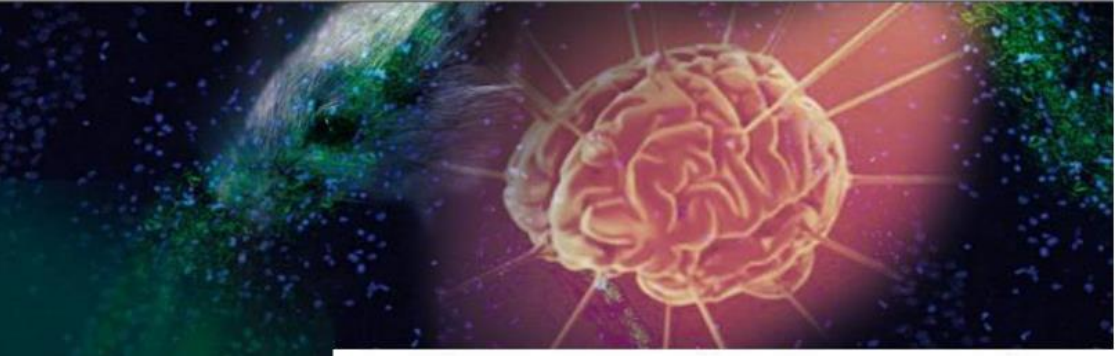

Fourth International Conference on the FUNCTIONAL ARCHITECTURE OF MEMORY

May 23rd to 25th, 2018

The FAM conference aims at bringing new insights on today's major controversies in recognition memory, and bridging human and animal memory function.

World leading experts on the Medital Temporal Lobe will discuss findings obtained with complementary approaches (behavioral, imaging, functional neuroanatomy and electrophysiology).

Go to http://www.ruhr-uni-bochum.de/philosophy/famconference for preliminay schedule, further description of the event and registration.

Speakers

Jozsef **Csicsvari** (IST, Austria)
Düzel/Berron (DZNE MD, Germany)
Paul **Frankland** (Sickkids, CA)
James **Knierim** (Johns Hopkins Hosp., USA)
Pierre **Lavenex** (Univ. Freiburg, Switzerland)
Stefan **Leutgeb** (UCSan Diego, USA)
Thomas **McHugh** (RIKEN, Japan)
Charan **Ranganath** (UC Davis, USA)
Magdalena **Sauvage** (LIN/OVGU, Germany)
Steven **Siegelbaum** (Columbia U, USA)
Mike **Yassa** (UC Irvine, USA)
Clea **Warburton** (Bristol University, UK)
Menno **Witter** (Kavli Institute, Norway)
Thomas **Wolbers** (DZNE MD, Germany)
Motoharu **Yoshida** (DZNE/LIN, Germany)

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Prof. M. Sauvage, Leibniz-Institute for Neurobiology/ OvGU,
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Special thanks to

Laura Montero, Vivien Galant, Celia Fürst and Erika Atucha for administrative support and
David Berron for recreational information

The team of Prof. Albert Newen (Institute of Philosophy II) for help with the announcements

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Functional Architecture of Memory Conference

May 23rd – 25th 2018

General Information

Key Information

1. Way to the conference centre (see map page 9)

Address:
Leibniz Institute for Neurobiology (LIN)
Center for Learning and Memory Research
Ebbinghaussaal
Brenneckestr. 6
39118 Magdeburg

By car:

Coming from Berlin or Hannover via A2 depart at 'Magdeburg-Zentrum' and follow the city highway (Magdeburger Ring) to exit 'Wiener Straße' (approx. 12 km). Turn right 3 times and follow signage "Uniklinik Magdeburg". Enter the campus of the University hospital and turn left at the ZENIT building.

Coming from Halle/Leipzig via A14 depart at 'Sudenburg', follow signage Magdeburg-Zentrum on the city highway (Magdeburger Ring) to exit Fermersleber Weg (approx. 7 km). Turn right twice, follow signage "Uniklinik Magdeburg". Enter the campus of the University hospital and turn left at the ZENIT building.

By public transport:
From Magdeburg station "Hauptbahnhof" (main entrance) take the tram Line 6 (direction: "Leipziger Chaussee") to the stop "Universitätsklinikum" (approx. 10 min) or "Brenneckestraße" (approx. 15 min).
From the city center take the tram Line 9 (direction: "Reform") to the stop "Universitätsklinikum" (approx. 10 min) or "Brenneckestraße" (approx. 15 min).
From the tram stop "Brenneckestraße" turn right into Brenneckestraße and after approx. 400m the yellow-brown institute's building appears on the right (see map on page 9).

If you miss the transfer to the restaurant, you can go by tram (Line 6) from the stop “Brenneckestraße” or “Universitätsklinikum” to the final destination “Cracau (Pechauer Platz)”. This takes approximately 20 minutes. From there, walk along the main road towards the town exit Magdeburg-Pechau. After an 8 minute walk you will reach “Die Kirche”. Alternatively, you can call a cab (0049 391 / 737373).

In case that you miss your transfer from the restaurant, walk along the main road from “Die Kirche” to the town entrance of Magdeburg and use the tram (Line 6). This goes directly to the town center if you need to get off for Motel One (use the stop “Allee Center” and walk up Breiter Weg and take a left after the Grüne Zitadelle Building, then go straight towards Motel One). If you wish to go back to the LIN, keep going on tram line 6 until “Universitätsklinikum” or “Brenneckestraße” (see map page 9).

No specific events are organized for Wednesday 23rd or Friday 25th but speakers and participants are encouraged to reconvene for drinks at Hasselbachplatz at “The Lion” on the evening at 21:00. The meeting point is in front of the pub at Keplerstraße 7. Wearing your badges would help finding each other.

For participants, our tips for dinner on those two days:

Please refer to the map in the “Recreational Info” chapter of this booklet (page 54) to find a choice of restaurants you might like to visit.

Functional Architecture of Memory Conference

May 23rd – 25th 2018

Program

Time	Wednesday May 23rd	Time	Thursday May 24th	Time	Friday May 25th
09:30 – 09:40	*"Welcome" M. Sauvage*	09:30 – 10:10	***Magdalena Sauvage (LIN/ OvGU, Germany)*** *Imaging memory traces over half a life-time in the medial temporal lobe - a network shift?*	09:30 – 10:10	***Stefan Leutgeb (UC San Diego, USA)*** *Spatial and memory computations in the medial entorhinal cortex and hippocampus*
09:40 – 10:10	*Data Blitz Session*				
10:10 – 10:50	*Data Blitz Session*	10:10 – 10:50	***Paul Frankland (Univ. of Toronto, CA)*** *Brain Networks involved in recent and remote fear memory*	10:10 – 10:50	***Josef Csicsvari (IST, Austria)*** *Hippocampal reactivation during spatial memory tasks*
10:50 – 11:00	*Coffee*	10:50 – 11:20	*Coffee*	10:50 – 11:20	*Coffee*
11:00 – 12:00	*Data Blitz Session*	11:20 – 12:00	***Clea Warburton (Univ. of Bristol, UK)*** *The nucleus reuniens of the thalamus, a key pillar in the architecture of recognition memory*	11:20 – 12:00	***Thomas McHugh (RIKEN, Japan)*** *The physiology of the hippocampal engram*
12:00 – 13:50	*Lunch Break*	12:00 – 13:00	*Lunch Break*	12:00 – 13:00	*Lunch Break*
13:00 – 13:50	*Students/Speakers round table*	13:00 – 13:50	*Students/Speakers round table*	13:00 – 13:50	*Students/Speakers round table*
14:00 – 14:40	***Michael Yassa (UC Irvine, USA)*** *Deconstructing episodic memory: what, where and when*	14:00 – 14:40	***Menno Witter (Kavli Institute, Norway)*** *A reappraisal of parallel "what" and "where" pathways in the MTL-memory system, mediated by the lateral and medial entorhinal cortex*	14:00 – 14:40	***Pierre Lavenex (Univ. Freiburg, Germany)*** *Functional and structural organization of the medial temporal lobe following neonatal hippocampal lesion in monkeys*
14:40 – 15:20	***Motoharu Yoshida (DZNE/ LIN, Germany)*** *Hippocampal TRCP channels support temporal bridging*	14:40 – 15:20	***James Knierim (Johns Hopkins Hosp., USA)*** *Egocentric vs. Allocentric coding in the lateral and medial entorhinal cortex*	14:40 – 15:20	***Thomas Wolbers (DZNE, Magdeburg, Germany)*** *Mechanisms of navigational decline in old age*
15:20 – 15:40	*Coffee*	15:20 – 15:40	*Coffee*	15:20 – 15:40	*Coffee*
15:40 – 16:20	***Charan Ranganath (UC Davis, USA)*** *Event representation and episodic memory*	15:40 – 16:20	***Berron/Düzel (DZNE Magdeburg, Germany)*** *Effects of age and Alzheimer's Pathology on Mnemonic Discrimination of objects and scenes in medial temporal lobe pathways*	15:40 – 16:20	***Steven Siegelbaum (Columbia Univ., USA)*** *Navigating social behavioral space through the hippocampal CA2 region*
16:20 – 17:00	*Open Discussion – M. Yassa "Time processing"*	16:20 – 17:00	*Open Discussion – M. Witter "The what and where pathway revisited"*	16:20 – 17:00	*Open Discussion – S. Leutgeb "Relativity of time and space"*

Blitz Sessions – Wednesday morning, May 23rd

Time	Wednesday May 23rd	Time	Wednesday May 23rd
09:30 – 09:40	*"Welcome" M. Sauvage*	10:50 – 11:00	*Coffee*
09:40 – 10:50	***Data Blitz Session*** *(talk: 5 mins; questions: 1 min)*	11:00 - 12:00	***Data Blitz Session*** *(talk: 5 mins; questions: 1 min)*
	Shih-pi Ku (Sauvage lab., LIN Magdeburg, Germany) *Regional specific evidence for memory-load dependent activity in the Dorsal Subiculum and the Lateral Entorhinal Cortex.*		***Mael Dumenieu (Lopez-Rojas lab., LIN Magdeburg, Germany)*** *The low-threshold calcium channel Cav3.2 mediates burst firing of mature granule cells of the dentate gyrus*
	Bethany Frost (O´Mara lab., Trinity College, Ireland) *Investigating the role of the anterior thalamic nuclei in spatial memory*		***Elke Edelmann (Leßmann lab., OvG Univ., Germany)*** *Synaptic plasticity at single cell level: Diversity along hippocampal axes*
	Liv Mahnke (Sauvage lab., LIN Magdeburg, Germany) *Familiarity-induced activity patterns in the LEC and PER in the absence of functional hippocampus*		***Camilla Fusi (Kreutz lab., LIN Magdeburg, Germany)*** *The synapto-nuclear messenger Jacob alters nucleolar dynamics to facilitate protein synthesis in plasticity*
	Steffen Gais (Univ. Tübingen, Germany) *Sleep supports memory systems consolidation between the hippocampus and parietal cortex*		***Anil Annamneedi (Stork lab., LIN Magdeburg, Germany)*** *Conditional mutants for the presynaptic protein Bassoon display distinct changes in learning and memory*
	Monika Schönauer (Univ. Tübingen, Germany) *A fast track to the neocortex: long-term memory representations in the parietal cortex*		***Bertram Gerber (LIN Magdeburg, Germany)*** *It´s in the timing, …*
	Christopher Dillingham (O´Mara lab., Trinity College, Ireland) *Single-unit and oscillatory activity of the claustrum during sleep*		***Nicole Wetzel (LIN Magdeburg, Germany)*** *Pupil constriction predicts recognition memory performance in children*
	Anne Maass (Jagust lab., Univ. of California, USA) *Effects of tau and amyloid deposition on domain-specific memory function in old age*		***Olya Hakobyan (Cheng lab., Ruhr University Bochum, Germany)*** *Modelling recognition memory as a decision process based on generic memory Modules*
	Erika Atucha (Sauvage lab., LIN Magdeburg, Germany) *Spatial information is preferentially processed by the distal part of CA3: implication for memory retrieval.*		***Michael T. Lippert (LIN Magdeburg, Germany)*** *Thermal implications of optogenetic brain stimulation for learning research*
	Anne Albrecht (Stork lab., OvG Univ., Germany) *HIPP neurons in the dentate gyrus mediate the cholinergic modulation of background context memory salience*		***Oliver Speck (OvG Univ., Germany)*** *Unleashing the full potential of high-field MRI*
	Cornelia Helbing (Angenstein lab., DZNE Magdeburg, Germany) *How hippocampal Fimbria-Fornix-stimulation affects the dopaminergic mesolimbic system of the rat brain*		

Time	Wednesday May 23rd
9:30 – 09:40	"Welcome" M. Sauvage
09:40 – 10:50	Data Blitz Session
10:50 – 11:00	Coffee
11:00 – 12:00	Data Blitz Session
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14:40 – 15:20	Motoharu Yoshida (DZNE/ LIN, Germany) *Hippocampal TRCP channels support temporal bridging*
15:20 – 15:40	Coffee
15:40 – 16:20	Charan Ranganath (UC Davis, USA) *Event representation and episodic memory*
16:20 – 17:00	Open Discussion – M. Yassa „Time processing"

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10:10 – 10:50	**Paul Frankland (Univ. of Toronto, CA)** *Brain Networks involved in recent and remote fear memory*
10:50 – 11:20	**Coffee**
11:20 – 12:00	**Clea Warburton (Univ. of Bristol, UK)** *The nucleus reuniens of the thalamus, a key pillar in the architecture of recognition memory*
12:00 – 13:00	**Lunch Break**
13:00 – 13:50	**Students/Speakers round table**
14:00 – 14:40	**Menno Witter (Kavli Institute, Norway)** *A reappraisal of parallel "what" and "where" pathways in the MTL-memory system, mediated by the lateral and medial entorhinal cortex*
14:40 – 15:20	**James Knierim (Johns Hopkins Hospital, USA)** *Egocentric vs. Allocentric coding in the lateral and medial entorhinal cortex*
15:20 – 15:40	**Coffee**
15:40 – 16:20	**Berron/Düzel (DZNE Magdeburg, Germany)** *Effects of age and Alzheimer´s Pathology on Mnemonic Discrimination of objects and scenes in medial temporal lobe pathways*
16:20 – 17:00	**Open Discussion – M. Witter** **„The what and where pathway revisited"**

Time	Friday May 25th
9:30 – 10:10	**Stefan Leutgeb (UC San Diego, USA)** *Spatial and memory computations in the medial entorhinal cortex and hippocampus*
10:10 – 10:50	**Josef Csicsvari (IST, Austria)** *Hippocampal reactivation during spatial memory tasks*
10:50 – 11:20	**Coffee**
11:20 – 12:00	**Thomas McHugh (RIKEN, Japan)** *The physiology of the hippocampal engram*
12:00 – 13:00	**Lunch Break**
13:00 – 13:50	**Students/Speakers round table**
14:00 – 14:40	**Pierre Lavenex (Univ. Freiburg, Germany)** *Functional and structural organization of the medial temporal lobe following neonatal hippocampal lesion in monkeys*
14:40 – 15:20	**Thomas Wolbers (DZNE, Magdeburg, Germany)** *Mechanisms of navigational decline in old age*
15:20 – 15:40	**Coffee**
15:40 – 16:20	**Steven Siegelbaum (Columbia Univ., USA)** *Navigating social behavioral space through the hippocampal CA2 region*
16:20 – 17:00	**Open Discussion – S. Leutgeb** **„Relativity of time and space“**

Functional Architecture of Memory Conference

May 23rd – 25th 2016

Data Blitz Session

Regional specific evidence for memory-load dependent activity in the Dorsal Subiculum and the Lateral Entorhinal Cortex.

Ku SP[1], Nakamura NH[2], Maingret N[2], Mahnke L[1], Yoshida M[3], Sauvage MM[1,2]

[1]Leibniz-Institute for Neurobiology, Functional Architecture of Memory Dept., 39118, Magdeburg, Germany; [2]Ruhr-University, Bochum, Germany; [3]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

The subiculum and the lateral entorhinal cortex (LEC) are the main output areas of the hippocampus, which contributes to spatial and non-spatial memory. The proximal part of the subiculum (bordering CA1) receives heavy projections from the perirhinal cortex and the distal part of CA1 (bordering the subiculum), both known for their ties to object recognition memory. The extent to which the proximal subiculum contributes to non-spatial memory is however unclear. Comparatively, the involvement of the LEC in non-spatial information processing is well known, yet very few studies have investigated its role within the frame of memory function. Thus, it is not known whether its contribution depends on memory load and whether its deep and superficial layers could be differentially recruited within this frame as recently suggested. Here, we tested the extent to which the proximal part of the subiculum and the superficial and deep layers of the LEC contribute to non-spatial memory. To do so, we imaged brain activity at the cellular level in these areas in rats performing a delayed nonmatch to sample task based on odors with two different memory loads (5 or 10 odors) by detection *Arc* RNA by in-*situ* hybridization. We report for the first time that the proximal part of the subiculum is recruited in a memory-load dependent manner and that the deep layers of the LEC is only engaged under high memory load conditions during the retrieval of non-spatial memory, thus shedding light on the specific networks contributing to non-spatial memory retrieval.

Investigating the role of the anterior thalamic nuclei in spatial memory

Bethany Frost[1], Christopher Dillingham[1], John Aggleton[2] and Shane O'Mara[1]

[1]Institute of Neuroscience, Trinity College Dublin
[2]Cardiff University, Cardiff

Interactions between anterior thalamus (ATN), the hippocampal formation (especially area CA1 and subiculum) and retrosplenial cortex are critical to spatial mnemonic processes. ATN lesions induce significant deficits in spatial navigation. Activity-dependent gene expression studies suggest these deficits result in part from covert pathology in distal, network-connected regions. The principal output of hippocampal area CA1 comprises a major projection to the subiculum. The majority of CA1 neurons display a strong spatial signal, and are called place cells. Neurons of the subiculum show a heterogeneous spatial code, with place, head direction, place x head direction and grid cells among the neuronal phenotypes. To further our understanding of the basis of this anterior thalamus lesion-induced dysfunction, we have been conducting simultaneous single-unit and local field potential (LFP) recordings in the dorsal subiculum combined with LFP recordings in the retrosplenial cortex of awake-behaving, ATN-lesioned, sham or control rats. ATN-lesioned rats showed significant deficits in spatial tasks. Place cells, head-direction cells and grid cells recorded in the dorsal subiculum showed responses to visual cue rotation in open field recordings in non-lesioned rats. Unexpectedly, given the spatial input from CA1, spatial coding in subiculum appears absent in the ATN-lesioned animals. The loss of ATN input to the hippocampal formation causes a significant disruption in spatial signal processing in the subiculum. Thus, the spatial responses found in subiculum result in large part from thalamic rather than hippocampal inputs; the spatial output of the hippocampal formation appears to have subcortical anterior thalamic, rather than hippocampal, origin.

Familiarity-induced activity patterns in the LEC and PER in the absence of functional hippocampus

Liv Mahnke[1], Erika Atucha[1], Takashi Kitsukawa[4]& Magdalena M. Sauvage[1,2,3]

[1]Leibniz-Institute for Neurobiology, Functional Architecture of Memory Dept., 39118, Magdeburg, Germany; [2]Otto von Guericke University, Medical Faculty, Functional Neuroplasticity Dept., 39120, Magdeburg Germany; [3]Otto von Guericke University, Center for Behavioral Brain Sciences, 39106, Magdeburg Germany; [4]KOKORO-biology group, Osaka University, 565-0871, Osaka, Japan.

Recognition memory relies on the recollection and the familiarity processes. It is a consensus that the hippocampus supports recollection, but a major debate remains whether the hippocampus also supports familiarity or whether the parahippocampal region does, particularly the perirhinal (PER) and the lateral entorhinal (LEC) cortices. Using a high resolution molecular imaging technique based on the detection of the immediate-early gene *Arc,* tight to synaptic plasticity, we reported that the PER and the LEC are selectively recruited during familiarity-only judgements in rats with intact hippocampus, while the hippocampal subfields CA1 and CA3 are not (see Atucha et al., 2017). To test whether this recruitment is truly independent of hippocampal function, we imaged brain activity in the PER and the LEC of rats with lesioned hippocampus that rely on familiarity to solve a delay non-match to sample memory task. Lesioning the hippocampus led to memory deficits attributed to a loss of contribution of the recollection process to memory retrieval (Fortin et al, *Nature*, 2004). Conversely, familiarity-like patterns of activity in the PER remained unaffected while activity levels in the LEC increased. These results suggest that patterns of activity detected in the PER are independent of hippocampal function and might indicate that involving the recollection process under a 'hippocampal intact' condition simultaneously decreases the contribution of familiarity to memory performance by affecting LEC function. Altogether, these data give further support to the claim that the PER and the LEC support familiarity and not the hippocampus.

Sleep supports memory systems consolidation between the hippocampus and parietal cortex

Steffen Gais

Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany

The flexibility and stability of our memories has long been hypothesized to rely on interacting learning systems. A fast learning system in the hippocampus provides the ability for fast encoding while neocortical memory traces are thought to develop gradually and ultimately enable stable long-term memory. However, over learning repetitions, there is also the rapid emergence of a posterior parietal cortex (PPC) memory representation that develops while memory becomes increasingly independent of the hippocampus. Another factor that benefits memory systems consolidation is sleep. During sleep, memories are reactivated, leading to improved memory storage and later recall. Such reactivation might also provide the stimulation required to trigger systems memory consolidation in sleep. In several experiments, we tracked changes in brain activity with fMRI during the learning of several declarative memory tasks over learning repetitions and during recall after a following interval of wakefulness or sleep. We found a fast transition of memory systems contributions over repeated rehearsals. Hippocampus and medial prefrontal cortex (mPFC) activity decreased over repetition, PPC activity increased, in particular in the precuneus. Here, we demonstrate that this transition is stabilized over sleep, whereas wakefulness leads to a reset to naïve responses, such as observed during early encoding. The role of sleep seems therefore to go beyond providing additional rehearsal through memory trace reactivation, as previously thought. We conclude that repeated study induces systems consolidation while sleep ensures that these transformations become stable and long lasting. Thus, sleep and repeated rehearsal jointly contribute to long-term memory consolidation.

A fast track to the neocortex: long-term memory representations in the parietal cortex

Monika Schönauer

Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany; Max-Planck-Institute for Biological Cybernetics, Spemannstr. 41, 72076 Tübingen, Germany

Traditional models of systems memory consolidation postulate two interacting memory stores, with rapid encoding of new information supported by the hippocampus and a gradually developing, stable storage in neocortical circuits. Recently, the posterior parietal cortex (PPC), particularly the precuneus, has been proposed as a cardinal location of neocortical long-term memory. We have shown functional activity in this area over repeated learning that is memory specific, long-term stable and related to memory accuracy. To conclusively identify the PPC as a location of memory storage, learning-contingent, lasting structural changes have to be demonstrated as well.

Here, we used diffusion MRI to assess changes in brain microstructure, which reflect neuronal plasticity. 41 participants learned object-place associations over 8 learning-recall repetitions in two sessions. Task-related activity was tracked with fMRI. Structural changes were assessed with dMRI at three time points (before, 90 minutes and 13 h after learning). A non-learning condition measured at the same times was employed as control.

Functional PPC activity increases with learning repetitions, remains stable over a 13-h period and strongly correlates with recall performance. Furthermore, decreases in mean diffusivity indicate structural changes in the same area, which also develop after learning, remain stable for over 12 hours and correlate with behavioral performance.

We thus show functional and structural changes in the PPC that fulfill all requirements for a neocortical long-term memory representation: learning specificity, long-term stability and behavioral relevance. The confirmation of structural plasticity in particular proves the importance of the PPC as a site of neocortical memory storage.

Single-unit and oscillatory activity of the claustrum during sleep

Christopher M Dillingham

Trinity College Institute of Neuroscience, Trinity College Dublin, College Green, Dublin, Ireland

The claustrum is a elongated, subcortical nucleus that exhibits dense connectivity across the extent of the cortical mantle. Through these connections, it is thought to orchestrate cortical activity in a task and/or arousal-dependent manner.

Simultaneous single-unit and local field potential (LFP) recordings in the claustrum, alongside one or more cortical areas (anterior cingulate, retrosplenial) and/or the hippocampal formation revealed a dominant population of claustral units that exhibited a firing pattern which was preferentially-entrained to the down-state of delta-oscillations during slow-wave sleep. The same population of units showed no phase preference during wakefulness or paradoxical sleep but high levels of theta-entrainment during epochs of high-voltage spindle oscillations (HVS) that were observed during periods of wakeful immobilisation, and in the transistion fom wakefulness and slow-wave sleep. Claustral LFP recordings revealed high delta-band oscillatory coherence with both the retrosplenial cortex and the hippocampus during slow-wave sleep as well as high theta-band coherence during HVS.

While the role of HVS in the context of memory consolidation is unconfirmed, considerable evidence supports such a role for cortical slow-wave delta-oscillations. In light of the present findings, we propose a role for the claustrum in the coordination of cortical slow wave activity, potentially though the down-state inhibition of cortical unit activity.

Effects of tau and amyloid deposition on domain-specific memory function in old age

Anne Maass[1,2], David Berron[2,3], Theresa Harrison[1], Suzanne Baker[4], Jenna Adams[1], Taylor Mellinger[1], Rachel K. Bell[1], Kaitlin Swinnerton[1] , Emrah Duezel[2,3], William J. Jagust[1,4]

[1]University of California, Berkeley, Berkeley, CA, United States; [2]German Center for Neurodegenerative Diseases, Magdeburg, Germany; [3]Institute for Cognitive Neurology and Dementia Research, Magdeburg, Germany; [4]Lawrence Berkeley National Lab, Berkeley, CA, United States

Processing of spatial and object information relies on posterior-medial (PM) and anterior-temporal (AT) systems that converge in the hippocampus. Tau pathology in the temporal lobe (esp. transentorhinal cortex) is common by age 60 and can now be measured in vivo with PET. We tested how tau and Aβ deposition relate to object vs. scene memory function in old age.

Fifty cognitively normal older adults (OA; 78±6yrs) and 25 young adults (YA; 26±4yrs) performed a mnemonic discrimination task developed by Berron et al. (2018) that poses high demands on memory precision and dissociates object vs. scene memory. High-resolution fMRI data were acquired at 3T while subjects performed the task (1.5mm^3 isotropic resolution, whole brain). In OA, Aβ burden was measured with [^{11}C]PiB PET and tau accumulation with [^{18}F]AV-1451 PET.

OA performed worse than YA across both domains as reported previously. There was no relationship between Aβ and domain-specific memory performance. However, higher tau PET measures in AT regions were related to relatively worse object than scene memory. Initial whole brain analyses on domain-specific activation showed altered activation in several regions for OA with higher tau PET measures. Our data suggest that OA with high temporal lobe tau show a tendency towards worse object recognition memory relative to scenes. While our data did not reveal evidence for a specific effect of Aβ on scene memory performance, this could be present in later stages of AD. Subsequent analyses will delineate effects of Aβ and tau measures on MTL subregional activation.

Spatial information is preferentially processed by the distal part of CA3: implication for memory retrieval.

Atucha[1] and Flasbeck[4], Nakamura NH[3], Yoshida M[1], Sauvage MM[1,2,3]

[1]Leibnitz-Institute for Neurobiology, Magdeburg, Germany; [2]Otto-von-Guericke University, Medial Faculty, Functional Neuroplasticity Dept., Magdeburg, Germany; [3]Otto-von-Guericke University, Center for Behavioral Brain Sciences, Magdeburg, Germany; [4]Ruhr-University, Bochum, Germany

For the past decades, CA3 was considered as a single functional entity. However, strong differences between the proximal (close to the dentate gyrus) and the distal (close to CA2) parts of CA3 in terms of connectivity patterns, gene expression and electrophysiological properties suggest that it is not the case. We recently showed that proximal CA3 (together with distal CA1) preferentially deals with non-spatial information [1]. In contrast to proximal CA3, distal CA3 mainly receives and predominantly projects to spatially tuned areas. Here, we tested if distal CA3 preferentially processes spatial information, which would suggest a segregation of the spatial information along the proximodistal axis of CA3. We used a high-resolution imaging technique based on the detection of the expression of the immediate-early gene Arc, commonly used to map activity in the medial temporal lobe. We showed that distal CA3 is strongly recruited in a newly designed delayed nonmatching-to-location task with high memory demands in rats, while proximal CA3 is not. These results indicate a functional segregation of CA3 that mirrors the one reported in CA1, and suggest the existence of a distal CA3- proximal CA1 spatial subnetwork. These findings bring further evidence for the existence of 'specialized' spatial and non-spatial subnetworks segregated along the proximodistal axis of the hippocampus and put forward the 'segregated' view of information processing in the hippocampus as a reasonable alternative to the well-accepted 'integrated' view, according to which spatial and non-spatial information are systematically integrated in the hippocampus to form episodic memory.

HIPP neurons in the dentate gyrus mediate the cholinergic modulation of background context memory salience

Anne Albrecht[1,2], Syed Ahsan Raza[1], Gürsel Çalışkan[1], Bettina Müller[1], Yunus Emre Demiray[1], Susann Ludewig[1], Susanne Meis[3], Nicolai Faber[4], Roland Hartig[5], Burkhart Schraven[5], Volkmar Lessmann[2, 3], Herbert Schwegler[2,4], Oliver Stork[1,2]

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During Pavlovian fear conditioning background context memory is acquired in the presence of elemental stimuli for predicting an aversive event. Altered background context conditioning has been implicated in a disturbed specificity of trauma-related memories and their associated intrusive re-experiencing in posttraumatic stress disorder. While cumulative evidence points out a pivotal role of the hippocampal formation and its cholinergic modulation in these processes, the local circuits underlying this phenomenon are unknown. With pharmacogenetic inhibition, we here demonstrate that hilar perforant path-associated (HIPP) cells of the dentate gyrus mediate the devaluation of background context memory during auditory-cued Pavlovian fear conditioning. The salience adjustment is sensitive to reduction of hilar neuropeptide Y (NPY) expression via dominant negative CREB expression in HIPP cells and to acute blockage of NPY-Y1-receptors in the dentate gyrus during conditioning. We show that NPY transmission and HIPP cell activity contribute to inhibitory effects of acetylcholine in the dentate gyrus and that M1 muscarinic receptors mediate the cholinergic activation of HIPP cells as well as their control of background context salience. Our data provide evidence for an adaptive local circuit in the dentate gyrus that utilizes NPY to mediate the cholinergic encoding of background context salience during fear memory acquisition.

How hippocampal Fimbria-Fornix-stimulation affects the dopaminergic mesolimbic system of the rat brain

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The hippocampal formation in combination with the mesolimbic dopaminergic system plays important roles for the consolidation of learning directed processes. Electrical stimulation of one major hippocampal output system, the fimbria-fornix fibers, in combination with functional magnetic resonance imaging (fMRI) or fast scan cyclic voltammetry (FSCV) revealed that certain hippocampal activity drives mesolimbic dopaminergic activity. To examine how variations in hippocampal output activity affect global functional connectivity, fMRIBOLD changes were measured during electrical stimulation of fimbria-fornix fibers (FF). To monitor, how hippocampal output activity drives the mesolimbic dopamine system, we additionally measured dopamine release in one of the target areas of the ventral tegmental area/substantia nigra (VTA/Sn), the nucleus accumbens (NAcc), during stimulation of hippocampal FF with bursts of high-frequency pulses (5 or 20 pulses with an inter-pulse interval of 10 ms) or continuous low frequency (5Hz or 20 Hz) pulses. Dependent on the stimulation protocol, significant BOLD responses were observed in the right hippocampus, entorhinal cortex, vertical limb of the dorsal band (VDB), amygdala or in septal areas. BOLD responses were also detected in the mesolimbic circuit, in particular in the NAcc, the medial prefrontal cortex and VTA/Sn. Dopamine release in the NAcc could be detected during all tested stimulation protocols. These results clearly indicate that hippocampal output activity via the fimbria-fornix system effectively activates the dopaminergic mesolimbic system. The findings also demonstrate that hippocampal output activity activates different neuronal networks dependent on the prevailing frequency.

The low-threshold calcium channel Cav3.2 mediates burst firing of mature granule cells of the dentate gyrus

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The dentate gyrus is the first relay station of the hippocampal trisynaptic loop and is a key structure in many hippocampus-dependent learning tasks. Mature granule cells of the dentate gyrus rarely fire action potentials *in vivo*. They should therefore ensure a very efficient transmission of information to the next synaptic relay station: the CA3 area. We have found that the T-type calcium channel subtype Cav3.2, at the axon initial segment of mature granule cells, controls the efficacy of the dentate-to-CA3 communication by influencing the pattern of action potentials elicited by mature granule cells. In animals with reduced functionality of T-type channels, mature granule cells fire tonic spikes, while with intact T-type channels they do it more often in bursts. This burst firing mode, in turn, modulates the synaptic plasticity of mature granule cells and their probability to fire the postsynaptic CA3 pyramids. We propose that due to the low basal excitability of mature granule cells, their bursting capability is a crucial element for their physiological function.

Synaptic plasticity at single cell level: Diversity along hippocampal axes

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The hippocampal CA1 region is critically involved in learning and memory. Synaptic plasticity measured as long-term potentiation or depression in the CA1 circuitry is an accepted model underlying these processes. Several lines of experimental evidence suggest that the hippocampus exerts a multitude of different functions, which are executed by distinct hippocampal sub-regions (e.g. dorsal or ventral hippocampus). In this regard, several gradients in neuromodulation and connectivity along different hippocampal axes are described.
We focus on differences of synaptic plasticity along the longitudinal and radial gradients in the hippocampus. We employ different spike timing-dependent plasticity (STDP) protocols to assess synaptic plasticity mechanisms and underlying neuromodulation at the level of a single postsynaptic neuron. Our results show that distinct types of synaptic plasticity at Schaffer collateral–CA1 synapses can be generated and can be executed either independently or in a synergistic fashion depending on the employed STDP protocol. It is known that, neuromodulators and mediators significantly modulate hippocampal synaptic plasticity. Therefore, we now test for region-specific effects of these modulators in STDP.
Our current data suggest, that different information can be stored at defined parts along the proximo-distal extension of the dendritic tree, depending on the availability of stored mediators, modulatory inputs and the employed STDP paradigm. Our data reveal that the synaptic communication can be strengthened or weakened in a very distinct way regarding activated signaling cascades and expression patterns. These findings will help to understand the manifold ways, how the brain can store information during learning and memory processes.

The synapto-nuclear messenger Jacob alters nucleolar dynamics to facilitate protein synthesis in plasticity

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Jacob is a protein messenger that encodes and transduces the synaptic and extrasynaptic origin of GluN2Bcontaining
NMDA receptors (NMDARs) to the nucleus and couples NMDARs activity to CREB-dependent geneexpression (Karpova et al., 2013). Nuclear import of Jacob following activation of extrasynaptic NMDARs leads to long-lasting dephosphorylation of CREB, loss of dendritic arborization and possibly cell death. Vice versa, following activation of synaptic NMDARs Jacob induces plasticity related and CREB-dependent gene expression.
The nuclear functions of Jacob are, however, not very well investigated. Yet unpublished data show that, once in the nucleus, Jacob localises to nucleoli in hippocampal or cortical neurons. Nucleoli are sub-nuclear compartments where ribosomal RNA (rRNA) and pre-ribosomal subunits assembly take place. Decreased rRNA synthesis and nucleolar disruption are primary signs of cell stress associated with aging and neurodegenerative diseases (Pietrzak et al., 2011; Lee et al., 2014). Enhanced neuronal activity results in the nuclear translocation of Jacob and the synaptic protein AIDA-1d. AIDA-1d is known to increase protein synthesis by controlling nucleolar number and thereby regulating processing and maturation of rRNA (Jordan et al., 2007). Here we show that Jacob and AIDA-1d associate and co-localize in the nucleus. We propose that Jacob, possibly in association with AIDA-1d, links synaptic activity and control of *de-novo* protein synthesis, which is essential in the consolidation of long-term memory, by regulating nucleolar assembly.

Conditional mutants for the presynaptic protein Bassoon display distinct changes in learning and memory

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Bassoon, a large scaffolding protein present at the cytomatrix at the active zone (CAZ) of neurotransmitter release at excitatory, inhibitory and modulatory presynapses, involved in the development of presynaptic terminals and in the regulation of neurotransmitter release at both excitatory and inhibitory brain synapses. A previous study has shown that Bassoon is down-regulated upon auditory cortex-dependent learning. Its involvement in homeostatic plasticity, synapto-nuclear communication and presynaptic autophagy has been reported. Constitutive Bassoon-mutant mice develop seizures and display impaired presynaptic function and sensory impairments. We have generated two conditional Bassoon mutants, one lacking the protein in excitatory synapses of the forebrain (*B2E cKO*) and another one lacking the protein at dopaminergic release sites (*B2D cKO*), to study the role of Bassoon in learning and memory processes. We show that *B2E cKO* mice, when compared to the WT mice, display enhanced hippocampus-dependent background contextual fear memory and hyperactive behavior in home cage activity test. Interestingly, *B2D cKO* mice only display hyperactive behavior in home cage activity test, specifically during dark phase. Further analysis of *B2E cKO* mice revealed an enhanced performance compared to WT mice in a dentate gyrus (DG)-mediated pattern separation task. Indeed, lack of age-dependent decrease in excitability at MPP-DG and alterations in the expression of cellular maturation markers suggest an immature phenotype of the DG and augmented neurogenesis in *B2E cKO* mice. Taken together, this study suggests that Bassoon expression in excitatory neurons is important for normal maturation of DG and DG-mediated memory formation.

This work was supported by the DFG-CRC 779 to A.F., W.T., E.D.G., O.S.

It´s in the timing, …

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Obtaining rewards and avoiding punishment are evolutionarily deep goals of behavior. Strikingly, however, current research neglects half of the processes through which rewards and punishments affect behavior, learning, and memory. That is, we certainly can learn predictors of the OCCURRENCE of rewards and punishment, and past research as provided detailed insight into these processes. However, it is drastically understudied how we learn about the TERMINATION of reward and punishment. For example, reward occurrence feels good but reward termination feels bad. This results in appetitive and aversive learning, respectively, of cues associated with these experiences. Conversely, receiving punishment *vs* being relieved from it supports aversive and appetitive learning. Thus there are four, and not just two, types of predictive relation between stimuli and reinforcement (reviewed: Gerber et al 2014 Learn Mem). Exploiting that in *Drosophila* single, identified dopamine neurons (DANs) can be non-invasively activated by optogenetics we show that activation of the DAN named PPL1-01 neuron is sufficient to mediate memories of opposing valence– dependent on the timing of its activation (König et al in press Learn Mem, Saumweber et al 2018 Nat comm). Presenting an odor before DAN activation resulted in learned odor avoidance, while presenting the odor upon termination of DAN activation resulted in learned odor approach. Thus, DANs do not in themselves code valence.

Pupil constriction predicts recognition memory performance in children

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The ability to remember specific past events in time and place (episodic memory) significantly develops from infancy to adolescence. Much knowledge about the neuronal mechanisms of memory was gained from methods not suitable for healthy kindergarten and elementary school-age children. We therefore applied pupillometry to study memory encoding and recognition mechanisms in children. Nine-year-old children (N=24) and an adult control group (N=24) memorized a set of visual scenes to later distinguish them from new pictures in a retrieval phase. Children performed worse than adults. We identified three components contributing to changes in pupil diameter, which were associated with the activity of the parasympathetic (including light reflex) and sympathetic pathways of the autonomic nervous system. During memorization, pictures that were later recognized successfully, elicited a stronger pupil constriction than pictures later forgotten. This was observed for all components and both age groups. During retrieval, novel pictures showed increased pupil constriction compared to familiar pictures in both age groups for the component related to sympathetic nervous system activity. This so-called pupil old/new effect was observed for objectively familiar vs. novel pictures as well as for subjectively familiar vs. novel pictures; that is, when participants believed that a picture was familiar or novel. Interestingly, the effects of objective vs. subjective familiarity were statistically independent suggesting dissociable underlying brain mechanisms. Our results provide a promising base for future research on the development of episodic memory using psychophysiological methods that are suitable even for young children.

Modelling recognition memory as a decision process based on generic memory Modules

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Many of the existing computational models of recognition memory follow the well-accepted dual-process framework. The central idea of the dual-process approach is that recognition judgments arise from recollection and familiarity, two qualitatively different and specialized memory processes that are thought to be supported by hippocampus and perirhinal cortex, respectively. We propose an alternative account of recognition memory, which is both parsimonious and in accordance with a wide range of empirical findings. Our approach posits that recognition memory is a decision making process relying on information retrieved from general-purpose memory systems. Importantly, the memory stores in our model use the same retrieval mechanism.The memory stores differ in their ability to perform pattern separation, by which similar inputs are mapped to dissimilar representations. Since receiver operating characteristic (ROC) analysis has emerged as a customary tool to study recognition memory, we use this method to assess the performance of our model. We show that the two well-known features of recognition ROC-curves,curvilinearity and asymmetry, need not arise from two different processes, as suggested by dual-process models. Instead, our results suggest that improved retrieval of stored items in systems with pattern separation is sufficient for the emergence of asymmetric ROC-curves. In addition, the model is capable to account for the influence of multiple factors on the shape of the ROC-curves, such as input statistics, hippocampal lesions, list length, noise as well as the stimulus pairing in associative recognition.

Thermal implications of optogenetic brain stimulation for learning research

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Optogenetic stimulation is a crucial tool to investigate the neural circuits underlying learning. It is often used to demonstrate necessity of circuit elements by cell-type specific silencing of these elements. However, illumination of the brain leads to deposition of heat in the tissue, potentially reaching damaging levels or influencing firing rates. For example, planned inhibition can turn into excitation by an increase in tissue temperature and subsequently raised baseline activity of nearby neurons. Particularly for learning research, where often large tissue volumes are illuminated, it is critical to estimate safe levels of irradiance. While modelling has been used as a tool to theoretically determine such safe levels, here we use infrared thermography to show that such modelling can strongly underestimate real-world heating due to insufficient capture of hemoglobine-related effects. In addition, we present an online tool to estimate brain heating based on values derived from in-vivo measurements.

Unleashing the full potential of high-field MRI

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One driving force behind ultra-high field MRI is the realization of higher spatial resolution in anatomical and functional imaging. Frequently the resolution is not limited by hard- or software but by the ability of the subject to remain still, particularly for high resolution and long scan times. Head motion can thus dramatically reduce the achievable effective image resolution. A number of methods have been proposed to account for rigid body motion of the head. We have developed an optical motion tracking system and real-time prospective correction that enables correction of head motion during the acquisition without further modifications of the image reconstruction. The technology allowed the acquisition of the highest resolution in vivo human brain data to date and enables researchers to approach the nominal image resolution in human brain studies.

Functional Architecture of Memory Conference

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Invited Talks

Deconstructing episodic memory: What, Where, and When

Michael A. Yassa

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Memory is the bridge to our past and future. Without memory, we would be stuck in a constant present, unable to learn from our experiences and unable to plan for the future. Memory loss can have catastrophic impact on life and livelihood. Diseases that rob individuals of their memory capacity, such as Alzheimer's disease, place a tremendous burden on individuals, families, and global public health. This talk will discuss our approach to understanding the neural mechanisms underlying episodic memory (memory for 'what', 'where' and 'when'), and how this approach is informed by animal and computational models. I will highlight recent advances in determining the functional division of labor in the medial temporal lobes using a combination of targeted behavioral paradigms for what, where and when memory and high-resolution functional MRI. This fundamental understanding is then applied to examining memory in older adults and assessing susceptibility to Alzheimer's disease, providing potential avenues for clinical intervention.

Hippocampal TRPC channels support temporal bridging

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Persistent firing is believed to support temporal bridging tasks such as working memory and trace conditioning. Although recurrent synaptic excitation is widely believed to support persistent firing, recent studies have established that neurons can support persistent firing through an intrinsic cellular mechanisms. Here, I will demonstrate that individual hippocampal pyramidal cells support persistent firing under cholinergic receptor activation through the transient receptor potential-canonical (TRPC) channels. In contrast, this persistent firing is suppressed by noradrenaline (NA) and serotonin (5HT) through cAMP elevation, which is in line with impaired working memory in high NA and 5HT. Based on these, mice with hippocampal TRPC5 channel knockout (KO) were tested in a trace-fear conditioning task, which requires temporal bridging. TRPC5 KO mice were strongly impaired in trace-fear conditioning suggesting that hippocampal TRPC channels support temporal bridging function in vivo.

Event Representation and Episodic Memory

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Although it is well established that the hippocampus supports episodic memory, studies of hippocampal function in animal models and in humans typically do not capture many of the attributes of real-life events. In particular, we know that people parse experiences into discrete events that have a temporal structure and meaning that transcends any particular item or spatial context. I will present research showing how the hippocampus and parietal regions mediate the influences of event structure on memory, and I will present new work showing how this process may be influenced by memory consolidation.

Imaging memory traces over half a life-time in the medial temporal lobe - a network shift?

Magdalena Sauvage

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Whether retrieval still depends on the hippocampus as memories age or relies then on cortical areas remains a major controversy. Despite recent evidence for a functional segregation between parahippocampal cortical areas and between hippocampal subfields, their specific role within the frame of memory retrieval remains unclear. Especially, the contribution of the hippocampal subfield CA3 to the retrieval of very remote memories is questionable as cues used for 'pattern completion' are likely to be so degraded at this time point that pattern completion might no longer contribute to memory retrieval. We investigated the role of CA1, CA3, LEC, MEC, PER and POR by imaging brain activity in mice during the retrieval of recent to very remote memories (i.e. memories comparable to 40 year-old human memories) by detecting the immediate-early gene Arc (Lux et al, Elife, 2017). In addition, we are currently investigating the specific memory content CA1 and CA3 support by combining behavioral and optogenetics techniques and modelling information processing in the MTL as memory age. Our results show that at least part of the hippocampus is engaged in retrieving even very remote memories and put forward a new concept of 'network shift' between the trisynaptic loop and the temporoammonic pathway over time. This concept is currently tested using EC layer specific mutant mice in collaboration with S. Tonegawa (MIT, USA), 7T fMRI techniques in humans with E. Duezel (DZNE Magdeburg) and memory tasks devoid of fear components.

Brain Networks involved in recent and remote fear memory

Paul Frankland

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While memories for events may initially depend on the hippocampus, over time they are reorganized in the cortex for long-term storage. Our studies have 1) identified plastic processes necessary for cortical memory consolidation, 2) identified brain regions necessary for their retrieval at remote time points and 3) studied how changes in organization affect memory quality. In addition, we have developed activity-dependent gene mapping and graph theoretical approaches to identify brain-wide networks engaged in memory recall at both recent and remote time points. Using chemogenetic neuronal silencing, we recently showed that hub brain regions within these networks disproportionately influence memory consolidation.

The nucleus reuniens of the thalamus, a key pillar in the architecture of recognition memory

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Successful judgement of the prior occurrence of a stimulus may be achieved by remembrance of a stimulus and its associated information, such as the location in which the stimulus was previously encountered. We have shown previously that object-in-place associative recognition memory in rodents depends on a brain wide neural network in which the hippocampus (HPC) and medial prefrontal cortex (mPFC) are key regions. Both the HPC and mPFC have bidirectional connections with the nucleus reuniens of the thalamus (NRe). Here I present data from in my lab which demonstrate: firstly, that the NRe plays a selective role in the encoding and retrieval of long-term, but not short term associative recognition memory; and secondly that the encoding of such long-term memory is dependent on cholinergic neurotransmission and protein synthesis within the NRe. Finally, I will present a series of experiments in which we have utilise optogenetic and pharmacogenetic techniques to dissociate the neural pathways between the NRe, HPC and PFC that mediate object-in-place recognition memory formation. These experiments show that different NRe-HPC and NRe-mPFC pathways convey associative recognition memory information during encoding and retrieval. We propose therefore that the NRe is a crucial node within a recognition memory network, and that that this region does not act as a simple relay but rather interacts directly with the HPC and PFC and indeed may act as an important facilitator of HPC-mPFC interactions.

A reappraisal of parallel 'what' and 'where' pathways in the MTL-memory system, mediated by the lateral and medial entorhinal cortex.

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The medial temporal lobe memory system comprises the hippocampal formation (HF) and the parahippocampal region. The latter comprises the lateral and medial entorhinal cortex as well as the perirhinal and parahippocampal (primates) or postrhinal (rodents) cortex. The current, generally accepted organizational scheme is that the postrhinal-medial entorhinal complex conveys spatial information to HF, whereas the perirhinal-lateral entorhinal complex conveys information concerning objects or events to HF. Notwithstanding the fact that perirhinal and postrhinal cortex have interconnections, as do lateral and medial entorhinal cortex, the convergence between the two pathways is considered to take place at the level of HF circuitry.
In my talk, I will present recently obtained anatomical and electrophysiological data in rodents indicating that the two pathways actually show a strong convergence already at the level of the entorhinal cortex, before the information enters HF. Whereas the medial entorhinal projections to HF, in line with the current notion, likely carry spatial information, the lateral entorhinal projections likely provide more complex data to HF.

Egocentric vs. allocentric coding in the lateral and medial entorhinal cortex

James J. Knierim

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The lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) provide the major inputs to the hippocampus, which plays an essential role in spatial and episodic memory. The MEC is thought to function as as allocentric spatial representation that encodes the context of a memory. Much less is known about the function of the LEC. We investigated whether other behavioral variables, e.g. head direction, can modulate the firing of the LEC neurons. We recorded from the LEC and the MEC while the subjects foraged in open arenas or in a goal-directed task. Many LEC neurons showed egocentric bearing selectivity and/or distance tuning relative to the center of the box or the goal. In contrast, MEC neurons were more likely to encode allocentric head direction. These results demonstrate a novel functional dissociation between the LEC and the MEC. We suggest that the "content" of a memory is encoded by LEC neurons in an egocentric (self-referenced) frame of reference, whereas the spatial context of a memory is encoded by MEC in an allocentric (world-centered) frame of reference. The egocentric coding of LEC is consistent with its hypothesized role of providing the "content" of an episodic memory, as the most recent and vivid recollections of past experiences often preserve a person's original (egocentric) perspective. This functional segregation of egocentric vs. allocentric information may reflect a fundamental organizing principle of the medial temporal lobe memory system.

Effects of Age and Alzheimers's Pathology on Mnemonic Discrimination of Objects and Scenes in Medial Temporal Lobe Pathways

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Subregions in the medial temporal lobe (MTL) are differentially involved in memory for objects and scenes and also differentially affected by Alzheimer's disease (AD). However, it is unclear whether object or scene memory is affected earlier in ageing and preclinical AD. I will present data from a novel mnemonic discrimination task where individuals had to discriminate similar versions of objects and scenes. In a first functional magnetic resonance imaging (fMRI) experiment in young adults, we found that object and scene discrimination each rely on different MTL pathways. In the following experiment including healthy older individuals, we found that while young individuals showed a clear dissociation of object and scene related activity in the perirhinal cortex, older individuals showed a significant reduction which was associated with reduced object discrimination performance. In order to test whether AD pathology is associated to domain-specific memory impairment in older individuals, we investigated the relationship of phosphorylated Tau (p-Tau) levels on memory function and MTL BOLD activity in cognitively normal older adults from the DELCODE study. Here we could replicate the relationship of an imbalance in domain-specific activity in the transentorhinal region and reduced object discrimination performance. In addition, p-Tau levels were associated to hippocampal hyperactivity and reduced object memory performance. Our findings demonstrate that the object pathway is affected predominantly in ageing and that tau pathology is associated to impairment in object but not scene memory. However, a longitudinal approach will be necessary to further understand the time course of object and scene memory impairment.

Spatial and Memory Computations in the Medial Entorhinal Cortex and Hippocampus

Stefan Leutgeb

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The hippocampus and entorhinal cortex are at the core of a circuit for the formation and retrieval of episodic and spatial memories. After the discovery of grid cells in the medial entorhinal cortex, the prevalent hypothesis has been that the grid cell area within the entorhinal cortex primarily codes for space and is critical for context discrimination. We tested this hypothesis and found that the medial entorhinal cortex is not necessary for disambiguating between different environments, but primarily contributes to the stability of spatial coding over extended time. Furthermore, we also found that the medial entorhinal cortex is required for generating precisely timed neuronal activity on the time scale of theta oscillations. We then asked whether these impairments in spatial and temporal coding are critical for spatial working memory and found memory impairments with medial entorhinal cortex lesions that were as substantial as after hippocampal lesions. However, working memory performance partially recovered when either the hippocampus or medial entorhinal cortex remained intact, while combined lesions of the hippocampus and medial entorhinal cortex resulted in a persistent memory impairment. To identify neuronal circuit mechanism for the recovery of function after medial entorhinal cortex lesions, we performed hippocampal recordings in the spatial working memory task and show that retained spatial coding in CA3 substantially contributes to the preserved hippocampal function. Inputs to hippocampus from sources other than the medial entorhinal cortex are therefore sufficient to at least partially support and restore hippocampal spatial and temporal coding.

Hippocampal reactivation during spatial memory tasks

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In the first part I present result that demonstrate the direct involvement of goal-specific reactivation in the stabilisation of spatial memories. To this end we have developed a method that involved the online identification of cell assemblies and the optogenetic disruption of a selective subgroup of them during reactivation. We trained animals to locate goals in two different environmental context (i.e. two cheeseboards at different location with different distal cues), with each associated with a different goal location. After learning we disrupted the reactivation of assemblies representing one of the goals using our online assembly detection procedure during rest/sleep. Following the disruption, we observed a selective memory impairment of the disrupted goal but not the other. Altogether, these results suggest that reactivation of learned goals during sleep has a role in in the consolidation of spatial memories.

The second part covers the results of another project where we examined waking reactivated trajectories during three different radial 8-arm maze spatial tasks. We found that waking reactivated trajectories at the decision point in the central stem of the maze predicted the future arm choice of the animal when the task had a reference memory component but not when it was a pure working memory task. This work suggests that waking trajectory reactivation is involved in decision making in a spatial task when a reference memory is needed to be recalled.

The Physiology of the Hippocampal Engram

Thomas McHugh

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Episodic memories are encoded by a sparse population of hippocampal neurons. In mice optogenetic manipulation of this memory “engram” established these neurons are necessary and sufficient for memory recall. However, little is known about their in vivo activity or precise role in memory. Using tetrode recordings and optoID approaches in cFos-tTA mice we have found that during memory encoding only a fraction of the CA1 place cells are engram neurons. This subset of cells can be distinguished by firing repetitive bursts paced at the theta frequency, a pattern effective in strengthening synapses. Surprisingly, during memory recall these neurons remained highly context specific, yet demonstrated preferential spatial remapping of their place fields. These data demonstrate a dissociation of precise spatial coding and contextual indexing by distinct hippocampal ensembles and suggest the hippocampal engram serves as an index of memory content.

Functional and structural organization of the medial temporal lobe following neonatal hippocampal lesion in monkeys

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We have previously shown that hippocampal lesion in adult monkeys prevents allocentric spatial relational learning, whereas spatial learning persists following neonatal lesion. In a first study, we quantified the number of cells expressing the immediate-early gene c-fos, a marker of neuronal activity, to characterize the functional organization of the medial temporal lobe memory system following neonatal hippocampal lesion. In unlesioned monkeys, we found high levels of c-fos expression in the intermediate and caudal regions of the entorhinal cortex, and in the perirhinal, parahippocampal, and retrosplenial cortices. In lesioned monkeys, spatial exploration induced an increase in c-fos expression in the intermediate field of the entorhinal cortex, the perirhinal, parahippocampal, and retrosplenial cortices, but not in the caudal entorhinal cortex. These findings suggest that different regions of the medial temporal lobe memory system may require different types of interaction with the hippocampus in support of memory. The caudal perirhinal cortex, the parahippocampal cortex, and the retrosplenial cortex may contribute to spatial learning in the absence of functional hippocampal circuits, whereas the caudal entorhinal cortex may require hippocampal output to support spatial learning. In a second study, we quantified the number of cells expressing Bcl2, a marker of immature neurons, to characterize the possible structural changes of medial temporal lobe structures following hippocampal lesion. We showed that neonatal hippocampal lesion increased the number and/or differentiation of immature neurons in the perirhinal cortex and the amygdala. Such lesion-induced plasticity may shed new light on potential mechanisms that may facilitate functional recovery following brain injury.

Mechanisms of navigational decline in old age

Thomas Wolbers

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While decades of research into cognitive aging have focused on functions such as memory and attention, spatial navigation has been understudied. This is surprising because key structures of the brain's navigation circuit are particularly vulnerable to the deleterious consequences of aging. In addition, deficits with spatial orientation are often among the first noticeable symptoms in patients with Alzheimer's Disease. Given the recent breakthroughs in understanding the cellular components of basic navigational circuits in rodents and non-human primates, we are now in the position to identify changes in the navigation network that occur as a result of normative aging processes and specific neuropathological conditions.
In this talk, I will first present functional neuroimaging studies that have identified key navigational computations in the human brain. In the second part, I will outline recent studies that have begun to elucidate age-related changes in navigational processing, using novel paradigms that target specific spatial computations. Importantly, these studies also offer novel insights into general mechanisms of brain ageing that could affect processes beyond the spatial domain. Finally, I will conclude with a discussion on how navigational indicators could (i) aid early detection of neuropathological conditions, (ii) be sensitive markers of treatment-related improvement or disease-related decline, and (iii) support behavioral interventions to maintain cognitive wellbeing.

Navigating social behavioral space through the hippocampal CA2 region

Steven Siegelbaum

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Although hippocampus is well known to play a central role in declarative memory, it has also been implicated in motivated behaviors, such as feeding, mating and aggression. Is the mnemonic function of hippocampus responsible for regulating motivated behaviors or are circuits distinct from those involved in memory recruited? We have focused on the CA2 subregion of the hippocampus, a relatively small and understudied area located between CA3 and CA1 that has been difficult to study using conventional lesioning. We developed a genetic approach to examining CA2 by generating an Amigo2-Cre line that allows for selective expression of genetically encoded tools and sensors in CA2 pyramidal neurons. Our previous results using genetic silencing of CA2 through tetanus toxin expression revealed that dorsal CA2 is critical for social memory, the ability of an animal to recognize and remember a conspecific. Our more recent findings show that dorsal CA2 also promotes social aggression. Circuit tracing and targeted silencing of CA2 output paths demonstrate that social memory is mediated by dorsal CA2 projections to regions of ventral CA1 that project to the nucleus accumbens. In contrast we find that CA2 promotes social aggression by sending outputs to lateral septum, which trigger a disynaptic disinhibitory circuit that enhances activation of ventro-medial hypothalamus, a region known to promote aggression. Thus distinct CA2 intra- and extra-hippocampal circuits selectively control social memory versus social aggression.

Functional Architecture of Memory Conference

May 23rd – 25th 2016

Recreational Info

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