The hippocampal learning-behaviour translation and clinical implications

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Translating hippocampal memory into behaviour

Rapid encoding and subsequent retrieval of place and declarative memory

Visuo-spatial information (dorso-lateral band of entorhinal cortex)

Synaptic plasticity

Behavioural control (prefrontal cortex and subcortical sites, including midbrain dopamine projections)

Translation into appropriate behaviour

Functional differentiation along the longitudinal axis of the hippoc. 1

Accuracy of place-related neuronal firing declines from septal to temporal pole

Involvement in fear/anxiety and the modulation of sensori-motor processes declines from temporal to septal pole


NMDA stimulation of temporal-intermediate, but not septal, hippoc. drives locomotion


Functional differentiation along the longitudinal axis of the hippoc. 2

Temporal to intermediate hippoc. drives nucleus accumbens and prefrontal cortex dopamine transmission

- Meso-corticolimbic dopamine transmission is implicated in a wide range of behavioural functions, including emotional, motivational, executive and sensorimotor processes, and may provide a key gateway to behavioural control for the hippocampus (Phillips et al, 2008, PharmBiochemBehav 90:236).

- The temporal to intermediate, but not septal, hippoc. has indirect anatomical links to the VTA and direct projections to dopaminergic terminals in the PFC and the NAC.

- Via these links, activity of the temporal to intermediate hippoc. stimulates dopamine transmission in the PFC and the NAC.

Microdialysis studies: increased NAC and PFC dopamine during hippocampal stimulation

Stimulation sites in temporal or septal hippoc. Microdialysis in NAC

NMDA stim. of temp. Microdialysis to interm. hippoc. in PFC

Microdialysis studies: increased NAC and PFC dopamine during hippocampal stimulation


Peleg-Raibstein et al. (2005) Neuroscience 132:219
Translating memory into behaviour – functional integration in the intermediate hippocampus

Rapid encoding and subsequent retrieval of place and declarative memory

Translation into appropriate behaviour

Some predictions derived from the model:
- Intermediate hippocampus, where substrates of rapid place learning and links to behavioural control converge, is critical for behaviour based on rapid place learning.
- Neither septal nor temporal pole can sustain such behaviour, as both possess only one of the two complementary sets of functional connectivity.
- Septal pole, through its connectivity with entorhinal cortex, can mediate rapid place encoding (even though not translate this information into behaviour).

Experimental strategy:
To examine the impact of partial hippocampal lesions, sparing different septo-temporal levels, on:
- Behavioural performance on a task requiring rapid, one-trial, place learning
- Electrophysiological models of rapid encoding in the septal hippocampus (LTP and place-related firing)

Rapid (one-trial)-place-learning task in the watermaze

Trial 2:
- Navigation depends on place memory encoded very rapidly, during T1
- Occasionally run as probe trial, with the platform not coming up before 60s

Time spent in ‘correct’ zone on probe trials

\[
\text{Time in correct zone} \times 100\% = \frac{t_{\text{correct zone}}}{t_{\text{all 8 zones}}}
\]
Ibotenate lesions sparing hippocampal tissue at different levels along the septo-temporal axis

<table>
<thead>
<tr>
<th>Sham lesion</th>
<th>Intermediate</th>
<th>Temporal</th>
<th>Septal</th>
<th>Compl. lesion</th>
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40% of hippocampal volume spared:

- Sham lesion
- Intermediate
- Temporal
- Septal
- Compl. lesion

Intermediate, but not septal or temporal, hippocampus can sustain performance based on one-trial place learning.

Rapid vs. incremental place learning

Day 1
T1 > T2 > T3 > T4 > T5 > T6 > T7 > T8
10-min trial spacing

Day 1, T2
After 1-trial learning

Day 2 to Day 5
T1 > T8

Day 6
T1

Visuo-spatial information (dorso-lateral band of entorhinal cortex)

Intact place learning, no translation into behaviour!

A residual hippocampal circuitry at the septal pole can ‘learn’: Electrophysiological models of hippocampal information encoding

Plasticity at entorhinal-hippocampal synapses

Entorhinal cortex

Evoked field potentials

% Baseline slope

Tetanus

LTP

5-min blocks

Functional integration in intermediate hippocampus is required for performance based on rapid place learning.

**Intermediate hippocampus**
- Visuo-spatial information
- Functional integration
- Performance
- Behavioural control

**Septal and temporal tips w/o intermediate hippocampus**
- Visuo-spatial information
- Functional integration
- Performance
- Behavioural control

Conclusion and future directions

Rapid encoding and subsequent retrieval of place memory

Visuo-spatial information (dorso-lateral band of entorhinal cortex)

Synaptic plasticity

Behavioural control (prefrontal cortex and subcortical sites, incl. midbrain dopamine projections)

Translation into appropriate behaviour


Functional interactions relevant for the learning-behaviour translation
• Hippocampal-prefrontal/subcortical interactions

Functional significance of hippocampal dysfunction in neuropsychiatric diseases: ‘integrative’ model of hippocampal function suggests new hypotheses concerning symptom generation
Functional implications of hippocampal overactivity?

**Hypotheses:**

- Generally, hippocampal overactivity, disrupting appropriately tuned hippocampal neuron firing, may impair performance on hippocampus-dependent memory tasks by interfering with accurate visuo-spatial encoding or the translation of such encoding into adaptive behaviour.
- Strong overactivity involving temporal to intermediate hippocampus may drive projections to prefrontal cortex and subcortical sites, including dopaminergic inputs. This may cause:
  - Psychosis-related behavioural disruptions related to dopamine hyperfunction (compare Howes & Kapur, 2009, Schizophr. Bull. 35:549);

**Experimental strategy:**

To examine how hippocampal overactivity relates to network alterations in cortical and subcortical circuits and to behavioural impairments.

- Combination of functional imaging (MRI and PET) and neuropsychological testing in patients.

Anterior (temporal) hippoc. overactivity is associated with psychosis in humans

Study compared regional cerebral blood volume (rCBV) in schizophrenia patients, prodromal patients, and healthy control subject and looked for correlations with symptoms.

rCBV in CA1 of anterior hippocampus . . .

. . . is increased in schizophrenia patients as compared to healthy control subjects

. . . is increased in prodromal subjects who progress to psychosis as compared to those who don’t

. . . correlates with delusional symptoms

Hippocampal overactivity is associated with cognitive impairments in SZ patients

Hippocampal neural disinhibition causes aberrant neural firing, as well as attentional and memory impairments.

**Hippocampal neural disinhibition**
- GABA receptor blocker (picrotoxin)

**Aberrant neural spiking and bursting**
- Neural activity
  - Picrotoxin 150 ng (n=8)
  - Saline (n=7)

**Rapid place learning performance in watermaze**
- Infusion
  - Novel location
  - T1 → T2

**Attentional performance on 5-choice-serial-reaction-time test**
- 5CSRT test is highly dependent on prefrontal function (Pezze et al., 2014, J Neurosci)

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 articles:**


Some questions for revision

• Which memory and not primarily memory related functions have been linked to the hippocampus? By which type of empirical evidence?

• 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 of concrete examples for 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?

• How may the hippocampus mediate the translation of rapid place learning into appropriate behaviour?

• How may hippocampal dysfunction contribute to symptoms that characterise schizophrenia?

• How could we study how hippocampal dysfunction contributes to symptoms of schizophrenia?