Multiple memory mechanisms? The long and the short of it

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Synaptic plasticity is known to be intrinsically linked to cytoskeletal remodelling. In a new study published in this issue of *The EMBO Journal*, Rust *et al* have therefore generated and analysed a forebrain-specific mouse knock-out of the actin-severing factor n-cofilin. Intriguingly, these mice exhibit a particular form of learning impairment-intact working memory but impaired spatial reference memory, correlating with a deficit in long-lasting long-term potentiation (LTP).

Rust *et al* (2010) have generated genetically modified mice that lack the actin filament depolymerizing protein n-cofilin (n-cof^{ΔFB}) in the adult forebrain, a protein important for remodelling of the cytoskeleton in neurons and thus for both regulating spine morphology and receptor trafficking. The authors show that these cytoskeletal changes are important for altering the efficacy of the synaptic connections between neurons, and for certain kinds of learning. Notably, the n-cof^{ΔFB} mice were impaired on the classic Morris water-maze task, in which they are required to form a long-term association between a particular spatial location and a hidden escape platform (a spatial reference memory task). In contrast, the n-cof^{ΔFB} mice were unimpaired on two tests of spatial, short-term working memory (spontaneous and rewarded alternation), which required the animals to choose arms on the basis of their relative familiarity (i.e. choose the arm that has been visited less recently). Strikingly, the n-cof^{ΔFB} mice performed as well as the controls on the spatial working memory tasks but showed no evidence of any learning whatsoever on the associative, spatial memory water-maze task.

What is equally striking is that the pattern of results obtained with n-cof^{ΔFB} mice is an inverse mirror image of data obtained from GluA1 AMPA glutamate receptor subunit knockout mice. GluA1^{-/-} mice show normal acquisition of associative long-term spatial reference memory tasks like the Morris water-maze but are impaired on short-term spatial memory tasks, including the same spontaneous and rewarded alternation tasks as used by Rust *et al* (Zamanillo *et al*, 1999; Reisel *et al*, 2002; Sanderson *et al*, 2007). Furthermore, on a six-arm radial maze task, GluA1^{-/-} mice are as good as wild-type controls in learning to discriminate between which three arms contain food rewards and which three arms are never baited (normal spatial reference memory), but are unable to discriminate between arms based on

recent familiarity, and thus are unable to avoid going back into arms that they have already been into on that visit to the maze (impaired spatial working memory; Schmitt *et al*, 2003).

Thus, the complementary learning deficits in n-cof^{ΔFB} and GluA1^{-/-} mice provide independent genetic proof for a double dissociation of short- and long-term spatial memory processes, thus confirming the existence of two distinct memory mechanisms. It has been argued that spatial working memory tasks are simply more sensitive to hippocampal disruption than spatial reference memory tasks. The double dissociation argues against this. Furthermore, whereas other dissociations between different kinds of memory are based on the processing of different kinds of information (e.g. spatial versus non-spatial), the distinction between n-cof^{ΔFB} and GluA1^{-/-} mice is based on different processing of the same information type (i.e. using spatial cues).

Rust *et al* also investigated putative neurobiological substrates that might underlie associative long-term memory. According to the authors, the n-cof^{ΔFB} mice fail to exhibit a robust, long-lasting form of LTP. The correlated inability to form long-term memories supports the idea that the neurobiological substrates underlying associative memory is long-lasting LTP in the forebrain. It is also tempting to speculate that the short-term memory deficits in GluA1^{-/-} mice could reflect the absence of a short-lasting plasticity in these animals (Hoffman *et al*, 2002; Romberg *et al*, 2009). However, caution is required when equating short- and long-term forms of LTP to short and long-term memory. Earlier studies with gene-targeted mice disprove a simple correlation between LTP and learning. For example, GluA2-deficient mouse lines exhibit normal or even enhanced LTP but dramatic spatial learning impairments (Shimshek *et al*, 2006). These results are also potentially at odds with Rust *et al* (2010), who suggest that the trafficking of GluA2 containing AMPA receptors during synaptic remodelling might underlie LTP. Unfortunately, the involvement of GluA1 and GluA3 during synaptic remodelling by n-cofilin was not investigated. It may be that GluA1 actually interferes with the n-cofilin-dependent mobilization of GluA2 containing receptors. Interestingly, we recently showed that GluA1^{-/-} mice, despite exhibiting impaired short-term spatial memory, actually display enhanced long-term spatial memory under certain conditions (Sanderson *et al*, 2009). This reflects the fact that in normal animals, short-term memory can be

detrimental to associative long-term memory formation. It may also suggest that this short-term spatial memory may actually reflect a non-associative, habituation process and thus might be better served mechanistically by a short-lasting reduction in neuronal excitability (Sanderson *et al*, 2010).

To conclude, the new data of Rust *et al* (2010), when taken with data from GluA1^{-/-} mice, potentially provide an important double dissociation of two spatial memory processes. It would obviously be of value to compare directly

the performance of the two mouse lines on a task like the radial maze that allows both spatial working and reference memory to be assessed simultaneously, using the same spatial cues, as well as to compare their molecular and electrophysiological properties.

Conflict of interest

The authors declare that they have no conflict of interest.

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