomly generated non-familiar picture. The monkeys make their selection by tapping the appropriate part of the touchscreen, which provides them with a treat (reinforcer). The same scenes are presented numerous times so that over time the monkey learns the correct part of the scene by trial and error; this naturally means that the error-rate of the monkeys' choice diminishes over successive trials. Monkeys with mammillary body lesions, however, despite showing some improvement over time, displayed a higher error rate than the control group. Trial and error should diminish as the monkeys learn what they had to do previously in order to gain reinforcement (or avoid the choice that gave no reinforcement), but this is hindered in the monkeys with mammillary body lesions. Essentially, the rhesus monkeys with the mammillary lesions are unable to learn from past experiences to get the most out of the repeated environments placed before them.

[2] This is important, because it suggests that mammillary bodies in humans (also primates) could also perform similar roles in episodic memory.

After comparing mammillary body lesioned monkeys to control monkeys in the object-in-place task, Parker and Gaffan lesioned the fornix in both of these groups. The group that had prior mammillary body lesions performed with almost the exact same error rate as before, but the control group, who never had the mammillary body lesions, performed with about the same error rate as the group who had the initial mammillary body lesions. This overlap in performance led Gaffan and Parker to conclude that the mammillary bodies and the fornix in primates are part of the same functional unit in the hippocampal-thalamic memory circuit.

By injecting retrograde tracers into the medial thalamus of macaque monkeys, Vann et al. (2007) were able to identify two very distinct pathways from the mammillary bodies to the thalamus, and according to the authors these pathways are the principal output of the mammillary bodies. The medial mammillary nucleus outputs to the anterior medial and anterior ventral nuclei of the thalamus, and the lateral mammillary nucleus outputs to the anterior dorsal nucleus of the thalamus. The functions of these two different pathways in episodic memory appear to be vastly different based upon their morphology. Indeed Vann and Aggleton (2004) state that the anterior medial nucleus stands out from the other anterior nuclei because it has a more intimate connectivity to the cingulate and the frontal cortex; the significance being that the medial mammillary body connects to this nucleus and the lateral mammillary nucleus does not – this is therefore indicative of two separate systems.[3]

Using recording electrodes, numerous studies have now shown the presence of head-direction cells in the anterior thalamic nuclei (Taube, 1995; Stackman and Taube, 1997; Taube

[3] I could not find any studies since Vann and Aggleton (2004) that have really shed any light on this two system phenomenon.

and Muller, 1998). Taube (1995) trained rats in a small arena where they had to retrieve randomly scattered food pellets. During the experiment he recorded from the anterior thalamic nuclei of rats and found that when the rats faced a particular direction, certain cells became the most active depending on the head direction; indeed, as the head direction approached the degree that caused the most firing, the activity of the neuron increased, and if the rat continued to turn passed the optimal degree, the activity of the neuron declined. The orientation of an animal is of key importance in episodic memory, because the direction of the animal is a crucial characteristic of the memory; this is evident in the use of dead-reckoning when an animal has to be able to remember how it oriented itself to its current position from a home-base so that it may work backwards upon completion of its foraging task.

Head-direction cells in the thalamus seem an oddity, however, in the sense that place cells (cells that fire when an animal is in a specific location) have been found in the hippocampus (O'Keefe and Speakman, 1987). This shows that the different components of episodic memory (such as time and space) seem to be located at different parts of the episodic memory circuit (Aggleton and Brown, 1999). Head direction cells have also been found in the mammillary bodies (Blair et al., 1998), and in the postsubiculum (Taube, 1998). But not only are the head cells not in the hippocampus, they are located at the tail end of a circuit that might not have a direct connection back to the hippocampus (mammillary bodies and thalamus); this means that the head direction cell information has to go to the cortex before it gets back to the hippocampus, or it means the thalamus communicates to the hippocampus via the fornix, or it means the head cells in the postsubiculum are able to communicate directly to the hippocampus. Why there should be head direction cells in at least these three distinct areas

appears to remain a mystery, but this could reflect the fact that damage to any part of this circuit results in a similar kind of amnesia (Delay and Brion, 1969).

Human Studies

In humans, the mammillary bodies are included in the Papez circuit (Papez, 1937), which was a circuit proposed by Papez that was supposed to underlie a system for emotion within the brain.[4] Papez seems to have thought that the role of the mammillary bodies was to receive information from the hippocampus and relay it to the Thalamus (Eichenbaum, 2002). We know today that the mammillary bodies do indeed communicate to the thalamus via the mammillothalamic tract (Vann et al., 2007), even if it might not be a system involved in emotion as Papez suspected, and we know that damage to this tract has been seen in a number of patients with memory impairment (Kwon et al., 2010); in fact Kwon et al. (2010) have developed a technique based on diffusion tensor imagining to determine the neural integrity of the mammillothalamic tract in patients.

A number of studies have looked at the result of mammillary atrophy in humans and how this subsequent damage seems to have affected their memory (Kapur et al., 1994; Tanaka et al., 1997; Hildebrant et al., 2001). Tanaka et al. (1997) studied a patient known as "S.S.", who was a 57 year old ironworker. S.S. had the onset of memory problems and so decided to see a physician. He was aware of the place and the year, but he was unsure of the month and day. When he was distracted for 5 minutes he was unable to remember three objects that had

[4] Papez believed the emotional circuit to be circular, whereby the stream of communication went cingulate, hippocampus, mammillary bodies, thalamus, cingulate (Eichenbaum, 2002)

previously been presented to him. At this point the amnesia seems comparable to H. M. when he was asked to perform on a delayed match-to-sample test (Sidman et al., 1968)[5], whereby the longer a delay, the less likely the patient is to remember the object. However, as we have noted previously, damage to numerous parts of the hippocampal-thalamic circuit can result in similar amnesia.

Using MRI, Tanaka et al. (1997) discovered a large avascular mass compressing the base of S.S.'s hypothalamus, and it extended further into his 3rd ventricle. S. S. had corrective surgery to remove the mass and went through a recovery period. After the recovery period, he received another MRI and it was revealed that S. S. had small atrophied mammillary bodies. When his memory was tested again, S. S. demonstrated moderate anterograde amnesia[6] and was impaired on delayed recall tasks. When compared to other patients, it was suggested that damage to the mammillary bodies does not result in retrograde amnesia as seen in patients with Korsakoff's, so Korsakoff's patients must have damage that goes beyond the mammillary bodies.

Hildebrant et al. (2001) studied another patient, T. S., who was a 24 year old man who presented with a stiff neck and dizziness. A tumor was found close to T.S.'s pituitary glands and he underwent a series of treatments. After these treatments many of the initial complications had subsided, but he was experiencing memory deficits; an MRI scan revealed small atrophied mammillary bodies. In order to test his memory, Hildebrant et al. told him a short story and then asked him to recall certain parts of it; this was done on an immediate recall basis straight

[5] It is unclear from Tanaka et al. (1997) if they used a delayed match-to-sample test or not.
[6] Retrograde amnesia is a failure to recall events prior to the neurological damage, whereas anterograde amnesia is a failure to recall events that happened after the neurological damage.

after the story, and after a ten minute delay. T. S. was drastically hindered in both parts of this test when compared to a healthy control subject (again, this is comparable to H. M.). Kapur et al. (1994) had found similar results to Tanaka et al. (1997) and Hildebrant et al. (2001). A patient, K. K. had come into their care with damage to his mammillary bodies, but also his medial thalamus and brainstem. K. K. was impaired in recalling stories, especially after a significant delay, and also displayed some mild retrograde amnesia.

As memory deficits are common in those with heart failure (both ischemic and idiopathic), Kumar et al. (2009) carried out a study using MRI to see if the structures within the hippocampal-thalamic circuit differed volumetrically from a healthy control group. Interestingly enough, all of the heart failure patients showed reduced mammillary body volumes and a reduced fornix volume, even when the patients were matched for age and gender with the control group. The memories of the patients were not tested, but based upon previous evidence it seems likely that reduced mammillary bodies and a smaller fornix is likely to hinder the patient's ability to remember.

One of the best human studies to date that explored memory deficits in humans and correlated performance with fornix and mammillary atrophy was carried out by Tsivilis et al. (2008). In this study, Tsivilis et al. examined 38 patients who all had colloid cysts[7] surgically removed. Whether as a result of the cyst or its surgical removal, the patients all had mammillary and fornix deficits. The two types of memory test used in this study were recall tests (being able to recall past occurrences) and recognition (remembering the presentation of either a sound or sight from earlier). A number of different standardized tests were used for

[7] Colloid cysts are gelatinous cysts that typically form near the third ventricle.

recognition testing (Weschler Memory Scale III (WMS III), Recognition Memory Test (RMT), and the Doors and People test), whereas recall was measured only by one test, the WMS III.

Using MRI to determine the volumetric size of the mammillary bodies, the fornix, hippocampus, entorhinal cortex, perirhinal cortex, and the parahippocampal cortex, Tsivilis et al. (2008) correlated volume with test performance. The volume of the mammillary bodies was positively correlated with success in the recall tasks and weakly correlated with success at the recognition tasks. Fornix volume was positively correlated with the success of the RMT task (but not the WMS-III task), and with certain aspects of the recognition task. The rest of the areas mentioned had negligible to no correlation with performance. The fact that mammillary and fornix deficits seem to lead to episodic memory impairments could lend support to the Parker et al. (1997) study that showed the fornix and the mammillary bodies to be part of the same functional unit. Interestingly enough, hippocampal volume was not correlated with success of the recognition or recall tasks.

Theta Waves and the Hippocampal-Thalamic circuit

A key feature of the hippocampal-thalamic circuit is its production of theta waves (Green and Arduini, 1954; Stumpf et al., 1961; O'Keefe and Recce, 1993; Buzsaki, 2002; Royer et al., 2010). In 1954, Arduini and Green discovered theta waves in the hippocampi of rabbits and determined that it was a specialized wave with an unusual pattern that was somehow correlated with distinct functional or morphological parts of the brain. Today we know that Arduini and Green's work was highly prescient towards understanding the functional

neuroanatomy of episodic memory. Vertes et al. (2001) estimated that 75% of cells in the anterior ventral nucleus of the thalamus fired in synchrony with hippocampal theta rhythms. This synchronization, at the very least, suggests a highly coordinated circuit that is necessary for the retention of episodic memory, and suggests another reason that damage to any area in the hippocampal-thalamic circuit could result in a similar memory deficit due to the lack of synchronization.

Theta rhythms have also been associated with Long Term Potentiation (Vertes and Kocsis, 1997). Vertes and Kocsis (1997) discuss that LTP is optimally delivered in the hippocampus when the tetanic stimulation is at theta frequency. LTP has long been associated with memory retention in the hippocampus, mainly because it was discovered that late LTP requires protein synthesis and if protein synthesis is blocked in the hippocampus, then memory retention is hindered (O'Dell and Kandel, 1991; Guzowski et al., 2000). The mantra for LTP has always been "neurons that wire together, fire together," but in terms of a memory circuit it also looks like, "neurons that theta together, synchronize together."

There are populations of cells in the hippocampus that appear to act as theta generators; neurons that oscillate at theta frequency and function as what are known as "seed populations", which control the rest of the neurons not in those populations, such as place cells (Geisler et al., 2009). This essentially means that each seed population helps to coordinate the activity within the hippocampus, and has led some to believe that the temporal nature of the coordination facilitates the aligning of episodes, in a temporal manner, within the hippocampus (Guderian et al., 2007). Geisler et al. (2009) wanted to know why neurons outside of the seed population could oscillate faster than theta frequency, given the huge coordinating effect of the

seed population. They found that cells in CA3, despite oscillating faster than theta, generated a theta oscillation in the CA1 region. The fact that a faster frequency should cause a lower frequency seems like an oddity, and the fact that the lower frequency is specifically at the theta level seems to reinforce the significance of theta activity in the hippocampus.

Theta rhythms have also been associated with neurotransmitter activity in the hippocampal region; theta oscillations are modulated by cholinergic, GABAergic, and glutamatergic activity from the medial septum (Young and Jackson, 2011). As the activity of acetylcholine in this region has remained controversial, Young and Jackson (2011) tried to narrow down its role. While they found that acetylcholine was not correlated with theta frequency (even though choline – a metabolite of acetylcholine – is correlated), they hypothesized that high release of acetylcholine suppressed excitatory intrahippocampal pathways and facilitated entorhinal cortex inputs, but low acetylcholine activity could promote memory retrieval by releasing CA1 and CA3 inhibition (Young and Jackson, 2011). The authors concluded that while cholinergic activity is not correlated with theta activity it does help to modulate it.

Summary

Since Delay and Brion (1969), studies in episodic memory have advanced considerably, each new study building on the rich research and findings of the previous studies. Using animal models, researchers have been able to gain some insight into the role of the hippocampus in episodic and spatial memory. We also know that the hippocampus is not needed to help locate specific hidden areas if they are marked by a cue. The fornix also needs to be intact to assist in

spatial memory, but if the fornix is lesioned the organism could actually be more efficient at locating areas with cues; it would be interesting to see if a hippocampectomy would result in the same phenomenon, even though fornix lesions and hippocampectomies have been treated the same. We have also seen that an intact fornix is needed for dead-reckoning in rats as it is needed to correctly sequence a set of movements from a home base to a food location so that it may return to the home base after retrieving the food.

Animal studies have also been useful in exploring the role of the mammillary bodies and the thalamus in episodic memory. Rhesus monkey studies have helped us to see that mammillary body and fornix lesions tend to result in the same learning deficits, reinforcing the Delay and Brion (1969) idea that damage at different locations in the hippocampal-thalamic circuit results in similar memory problems. Rhesus monkeys have also been used to study and identify the complexity and profundity of the connections between the mammillary bodies and the thalamus. More studies are clearly needed to note how the two different pathways from the medial and lateral mammillary nuclei to the thalamus affect memory.

Animal studies have also helped us to see that there are specific place cells and head direction cells in the hippocampal-thalamic circuit; place direction cells in the hippocampus, but head direction in the post subiculum, the anterior thalamic nuclei, the mammillary bodies, and in the hippocampus. These studies show us that components of episodic memory seem to be represented on the cellular level in the hippocampal-thalamic circuit.

Human studies have also been useful, despite the variation in damage to the mammillary bodies and the fornix. Most of the human studies seem to be in agreement that damage to the mammillary bodies results in anterograde amnesia, and the ability for recall and

recognition is different. This is comparable to H.M., even though had his hippocampi removed; this is another reason to assume that deficits anywhere in the hippocampal-thalamic circuit result in similar deficits.

Theta wave studies have also proven pivotal in understanding episodic memory. Theta activity appears to help coordinate neural activity within the episodic memory circuit, and some believe this synchrony might assist in providing a time signature to memory events. Either way, it shows us that this system is highly dynamic and relies on the activity and coordination of all areas. Theta waves also appear to assist Long Term Potentiation in the hippocampus and can be modulated by neurotransmitter activity. Theta wave studies are clearly going to remain exciting and fruitful in helping us to understand episodic memory.

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