Memory Allocation

Memories are thought to be represented in the brain as enduring physical changes in ensembles of neurons, the 'engram'. How are neurons chosen (or allocated) to become part of the engram? Is this process random? Evidence suggests it is not. We (Han *et al*, 2009) and others (Zhou *et al*, 2009) examined how fear/threat memories are encoded in the brain. In this paradigm, rodents learn to associate a tone with a shock and this association critically depends on the lateral amygdala (LA) (Repa *et al*, 2001). Manipulating levels of the transcription factor CREB in LA neurons influenced the likelihood of a neuron becoming part of a fear/threat memory engram. To determine 'engram membership' we quantified expression of the activity-regulated gene *arc* after encoding and/or retrieval. When CREB was virally overexpressed in random LA neurons, those infected neurons were more likely to be allocated to the engram than their non-infected neighbors. Conversely, when CREB function was virally suppressed, infected neurons were excluded from the engram (Han *et al*, 2009). These findings suggested that neurons with relatively higher CREB are more likely to 'capture' the memory. Definitive evidence for this emerged from subsequent experiments: genetic ablation or suppression of the CREB overexpressing cells (and not an equivalently sized random population of LA neurons) was sufficient to erase the memory (Han *et al*, 2009; Zhou *et al*, 2009).

CREB is involved in many biological processes. Which process is responsible for the increased likelihood of allocation? One candidate is neuronal excitability. Overexpression of CREB increases a neuron's intrinsic excitability (Dong *et al*, 2006; Zhou *et al*, 2009). Might changes in neuronal excitability allow LA neurons with high CREB function to win the neuronal competition and become allocated to the engram? To test this, we manipulated excitability in LA neurons by targeting K^+ channels and using genetic mediators of excitability (DREADDs, optogenetics). Remarkably, we found that increasing neuronal excitability via different methods mimicked the effects of CREB overexpression: Fear/threat memories were funnelled into these more excitable neurons. Conversely, blocking CREB-induced increases in neuronal excitability (by co-expressing Kir2.1, an inwardly rectifying K^+ channel, which reduces neuronal excitability) prevented their preferential allocation (Yiu *et al*, 2014). Our finding that neurons are recruited to an engram based on neuronal excitability was predicted by a recent biophysical modeling study (Kim *et al*, 2013).

Why allocate? Recalling a particular event might conjure up memories of closely related episodes. This phenomenon may reflect some underlying structure of the way in which our memories are organized, with memories that are related either in content or in time encoded by overlapping ensembles of neurons. Within this associative network, fluctuations in CREB/excitability determine whether memories are linked or, alternately, segregated. Is it possible to alter the structure or function of this fundamental associative network by hijacking the allocation process? For example, manipulating CREB levels in different neuronal ensembles might artificially link otherwise unrelated memories or, conversely, uncouple memories that would normally be allocated to overlapping populations of neurons. Understanding the rules of allocation might provide insights into a range of psychiatric conditions that are characterized by inappropriate associations such as schizophrenia. We wonder, therefore, to what extent different psychophathologies can be thought of as disorders of mis-allocation.

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Oxytocin, Social Cognition and Psychiatry

Oxytocin (OT) has an ancient role in modulating sensing and responding to social stimuli, from nematodes to man. OT regulates not only mammalian labor and nursing, but also maternal behavior. There is increasing evidence that OT influences human parenting and mediates the impact of parenting