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Spatial memory and hippocampal enhancement

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Given the central role of hippocampal function in spatial and episodic memory, the concept of enhancing it when compromised is attractive. This might be realised behaviourally, pharmacologically or via more radical routes such as brain stimulation. Successful approaches in each of these domains include trial-spacing, rest, and NMDA or cholinergic receptor modulation, but the goal of enhancement has to be clear as some approaches can enhance in one domain but inhibit in another. Enhancement may also extend the duration of memory rather than augment encoding, an idea conceptually embedded into the synaptic-tagging-and-capture theory of memory persistence. In addition, recent work on human spatial memory reflects new findings about the interacting components of egocentric and allocentric processing of human navigation.

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Introduction

The famous opening sentences of O'Keefe and Nadel's (1978) book '**The hippocampus as a cognitive map**' [1••] remind us of the importance of spatial memory: '*Space plays a role in all our behaviour. We live in it, move through it, explore it, defend it. We find it easy enough to point to bits of it: the room, the mantle of the heavens, the gap between two fingers, the place left behind when the piano finally gets moved.*' In 2015, shortly after the award of the Nobel Prize for the discovery of place and grid cells (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2014), we have good reason to celebrate the progress that has been made by systems neuroscientists in understanding spatial memory.

Our story begins, however, with the earlier discovery of the critical role of the hippocampal system in human memory [2••]. This triggered an explosion of research leading to our present understanding of hippocampal function and its role in memory. Aspects of this work have enabled translational research and drug discovery with the aim of improving cognition, including spatial memory. Such work forms one part of a wider project to support the 'mental wealth of nations' [3•]. Memory enhancement has been discussed in the context of more effective attention, better encoding or consolidation of information and, although less frequently, of improving memory retrieval. There are mechanistic implications of each of these distinct processes (Box 1). Post-trial enhancement of consolidation has been a longstanding theme of memory research [4]. More recently, the opportunity for exploiting new advances in the molecular neurobiology of memory has been raised [5], and a strong case advanced for paying more attention than hitherto to the mechanisms of activity-dependent synaptic plasticity, such as long-term potentiation [6•]. Molecular insights and synaptic plasticity offer potentially important neurobiological anchors to behavioural observations.

Within the spatial domain — the specific focus of this contribution — there is the prospect of enhancing spatial memory in everyday life. This would include helping older people remember where things are around the house through to preventing them from getting lost when finding their way. More effective spatial memory and navigation involve a number of interacting processes and mechanisms including remembering the location of a goal, planning a route, greater flexibility in coping with unexpected detours and so on. Exploring this in animal models, and more recently humans also, has been guided by neuroscience discoveries such as those of place cells [7••], head-direction cells [8••], and grid-cells [9••]. Collectively, these provide a neural structure for spatial memory. Whether such a finely tuned system, dependent on intricate excitatory and inhibitory circuitry [10,11], can reliably be enhanced is unclear.

However, spatial memory and other types of 'memory space' [12], do surely serve to anchor and enhance other aspects of memory. There is a long history of methods, such as the '*method of loci*' celebrated in Frances Yates

classic book 'The Art of Memory' [13], in which people train themselves to use buildings or towns with which they are familiar to provide a structure for remembering the content and sequence of new information. This was a favoured method of orators in remembering their speeches, and used to this day by people who perform extraordinary memory feats (such as remembering absurdly long numbers). Other behavioural 'tricks' involve the disciplined use of existing mental structures or schemas to organise new information, or the imposition of a short rest after learning. However, the discipline of doing these (even though they work) is beyond most people.

The usual assumption about enhancement is that, behavioural approaches aside, a pharmacological intervention might be found such as a nicotinic partial agonist (e.g. of the α7 subunit) or a phosphodiesterase inhibitor (e.g. of PDE4). Considerable efforts are being made in pharmaceutical and biotech companies to develop such compounds, with a major focus on improvement of cognitive dysfunction in neuropsychiatric conditions [14•]. '*Enhancement*' induced by such drugs is likely mediated by mechanisms that potentiate some plasticity-related mechanism (such as increased membrane excitability or protein-synthesis). However, there are other possibilities such as improved signal-to-noise ratio of target relative to interfering material rather than 'bigger' in a literal sense — as in the process of pattern separation that might be affected by the balance between excitation and inhibition in the dentate gyrus. In addition, a memory might be enhanced in the sense of being more persistent over time than stronger at the time of encoding. Indeed 'strength' and 'persistence' may be orthogonal parameters with distinct possibilities for behavioural or pharmacological interventions.

In effect, the goal of enhancement is context-dependent — what is the specific aim of altering some cognitive process? We next illustrate some relevant complexities with reference (a) to work on D-cycloserine and NMDA receptors [15••], and (b) to the contribution of synaptic tagging and capture (STC) to the place of enhanced protein-synthesis in memory enhancement [16,17].

Complexities and assumptions

The simple theme of this section is to point out that 'bigger is not always better' (Box 1). This is not to imply that enhancement is not possible and certainly not to

Box 1 Enhancement of spatial memory: concepts and putative mechanisms

Enhancement includes memory traces being stronger (mechanistically due to enhanced synaptic plasticity), but there are other possibilities. These include, firstly, improved signal-to-noise ratio of target relative to interfering material (due to more effective pattern separation by the dentate gyrus via alterations in excitatory-inhibitory balance, or neurogenesis); secondly, more effective persistence over time (due to capture of plasticity-related proteins [PRPs] at tagged synapses).

Spatial memory refers to memory of the places of events or things in the world, and can include paired-associate and map-like representations, representations of the value of the sought object, and/or of the route that should be taken to get from the present location to a remembered location. In this respect, spatial memory is generally considered a 'catch-all' term for diverse aspects of spatial learning and navigation.

Encoding, storage, consolidation, retrieval refer to successive stages of the processing of information entering long-term spatial memory. *Encoding* is the process of transforming perceptual information into single or associated items into memory traces. Effective encoding may involve pattern separation and filtering of target relative to interfering material. *Storage* is the process by which such traces last over time — usually thought to be a passive process involving an initial alteration of synaptic strength that is distributed across synapses and neurons in DG, CA3 and CA1. *Consolidation* is the further process that helps ensure that stored information is less likely to decay over time, that is, to become stabilised. This is likely a process where enhanced synthesis, distribution and utilisation of plasticity-related gene products will be especially important. *Retrieval* refers to the putative process by which neural activity interacts with stored traces and so, possibly engaging pattern separation, reactivates representations that, at least in humans, have the phenomenological experience of implicit or explicit remembering. Retrieved information may affect processing speed or choice in the absence of awareness, or it may enter consciousness in an explicit manner and so constitute an experienced event. Retrieval of, for example, context fear conditioning has been shown to affect immediate early gene activation in diverse brain areas, with the areas preferentially activated changing with the passage of time.

The hippocampal formation consists of the entorhinal cortex, dentate gyrus, CA3, CA1, and subiculum (Andersen *et al*., 2007). There is debate about whether the medial and lateral septum should be considered part of the hippocampal formation, but the importance of the cholinergic and GABAergic modulatory input via the septum, particularly in relation to encoding, cannot be ignored. Mechanistically, nicotinic agonists and GABAergic inverse agonists act by altering membrane depolarization at the time of memory encoding. Dopaminergic modulation is relevant because of the importance of D1 receptor signalling for the persistence of hippocampal synaptic plasticity and memory, possibly acting via the pKA-cAMP pathway, DARPP-32 and inhibition of protein phosphatase 1 (PP1). Importantly, the hippocampal formation does not work in isolation — it works in partnership with numerous other brain areas, including the neocortex for systems memory consolidation, such that enhancement of hippocampal memory processing may have its impact in other brain areas where memory traces may be stored. The mechanisms of 'initial' or cellular consolidation impact on the effectiveness of subsequent systems consolidation.

Animal model refers to any animal based research strategy usually using *Drosophila*, rodents or non-human primates, often using interventional approaches that are ethically impossible in humans. The supposition is that memory processing has evolved over time, retaining many features that are quite old in evolutionary terms and that therefore can be successfully investigated in animal models. However, we should be sensitive to many differences between humans and animals — including anatomy, language and prior-knowledge — that may collectively impact successful translation of cognitive enhancing drugs from animal proof-of-concept studies through to phase 3 studies in humans. The puzzle of 'lost in translation' is important in drug development.