THE Science BREAKER
SCIENCE MEETS SOCIETY

December 14, 2015

Neurobiology

Where is the Engram?

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This Break was edited by Dr. Tobias Preuten, *Editorial Advisor* - TheScienceBreaker

The human brain is composed of over 100 billion electrically-active brain cells (called neurons), and what makes the neuron a special cell type is that it sends out extensions (known as axons) that form connections with other neurons. These connections are known as synapses, and allow for the direct communication of neurons with one another through the release of chemical substances called neurotransmitters. Populations of neurons form intricate wiring networks in the brain, resulting in trillions of different synapses. Intriguingly the structure and strength of synaptic connections can change with experience. Because of this plasticity, and the inherent complexity of synaptic networks, it has long been assumed that memories are stored through these connections. Yet it has been difficult for scientists to study this in detail because looking for the neurons involved in any particular memory is like looking for a particular grain of sand at the beach. The challenge therefore is to identify which neurons are holding a given memory, which we refer to as the memory engram, and then to study their synaptic connections.

In Arthur Conan Doyle's "A Scandal in Bohemia", Sherlock Holmes devises a plan to retrieve a compromising photograph of the King of Bohemia hidden in Irene Adler's home. Dr. Watson questions how Holmes will know where to look for it. Holmes retorts – "I will not look...I will get her to show me". By releasing smoke, the photograph's location is revealed through Adler's behaviour because "when a woman thinks that her house is on fire, her instinct is…to rush to the thing which she values most". If we are to identify a specific memory we can take a similar approach, by hijacking the biological mechanisms of memory allocation. One of the ways that the brain allocates information is through specific genes that are induced by brain activity to produce specific proteins. We modified these brain-activity induced genes to produce a fluorescent protein that can easily be observed. This way, we genetically engineered a mouse whose brain cells lit up brightly when a certain memory was triggered and were able to identify some of the cells that store a specific memory—the memory engram cells.

Having identified these cells, we could study their biology directly. In doing so, evidence was found implying that engram cells carrying a specific memory have more synaptic input than other neurons. Furthermore, when these particular synapses were experimentally disrupted by drug treatment, the mice displayed amnesia for the associated memories; in other words, they could no longer remember the events stored in these places. Thus, these engram cell properties seem to be important for memory function.

But are these memories lost or just not accessible? The ultimate evidence for a memory being present is the behavioural fact of the animal recalling the memory. We developed a method to directly switch on a particular memory in the mouse by specifically activating the associated engram cells. Upon activation of these cells, memory recall occurs as shown by the expected behaviour of the mouse. When we stimulated engram cells whose synapses had been disrupted before, leading to amnesia, the mice still showed the expected behaviour, i.e. they remembered what was stored in these cells. This means that the memory survived the

amnesia and was still present in the brain.

How, then, is the memory stored in the brain in the absence of the strengthened engram synapses? Further analysis revealed that engram cells showed a unique pattern of synaptic connectivity with other engram cells in different brain regions. Though the strength of these synapses was compromised by the amnesia, the basic pattern of connection in the network remained intact. This is why the memory could be recovered by directly switching-on the engram cells.

When learning occurs, small populations of neurons are simultaneously activated in different brain regions relevant to that experience, and become engram cells. These engram cell populations form preferential networks across brain regions which likely represent the storage of the memory information itself. In parallel, the synaptic connections between engram cells are reinforced which facilitates efficient access and allows them to be easily retrieved when a memory is needed. These dual properties of engram cells provide adaptive value to the organism: stable synaptic networks allow long-term memories to be stored for a lifetime. On the other hand, dynamic changes in synaptic strength permit the organism to quickly and reversibly alter the relative accessibility of existing memories, without the cost of losing them entirely. Based on these findings, it is likely that many cases of clinical amnesia such as Alzheimer's disease, stroke, and traumatic brain injury are caused by disruption of the brain's access to specific memory engrams. "Lost" memories may still be present in the brains of patients suffering from these conditions, and could be retrievable if novel clinical interventions are developed. The trick, as Sherlock Holmes might suggest, will be to get the brain to show us where they are.