Fear knot

Neurobiological disruption of long-term fear memory

PAUL D. MORRISON, JUDITH ALLARDYCE and JOSEPH P. McKANE

Research in the neurosciences offers valuable insights for psychiatry. Recent animal work qualifies the well-established consolidation hypothesis and suggests long-term memories may be vulnerable to disruption. Following memory reactivation, molecular manipulation of the neuronal systems within a critical time window may result in loss of previously consolidated learned behaviours. An improved understanding of the neurobiology of memory should lead to the improved ability to treat and prevent traumatic memories. Here, we focus on the vulnerability of amygdala-encoded fear memory, although hippocampus-dependent memories also appear susceptible to disruption.

MEMORY SYSTEMS

There is no single entity in the mind called memory and no single brain structure or process which can be labelled the seat of memory (Squire & Kandel, 1998). Instead, research posits several memory systems with discrete interacting anatomical substrates sub-served by long-evolved molecular components.

Long-term memory is subdivided into explicit (declarative) and implicit (procedural) memory. Explicit memory provides factual knowledge of the world (semantic) and personal past (episodic). Explicit memories are recollected in consciousness, with long-term encoding dependent on the hippocampus (Squire & Kandel, 1998). Implicit memory stores our skills, tasks, habits and emotional reflexes; however, their expression does not necessitate immediate transfer into the consciousness or require the hippocampus for long-term encoding, but is likely to be mediated through the cerebellum, basal ganglia and amygdala (Squire & Kandel, 1998).

In memory consolidation, information is transferred from a vulnerable short-term buffer into a stable long-term store (the engram) (Squire & Kandel, 1998). Modern explanations focus on anatomical, molecular or neuromodulatory factors. The anatomical account emphasises information storage in the cortex following transfer from the medial temporal lobe (Squire & Kandel, 1998). In the molecular account, a transiently enhanced neuronal assembly is strengthened via protein synthesis and synaptogenesis (Squire & Kandel, 1998). The neuromodulatory account emphasises subcortical neuromodulation and stabilisation of memory traces (Cahill & McHaugh, 1996). Recent animal studies involving manipulation of the structural and functional substrates challenge the notion of the stability of long-term memories.

The amygdala: fear memory processing

To investigate fear memory processes, the technique of fear conditioning is used. For example, if a mild electric shock to the foot (unconditioned stimulus) is paired with a tone (conditioned stimulus), subsequently the tone alone is sufficient to elicit the fear response. Therefore, 'novel environment events' can access hard-wired circuitry. The neuroanatomy and functional plasticity which underpin learned fear have been described in detail (Ledoux, 1995).

In early fear-conditioning studies application of an electroconvulsive shock 30 seconds after pairing interrupted consolidation. A shock delayed until the following day had no effect. However, if prior to the following day's shock animals were again exposed to the tone (conditioned stimulus), the paired association was disrupted. That is, activity of the memory (rather than its age) appeared to confer susceptibility to disruption (Miansin *et al*, 1968).

In the intervening years, studies have shown the amygdaloid complex to be essential for fear conditioning and an important component in the emotion of fear (Ledoux, 1995). Located in the medial temporal lobe, the amygdala's extrinsic connectivity fits with its postulated role as an important processor in an integrated fear system (Davis, 1999).

Nader *et al* (2000) used fear-conditioning methodology, except the electroconvulsive shock was replaced by a targeted infusion of the protein synthesis inhibitor anisomyosin directly into the lateral amygdala. Following memory reactivation, the drug infusion resulted in amnesia for 1- and 14-day-old fear memories. Inhibition of protein synthesis rather than a non-specific mechanism was indicated by the failure of an infused vehicle to produce the effect. Additionally, the amnesia did not manifest immediately, but began after 4 hours had elapsed. Furthermore, the timing of the drug administration was critical, since infusion 6 hours after reactivation left the memory intact. The authors concluded that old consolidated fear memories return to a labile state following reactivation and protein synthesis is required for their reconsolidation.

Human fear is clearly more than an inbuilt set of reflexes accessed via a plastic interface. Extensive bi-directional connectivity with, for example, the cingulate and medial prefrontal cortex shifts enquiry from the behavioural to the cognitive and phenomenological domains. Of more immediate significance empirically, is the influence of the amygdala on the hippocampus and, therefore, explicit memory, or memory processed in consciousness. An impressive body of work shows that activation in the amygdala facilitates hippocampus-dependent learning and memory (Cahill & McHaugh, 1996). In addition, the question arises of whether hippocampus-dependent long-term memories themselves show the same vulnerability following reactivation.

HIPPOCAMPUS-DEPENDENT MEMORY

Recent work suggests that hippocampus-dependent memory is also prone to disruption after reactivation. Nadel & Land (2000) utilise a signalled avoidance task, in which a tone predicts a shock to the foot which the animal quickly learns to avoid. If

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two days after training a lesion is made in the dorsal hippocampus, memory for the task remains intact, consistent with the consolidation hypothesis. However, if reactivation occurs shortly before the lesion is made in the dorsal hippocampus, memory for the task is lost. Hippocampus-dependent memories are also studied in a paradigm where animals learn to negotiate a radial maze for a food reward. Using a pharmacological approach Sara (2000) demonstrated that following reactivation (in this case an errorless retrieval), antagonism at the glutamate *N*-methyl-D-aspartate (NMDA) receptor produced a robust and selective amnesia for the task. In contrast, without prior reactivation the memory remained intact. Earlier studies using the same task had shown that electroconvulsive shock could produce selective disruption of reactivated appetitive memories. Sara's group refined the earlier work by targeted manipulation of a specific neurochemical signalling system.

MOLECULAR MECHANISMS: GLUTAMATE AND THE NEUROMODULATORS

Glutamate is the principal excitatory neurotransmitter in the mammalian central nervous system. Over the past two decades, research has focused on its role in learning and memory (Malenka & Nicoll, 1999). If excitatory synapses are activated, their signal strength increases over time. This process, known as long-term potentiation, was first observed in the hippocampus, and has subsequently been demonstrated in other areas including the amygdala. The molecular events underlying long-term potentiation involve NMDA receptor agonism and activation of intracellular cascades. A synapse can be strengthened transiently for a few hours or remain potentiated indefinitely. The latter involves protein synthesis downstream of the intracellular cascades.

Classical neurotransmitters (neuromodulators), also play a role in learning and memory. Squire & Kandel have teased out the molecular underpinnings of learning and memory in the marine invertebrate *Aplysia californica*. They have shown that serotonin acts through the cyclic adenosine monophosphate (cAMP) pathway to strengthen existing synapses and induce the formation of new synapses via gene transcription (Squire & Kandel, 1998). In the mammalian central nervous system, brain stem neuromodulators such as serotonin, dopamine and noradrenaline may be important in memory formation for salient events. The dopamine (D_1/D_5) and noradrenaline (β1) ascending systems, like serotonin, mediate their post-synaptic effects via activation of the cAMP pathway. At the experimental level D_1/D_5 agonists enhance learning and long-term potentiation, while antagonists have the opposite effect (Bailey *et al*, 2000).

In addition, blockade of β-adrenoceptors interferes with the formation of emotional memory in humans, while agonists enhance memory consolidation in animals (Cahill & McHaugh, 1996; Bailey *et al*, 2000). At the phenomenological level it is accepted that ongoing experience concurrent with attention or arousal (noradrenaline-mediated) or with reward (dopamine-mediated) is more likely to be encoded into long-term memory.

As with glutamate, animal paradigms have been utilised to demonstrate the importance of noradrenergic modulation in memory consolidation and reconsolidation. The odour discrimination task involves animals learning to associate one of three odours with a food reward. However, injection of intra-cerebro-ventricular adrenoceptor antagonists, within 2 hours disrupts the consolidation of information into long-term memory. Central adrenoreceptor β-blockade beyond this time-period has no effect, presumably missing the molecular events of consolidation. Following reactivation the memory again becomes sensitive to β-blockade, suggesting efficacy is reactivation- and time-dependent (Sara *et al*, 2000).

DISCUSSION

A prior review suggested pharmacological manipulation of neurotransmission could be clinically useful in post-traumatic syndromes by disrupting the consolidation of traumatic experiences into long-term memory (O'Brien & Nutt, 1998). In animal models, NMDA channel or specific peptide receptor blockers inhibit the physiological and behavioural corollaries of post-traumatic stress disorder (Adamec, 1997).

The timing of drug therapy may be important. Drug treatment started beyond the critical period may be too late in preventing the laying down of the 'immutable brain traces' which constitute post-traumatic stress disorder (O'Brien & Nutt, 1998). However, the recent re-discovery that upon reactivation 'immutable' long-term fear memories are vulnerable to disruption offers the possibility of pharmacological treatment well beyond the initial trauma.

The recent findings show that a variety of cell surface proteins, such as the NMDA receptor or β-adrenoceptor, are potential targets in the pharmacotherapy of maladaptive engrams. Efficacy depends on memory reactivation followed by drug delivery within a time window.

The clinical value of the above observations remains controversial; can a memory trace be removed individually without unwanted disruption to other memories? Is the web of connections in human memory too extensively interlinked to allow for the possibility of therapeutic erasure? These new findings are, however, exciting in theory and offer the possibility that adverse experiences, or their biological correlates, need not be an organising principle or factor at all in psychic life.

DECLARATION OF INTEREST

None.

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