From rapid place and ‘declarative’ learning to the efficient control of behaviour – functional organisation of the hippocampus and clinical implications of hippocampal dysfunction

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From memory to behaviour - functional integration in the hippocampus

Multiple functions associated with the hippocampus:

- Rapid place and declarative learning
- Behavioural control, including emotional, motivational, and sensorimotor functions

Integration of these functions may be a key feature of the hippocampus.
Today
Hippocampal learning & memory mechanisms – selective review of some key points
• Hippocampal amnesia: case studies and animal models
• Rapid vs. incremental learning
• Hippocampal firing correlates of learning and memory
• Neuroanatomical basis of hippocampal learning: cortico-hippocampal connectivity
• Physiological basis of hippocampal learning: synaptic plasticity
• A consensus view of hippocampal memory mechanisms
• Experimental study testing key predictions of the consensus view
• Hippocampal dysfunction in normal age-related and pathological memory decline

Hippocampal dysfunction in schizophrenia
• Neuroimaging evidence
• Relation between hippocampal dysfunction and schizophrenia symptoms?

Next lecture
Hippocampal learning-behaviour translation and clinical implications
• Translating hippocampal memory into behaviour: a functional-anatomical model
  - Functional differentiation along the longitudinal axis of the hippocampus
  - Functional integration in the intermediate hippocampus
• Experimental study testing some predictions of the functional-anatomical model
• Hypotheses on the relation between hippocampal dysfunction and schizophrenia symptoms
Hippocampus in learning and memory – a selective review of some key points
Hippocampal amnesia – human case studies

Selective memory deficits in patients with hippocampal lesions

Patient HM: Hippocampal damage following temporal-lobe resection

Anoxia-induced hippocampal damage


• Patients with selective and extensive hippocampal damage show marked deficits in declarative memory (especially episodic memory with semantic memory often quite intact), place and contextual memory.

• Other types of memory and general intellect are largely spared (reviewed in Spiers et al, 2001, *Neurocase* 7:357)
Hippocampal amnesia – human case studies

Movie ‘Memento’ (2000) by Christopher Nolan

Suzanne Corkin (2014)
Permanent present tense
Hippocampal amnesia – animal models

Place learning deficits in rats with hippocampal lesions

Annulus crossing on probe trials (▲) without platform

Hippoc. lesion
Cortical lesion
Control

Sample swim paths on trial 28

Training trials

Hippocampal lesion
Watermaze

Rapid vs. incremental learning

Rats with hippoc. lesions can very slowly acquire good place memory in the water maze

H.M. can incrementally acquire accurate place memory

Drawings of floor plan of house where H.M. lived from 1958 (five years after operation) to 1974

There is also evidence for post-morbid acquisition of semantic memory by H.M. and other patients with hippoc. amnesia.


Complementary learning systems theory: Hippocampus mediates rapid learning of place and declarative information, while extra-hippocampal (neocortical) sites can mediate slow incremental learning of such information. Like this, the two goals of rapidly learning about specific experiences and of extracting generalities from routine experiences can be reconciled (see O’Reilly & Norman, 2002, Trends Cogn Sci 6:505).
Hippocampal firing correlates of learning and memory

Place cells in the rat hippocampus


Place cells in the human hippocampus

Virtual environment


Place-responsive hippoc. neuron during virtual navigation

Beyond places . . .

Neuronal firing in the rat hippocampus also codes for other types of event information stored in the animal’s memory (reviewed in Eichenbaum et al, 1999, Neuron 23:209).

Trial-type specific firing on a spatial-alternation task

Rats are rewarded for alternating between left and right turns. Hippocampal firing codes for right- or left-turn trials.

Watching film clips


Free recall of film clips


Neurons in human hippoc. fire during encoding and free recall of film-clip episodes
Through the parahippoc. region, especially the entorhinal cortex, highly processed and multimodal sensory information from the sensory association cortices converges in the hippocampus.
John O’Keefe discovered, in 1971, that certain nerve cells in the brain were activated when a rat assumed a particular place in the environment. Other nerve cells were activated at other places. He proposed that these “place cells” build up an inner map of the environment. Place cells are located in a part of the brain called the hippocampus.

May-Britt Moser and Edvard I. Moser discovered in 2005 that other nerve cells in a nearby part of the brain, the entorhinal cortex, were activated when the rat passed certain locations. Together, these locations formed a hexagonal grid, each “grid cell” reacting in a unique spatial pattern. Collectively, these grid cells form a coordinate system that allows for spatial navigation.

Grid cells, together with other cells in the entorhinal cortex that recognize the direction of the head of the animal and the border of the room, form networks with the place cells in the hippocampus. This circuitry constitutes a comprehensive positioning system, an inner GPS, in the brain. The positioning system in the human brain appears to have similar components as those of the rat brain.

http://www nobelprize org nobel prizes medicine laureates 2014 press html
Physiological basis of hippoc. learning: synaptic plasticity

Hebb’s hypothesis (1949)
Neurons that fire together wire together and this synaptic plasticity may be the physiological basis of learning.

Hebbian synaptic plasticity in the hippocampus
All excitatory pathways in the hippoc. show long-term potentiation (LTP), i.e. long-lasting increase in synaptic strength in response to tetanic stimulation (which involves strong concurrent stimulation of many synaptic connections making up the pathway).

The NMDA-type of glutamate receptors is critical for the induction of LTP in most hippoc. pathways.

Long-term potentiation (LTP): the basics

Neuroscience - Science of the Brain: An Introduction for Young Students; p. 28 (http://www.bna.org.uk/publications/brain_sci.html)
Further reading: Carlson, Physiology of Behavior, Chpt. 13 or 14 (depending on edition); Bliss & Collingridge (1993) Nature 361:31
Physiological basis of hippoc. learning: synaptic plasticity

Hebb’s hypothesis (1949)

Neurons that fire together wire together and this synaptic plasticity may be the physiological basis of learning.

Hebbian synaptic plasticity in the hippocampus

Many pathways in the hippocampus show long-term potentiation (LTP) in response to tetanic stimulation, i.e. strong concurrent stimulation of a large proportion of the synaptic connections that make up the pathway.

The NMDA-type of glutamate receptors is critical for the induction of LTP in most hippocampus pathways.


Blockade of hippoc. long-term potentiation and of place learning by the NMDA receptor antagonist AP5

The Brain Prize for 2016 is awarded to Timothy Bliss, Graham Collingridge and Richard Morris for their ground-breaking research on the cellular and molecular basis of Long-Term Potentiation and the demonstration that this form of synaptic plasticity underpins spatial memory and learning.

http://www.thebrainprize.org/flx/prize_winners/the_brain_prize_winners_2016/
A consensus view

A common theme of theories of hippocampal memory functions is the importance of the hippocampus for the rapid encoding and subsequent retrieval of memory representations conjoining features and their mutual relations.

Encoding

Retrieval

Configuration of stimuli (e.g., one defining a place) evokes neocortical activity pattern, which excites a hippoc. ensemble. As a result of concurrent activity, cortico-hippoc. connections and connections between hippoc. neurons are strengthened through the induction of synaptic plasticity.

Original neocortical pattern is partly reactivated, by a part of the original stimulus configuration, and excites a part of the hippocampal pattern. Via transmission through synapses that were strengthened during encoding, the complete original neocortical pattern, representing the original configuration, is reactivated.

Consolidation: A matter of intense debate is if memories encoded by hippoc. plasticity remain permanently hippoc.-dependent for their storage and/or retrieval or become hippoc.-independent and solely dependent on the neocortex after a period of systems consolidation (see Frankland & Bontempi, 2005, NatureRevNeurosci 6:119).

Rapid encoding and subsequent retrieval of memory by the hippocampus

**Predictions:**
- Hippocampal NMDA receptors, supporting induction of synaptic plasticity, are important for encoding, but not retrieval, of one-trial place memory.
- Hippocampal AMPA receptors, mediating fast synaptic transmission, are also important for retrieval of one-trial place memory.

**Experimental test:**
Measurement of one-trial place memory when hippocampal NMDA or AMPA receptors are reversibly blocked during encoding or retrieval by intra-hippocampal infusion of specific receptor antagonists (AP-5 or CNQX, respectively)
Rapid encoding and subsequent retrieval of place memory – Distinct contributions of hippocampal NMDA and AMPA receptors

One-trial place memory task in the Event Arena

Effects of hippocampal NMDA or AMPA receptor blockade on encoding and retrieval

AP5

CNQX

D-AP5 (30 mM, 1 µl)
CNQX (3 mM, 1µl)
ACSF as control

20-min retention delay

Before Encoding

Before Retrieval

ACSF

AP-5

ACSF

AP-5

Correct

Aver. incorrect

Correct

Aver. incorrect

% Dig time at sandwell

% Dig time at sandwell

Chance

Chance

5 60 180 360

Delay between encoding and retrieval (min)

Distinct electrophysiological effects of AP5 and CNQX

CNQX, but not AP5, reduces synaptic baseline transmission

AP5 blocks induction, but not expression or maintenance, of LTP

### Graphs

**Graph 1:**
- **X-axis:** 5-min blocks
- **Y-axis:** % Baseline EPSP slope
- **Legend:**
  - ACSF
  - AP5
  - CNQX
- **Time:** 15-20 min after infusion

**Graph 2:**
- **X-axis:** 5-min blocks
- **Y-axis:** % Baseline EPSP slope
- **Legend:**
  - ACSF before tetanus
  - AP5 before tetanus
  - AP5 after tetanus
- **Tetanus:**

### Diagram

- **Entorhinal cortex**
- **PP**
- **DG**
- **Evoked field potentials**
- **Injections:**
  - D-AP5 (30 mM, 1 µl)
  - CNQX (3 mM, 1 µl)
  - ACSF as control
Hippocampal dysfunction in normal age-related and pathological memory decline

Both normal age-related memory decline and pathological memory decline in early stages of Alzheimer’s disease, and its precursor stage mild cognitive impairment (MCI), mainly involve deficits in rapid learning of place or episodic information (for overview, see Hedden & Gabrieli, 2004, *Nature Rev Neurosci* 5:87).

*As I get older, I find I rely more and more on these sticky notes to remind me.*

Disorders in which hippocampal dysfunction has been implicated

* recently also evidence for hyperexcitability, especially in CA3; compare Gallagher & Koh, 2011, Curr Opin Neurobiol: Bakker et al., 2012, Neuron; Busche & Konnerth, 2016, Phil Trans Roy Soc B

Hippocampal dysfunction in schizophrenia

Schizophrenia symptoms

Schizophrenia is a severe neuropsychiatric disorder that involves disruption in a wide range of cognitive and behavioural functions, including psychosis (hallucinations, delusions, thought disorder), emotional, motivational, and psychomotor symptoms, and neuro-cognitive deficits (e.g., impaired executive function, working memory, episodic memory).

Neuroimaging evidence for hippocampal dysfunction in schizophrenia

**Decreased hippocampal volume in schizophrenia**


**Hippocampal function in schizophrenia**

Hippocampal overactivity at rest and impaired hippocampal recruitment in memory tasks


**Increased hippocampal activity during auditory hallucinations**


Converging evidence from human post-mortem and genetic studies and from animal models suggests hippocampal overactivity at rest as key feature of schizophrenia pathophysiology

A possible cause of hippocampal overactivity in schizophrenia: GABA dysfunction in the hippocampus

Excitation/inhibition balance

GABA synapse

Post mortem evidence for hippocampal GABA dysfunction in SZ

Reduced presynaptic markers of GABA neurons in hippocampus (e.g., GAD67)

Compensatory upregulation of postsynaptic GABA receptors

Selected key reviews:
Benes & Berretta (2001) Neuropsychopharmacology
Lisman et al. (2008) Trends Neurosci
Heckers & Konradi (2015) Schizophr Res
A possible link between hippocampal overactivity and atrophy in schizophrenia: early hyperactivity may cause atrophy at later stages

Imaging Patients with Psychosis and a Mouse Model Establishes a Spreading Pattern of Hippocampal Dysfunction and Implicates Glutamate as a Driver

Scott A. Schobel,1,4,8 Nashid H. Chaudhury,4,9 Usman A. Khan,2,5 Beatriz Paniagua,6 Martin A. Styner,6,7 Iris Asllani,3 Benjamin P. Inbar,4 Cheryl M. Corcoran,1,4 Jeffrey A. Lieberman,1,4 Holly Moore,1,2,* and Scott A. Small2,*

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http://dx.doi.org/10.1016/j.neuron.2013.02.011

Relation between hippocampal dysfunction and schizophrenia symptoms?

Deficits in hippocampus-dependent learning

Rivermead Behavioural Memory Test
(test of every-day memory)
(a) remembering a name;
(b) remembering a hidden belonging;
(c) remembering an appointment;
(d) picture recognition;
(e) immediate recall of a newspaper article;
(f) delayed recall of a newspaper article;
(g) face recognition;
(h) remembering a new route (immediate);
(i) remembering a new route (delayed);
(j) delivering a message;
(k) orientation questions;
(l) knowing the date.

Rapid place and declarative learning

How may hippocampal dysfunction (overactivity) contribute to other functional impairments characterizing schizophrenia?

- Delusions and hallucinations as pathological hippocampus-dependent memories: Abnormal interaction between hippoc. and sensory association cortices may cause sensory hallucinations. (Tamminga et al., 2012, SchizophrBull 38:927; also compare: http://www.schizophreniaforum.org/news/can-experimentally-created-memories-help-explain-delusions)

- Other mechanisms that are not primarily related to faulty hippocampus-dependent memory processing?

Overall, relatively selective deficits in “relational” types of learning are well-documented in schizophrenia, and there is good evidence they are due to hippoc. dysfunction (Ongur et al, 2006, ArchGenPsychiatry 63:356)
Selected reading

**Textbook:**
Carlson NR (any recent edition) The physiology of behavior. Chapter 13 (11th and 12th eds), Learning and memory; Chapter 16 (11th and 12th eds), Schizophrenia.

**Review articles:**


**Research article:**

**Interesting webpage on schizophrenia:**
www.schizophreniaresearchforum.com
Some questions for revision

• Many every-day problems require us to rapidly encode novel place information and subsequently to use this information to guide our behaviour. Can you think about concrete examples of this problem and comparable behavioural tests that are suitable for rats? How can we use such behavioural tests in rats to study the neural substrates that help us to solve this problem?

• Which neuro-anatomical connections and physiological mechanisms are considered critical for the role of the hippocampus in rapid place and declarative learning?

• Can disruption of the memory-related hippocampal mechanisms that we discussed in today’s lecture account for functional deficits observed in conditions that are characterised by hippocampal dysfunction?
The hippocampal learning-behaviour translation and clinical implications