USING TEMPORAL LOBE EPILEPSY TO STUDY HOW MEMORY WORKS

By David Sloan

Instructive Malfunctions and Memory Systems,

Very often, we can learn as much about a system by observing its malfunctions as we can from observing its normal operations. Just as hurricanes and earthquakes teach us about how our planet works, much of our knowledge of biology, including the workings of our own bodies, has come from studying detrimental genetic disorders, infections and lesions. Indeed, the presence of an anomaly challenges us to ask questions that wouldn't be considered otherwise.

This concept of "instructive malfunctions" extends to modern research into the intricate workings of the brain and nervous system. The complex web of connections that form our cerebral network, which we take for granted as the foundation of our entire life experience, can be altered on multiple levels and in a myriad of ways. Each of these alterations helps us to appreciate biology's wonderful inventiveness, and has the potential to teach us how to fix the unwanted alterations that interfere with our quality of life.

One of the facets that is both basic and mysterious in the brain is the capacity to receive, store, retrieve and integrate information in the form of memories. It is compelling to realize that an organ made almost entirely of salt water, fat and proteins can effectively store events, images, languages, contexts and feelings in ways that we are still just beginning to understand. While we know the general regions that are most important for memory and while the cellular mechanisms that underlie memory are becoming better understood, much of what goes on between these two levels is still unclear. This middle ground, the "systems" or "populations" level, is difficult to comprehend, let alone study. Nevertheless, a solid understanding of how neurons work at the systems level is critical to our eventually unlocking the secrets of memory to our practical, clinical benefit.

At the systems level, the brain can be thought of as a constellation of overlapping networks. Each network represents a functional connectivity between multiple structures that work together to carry out an important calculation (for example, the optic network inputs and analyzes visual information in a way that can be used by the rest of the brain). The network commonly designated as responsible for memory is the limbic system. This system comprises substructures like the hippocampus, amygdala, midline thalamus and a variety of cortical regions. Each structure is connected to every other within the limbic system, but each structure affects each other physiologically in different ways. We can study this system directly by stimulating different structures and recording the reactions that they cause. We can further dissect out these regions to study their cellular components out of context or use imaging scans (like MRI) to see how they react to environmental stimuli.

Much of what is currently known about the memory system has been gleaned from medically relevant brain lesions, both accidental and surgical. For example, we know that a surgery removing both temporal lobes causes a complete loss of the ability to store short-term memories but doesn't affect long-term memories that have already been stored. Close observation of patients with degenerative diseases like Alzheimer's or viral infections--diseases that cause some physical destruction to parts of the brain--have helped us to understand that there are distinctions between where different types of memory (explicit, implicit, working, etc.) are carried out. But these studies provide only broad, regional insights, and don't reveal what is actually going on within the lesioned structures. More detailed insights require much more sophisticated and creative experimentation.

Temporal Lobe Epilepsy as an Instructive Malfunction

The idea introduced at the beginning of this article is that malfunctions within a system can be just as instructive as normal operations. That being the case, it would be useful to examine ways in which some or all of the limbic system is altered or mutated. At least one naturally occurring disorder fits this description.

Epilepsy is a major neurological disorder worldwide. It is defined as the occurrence of multiple seizures, or inappropriate electrophysiological events, over a period of time. A common type of epilepsy in adults is Temporal Lobe Epilepsy (TLE), in which seizures appear to begin at some point in one or both temporal lobes (Engel 1996). TLE is often medically intractable, or resistant to medications, and may require surgical resection of the temporal lobe to control. Unlike other forms of epilepsy that are caused by simple chemical imbalances or genetic mutations, the evolution of TLE causes cellular damage and a rewiring of affected areas, rendering pharmacological interventions ineffective.

TLE, specifically a sub-type known as Mesial Temporal Lobe Epilepsy (hereafter just TLE) directly targets the limbic system. TLE seizures often initiate within the hippocampus, amygdala, or a neighboring cortical tissue, although the network is so tightly interwoven that it sometimes appears that seizure initiation can occur in any number of points within the system. Patients with TLE are known to show cell death and reduction of volume in the hippocampus as well as other areas. More importantly, the physiological balance at each point of the system appears to be altered. The same delicate, plastic mechanisms that form the basis of memory functions are used against the brain to perpetuate seizure activity. Essentially, TLE can be viewed as a malfunction, or warping, of the memory system.

Not surprisingly, mild memory defects are commonly reported in TLE patients. It is the most common self-reported complaint of patients (Eliasen et al. 2008, Piazzini et al. 2001, Corcoran and Thompson 1992). The extent to which real memory problems exist in a patient depends on a number of factors, including the age of onset, seizure severity and duration, the effects of anti-epileptic drugs, and factors introduced by lifestyle (drinking, high stress environments, etc.) The mildest problems are represented by a subset of TLE called Transient Epileptic Amnesia, in which the patient experiences brief electrical bursts that impede the reception of memories (Butler et al., 2008). The more severe the seizures and the longer they last, the more the memory of the individual is affected, leading to a graded variety of seizure-correlated memory disruptions.

It should be noted that a major limitation to these studies is identifying which test results reflect actual memory difficulties. A slew of studies over the past twenty years have suggested that some TLE patients perform poorly on memory tests because the seizures have affected the verbal centers that are also found in the temporal lobe. Further work suggests that epilepsy patients have high rates of depression or anxiety, which may exacerbate any mental occlusion, or at least magnify their own perception of the severity of their memory loss. Although many patients perform well on psychological tests, memory loss is generally well accepted as a result of TLE, particularly in working memory used on a day-to-day basis (Eliasen et al., 2008; Piazzini et al., 2001; Corcoran and Thompson, 1992; Van Rijckevorsel, 2004).

Lessons From TLE

The potential for exploring how memory works through the lens of TLE has not been lost on researchers. Still, many have limited their approach to that potential to the “top-down” approach, trying to extrapolate distinctions between different types of memory in patients with different degrees of TLE severity. Leritx et al. (2006), recently focused on how explicit and implicit memory is altered across TLE patients, with varied success. But the condition of TLE allows for much more precise investigations into memory circuitry, even with non-invasive technologies.

A close examination of epilepsy circuitry in humans can reveal much about how parts of the brain can compensate in memory functions. Recent work by Eliasen et al. (2008), examines how a number of cortical and subcortical areas (including the medial prefrontal and the thalamus) are involved with recollection and encoding in different learning contexts. They found that TLE on the left side can shift the distribution of computational tasks across hemispheres, so that computations that were primarily done on one side of the brain can be successfully delegated to the other. Furthermore, areas directly affected by seizures can force compensatory action by other cortical areas on the same side.

In another recent study, Takaya et al. (2008), issued a report on temporal lobectomies. A surgical concern in removing a seizure focus is the proximity of the focus to other axon tracts and cortical regions, like those that perform language functions. Removing these portions can cause unwanted side effects. In developing a more careful and localized procedure, they found that removing the epileptogenic zone led to improved glucose metabolism in other areas of the brain and improved cognitive scores on several tests. This indicates that brain regions modified in TLE were holding back nearby regions of the brain and that this restraint is lifted when the region is excised. One may reasonably extrapolate that a portion of the memory circuit does not have to be changed directly by seizure activity to be affected by it indirectly. It's like if somebody kidnaps a postal worker: the postal worker has a bad day, but there's also a lesser effect on all the people who don't get their mail. If the hippocampus, for example, can't send or receive accurate, uncorrupted and clear data, then all the synaptic targets of the hippocampus suffer, and the memory system doesn't work. The trick is to find out what exactly is interfering and fix it.

Limbic Circuit Studies in Animal Models of TLE

While much can be learned from studying memory in TLE patients, there's clearly a limit to which a patient's brain can be ethically examined in a controlled fashion. For this reason, animal models of mesial TLE seizures—mostly in rats—have been developed over the last fifty years (in careful conjunction with established ethical standards). These are known as Chronic Limbic Seizure (CLS) models. Having an animal analog allows for a more tactile approach to study the ways in which memory circuitry is altered following seizures.

An animal CLS model is typically created by the application of an electrical or chemical stimulant into the limbic system, usually in the hippocampus or amygdala. If the stimulation is strong enough, it induces an electrochemical event at the application point that severely damages, or at least rattles, all the circuits going in and out of that point. While the animal recovers, the effects of the event take shape. The most overstimulated cells die off within a week. The normal synaptic plasticity of the brain allows the surviving neurons to either strengthen their communication with intact pathways, or to seek out new connections to compensate for the ones that were lost. The result is a rewiring of almost the entire limbic network, and that leads to an environment in which spontaneous seizures can, and do, occur. While this is obviously not the way that TLE typically develops in humans, it is comparable in that the same structures are involved and that the basis of the problem lies in a warping of the hard wiring.

The primary goal of research in CLS models is to identify how spontaneous seizures initiate and spread in the animal's altered brain. This is done through procedures that attempt to catalog the changes that take place following convulsant event in each limbic structure, then to identify how communication between structures in the epileptic brain has changed. Further work is done to actually record seizure activity as it happens and to map out how the seizure flows, similar in some ways to using a few sensors to measure how flood water spreads out into a field. Data from all of these experiments can than be integrated to gain a clear conception of how each part of the limbic system interacts. In this way, a foundation is laid upon which memory research programs, focusing on the entire memory network, can be built.

Part of this work involves piecing together a clear understanding of how each individual circuit works. This requires a somewhat painstaking analysis of the connections between each structure and then expanding that analysis to include how a third, fourth or fifth influences the working of that circuit. An example of this work is being undertaken at the University of Virginia. Researchers at the Bertram lab are examining a variety of memory-relevant limbic circuits, with attention focused on how one particular structure, the midline thalamus, influences circuit dynamics.

The thalamus sits at the center of the brain, and acts much like a central router. It relays information between structures, modulates circuit activity as a kind of third party, and coordinates activity across structures. The medial portions of the thalamus are the most well-connected to the limbic system, and connect to virtually every node of the network. Naturally, it is a subject of interest in epilepsy research, as it would be quite capable of distributing and synchronizing seizure activity throughout the brain. Several studies have already established that the midline thalamus participates in limbic seizures, and is affected by them anatomically and physiologically (Bertram et al. 2001, 2008, Sloan and Bertram 2008). To explore how the thalamus affects circuits in the epileptic rat, it first becomes necessary to understand how it affects circuits in control animals.

For example, there exists a connection between the subiculum, which is the major output center of the hippocampus, and the prefrontal cortex (PC), where executive functions and decision-making computations are undertaken. The link between them is important for channeling memory information from the hippocampus to the PC in order to make effective behavioral decisions. The stimulation/response effect that the subiculum has on the PC can be measured electrophysiologically. Once measured, the role of the midline thalamus in that effect can be measured by either knocking down or hyperexciting the thalamus pharmacologically. Preliminary data obtained by the author suggests that while the subiculum is sending direct input to the PC, a secondary pathway from the subiculum through the thalamus creates an additional physiological response. In other words, the subiculum talks to the PC directly, and also sends a secondary signal indirectly through the thalamus.

This work, performed in an effort to better stand the circuitry of epilepsy, could also yield valuable information to the study of memory. The reason why this indirect pathway from the hippocampus through the thalamus exists is yet unclear. Perhaps it serves to reinforce or amplify subicular input, ensuring that the data is not lost or ignored. Perhaps it serves to provide an additional boost that will encourage the mechanisms of synaptic plasticity to strengthen or retreat from a specific avenue. Perhaps there is more than one reason. The point is that once this data is available, both epilepsy researchers and memory researchers alike can fit it into the grander models of how the limbic system works.

Potential for the Future of Memory and Epilepsy Research

Several key technological advances have come about in the last ten years that will make possible far more linkages between memory and epilepsy research than there have ever been. Advancements in multi-electrode arrays are leading to broader, three-dimensional views of brain interactions, and it is not unlikely that arrays designed specifically for recording across the subcortical limbic network can be created. Advances in computer modeling have already provided insight into seizure movements in generalized epilepsy. Future virtual simulations that can handle non-linear interactions will greatly aid in integrating all the data obtained from experiments thus far. Also, great steps in improving the resolution of fMRI and PET scans will help to draw comparisons between TLE patients and CLS models, while new methods such as Diffuse Tensor Imaging, which allows MRIs to create 3 dimensional images of specific fiber bundles, will help visualize how fiber bundles connecting limbic structures change in human epilepsy patients. Advances on all of these fronts are already being made and have contributed a great deal to our understanding of other types of epilepsy (Meeren et al., 2002; Shusterman et al., 2008; Szabo et al., 2005.)

Additionally, the various electrophysiology techniques that have supplied so much data over the years are not losing their effectiveness, and will continue to reveal multiple avenues of interest. The amount of data that is now known in both control animals and CLS models will need to be sorted, integrated and explored indefinitely. For example, we now have a greater understanding of how cells in the hippocampus are wired in a non-random fashion (Larimar and Stowbridge 2008). Those same hippocampal cells are rewired in epileptic animals (i.e., Sun et al., 2007). The potential for crossover research at the small-scale cellular level is enormous.

Obtaining a knowledge of how things have changed requires control experiments that test how things normally work. Every anomaly seen in an epileptic brain can lead to hypotheses that can be tested in a normal brain. Furthermore, epilepsy research forces a 'systems' perspective in the researcher, as well as a focus on how information flows down established pathways. After all, a seizure most likely flows down the path of least resistance, and that means that it may preferentially utilize pathways that have been developed to maximize memory functions. In other words, it is not unlikely that limbic seizures and important memories use the same neural highway systems (although there is much to that conjecture that remains to be tested).

The lines between fields of research often become blurred as the assumptions that originally divided them are changed. In the case of epilepsy and memory, our modern understanding should promote interest in what one they can teach one another.

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