Where do memories live?

September 8 2016, by Giuseppe Gangarossa

Memory is one of the many brain functions that have fascinated generations of neuroscientists. It is a cerebral phenomenon that accompanies us throughout our lives and gives a colorful meaning to our experiences. Good and bad memories shape our personality and our way of interacting with the world. Among the questions brain researchers and many others have long pondered are: How and where are memories born? Who or what is responsible for their creation? Where do they live?

And while the mechanisms involved in encoding, storing and retrieving

memories have attracted a great deal of attention, the processes that allocate individual memories to a specific subset of neurons within a complex neural network have not been fully elucidated. Obviously, a memory must be allocated somewhere in the brain and memory allocation is becoming an extremely fascinating field.

Memories depend on allocation: who and where

Memory allocation, a recently discovered phenomenon of memory formation, accounts for how specific neurons (neuronal allocation) or even synapses (synaptic allocation) are committed to storing a specific memory (Rogerson et al., 2014). Synaptic and neuronal allocation mechanisms work closely in building and governing the networks of neurons implicated in the acquisition, stabilization and retrieval of information within the black box which is our brain. Therefore, understanding the molecular, cellular and systemic mechanisms, as well as the implications of these processes, is essential since this knowledge may elucidate how memory allocations are coordinated and integrated during memory formation and consolidation.

In a recent research article published in *PLOS ONE*, Thomas Rogerson and colleagues had a closer look at how molecular and cellular mechanisms regulate the allocation of memories to discrete neurons in the amygdala, a brain region highly involved in learning and memory processes.

Molecular mechanisms of memory allocation

Increasing evidence suggests that the transcription factor cAMP-response element binding protein (CREB) plays a critical role in neuronal allocation in the lateral amygdala (LA) (Silva AJ et al., 2009, Sano Y et al., 2014), a structure required for learning the association

between a conditioned stimulus (CS, such as a tone) and an unconditioned one (US, such as a foot-shock) in auditory-fear conditioning (AFC). The AFC paradigm relies on the following principle: when a mouse receives a foot-shock in a particular context, an engram forms to encode the memory trace of that event. Once that memory forms, the set of neurons that make up the engram are more likely to be activated. Interestingly, the more excitable neuronal cells are, the more likely they are to be recruited into a specific engram.

Using cellular, behavioral and optogenetic tools, Rogerson and colleagues tested whether it was possible to recruit the encoding of an auditory-fear conditioning (AFC) memory to a subset of neurons with increased excitability, as it has been previously shown for CREB (Zhou Y et al., 2009). In fact, the same laboratory, led by Alcino Silva, a Professor of Neurobiology at the David Geffen School of Medicine at UCLA, has shown that CREB regulates neuronal allocation by modulating neuronal excitability (Zhou Y et al., 2009).

In this elegant study, optogenetic studies in the lateral amygdala (LA) were used to explore whether CREB and neuronal excitability regulate which neurons are to encode an emotional memory such as fear. Indeed, the authors were able to allocate an emotional memory to a subset of LA neurons using either CREB or a transient optogenetically-controlled increase in excitability during learning. Surprisingly, "opto-activation of this specific subset of LA neurons resulted in recall of the memory" said Thomas Rogerson, the leading author of the study. In fact, post-training optogenetic activation of neuronal cells infected with a viral CREB was sufficient to elicit recall of an auditory-fear conditioning memory. Memory recall, triggered by light-driven stimulation of Channelrhodopsin-2 in neurons virally expressing CREB, was higher than that observed after activating a similarly infected population of neurons with a control virus. These results "suggest that the AFC memory was disproportionately allocated to the neurons with higher

CREB, so that Channelrhodopsin-2 activation of these neurons post-training resulted in more robust recall than activation of a similar number of neurons with normal levels of CREB in controls," concluded the authors. In addition to these experiments, the team of Dr. Alcino Silva showed that "increasing neuronal excitability in a subset of lateral amygdala neurons right before training increased the probability that these neurons would be involved in memory." These results suggest that increases in excitability can bias memory allocation only when they takes place during training, whereas increases in excitability immediately after learning do not affect neuronal allocation. As discussed in the article, "altogether, these results strongly support the hypothesis that increases in neuronal excitability are a mechanism by which higher levels of CREB bias memory to a subset of neurons in a neural circuit."

Could increased excitability solely explain the phenomena of memory allocation? This is unlikely since "the refinement of a memory trace to a subset of eligible neurons relies on a number of other cellular and circuit mechanisms, such as lateral inhibition mechanisms in which the most excitable neurons inhibit the formation of the memory in less excitable neurons," reported the authors.

In conclusion, this research remarkably contributes to unfolding the various mysteries of memory processes, suggesting that increases in neuronal excitability and cell tagging may together determine the exact sites where, and how, memories are to be stored and recalled. It is thus tempting to hypothesize that the research of these authors may lead to important, groundbreaking discoveries aiming to repair broken neural circuits involved in memory-related dysfunctions as observed in Alzheimer's disease or post-traumatic stress disorder.

More information: Thomas Rogerson et al. Molecular and Cellular Mechanisms for Trapping and Activating Emotional Memories, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0161655

A. J. Silva et al. Molecular and Cellular Approaches to Memory Allocation in Neural Circuits, *Science* (2009). DOI: 10.1126/science.1174519

Yoshitake Sano et al. CREB Regulates Memory Allocation in the Insular Cortex, *Current Biology* (2014). DOI: 10.1016/j.cub.2014.10.018

Yu Zhou et al. CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala, *Nature Neuroscience* (2009). DOI: 10.1038/nn.2405

Thomas Rogerson et al. Synaptic tagging during memory allocation, *Nature Reviews Neuroscience* (2014). DOI: 10.1038/nrn3667