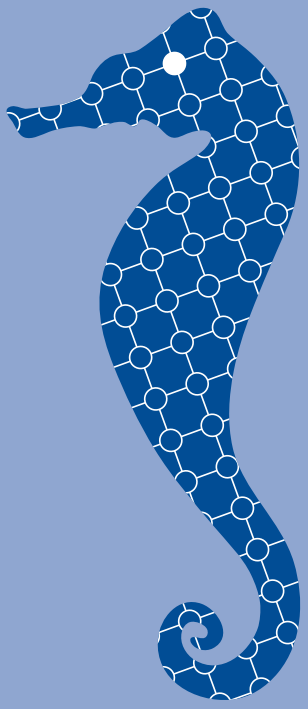

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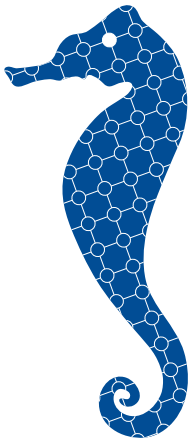
Hippocampal Network Across the Lifespan:
Circuit | Code | Cognition

Symposium

May 24–26, 2018

Budapest, Hungary



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Program

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May 24, Thursday

18:00–18:05 Opening remarks:

Zoltán Vidnyánszky
Hungarian Academy of Sciences
Attila Keresztes, Markus Werkle-Bergner
Max Planck Institute for Human Development

18:05–18:25 Welcome messages:

György Pokol
Director, Research Centre for Natural Sciences,
Hungarian Academy of Sciences

Tamás Freund
Director, Institute of Experimental Medicine,
Hungarian Academy of Sciences /
Head, Department of Neurosciences,
Pázmány Péter Catholic University

I. Circuitry: insights from animal models

Chair: Zoltán Vidnyánszky

18:25–19:10 Opening talk

Attila Losonczy
Columbia University Medical Center
Dissecting hippocampal circuit dynamics
for navigation and learning

19:10–19:25 Discussion

19:25 Reception

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May 25, Friday

II. Computational and human models

Chair: Attila Keresztes

9:30–10:00 **Anna Schapiro**
Beth Israel Deaconess Medical Center/ Harvard Medical School
Rethinking memory systems for statistical learning

10:05–10:35 **Kimberly Stachenfeld**
Princeton Neuroscience Institute/Google DeepMind
The hippocampus as a predictive map

10:35–10:50 Discussion

10:50–11:20 Coffee break

III. Coding mechanisms

Chair: Markus Werkle-Bergner

11:20–11:50 **Simon Hanslmayr**
University of Birmingham
How a desynchronized cortex and a synchronized hippocampus cooperatively form and retrieve memories

11:55–12:25 **Nikolai Axmacher**
University of Bochum
Oscillatory reinstatement in hippocampus and neocortex

12:25–12:40 Discussion

12:40–13:40 Lunch

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May 25, Friday (continued)

IV. Hippocampal structure and function across the human lifespan

Chairs: Zoltán Vidnyánszky and Markus Werkle-Bergner

13:40–14:10 **Brock Kirwan**
Brigham Young University
Encoding, Retrieval, and Consolidation Effects on Hippocampal-Dependent Memory Discrimination

14:15–14:45 **Pamela Lavenex**
University of Lausanne
Learning to find our way in the world:
The development of allocentric spatial memory in toddlers and its underlying hippocampal substrates

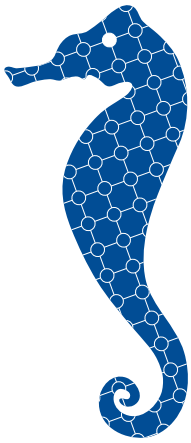
14:50–15:20 **Attila Keresztes**
Max Planck Institute for Human Development
Hippocampal contributions to memory specificity across the lifespan

15:20–15:35 Discussion

15:35–16:05 Coffee break

16:05–16:35 **Gael Chetelat**
Université de Caen-Normandie
A multimodal neuroimaging perspective of the human hippocampal circuitry involvement in normal and pathological aging

16:40–17:10 **Ádám O. Kettinger**
Hungarian Academy of Sciences /
Budapest University of Technology and Economics
Simultaneous multislice imaging: New horizons in accelerated MRI



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May 25, Friday (continued)

17:10–17:25 Discussion

Evening talk
Chair: Markus Werkle-Bergner

17:25–18:10 **Christian Doeller**
Kavli Institute for Systems Neuroscience / Norwegian University of Science and Technology
Grid-like coding for vision and navigation in human entorhinal cortex

18:10–18:25 Discussion

19:00 Conference Dinner

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May 26, Saturday

V. Beyond the hippocampus

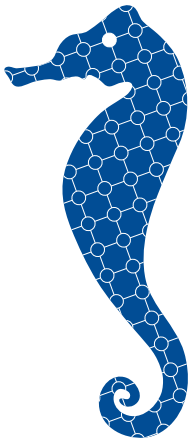
Chair: Attila Keresztes

10:00–10:30 **Gyula Kovács**
University of Jena
Of priming and predictions: neuroimaging and TMS evidences of the predictive interpretation of priming

10:35–11:05 **Zoltán Vidnyánszky**
Hungarian Academy of Sciences
Separation of task-relevant and irrelevant object representations in visual working memory

11:05–11:20 Discussion

11:20–11:35 Closing remarks:
Markus Werkle-Bergner
Max Planck Institute for Human Development



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Abstracts

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Abstracts are shown with speakers in alphabetical order.

Nikolai Axmacher
Oscillatory reinstatement in hippocampus and neocortex

EEG oscillations reflect fluctuations of excitability and thereby provide "windows of opportunity" for neural firing. Abundant evidence has shown that oscillations play a general role for basic brain operations that are recruited by various cognitive functions. More recently, it has been shown that the time-frequency pattern of EEG activity can also be used to decode specific contents that can then be tracked across subsequent stages of memory processing. In my talk, I will provide an overview of these results based on intracranial EEG recordings. In a first set of studies, oscillatory reinstatement was identified in distributions of high-frequency activity across electrodes. This was related to reinstatement at individual electrodes. A similar approach has been used to measure reinstatement during offline resting states and sleep, i.e., related to memory consolidation. Finally, we recently found evidence for a dissociation of different representational formats in hippocampus and neocortex. Together, these studies show that time-frequency patterns of EEG oscillations provide a window into the reactivation of unique memory traces.

Gael Chetelat
A multimodal neuroimaging perspective of the human hippocampal circuitry involvement in normal and pathological aging

The hippocampus is vulnerable to a multitude of conditions and diseases. Normal and pathological aging for examples are associated with hippocampal volume decrease; yet, they are discrepancies in the relative involvement of the different parts of the hippocampus – in terms of hippocampal subfields and/or through the antero-posterior axis of the hippocampus. For instance, hippocampal volume loss predominates in the subiculum in normal aging, in CA1 in Alzheimer's disease, and in the anterior hippocampus in semantic dementia. Hippocampal alterations have distant effects, affecting the functioning of other brain areas that are connected to the hippocampus. Thus, beyond hippocampal alterations, the different states and disease are associated with the disruption of spe-

cific hippocampal networks. The specificity of the hippocampal networks that are involved at least partly depends on the topography / specificity of the hippocampal alterations. Alzheimer's disease and semantic dementia, while both associated with hippocampal atrophy, are associated with the disruption of distinct hippocampal networks – and this specificity itself explains the specificities of the clinical manifestation of the diseases and more particularly the associated cognitive deficits. Indeed, over and above local alterations, the disruption of brain connectivity and network function underlie cognitive deficits. The richness and complexity of the hippocampus function reflect not only the heterogeneity of this structure, but also all the possible interactions of the hippocampus with other brain structures through connectivity, which would themselves determine this function.

Christian Doeller
Grid-like coding for vision and navigation in human entorhinal cortex

Entorhinal grid cells map the local environment, but their involvement beyond spatial navigation remains elusive. During my talk I will present evidence from human fMRI and MEG studies showing that entorhinal cortex exhibits a hexadirectional signal encoding gaze direction. These results provide evidence for a grid-like entorhinal code for visual space and suggest a more general role of the entorhinal grid system in coding information along continuous dimensions.

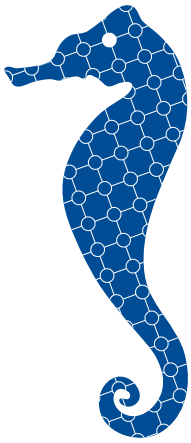
Simon Hanslmayr
How a desynchronized cortex and a synchronized hippocampus cooperatively form and retrieve memories

Brain oscillations have been proposed to be one of the core mechanisms underlying episodic memory. But how do they operate in the service of memory? Reviewing the literature a conundrum emerges as some studies highlight the role of synchronized oscillatory activity, whereas others highlight the role of desynchronized activity.
In this talk, I will describe a recently published computational model that resolves this conundrum and parsimoniously shows how these two opposing oscillatory behaviours may cooperate in the service of memory.

Building on empirical evidence, I will argue that the synchronization and desynchronization reflect a division of labour between a hippocampal and a neocortical system, respectively. Specifically, whereas desynchronization is key for the neocortex to represent information, synchronization in the hippocampus is key to bind information. I will then derive specific predictions that arise from this model about how the interaction between a synchronized hippocampus and a desynchronized neocortex is supposed to look like. A test of these predictions will be presented via intracranially recorded data in human epilepsy patients where we can simultaneously record from both regions and thereby study the interaction between the two systems in the service of memory.

Attila Keresztes
Hippocampal contributions to memory specificity across the lifespan

Adaptive learning systems need to meet two complementary and partially conflicting goals: detecting regularities in the world versus remembering specific events. The hippocampus (HC) keeps a fine balance between computations that extract commonalities of incoming information (i.e. generalization through pattern completion) and computations that enable encoding of highly similar events into unique representations (i.e. memory specificity through pattern separation). During early ontogeny, the rapid and cumulative acquisition of world knowledge through generalization contrasts slower improvements in the ability to lay down highly specific, long-lasting episodic memories. At the other end of the lifespan, an early decrease in memory specificity is paralleled with relatively intact generalization. In this talk, we will highlight recent behavioral and neuroimaging evidence suggesting that maturational differences among subfields within the hippocampus contribute to the lead-lag relation between generalization and specificity during childhood and adolescence, and present preliminary results of a study investigating how scenescent changes within the hippocampus affect specificity and generalization. In sum, we propose that developmental changes within the hippocampus affect the fine balance between specificity and generalization across the human lifespan.



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Brock Kirwan
Encoding, Retrieval, and Consolidation Effects on Hippocampal-Dependent Memory Discrimination

Long-term memory for facts and events is critically dependent on the medial temporal lobe, and specifically on the hippocampus. Computational models of hippocampal function propose that one of the essential functions of the hippocampus is pattern separation, whereby similar or overlapping memory representations are orthogonalized or made as dissimilar as possible. We and others have tested these predictions and demonstrated that the hippocampus is indeed involved in pattern separation at the time of encoding. However, it is less clear how these orthogonalized memory representations are affected by retrieval and sleep-dependent consolidation. Further, it remains to be tested how the hippocampus interacts with the cortex during mnemonic discrimination tasks. Here we present data demonstrating that the orthogonalized memory representations are sensitive to target-lure similarity, that they are robust to interference during retrieval, and that they are strengthened by sleep-dependent consolidation.

Gyula Kovács
Of priming and predictions: neuroimaging and TMS evidences of the predictive interpretation of priming.

Repeating a stimulus reduces the neural activity, which leads to lower BOLD signal in fMRI experiments. This phenomenon has recently been interpreted in the predictive coding framework and it was argued that stimulus repetitions reduce the predictive error of the system and this is manifested in the lower BOLD signal. However, theoretically the predictive error of a system can also be reduced by related sensory or semantic cues (primes) as supported by many experiments with image repetitions or with name-picture stimulus priming arrangements. Here we first tested in an fMRI experiment if the fusiform and occipital face areas (FFA/OFA) show reduced BOLD signal for faces presented after congruent as compared to incongruent names in a famous/non-famous task. We found, in addition to a strong behavioral advantage of the congruent trials, a significant response reduction in the bilateral FFA and rOFA, suggesting

that these areas are playing a role in the computation of prediction errors, based on semantic cues/primes. Second, in a series of TMS experiments we found that the stimulation of the right OFA eliminates the behavioral advantage of both the repetition of a face and of the congruent cross-domain cues/primes, suggesting the causal role of the OFA in creating identity-specific memory-traces, presumably via the estimation of predictive errors within and cross-domain situations. Overall these results show, for the first time, that the core face-processing areas play a role in implicit memory processes across sensory domains and support the idea that priming is related to the reduction of predictive error.

Pamela Lavenex
Learning to find our way in the world: The development of allocentric spatial memory in toddlers and its underlying hippocampal substrates.

Episodic memories for autobiographical events that happen in unique spatiotemporal contexts are central to defining who we are. Yet, before 2 years of age, children are unable to form or store episodic memories for recall later in life, a phenomenon known as infantile amnesia. In order to better understand the emergence and maturation of episodic memory in children from 2 to 7 years of age, we have studied the development of allocentric spatial memory, a fundamental component of episodic memory. Our investigations have revealed that basic allocentric spatial memory abilities are reliably observed in children after 2 years of age, coinciding with the offset of infantile amnesia. Interestingly, evidence from our parallel investigations of the neuroanatomical and molecular development of the monkey hippocampal formation reveals that numerous features of the CA1 region of the hippocampus become adult-like at the same time, thus suggesting that the functional maturation of CA1 may underlie the emergence of allocentric spatial capacities and the offset of infantile amnesia in young children. I will discuss several theories regarding why the tardive development of a structure critical for relational memory functions such as allocentric and episodic memory may actually be adaptive in an evolutionary context. Altogether, our molecular, neuroanatomical and behavioral findings support the hypothesis that the differential maturation of distinct hippocampal circuits underlies the differential emergence of specific “hippocampus-dependent” memory processes, culminating in

the emergence of adult-like episodic memory concomitant with the maturation of all hippocampal circuits.

Attila Losonczy
Dissecting hippocampal circuit dynamics for navigation and learning

Learning and remembering where and when salient events occur in space and time are essential for adaptive behaviors. Both spatial navigation and episodic memory have been linked to the mammalian hippocampus, but the detailed mechanisms at cellular and circuit levels remain poorly understood. To address these questions, we use in vivo functional imaging to monitor the activity of identified excitatory, inhibitory and neuromodulatory circuit motifs in the hippocampus of behaving mice during spatial exploration, fear learning and goal-directed learning. The talk will focus on our recent efforts aimed at dissecting functional roles of multimodal microcircuits at the dentate gyrus input and at the CA1 output nodes of the hippocampus. I will summarize how various types of dentate gyrus principal neurons – adult-born and mature granule cells, and hilar mossy cells contribute to context encoding and discrimination. We also monitored activity in deep and superficial subpopulations of CA1 pyramidal cells, and assessed the relationship between sublayer dynamics and learning. Relatedly, I will present findings on how goal-oriented spatial learning is supported by disinhibitory GABAergic circuits in CA1. Finally, I will discuss our most recent efforts to dissect hippocampal population dynamics supporting temporal associative learning. Together, our results demonstrate a functional division of labor among subpopulations of principal neurons and their GABAergic counterparts during hippocampal-dependent behaviors.

Anna Schapiro
Rethinking memory systems for statistical learning

There is a fundamental tension between storing discrete traces of individual experiences, which allows recall of particular moments in our past without interference, and extracting regularities across these experiences, which supports generalization and prediction in similar situations in the future. This tension is resolved in classic memory systems theories

by separating these processes anatomically: the hippocampus rapidly encodes individual episodes, while the cortex slowly extracts regularities over days, months, and years. This framework fails, however, to explain how we often learn regularities quite quickly—within a few minutes or hours. I will present empirical evidence suggesting that the hippocampus, in addition to its well-established role in episodic memory, is in fact also responsible for our ability to rapidly extract regularities. I will then use a neural network model of the hippocampus to demonstrate how these two competing learning processes can coexist in one brain structure. The proposal is that the trisynaptic pathway of the hippocampus specializes in episodic memory, while the monosynaptic pathway supports statistical learning. This framework provides a new perspective on how changes in the structure of the hippocampus across the lifespan may relate to changes in the nature of memory ability, and suggests new tasks that may be useful in assessing this relationship.

Kimberly Stachenfeld
The hippocampus as a predictive map

A cognitive map has long been the dominant metaphor for hippocampal function, embracing the idea that place cells encode a geometric representation of space. However, evidence for predictive coding, reward sensitivity, and policy dependence in place cells suggests that the representation is not purely spatial. We approach this puzzle from a reinforcement learning perspective: what kind of spatial representation provides a useful basis for estimating expected future reward? We show that the answer takes the form of a predictive representation. This representation captures many aspects of place cell responses that fall outside the traditional view of a cognitive map. Furthermore, we argue that entorhinal grid cells encode a low-dimensional basis set for the predictive representation, useful for suppressing noise in predictions and extracting multiscale structure for hierarchical planning.

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Zoltán Vidnyánszky
Separation of task-relevant and irrelevant object representations in visual working memory

The ability to select task-relevant information and maintain it in working memory is of critical importance while interacting with cluttered visual environment. However, the neural processes underlying selection and separation of task-relevant object representations in working memory from irrelevant and distracting information is still poorly understood. I will present the results of our recent neuroimaging research aiming at uncovering the brain networks and computations subserving separation of task-relevant and irrelevant object representations in visual working memory as well as their age-related impairment. Special emphasis will be given to the interaction between the hippocampus and the downstream object-selective visual cortical areas enabling proper binding of attended, task-relevant object representations.

Ádám Ottó Kettinger
Simultaneous multislice imaging: new horizons in accelerated MRI

The lengthy data acquisition is one of the main drawbacks of magnetic resonance imaging. In the last decade, scan time reduction by measuring only a fraction of k-space became commonly used even in clinical practice. However, the increased acquisition speed comes at a price of degraded SNR, consisting of an inherent decrease due to the smaller amount of measured data, and a spatially varying noise amplification caused by the reconstruction. Recently, another form of acceleration method, called simultaneous multislice imaging, has emerged, spreading rapidly in the research community. In this technique, the inherent SNR decrease caused by smaller amount of measured data is not present, allowing a higher acceleration without spoiling the image quality. Furthermore, new reconstruction methods to decrease the reconstruction noise are being actively developed, with the participation of the Brain Imaging Centre of the Research Centre for Natural Sciences. Using these acquisition and reconstruction techniques, MR image acquistion time can be decreased by an order of magnitude, providing exciting new opportunities in both anatomical applications and functional neuroimaging.