Interactive Memory Systems in the Mammalian Brain

Poster · April 2018

DOI: 10.13140/RG.2.2.30679.50088

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Interactive Memory Systems in the Mammalian Brain

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Abstract

Following the famous case of H.M. who received a bilateral medial temporal lobectomy causing severe anterograde amnesia, animal researchers investigated the role of different structures in cognitive memory formation, with spared habit formation as in H.M. These investigations eventually led to a dissociation of memory systems that can function independently and in parallel. The first evidence for an interaction between memory systems revealed that they compete for behavioral control. Several follow-up experiments have supported the competitive nature of interactions. More recent studies, however, have shown that under different testing conditions memory systems often cooperate in spatial-cognitive tasks. Neuroimaging studies have reinterpreted what appeared to be competition at a neural level to functional cooperation at a behavioral/cognitive level. The acknowledgment of cooperative interactions was met with initial resistance according to Morgan's cannon. However, such interpretations were oversimplified, and impeded research on the many instances where the systems cooperate, and who's dysfunction may contribute to several psychological and neurodegenerative disorders in need of improved treatments based on more realistic views of interactive brain functions, including the synaptic level where the role of astrocytes and glio-transmitters are beginning to reveal new therapeutic targets for memory dysfunction in Parkinson's, Alzheimer's and other neurodegenerative conditions.

Background

H.M. bilateral removal of the medial temporal lobe (MTL) (Scoville & Milner, 1957), as an experimental treatment for intractable epilepsy, resulted in severe anterograde amnesia, an inability to form new long-term cognitive memories. H.M. could form new unconscious skills, procedures and habits (e.g. Mirror drawing) despite having no cognitive memory recollection of ever performing these tasks (Milner, 1962).

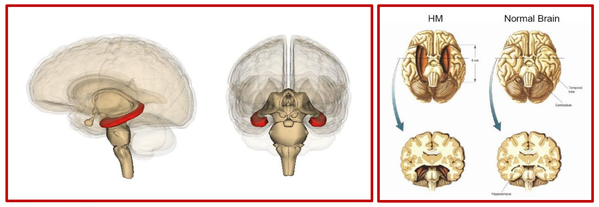
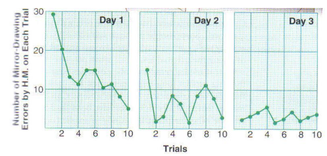


Fig.1 (A) The location of the hippocampus (red) with the medial temporal lobe of the ghosted brain. (B) The extent of tissue excised in H.M.'s bilateral medial temporal lobectomy compared to a normal brain.



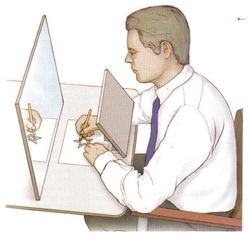


Fig.2 Despite his anterograde amnesia, HM was able to learn skills over several days despite not knowing he had previously completed the task.

Conclusion: the brain contains multiple memory systems that may function independent of each other

Animal models

Researchers attempted to model H.M.'s impairment, concerned mostly with the necessary structures removed in the surgery (hippocampus, amygdala and rhinal cortex among others) rather than the task components, leading to mixed findings (Hirsh, 1974). Tasks requiring flexible knowledge of multiple stimulus (S-S) associations were impaired by hippocampal lesions, while those that could be solved using a simple stimulus-response association (S-R) or habit formation was spared following MTL damage.

Radial maze tasks with different associative contingencies were used to dissociate three memory systems: the hippocampus (cognitive, S-S), striatum (habit, S-R), and the amygdala (affect, S-A) (McDonald & White, 2013). One effect in the figure matrix stood out and suggested that a normal competition occurs between the hippocampus and striatum during win-stay (S-R) learning. By removing the hippocampus, unconscious habit formation is improved due to a lack of cognitive interference.

Note: This is a causal inference because it includes a manipulation of the brain and random assignment to lesion groups in attempt to control all other extraneous variables.

Radial Arm Maze Findings Including the Original Double and Triple Dissociation Experiments

Double Dissociation - 1989

Double Dissociation	Spatial Win-shift: Cognitive (S-S)	Cued Win-stay: Habit (S-R)	CCP task: Reward (S-SR)
Hippocampus (fornix-fimbria)	Impaired	Facilitated	No Difference
Striatum (dorso-lateral)	No Difference	Impaired	No Difference
Amygdala (baso-lateral n.)	No Difference	No Difference	Impaired

Packard, Hirsh & White (1989) Double Dissociation
McDonald & White (1993; 2013) Triple Dissociation

Neuroimaging

A similar claim of a competitive interaction between systems was based on a functional Magnetic Resonance Imaging (fMRI) study of probabilistic classification in humans (Poldrack et al., 2001). Inverse correlations were reported for striatal and MTL activation, with an initial increase in MTL activity followed by a decrease, and the opposite pattern observed for the striatum across trials, suggesting a possible causal inhibition among systems as in the rat radial maze studies above.

The author's even state "The results presented here provide the first substantive evidence, to our knowledge, for competition between memory systems in the human brain."

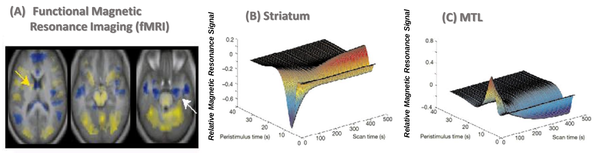


Fig. 4 (A) Regions exhibiting significant **evoked activation** (yellow) or **deactivation** (blue) for classification trials. Yellow arrow highlights region of caudate activation, white arrow highlights region of MTL deactivation. b, c, Change in haemodynamic response. Red indicates positive, event-related response, blue indicates negative event-related response for (B) striatum and (C) MTL across the initial 450-s scanning run (averaged across subjects). *Adapted from Poldrack et al. (2001)*

However, the authors also state that their computational theory:

"…interprets both the earlier animal data and the present human imaging data as implying an interaction between the hippocampus and other brain structures, in which the hippocampus has a modulatory role in learning by developing new stimulus representations during early phases of training which are used by the striatum to develop complex stimulus response associations."

In other words, the hippocampus *provides* complex stimulus representations to the striatum so that *it can form* complex S-R habits, what we have termed (S-S)-R, or higher-order habits (Devan, Chaban, Piscopello, Deibel, & McDonald, 2016; Devan, Hong, & McDonald, 2011), through a process of cooperation, not competition.

Comparison of Human and Animal Studies

Parallel processing at the systems level was demonstrated when the hippocampus was ablated (H.M. and rat studies). Neuroimaging findings do not manipulate the brain and therefore cannot make such assertions or claim that they provide evidence of competition in the human brain, as was demonstrated in the rat studies. This apparently is a difficult concept for some researchers to grasp given the further insistence that the findings converge (Poldrack & Packard, 2003). Consequently, consider the following conclusions:

1. Poldrack et al. 2001 – inverse, negative correlations = competition between systems AND cooperation (i.e., hippocampus → striatum = complex, S-R associations, see above statements).
2. McDonald & White, 2013 – removal of the hippocampus eliminates cognitive S-S interference with incremental S-R learning of the striatum.
3. This misunderstanding derives from trying to substitute correlational activation data for ablation data. Neural activation or deactivation ≠ function, incidental activity, i.e., **McDonald, Hong, & Devan (2004)** has been widely demonstrated by many means, whereas lesion/ablation = impaired or enhanced function of the whole behaving organism.

Competition and Cooperation

As Hirsh and Krajden (1982) expressed so eloquently:

"When two different systems appearing to address the same substantive matters are present, it is worthwhile to ponder how they might interact. We think that on some occasions the two systems compete; on others they cooperate. Once the fundamental differences between the two systems are understood, their differing capacities become clear. Each has capabilities that the other does not. There are certain features of knowledge that cannot be attained without using the capacities of both."

General Neuroanatomy: Rat Brain Dissection

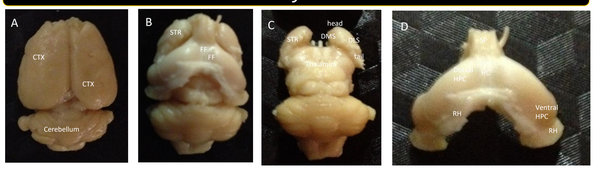


Fig. 5 Dissection of the rat brain. (A) intact brain with cortex (CTX) and cerebellum showing. (B) The cortex has been removed revealing the hippocampus (HPC) and striatum (STR). (C) HPC removed to show underlying thalamus and the prominence of the STR at the top of the image. (D) The HPC removed from the brain, showing the septum (SP) at the top, fibers of the Fornix/fimbria (FF) and the curved structure of each HPC joined by the HPC commissure (HC) with significant posterior fibers in the retrohippocampal (RH) region. The dorsomedial striatum (DMS) and dorsolateral striatum (DLS) are also identified along with the head and tail of the STR.

Histology

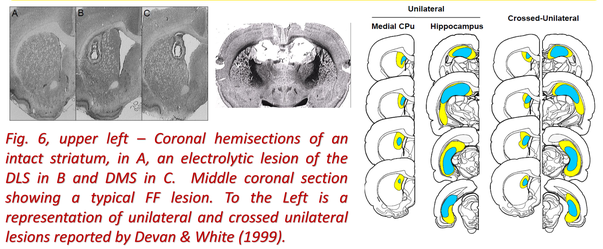


Fig. 6, upper left – Coronal hemisections of an intact striatum, in A, an electrolytic lesion of the DLS in B and DMS in C. Middle coronal section showing a typical FF lesion. To the Left is a representation of unilateral and crossed unilateral lesions reported by Devan & White (1999).

The water maze task developed by McDonald & White (1994) trained rats to learn a concurrent cue-place response in one location/quadrant, and then made the place inconsistent with the cue location (Fig.7). Different competition tests reveal roughly a 50/50 split among control place and cue responders (Devan, McDonald, & White, 1999; Devan & White, 1999; McDonald & White, 1994) (Fig.8), allowing assessment of lesion effects: A cue response prevails with damage to the hippocampus (HPC, FF or the DMS, suggesting *cooperation* between systems, whereas place response prevails with DLS damage, indicating a *competition* with the other two areas/systems (Fig.8).

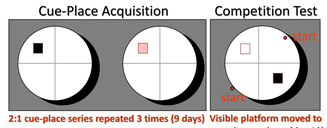


Fig.7 Competitive cue-place water maze task used to test the effects of the different lesions in the three original studies cited above.

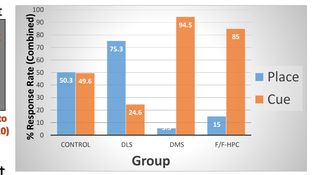
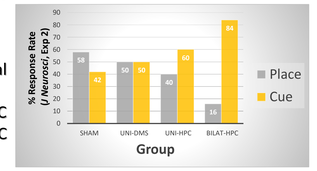


Fig.8 The results of combining the 3 original cue-place water maze studies. The results demonstrate competition between the HPC and DLS, and cooperation between the HPC and DMS.



Neurodegeneration and Treatment

Understanding interactive memory systems is beginning to shed light on psychological disorders and neurodegenerative diseases of aging with multiple cofactors being identified (McDonald, 2002; McDonald, Devan, & Hong, 2004). In addition to neurotransmitter depletions, synaptic receptor changes, inflammation, ministroke, sleep dysrhythmia, among others. The goal in identify these and other processes early has become a major focus of research. For example, the gut microbiota influences brain development and neurodegenerative processes leading to Alzheimer's and Parkinson's neuropathology (Dinan & Cryan, 2017; Hu, Wang, & Jin, 2016; Mancuso & Santangelo, 2018). Future studies could improve detection of PD and the beginning of AD through early olfactory detection (Park, Kwon, Choi, Park, & Yoon, 2018; Xydakis & Belluscio, 2017), and as a case in Manchester suggests (Knapton, 2017), through the very early olfactory smell of PD, a decade before disease detection began in her husband, as scientists are just beginning to study her ability.

Glia cells make up 90% of human brain cells on average. Given the prevalence of glia, they not only interact with the gut-brain-microbiota axis and are involved in many processes, including spatial learning and memory. The gliotransmitter, D-serine promotes spatial memory in the water maze but in a way that suggested enhanced striatal habit function (Stouffer, Petri, & Devan, 2004). More recently D-serine specifically enhanced spatial memory retrieval in the water maze through gliotransmission in the hippocampus (Zhang, Gong, Wang, Xu, & Xu, 2008). Our own data suggests that using a competitive place task, D-serine supplementation may rescue functional plasticity in the aging hippocampus (Billard, 2015). D-serine in changes in functional plasticity that occur in the aging hippocampus since deficits are rescued by D-serine supplementation

Screening potential neurodegenerative therapeutics in preclinical models has been criticized recently for lack of translational development in the clinic. One potential hurdle may be the time that it takes some therapeutics to work preclude success in the multitude of disease processes through the gut microbiota-brain axis. If intervention occurs earlier than currently possible the success of individualized treatment based on the complexity of how memory systems may interact at the systems level and the early microbiota age-related neurological processes, the onset of neurodegenerative processes may be delayed or even avoided to alleviate the most devastating diseases of the aging brain (Calvani et al., 2018).

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