Re*hebb*ilitating Memory

Amnesia is a deficit of memory function that can result from trauma, stress, disease, drug use, or ageing. Though efforts are being made to prevent and treat the various causes of amnesia, there remains no treatment for the symptom of memory loss itself. Because the defining feature of amnesia is an inability to recall memory, any given case may be due to the possibility that the memory is gone, or the alternative that it is present but irretrievable (Squire, 1982). Discriminating between these two scenarios would be of scientific value, because the neurobiology of memory formation is anchored in experimental amnesia. From a clinical perspective, pathological cases of amnesia that are due to retrieval deficits may in principle be treatable rather than merely preventable. Amnesia could be attributed to a retrieval deficit if the ostensible 'lost' memory could be evoked through brain stimulation. The challenge here is to identify exactly where in the brain a particular memory is stored.

Our strategy to meet this challenge was based on Richard Semon's 100 and some year-old memory engram theory (Semon, 1904). In the contemporary version of this theory, formation of memory starts with learning-induced activation of a specific population of neurons, followed by an establishment of enduring physical or chemical changes in these neurons, referred to as an engram, which is the brain representation of the acquired memory. Furthermore, subsequent recall of the memory is evoked by reactivation of these engram-holding neurons by recall cues. Our approach took advantage of the activation of an immediate early gene, *c-fos*, in a specific population of neurons upon experiencing a certain episode. These neurons can be labelled upon learning with a light-sensitive protein like channelrhodopsin-2 (ChR2) in a transgenic mouse in which the promotor of the *c-fos* promoter controls the expression of ChR2 (Liu *et al*, 2012). Using this genetic technology, the memory engram cell population in the hippocampus could be identified, and their subsequent reactivation by light of a specific wavelength was sufficient for eliciting recall of the specific memory. Furthermore, these engram cell populations were shown to be essential for natural memory recall (Tonegawa *et al*, 2015).

We employed engram technology to investigate retrograde amnesia due to disrupted memory consolidation (Ryan *et al*, 2015). Memory consolidation is the process whereby a newly formed memory is temporally susceptible to disruption by interventions such as protein synthesis inhibitors (PSIs), and represents the dominant neurobiological paradigm for memory formation. We found that contextual fear memories could be retrieved from a range of cases of amnesia due to disrupted consolidation, by direct optogenetic activation of amnesic memory engram cells. These findings provide positive evidence that retrograde amnesia due to disrupted consolidation is a deficit of memory retrievability.

If a memory survives amnesia, what causes the retrieval deficit? We observed an engram cell-specific plasticity of enhanced dendritic spine density and synaptic strength that was abolished by PSI administration. How then are memories stored in amnesic engram cells? A transynaptic engram cell connectivity pattern across brain regions was observed in normal mice and it persisted in the amnesic case, being unaffected by PSIs. Thus, the engram cell circuit is a plausible candidate mechanism for robust and persistent storage of memory. These data lead to a hypothesis that engram cell-specific enhanced synaptic plasticity is necessary for the efficient retrieval of the memory, and that amnesia is caused by inefficient access of natural recall cues to the engram cell somata due to the lack of enhanced synaptic density and strength (Ryan *et al*, 2015; Tonegawa *et al*, 2015).

The experimental design employed here may be expanded to clinical cases of amnesia, including early stages of Alzheimer's disease and other neurodegenerative disorders. If memory content endures in engram circuits of clinical amnesia, then seemingly lost memories may be reinvigorated by targeted stimulation of amnesic engram cells. Indeed, when an amnesic contextual engram was artificially updated with a fear association, the amnesic contextual memory became accessible to natural recall (Ryan *et al*, 2015). Beyond amnesia, affective disorders such as depression might be ameliorated by potentiating access to positive engrams (Ramirez *et al*, 2015). A paradox of memory is that it is simultaneously an enduring biological property, and yet one that is intrinsically fragile. Embracing a theoretical dissociation of the dual features of storage and access may account for this discrepancy and should lead to novel lines of research into the neurobiological mechanisms of memory storage and memory retrieval.

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Extracellular Vesicles: Goodies for the Brain?

Brain homeostasis requires extensive signaling and information exchange between all types of neural cells, including neurons and glia. Recent studies indicated a pivotal role of extracellular vesicles (EVs) in communication between neural cells and furthermore, in the conversation between neural cells and the periphery. EVs comprise a group of varied secreted vesicles (plasma membrane-derived microvesicles and endosome-derived exosomes), which recently came into focus regarding their ability to shuttle biomolecules including RNA between cells and their potential to phenotypically modulate target cells. Apparently, all types of neural cells release EVs, which have been implicated in several physiological and pathological processes such as neuromodulation, synaptic plasticity, neuron-glia-interaction, and the spreading of neuropathological agents. Notably, EVs with the characteristics of exosomes seem to have a remarkable role in neuroprotection and neuroregeneration. Oligodendrocytes release exosomes in response to neurotransmitter signaling, that transfer cargo to neurons and enhance the tolerance of recipient neurons toward different types of cell stress (Frühbeis *et al*, 2013). These exosomes convey multilevel information by transferring stress-protective enzymes (Hsp70, SOD1, and catalase), activation of pro-survival signaling pathways and modulation of gene expression. In similar fashion, EVs secreted by Schwann-cells are internalized by neurons in the peripheral nervous system and promote axonal regeneration after injury by increasing axon elongation (Lopez-Verrilli *et al*, 2013). Thus, EVs transferred from myelinating glia cells to neurons convey neuroprotective and pro-regenerative messages and provide local support to facilitate axonal maintenance, homeostasis, and axonal growth. It is therefore conceivable that application of glial exosomes may offer a therapeutic opportunity to benefit neurons and prevent axonal death in the course of demyelinating diseases or other sorts of neural injury.

Moreover, there is compelling evidence that EVs released by cells in the periphery can enter the CNS and accomplish pro-neural activity. EVs derived from hematopoietic cells are able to pass the blood–brain barrier and deliver genetic information in form of mRNA and miRNAs to CNS neurons, in particular under inflammatory conditions (Ridder *et al*, 2014). It has been suggested that IFNγ-stimulated dendritic cells release EVs that promote CNS myelination and might be applied for remyelination therapies (Pusic *et al*, 2014). Furthermore, recent developments in the field of cell therapy strongly suggest that the systemic regenerative potential of stem cells observed in several neurological disorders is not revealed by cell engraftment, but largely due to paracrine signals delivered by EVs entering the CNS or modulating inflammatory responses. In a rat model of ischemia, intravenous administration of EVs originating from mesenchymal stromal cells improved functional recovery, which was related to enhanced neurite remodeling, neurogenesis, and neovascularization due to EV-mediated transfer of miRNAs to neural target cells (Xin *et al*, 2013). Neural stem cells (NSCs), which facilitate functional recovery upon systemic application in a number of neural diseases, release EVs after exposure to pro-inflammatory cytokines that are considered to mediate immunomodulation in the host environment (Cossetti *et al*, 2014).

In conclusion, EVs derived from cells within the nervous system as well as EVs entering the CNS from the periphery emerge as potent conveyors of complex messages in benefit of neural health. Future studies will be needed to uncover their full potential as therapeutic agents and to unravel their mode of action.

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