LIN

LEIBNIZ INSTITUTE
FOR NEUROBIOLOGY
MAGDEBURG

Research Magazine
Edition 2020/21

NEWS FROM OUR RESEARCH

Our vision:
Making brain processes understandable

s. 20
Before the plaques come

s. 40
In Rain Man´s synapses

s. 63
Somewhere else with your mind

RESEARCH MAGAZINE 2020/21

Mitglied der
Leibniz
Gemeinschaft

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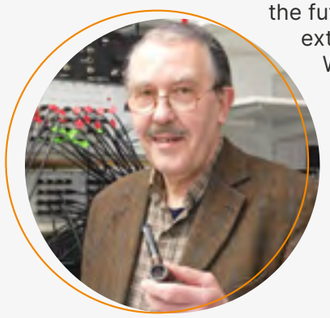
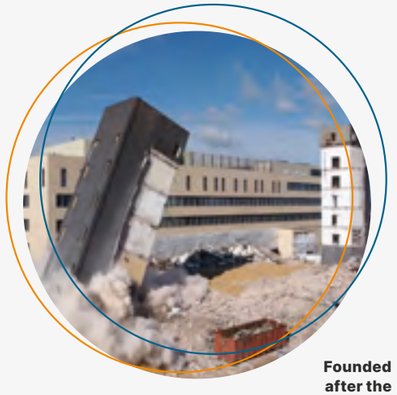
LIN Turns 30



From the memory perspective, the present is always the past - as soon as you think about it. Paradoxically the future is also mainly extrapolation from memory. Without experience we could say nothing meaningful about the future.

Prof. Dr. Henning Scheich (Founding Director, 1992 – 2010)



Founded after the reunification:

The LIN emerged from the Institute for Neurobiology and Brain Research of the Academy of Sciences of the GDR.

228
Doctoral degrees

When I came to Magdeburg in 1992, we had identified a whole series of synaptic proteins that we knew had to work in harmony in order to functionally orchestrate synapses, but is was unknown how they act in the brain. The LIN with its concept of comprehensive research into learning and memory seemed to the ideal place to explore this. Today, 30 years later, we know the significance of many of these synapse components for brain processes. Perhaps the most important finding: almost all members of the synaptic "protein orchestra" that we identified and studied out of scientific curiosity are now known to be associated with brain diseases and learning and memory disorders.

Prof. Dr. Eckart Gundelfinger (Former Managing Director, 2010 – 2020)

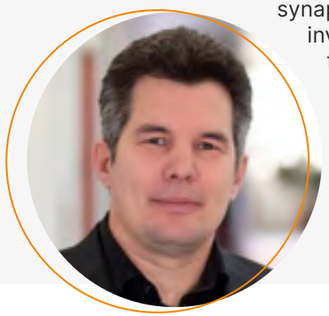
108 MIO. EUR
Third Party Funds

30 years of LIN and exactly half of this time I have been with the LIN and its members. It has been turbulent, intense, challenging, emotional, exciting, fun, consistently changing, colourful, hair-raising, astonishing, fascinating and NEVER boring. The potential of the LIN and especially of the people was, is and will remain great, so that also the next 30 years will be nothing but exciting. Promised!

Thekla Thiel (Head of the Administration since 2008)

23
Habilitations

2472
Scientific publications



This institute is the perfect place to decipher the memory code. Here, engrams are identified, neurons are manipulated by light, synaptic plasticity studied, and learning and memory are investigated in humans and in model systems - the fruit fly larva, the mouse, non-human primates, during early childhood development and in patients. We will explore new ways to understand the complexity of the brain and make it understandable, and to make science open, transparent and reproducible.

Prof. Dr. Stefan Remy (Managing Director since 2020)

LIN in the Time of Corona

→ In early March 2020, we had to cancel the XIV Magdeburg International Neurobiological Symposium after the first cases of COVID-19 occurred in Europe.

→ Germany went into lockdown for a few months and most of our colleagues switched to home office. We prepared hygiene and emergency plans, ordered disinfectants and face masks to make sure that at least work in particularly sensitive areas can continue.

→ Many international conferences (such as the "Functional Architecture of Memory" conference or the "International Conference on Auditory Cortex") had to be cancelled or postponed several times. Instead we tried out digital formats of coming together and institutional life in a tile format.

→ The email account corona@lin-magdeburg.de was set up to bundle all inquiries.

→ The Long Night of Science was cancelled in 2020. In 2021, it only took place in a digital format.

→ Many of our foreign colleagues couldn´t visit their families for a long time.

→ From early summer 2021, the first Covid-19 vaccination campaign was organized by the LIN. This offer was used intensively, and by the end of 2021, the LIN had a vaccination rate of almost 100 per cent.

→ In January 2022, the members of our Corona team (see photo) were honoured as "Employees of the Year". They tested our probands, helped out at the university's test centres, coordinated vaccination appointments and dealt with all questions regarding quarantine measures, hygiene plans, home office, contact tracking and room occupancy.

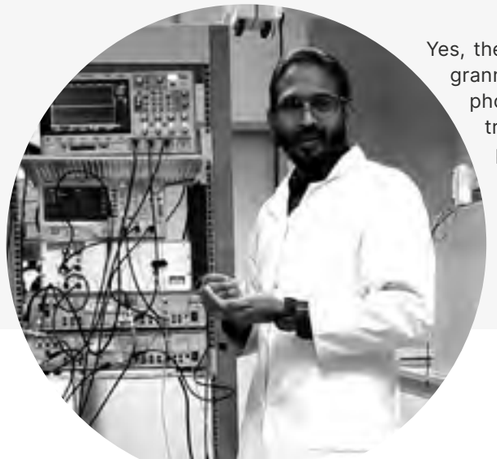
→ By the end of March 2022, the nationwide restrictions ended and the LIN went back into cautious normal operation.

“Resilience“ is the word that I have better understood the meaning in 2020. The COVID-19 pandemic feels like a Sci-Fi movie. I am worried about my health, my career, the country that I live in and particularly my family in Turkey. I have spent the first lockdown by myself while struggling between my home office-tasks and the coronavirus news, having video calls with my family and my best friends who all live in different countries. The pandemic presumably brings more or less the same issues for everyone. However, I see that immigrants experience it slightly different from locals by having double concerns about the country of residence and their home countries. All I can do is being patient and hope for the best. I believe in the power of science which gives me motivation and strength for the future. Resilience is the new black!

Dr. Ayse Malci

The corona virus came to remind us that - no matter how much technology or knowledge we have - something we do not see or feel can kill us or change our lives. This pandemic has exposed the best and worst in each of us, and it reminded me of a book by the writer José Saramago “Essay on Blindness”. This critical situation has taught us to value life, the freedom to do what we like, to appreciate even more what it means to hug a loved person. The loss of a family member and not being able to sayfarewell to him has been very hard for me. Thinking that my grandparents are old and maybe I won't see them again is something that saddens me. But at the same time it reminds me that to overcome this and be with our loved ones, we must learn to live with the virus, to control it, take precautions, to think as scientists how we can contribute and help to solve this in some way, for example by passing on information, educating people.

Dr. Carolina Montenegro



Yes, the pandemic threat was horrifying. I lost my granny during this period, and it was through phone I had to make my goodbye. I experienced travel restrictions, was concerned about my parents´ health. Later I realized, pandemics are about breaking the past and reconceiving the world new.

Vivekanandhan Viswanathan

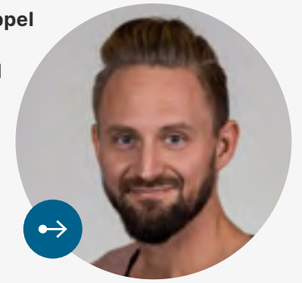
Who Came? Who Left?

→ On 9 January 2020, **Stefan Remy** was inaugurated as the new director of the LIN in a festive ceremony. The medical scientist and physiologist previously worked as research group leader at the DZNE in Bonn. Stefan Remy took over the office from **Eckart Gundelfinger**, the longstanding head of the Department of Neurochemistry and Molecular Biology who had run the institute since 2010. Eckart Gundelfinger retired at the end of 2020 and has been a guest scientist at the LIN since then.

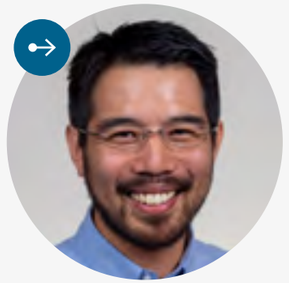
→ **Sanja Bauer Mikulovic** studies the neurobiology of prosocial behaviour and solidary action in mice. She started her research group "Cognition and Emotion" at the LIN in 2021.

→ Since autumn 2021, **Hongbo Jia** has been working as the new CNI Coordinator at the LIN. He takes over responsibility for the microscopy facility from the long-serving head Werner Zuschratter who will be retired. Together with André Brechmann, Hongbo Jia heads the Core Facility CNI.

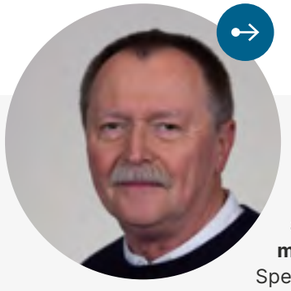
→ In early 2022, the Italian neuroscientist **Alessio Attardo** and his research group from the Max Planck Institute of Psychiatry in Munich moved to the LIN. They study plasticity mechanisms in the hippocampus.



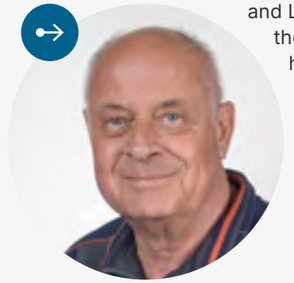
→ In April 2021, **Max Happel** became a professor of physiology at the Medical School Berlin. He will continue to collaborate with the LIN.

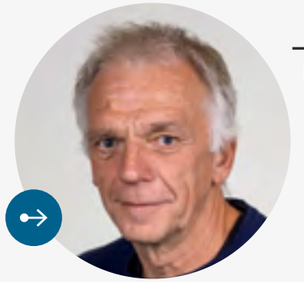


→ Working group leader **Kentaroh Takagaki** has accepted a professorship at the Bio-Innovation Research Center at the University of Tokushima, Japan.



→ **Karl-Heinz Smalla** and **Wolfgang Tischmeyer,** two long-time Special Lab managers and LIN employees from the very first hour who helped to establish the predecessor institute in the 1980s, went into retirement, but still remain associated with the institute.





→ After 23 years at the LIN, **Peter Heil** also said goodbye at the end of 2021. He led the work group on Hearing and had served as LIN ombudsman for 18 years.

Obituary:

We had to say goodbye to **Wolfram Wetzel**, the former head of our behavioural pharmacology lab. Wolfram also belonged to the generation of LIN founding members.

He published internationally recognized research on the neurobiological mechanisms of learning and he shaped the research at the institute with his collegiality, knowledge and original ideas. We honour his memory as a distinguished scientist, trustful colleague and reliable friend.

Reasons to Celebrate?

NEURALE RESSOURCEN DER KOGNITION

→ At the limit: It is well known that stress or lack of sleep have an influence on our performance. Now researchers of the LIN, OVGU and DZNE in Magdeburg want to find out which neurobiological causes and mechanisms in the brain can limit our perceptual and cognitive performance. In the Collaborative Research Centre CRC 1436 "Neuronal Resources of Cognition", headed by Emrah Düzel and Michael R. Kreutz as spokespersons and funded by the German Research Foundation (DFG) since January 2021, interdisciplinary research is being conducted on this topic.

→ Newly established: In March 2021, a partner site of the German Centre for Mental Health was established in Jena, Magdeburg and Halle.

A team of more than 60 experts from the fields of psychiatry, neuroscience, psychotherapy and psychology, including 10 LIN researchers, has launched a joint initiative under the name C-I-R-C to develop novel concepts for the prevention, diagnosis and treatment of mental disorders. C-I-R-C is based on the English word "circuit" and refers to the networks of nerve cells in the brain and how they are connected to the body, and also to the network of experts in the three mid-German university cities of Magdeburg, Jena and Halle.
(photo below)

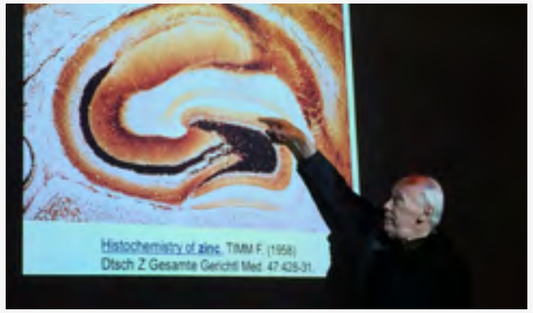
→ Excellent rating: Excellent rating: The senate of the Leibniz Association recommends to the federal and state governments to continue funding the LIN for the next seven years. This recommendation is based on a comprehensive evaluation of the institute's performance by an independent commission of experts after a long preparatory process involving all colleagues. The evaluation report published on 1 July 2021 praises in particular the LIN's coherent research concept. *(Photo above)*

→ Keeping an eye on tissue changes: The LIN Core Facility Combinatorial NeuroImaging (CNI) is involved in the joint project "Time-resolved Raman and Metabolic Imaging Spectroscopy Unit" (TIRAMISU for short) funded by the Federal Ministry of Education and Research (BMBF) since August 2021. The aim of the project is to study microorganisms in the mouth and throat. With the help of the ultra-sensitive, time-resolving camera developed by Werner Zuschratter and his team at the LIN, critical tissue changes as well as head and neck tumours are to be investigated in order to develop biomarkers for early diagnosis.

→ Synaptic proteins in balance: 17 researchers from Magdeburg, Berlin, Bremen and Haifa have been jointly investigating protein balance in nerve cells since August 2021. In fact it is a central question of modern cell biology how this process is regulated locally in the presynapse and how the complex interplay of protein synthesis and degradation processes - proteostasis - is dynamically organised. The DFG funds the Research Group 5228 "Membrane Transport Processes for the Regulation of Presynaptic Proteostasis", whose spokesperson is Michael Kreutz, initially for four years.

SYNTOPHAGY FOR 5228

The LIN Hosts the Scientific World



→ **Matthies Honorary Lecture:** On 2 March 2020, Tim Bliss, fellow of the Royal Society and one of the discoverers of the long-term potentiation of nerve cells, gave the 3rd Matthies Honorary Lecture, which was like a journey through the history of neurobiology. In his lecture he honored the founder of the neurosciences in Magdeburg, Hansjürgen Matthies.

→ **Looking through the LINdoscope:** From 6 to 19 September 2021, Sanja Bauer Mikulovic, Pavol Bauer, Oliver Barnstedt and Matthias Prigge from the LIN together with Janelle Pakan from the OVGU organised a Summer School. The international participants attended top-class lectures and practical courses on microscope techniques, imaging approaches, optogenetics and pupillometry.

→ **Theory and practice:** Rodrigo Herrera-Molina, Oliver Kobler, Torsten Stöter, André Weber and Werner Zuschratter from the CNI lab as well as Sanja Bauer Mikulovic and Pavol Bauer organised the microscopy methods course "Imaging Techniques in Neuroscience" in cooperation with the German Neuroscience Society. Young researchers from all over Germany came to the

LIN to learn about various techniques of modern light microscopy in lectures and practical exercises.

→ **Children's brains:** From 13 to 14 September 2021 Nicole Wetzel and her team conducted the online workshop "Attention & Memory in Development (AMiD)" with international guests. The focus was on the development of attention and memory in childhood and adolescence from a neurocognitive perspective.

→ **Listening to the brain:** the International Conference on Auditory Cortex had to be posponed twice due to the pandemic. In order to keep up to date and continue the scientific exchange between the expert laboratories worldwide, the hearing specialists from Magdeburg organised a virtual meeting on 5/6 October 2021 with over 200 participants from 26 countries.

Events for the Public

→ Science needs urban culture, so Magdeburg's application as European Capital of Culture was supported also by the LIN and the other research institutions with a lot of enthusiasm and ideas. During the digital jury visit to the Elbe Dome in **October 2020**, researchers and cultural workers presented Magdeburg as an innovative science location with crossover projects between science, art and urban culture.

→ The 2020 Long Night of Science had to be cancelled due to Corona, but the 2021 event took place on **29 May** in a fully digital format.

Science fans could follow the experiments from the broadcast studio, and interactive formats such as "Meet a scientist" enabled viewers from all over the world to ask their questions via chat.

Check our LIN YouTube channel

→ Together with the Federal Cyber Agency, the LIN organised the public event "Private Brains: Can Machines Read Our Thoughts?" in Magdeburg's Johanniskirche on 22 September 2021. LIN Director Stefan Remy talked about the use of artificial intelligence technology for brain research and for direct brain-machine communication. Afterwards, the guests discussed with the audience the opportunities and risks of brain-computer interfaces. (Photo below)

→ Little microscopy fans were welcomed by Wener Zuschratter's team at the Mouse Dooropener Day on **3 October 2021.** The kids could take a look into the laboratories and do experiments. For example they could discover under the microscope tiny things floating in the water of the Elbe river.

→ On **4 October 2021**, the cinema tour for the film "Lost in face - Die Welt mit Carlottas Augen" stopped off at the Moritzhof. Carlotta, the protagonist of the film, can´t recognise any faces, because she suffers from prosopagnosia - face blindness. Together with director Valentin Riedl and the protagonist Carlotta, neurologist Ariel Schoenfeld from the LIN answered the audience's questions after the movie.

LIN life

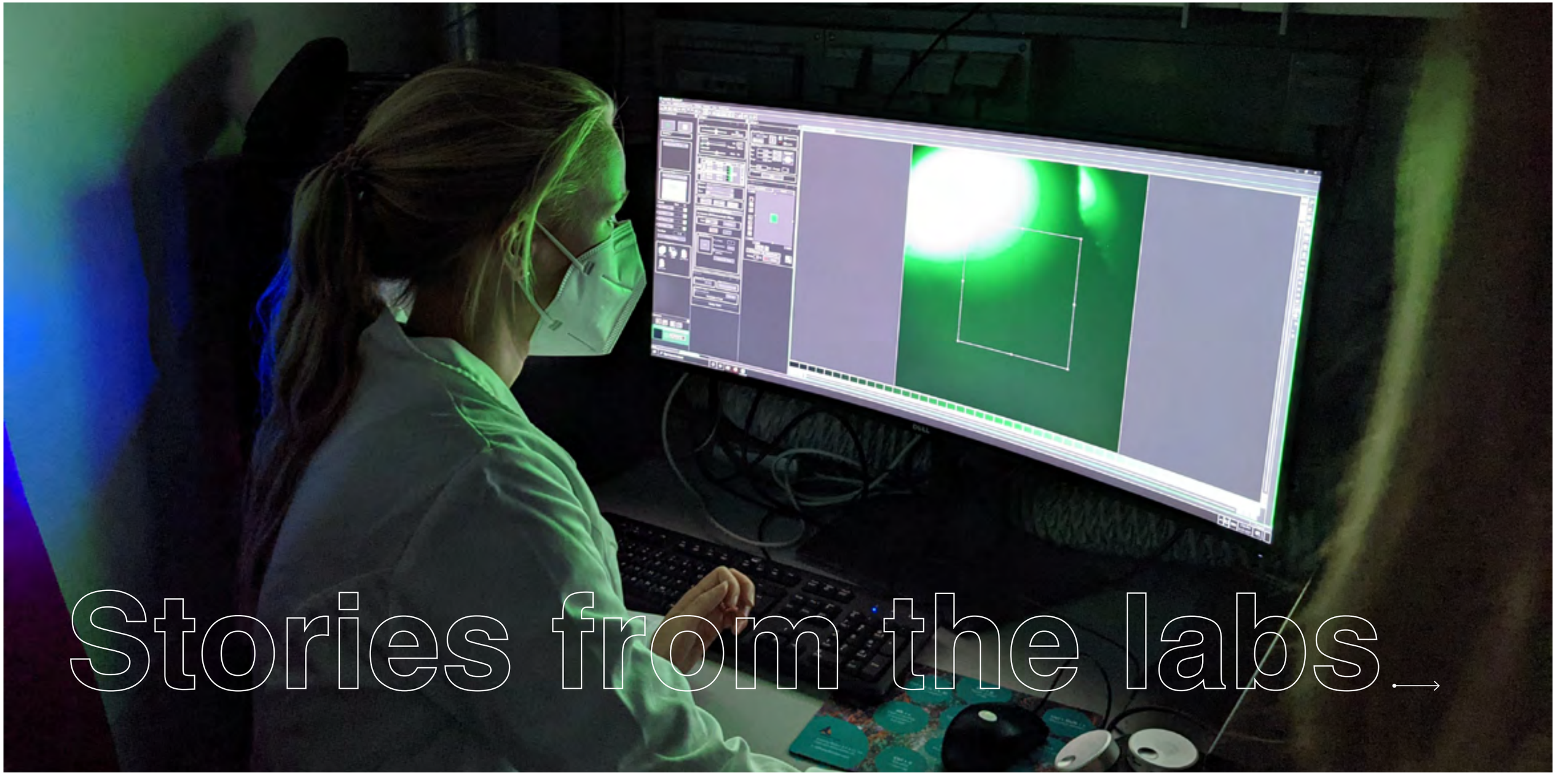
→ During the 2020 winter holidays, ten pupils could try out laboratory work at the institute: the trainees got to know experimental work starting from the measurement of brain waves, staining nerve cells, analysis of proteins, to experiments with fruit flies.

→ On **28 September 2020,** the Federal Drug Commissioner Daniela Ludwig visited the LIN. In a conversation with Nicole Wetzel and Christian Merkel, the politician informed herself about current research on attention, motivation and learning in connection with social media use.

→ The Brazilian researcher Thomaz Fabrin has been a fellow of the Alexander von Humboldt Foundation at the LIN since 2021. In Matthias Prigge's research group he works on the use of different opsins - proteins that occur in visual pigments and react to light..

→ In **July 2021**, a Germany-wide initiative for transparent animal experiments was launched. Its goal: to promote a transparent and open discussion on research involving animals. A total of 75 institutions have already joined this initiative with the LIN being one of the first signatories.

Initiative Transparente Tierversuche



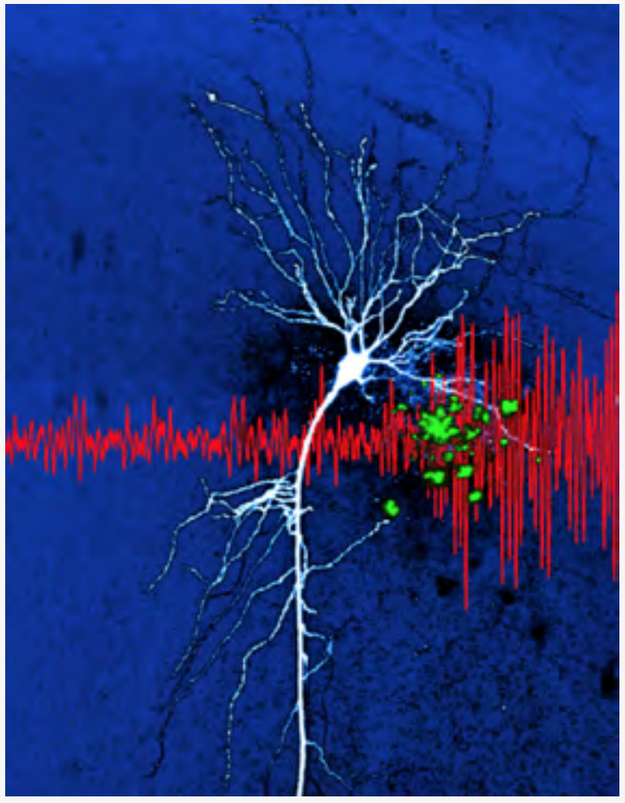
Stories from the labs

Before the plaques come: Altered nerve cells point to Alzheimer's dementia

An important cause for the cognitive decline and loss of cognitive vitality in old age is dementia. The most common form of dementia is Alzheimer's disease, for which age is the most important risk factor. An international team led by LIN postdoc Liudmila Sosulina was able to demonstrate hyperexcitability of neuronal networks and neurons long before the typical deposits appeared in the brain.

According to the German Alzheimer's Association, about 1.6 million people in Germany alone live with dementia. "We still know too little about the mechanisms by which Alzheimer's disease develops. But if you want to develop biomarkers for its detection or therapeutic approaches, it is very important to understand what is going on in its early stages," explain study leaders Prof. Dr. Martin Fuhrmann (DZNE Bonn) and Prof. Dr. Stefan Remy (LIN). It is known from previous Alzheimer's studies that protein deposits - so-called plaques - contribute to the loss of nerve cells and their connections - the synapses - in the brain. Those affected develop dementia. In the study, first author Dr. Liudmila Sosulina examined the hippocampus of rats in connection with the disease, because this area plays a crucial role in learning and memory processes. She explains, "Using different methods, we were able to demonstrate that there is hyperexcitability of neurons in the animals' hippocampus, even before Alzheimer's plaques have spread."

Typically, Alzheimer's disease causes dysfunction in neuronal networks. Previously, this has been shown in mice and it is assumed to be a pathomechanism in humans. Evidence in other species, such as the rat, which is also an important model animal for learning and memory research, suggests that it is a cross-species disease phenomenon. "In our study, we examined the micronetwork in the hippocampus of transgenic rats at the onset of the disease and found that the changes that occurred



Beta-amyloid deposition is typical of Alzheimer's disease. Amyloid accumulation (green) near a pyramidal cell in the hippocampus.

Altered nerve cell excitability shows up in more irregular oscillations (shown here in the local field potential, red).

were initially exclusive to glutamatergic, so called excitatory, networks. We hypothesize that inhibitory circuits are also affected, but later," Sosulina said.

"The methodological novelty of the study is that imaging techniques were established in Alzheimer's rats to measure calcium activity in the cells." Using two-photon microscopy, the researchers involved were able to detect hyperactivity of CA1 neurons in the hippocampus of the animals. In brain slices, using single-cell recordings and multi-electrode arrays, they also detected increased excitability and altered action potential properties in the CA1 pyramidal neurons. The inhibitory networks that later cause typical Alzheimer's symptoms were not affected at this time.

The study shows that even before protein deposits are visible in the brain, it is possible to measure the hyperexcitability of neurons in the hippocampus, because glutamatergic neurons have already changed there in the early stages of Alzheimer's disease. Understanding the mechanisms behind this is important so that new biomarkers can be developed and therapeutic measures researched. In current studies, the CNeu department is investigating whether early behavioral changes occur in animal models of Alzheimer's disease that remain unnoticeable in conventional behavioral tests, but could one day become important for early detection. To this end, the department is using machine learning to quantify behavior in image observations and divide it into hierarchical behavioral modules, known as motifs. First promising results have already been published as a preprint (Luxem et al. 2020). A larger series of measurements is currently being conducted in cooperation with the Gladstone Institute for Neurological Research in San Francisco.

Read more

Sosulina L, Mittag M, Geis HR, Hoffmann K, Klyubin I, Qi Y, Steffen J, Friedrichs D, Henneberg N, Fuhrmann F, Justus D, Keppler K, Cuello AC, Rowan MJ, Fuhrmann M, Remy S. Hippocampal hyperactivity in a rat model of Alzheimer's disease. J Neurochem. 2021 Jun;157(6):2128-2144.

Luxem K, Fuhrmann F, Kürsch J, Remy S, Bauer P, Identifying Behavioral Structure from Deep Variational Embeddings of Animal Motion. bioRxiv 2020.05.14.095430

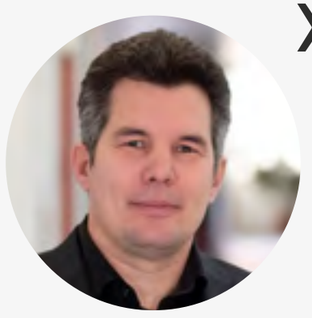
Cellular Neuroscience

Our department was founded in 2020 and has grown steadily since then. Our research focus is on neuronal circuits. Changes in the way neurons communicate in circuits underlie all learning and memory prcesses. In four research groups we investigate how synaptic signals are generated, plastically modified and processed by neurons and their networks. Thus, we aim to understand basic mechanisms of memory formation and its disorders. In terms of disorders, we are not only interested in neurodegernerative diseases but also in the maladaptation of circuits in neuropsychiatric disorders.

The Thomas group uses the fruit fly Drosophila as a model organism to characterise the role of calcium-regulating protein complexes for the structure, function and plasticity of glutamatergic synapses by means of genetics, cell and molecular biology.

The Attardo group investigates cellular and circuit mechanisms underlying memory storage and retrieval in the hippocampus. We use intravital imaging to visualise the neuronal activity patterns corresponding to the representation of experience in the hippocampus in mice undergoing a learning task, and use molecular and genetic tools to manipulate the activity of specific neurons. The Remy group is investigating the functional and molecular diversity of synaptic circuits and micro-networks in the hippocampus, and in the future increasingly behavioural network activity patterns that span multiple brain regions ("brain states"). We are deciphering how subcortical circuits are involved in triggering behaviour such as locomotion and exploration. Machine learning allows us to quantify behaviour and relate it to neuronal activity.

The Dürschmid group analyses functional mechanisms of learning and decision-making in the human brain in terms of single cell activity, their integration into cortical activity patterns and as network activity. We decode cortical activity to capture the exact temporal dynamics of different brain states.



» **True for neuronal circuits and for departments: Coming together is a beginning, staying together is progress, and working together is success.**

Prof. Dr. Stefan Remy

Team

Head
Prof. Dr. Stefan Remy

Group leaders
Dr. Alessio Attardo (ab 01/2022)
Dr. Stefan Dürschmid (ab 01/2022)
Dr. Ulrich Thomas

Postdocs
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Dr. Pavol Bauer (bis 09/2021)
Dr. Falko Fuhrmann (bis 08/2021)
Dr. Hiroshi Kaneko
Dr. Stefano Pupe
Dr. Liudmila Sosulina
Alessandro Francesco Ulivi (ab 01/2022)

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Damaris Holder
Bhargavi Keerthana Boovaraga Murthy (ab 01/2022)
Hannah Klimmt (ab 01/2022)
Felix Kuhn
Xiao Lin (bis 12/2021)
Kevin Luxem
Petra Mocellin
Nikhil Tiwari

Students, guests and trainees
Benedikt Auer
Johannes Kürsch

Technicians and lab service
Jorge Bergado Acosta
Janina Juhle
Chris Theuerkauf
Silvia Vieweg

Secretary
Juliane Jäger

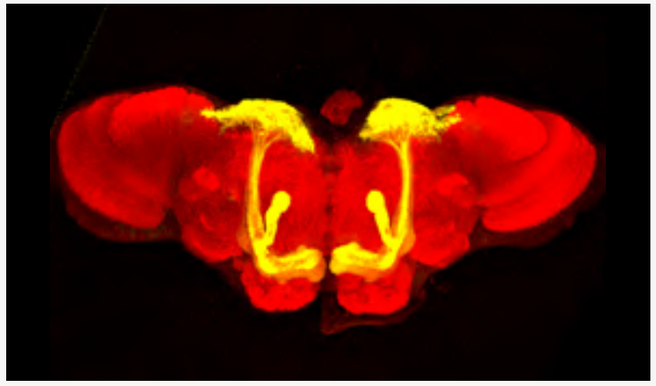
You have to be able to switch!

Compared to humans and mice, the brain of the fruit fly Drosophila melanogaster has far fewer nerve cells, totalling only about 100,000, and the brain of fly larvae is much simpler still. Indeed, fruit flies, like butterflies, are insects with complete metamorphosis: a female fly lays her eggs on a ripe apple, for example, and an insatiable larva hatches from each egg, eats as fast and as much as it can, pupates after a few days, and begins the cycle of life anew as an adult fly after barely a week. For the neurobiology of learning, the larvae thus offer particular advantages as research objects – they are small, have only about 10,000 nerve cells and a clear and simple motivation: to search for food!

This has allowed us to develop a robust experiment for learning in the larvae. In this experiment, the larvae only get a food reward in the presence of a certain odour stimulus. If this odour stimulus is presented to them in a later test, they direct their food search towards that odour, because food is to be expected with it. However, as soon as the food is found it is time to switch gears from such exploratory search behaviour and instead exploit the food resource and eat. In a recent study, we identified a single nerve cell that can cause such a switching off of learned search (Schleyer et al., 2021).

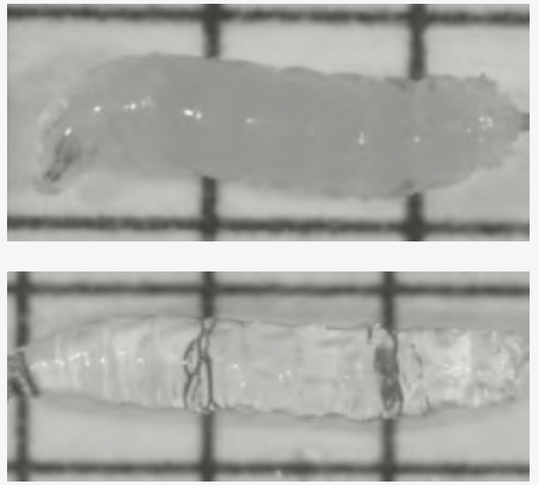
As part of a long-term international research collaboration, we had already mapped all the nerve cells in the larval brain, including all the synaptic contacts between these nerve cells (Saumweber et al., 2018, Eschbach et al., 2020). Some of these nerve cells use dopamine as a messenger, which plays an important role in reward learning in humans and rodents as well as in insects. We were able to show that the activation of even a single one of these dopamine cells (DAN-i1) in the larval brain can act as a reward. To do this, we used methods of optogenetics, allowing us to make individual cells in the larval brain sensitive to light such that when the light is switched on, the cell fires. Surprisingly, the DAN-i1 "happiness cell" not only acts as a reward, but also has a second function: it can switch off the learned search behaviour. How can one and the same nerve cell perform two such different functions?

The explanation lies in the initially enigmatic connectivity of the dopamine cells as revealed during the mapping of the larval brain. Indeed, DAN-i1 and all comparable dopamine cells of the larvae and of adult flies have two targets. The first and previously known targets are the nerve cells of the so-called mushroom body, the highest brain centre in the insect brain, where learning takes place. The second, previously unknown targets, however, are the neurons that connect the memory centre with the neurons that steer learned search behaviour! In view of the evolutionarily conserved role of dopamine in humans and animals, the question arises as to whether such a dual connectivity motive and the corresponding dual function of the dopamine cells , to mediate reward and to switch off learned search, represent a more general principle.



(Heisenberg & Gerber 2008)

The so-called mushroom bodies (yellow) are the highest brain center for learning processes in the relatively simply constructed brain of a fruit fly.



(Kobler et al., 2021)

A "glass" fruit fly larva: Through tissue clearing the body of a larva can be made transparent. This gives us a a clear view of the larva's nervous system with a so-called light sheet microscope - within the intact, full body.

Read more

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» **The connectome of the Drosophila brain has revealed a baffling complexity of neuronal circuits – prompting new exploration of the cognitive capacities that such circuit complexity can confer.**

Prof. Dr. Bertram Gerber

Genetics of Learning and Memory

Our aim is to understand the organisation of behaviour through the molecular and cellular structure of the brain. We investigate how experiences are turned into memories and how such memories are stored and turned into learned behaviour. We do this at the level of molecules, nerve cells and neuronal circuits, in the fruit fly Drosophila and its larvae. The experiments we perform use genetic methods that allow any gene or transgene of interest to be read out only in the cells and time periods of our choosing. Because many memory processes in Drosophila, in mice and in humans function on the same principles, this research is of biomedical interest. Furthermore, due to the small number of nerve cells in Drosophila, minimal adaptive neuronal circuits can be described at the synaptic level (connectomics). Together with the possibility of functionally manipulating single cells, it is thus possible to understand how the adaptability and reliability of behaviour can be kept in balance – and this can be inspiring for applications in robots or other technical devices.

However, an understanding of behaviour and brain function remains incomplete if one does not keep in mind the psychological processes that accompany behaviour and the activity of the nervous system. We therefore try to understand how key psychological processes (e.g. perception, expectation, knowledge) are reflected in behaviour.

Our current projects focus on the memories established through the occurrence as compared to the termination of punishment in particular, which are of opposing emotional and behavioural valence; the decision process to translate a memory into learned behaviour – or not; and the structure and function of the mushroom body, the highest brain centre of insects.

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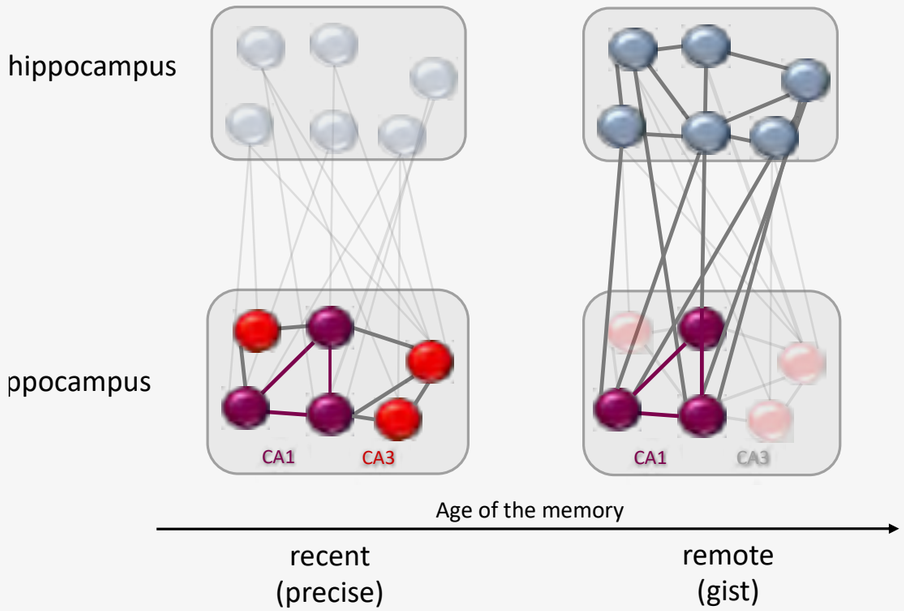
How do we recall precise or vague memories over time?

Retrieving past memories is a crucial element for dealing with daily-life events. Still, the precise mechanisms underlying memory recall is not known, especially when it comes down to very remote events such as childhood memories or traumatic memories that often occur decades before therapy in the case of post traumatic disorders.The medial temporal lobe (MTL) of the brain, especially a brain area called the hippocampus, plays a crucial role in retrieving memories. Indeed, damage to this brain area leads to severe memory deficits as reported in aging and in patients with amnesia. Whether or not the hippocampus contributes to retrieving memories when they are remote has been the subject of a heated debate for the past decades. This debate partially stems from the limited spatial resolution of the imaging techniques used at the time. To overcome this technical limitation, we used high-resolution molecular imaging techniques in mice and imaged activity in MTL subareas during the recall of memory over a time window comparable to that used in humans. This extended time window, up to 1-year-old memories, is comparable to 40 years-old memories in humans and was used for the first time in the rodent literature in an attempt to better transfer findings to humans.

With these experiments, we previously showed that only a very specific part of the hippocampus, the hippocampal subfield CA1, remained engaged during the recall of the most remote memories and that other parts of the MTL, the parahippocampal areas (cortical areas surrounding the hippocampus: LEC, MEC, PER, POR), were optimally engaged at this time point. In striking contrast, the involvement of the hippocampal subfield CA3 was limited to recalling recent and early remote memories during which parahippocampal areas were minimally involved, suggesting that distinct MTL subnetworks contribute to memory recall over time (Lux et al 2016).

More recently, we have focussed on memory precision and showed that CA3 selectively bares a crucial but time-limited role for retrieving memory precision, using optogenetics. In contrast, CA1 specifically dealt with the essence of the memory independently of their age and received support from the parahippocampal areas for the most remote memories (Atucha et al, 2020). These new findings complement the system consolidation and the multiple trace theories by identifying the specific role of CA1 and CA3 in terms of the recall of memory precision over time.

In addition, in an independent study, we reported that the selective disengagement of CA3 over time likely reflects a fundamental mechanism of memory consolidation as it takes place for the recall of different types of memory. Currently, we aim at disentangling the specific contribution of the two main information input pathways to the hippocampus, the temporoamonic and the trisynaptic pathways, to the recall of memory overtime by optogenetically manipulating synaptic plasticity in collaboration with S. Tonegawa (MIT, USA), at investigating the in- vivo electrophysiological mechanisms underlying recent and remote memory retrieval with K. Allen (Heidelberg) and M. Yoshida (DZNE, MD) and at collecting evidence for a CA3 disengagement in humans using 7TfMRI together with E. Duezel (DZNE).



Precise or vague memory? While recalling precise memories require CA1 and CA3 retrieving their gist involves CA1 and the parahippocmpal areas.

Read more

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» **How precise a memory is might not depend on how old it is, but rather which Medial Temporal Lobe brain subnetwork is engaged at the time of recall.**

Prof. Dr. Magdalena Sauvage

Functional Architecture of Memory

Remembering specific events of our past is crucial for present and future daily-life decisions. Our department is dedicated to uncover the fundamental principles of memory recall by investigating its behavioral, network and cellular mechanisms. The Functional Architecture of Memory (FAM) department focuses on characterizing the role of the Medial Temporal Lobe (MTL) areas of the brain, a region that suffers damage in aging, in patients suffering from amnesia and Alzheimer's Disease (AD), within this framework.

The originality of our approach is to use for rodents behavioral experimental conditions similar to those used in humans, which we combine with light-induced modulation of cell activity (optogenetics), targeted stereotactic lesion, high-resolution molecular imaging and 9.4T fMRI in awake rats with the aim of bridging further human and animal memory research. This approach especially allowed us to recently put forward new concepts for the consolidation of memory over the lifespan and for the processing of spatial and non-spatial information in the brain, which will be tested in humans within the frame of a long-lasting collaboration with E. Düzel (DZNE, Magdeburg).

We also scrutinize the mechanisms underlying memory function at a more cellular level using highly selective molecular and genetic tools and in-vivo electrophysiology in collaborations with S. Tonegawa (MIT, USA), K. Kitamura (UT Southwestern, USA), S. Josselyn (Sickkids, CN) and J. Csicsvari (IST, Austria). In addition, we also study the neural basis of interindividual differences in memory within the frame of the CRC 1436. Knowledge transfer on these topics is facilitated by the organization of the biennial international and interdisciplinary FAM conference series.

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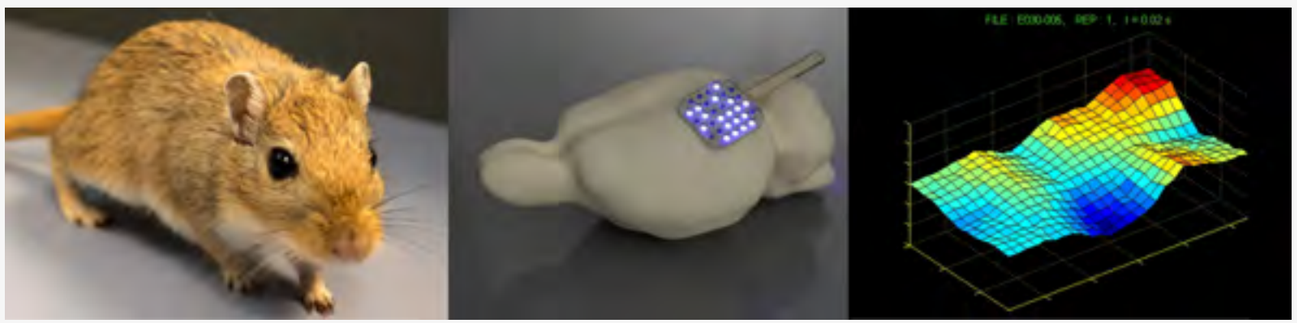
Quantum leaps in learning

Learning is usually understood as a continuous process of increasing knowledge or and skills. This is also expressed in the way learning outcomes are often represented - namely by smooth learning curves - and how we model them mathematically. In fact, however, learning seems to happen in smaller and larger discrete jumps, for which we have now also found physiological mechanisms. These discoveries were made possible by a combination of appropriately chosen learning tasks and improved measurement techniques of brain activity, as well as improved mathematical modeling of the experimental data.

Originally, we had targeted a learning process in which a clear "flip" is already proverbial: the so-called "aha" moment in concept learning and category formation. We found first evidence that the neural mechanisms on which these cognitive learning processes are based also exhibit such discrete transition events, often called "phase transitions". Subsequently, we have studied learning processes in which such turnarounds appear less drastic, such as the transition from detection learning (the learning organism can respond meaningfully to the occurrence of a stimulus) to discrimination learning (the learning organism attaches different meanings to different stimuli), or even the transition from the naive state to simple detection.

Our recent studies show that even in these supposedly simple learning processes, there are discrete cognitive processes that have physiological correlates. The discovery of the latter was supported by new, meanwhile patented, technical developments of our department, which allow us to measure neuronal activities in the brain in a spatially highly resolved manner and to manipulate them in a targeted manner, for example by otpogenetic methods. This has allowed us to show, for example, that in the neocortex, the layered and phylogenetically youngest part of our brain, discrete turnovers in learning processes are accompanied by recruitment of different neuronal functional groups (so-called assemblies) in different layers of the neocortex. The new data force us to develop also the mathematical modeling of neural processes during learning. Traditionally, such processes have been understood as dynamical systems and modeled with differential equations, an approach that idealizes continuous smooth structures in space and time. Using modern methods based on graph theory, we have succeeded, in cooperation with mathematicians, in mathematically describing the discrete state changes relevant for learning and in developing criteria to enable their detection in real data.

Our latest results not only help us to better understand the nature of learning processes and to better support them, especially in aging and disease, they also help to improve artificial learning systems by equipping them with new algorithms that we have been able to identify in biological learning systems. In collaboration with engineers, we have improved current so-called deep reinforcement learning algorithms to provide them with the robustness and generalizability that we know from biological systems.



Behavioural studies on learning rodents (left) with the help of newly developed opto-electrophysiological methods (centre) together with the mathematical mathematical modelling of brain activity (right) allow a deeper understanding of the neuronal mechanism of learning.

Read more

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We investigate neuronal mechanisms of learning at the level of neuronal circuits and also use the findings to improve artificial learning systems.

Prof. Dr. Frank Ohl

Systems physiology of learning

Our department investigates different forms and phenomena of learning at the level of neuronal circuits and interactive brain networks (systems level). Methodologically, we combine behavioral and psychophysical analyses, mainly in rodents, with electrophysiological recordings (from single cells, cell assemblies, local field potentials, electrocorticograms and EEG) with optical recordings (voltage-sensitive dyes, calcium imaging) and (optogenetic, electrical and pharmacological) brain stimulation. A particular focus of our work is on the auditory cortex and several brain systems connected to it. We investigate how neuroplastic changes in cells and circuits of the cortex mediate learning at the behavioral and cognitive levels.

In addition to standard learning paradigms such as detection learning and discrimination learning, we are particularly interested in the transfer of learned information in the context of reversal learning or concept formation. In the last two years, we have described the neuroplastic differential recruitment of different cortical layers in relation to the action of the neurotransmitter dopamine in auditory learning and to pathological disorders such as acoustic trauma. In collaboration with mathematicians and computer scientists, we are developing strategies for making learning mechanisms newly identified in biological systems applicable to artificial learning systems. Recently, two postdocs (Max Happel and Kentaroh Takagaki) have accepted professorships elsewhere.

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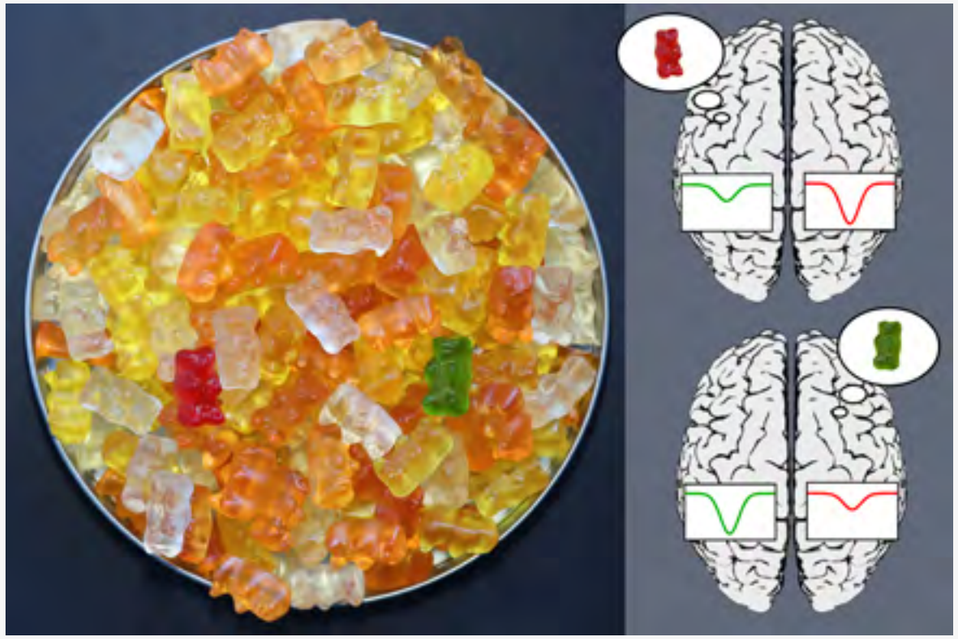
On the trail of attention, learning motivation and brain machine interactions

Some people claim that green gummy bears taste better than red ones. Picking out only the green bears is a piece of cake for us. Within a few milliseconds, we manage to locate the object of desire. Selectively directing our attention to certain features, such as the color of an object, plays an important role in many everyday situations, such as in front of the supermarket shelf. But how does this visual search work in the brain? Does our brain prioritize the processing of the target object or does it first suppress the processing of distracting objects?

To clarify this, we had participants pay attention to colored objects on a screen while we measured the electrical and magnetic changes on their head surface. The astonishing result: the unattended, potentially distracting color is processed temporally earlier than the target color, allowing irrelevant information to be eliminated early on ("selection for rejection"). Transferred to the gummy bears, our brain first actively ignores the red gummy bears in order to finally emphasize the green ones in our perception.



Red or green? The activity in our hemispheres depends on which side of our visual field a sought object is located. We use this phenomenon to control a BCI.

From the lab to the clinic

How can our knowledge of visual search processes help patients suffering from a motor neuron disease to communicate with their environment despite complete paralysis? We are applying our findings in so-called brain-computer interfaces (BCI) to use attention to color as a control signal. Here, we asked participants dichotomous questions (yes/no), which they answered by paying attention to colored symbols presented on a screen, while we measured their brain activity.

If the subjects paid attention to the green symbol in one of the visual hemi-fields without moving their eyes, they signaled positive feedback; if they paid attention to the red symbol, which was presented in the other visual hemi-field, they signaled negative feedback. In 89% of the questions asked, we were able to correctly decode the participant's intended response from the recorded brain activity. Since this approach does not require any eye movement, the results of our study in healthy subjects are promising for completely paralyzed patients who could benefit by regaining a communication ability.

Wait and see?

Whether it's a gummy bear hunt or brain-machine interactions, with the right motivation, we can usually learn well. But does our ability to learn through motivation change over the lifespan? To find out, we asked 247 people between the ages of 7 and 80 to respond to certain pictures by pressing a button, while withholding the response to other pictures to win money or avoid losing it. All participants found it easy to act actively for a reward and to hold back to avoid punishment. It was particularly difficult to remain passive in order to receive a reward. Young adults were better able to learn this because they were more sensitive to reward and punishment, although children and adolescents showed an underlying preference for active action regardless of gain or loss. The ability to flexibly relearn during childhood and adolescence is important for navigating the rules of life and maximizing gains. Older adults had poorer learning abilities in the experiment. But even if motivated learning declines with age, the ability remains basically intact - an important finding also with regard to lifelong learning. So just wait and see, not reacting to something right away can sometimes also be rewarding.

Read more

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» **Every thought we think, every feeling we experience, every dream and every hope have a specific brain signature, a unique spatio-temporal activity pattern of the nerve cells in the brain.**

Prof. Dr. Hans-Jochen Heinze

Behavioral Neurology

Human behavior has many facets: we go shopping, ride our bikes, learn new things, and sometimes we get distracted or just let our minds wander. Our department explores what neurobiologically underlies our behavior. How do we find the tomato on the supermarket shelf? How do we perceive touch or learn movement sequences? What influence do reward, punishment or even our age have on our learning success?

To find the answers to such questions, we have volunteers solve tasks on the screen while we record their response behavior and, depending on the study, also measure their eye movements or brain activity.
Our close cooperation with the Department of Neurology allows us to work with patients as well. A major goal here is to better understand neurological diseases and to be able to help patients directly with our findings.

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In Rain Man's synapses: Molecular consequences of autism mutations in the SHANK3 gene identified

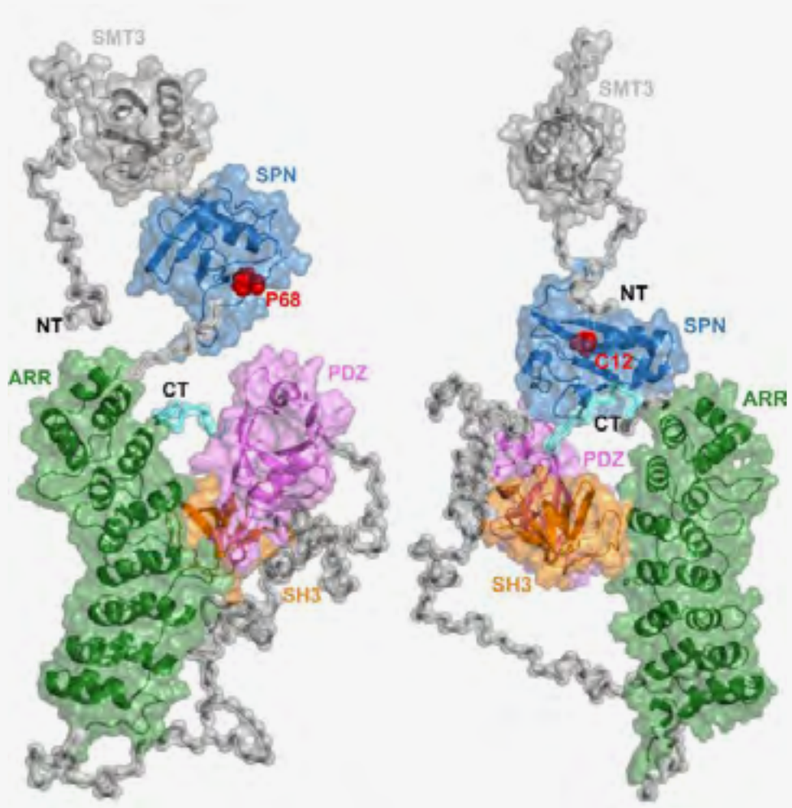
An international team of researchers led by Dr. Michael R. Kreutz and Dr. Marina Mikhaylova from the LIN, the Center for Molecular Neurobiology Hamburg (ZMNH) and Humboldt University Berlin, and Dr. Eunjoon Kim from the Korea Advanced Institute of Science and Technology (KAIST) has deciphered the molecular-level effects of mutations in the autism risk gene SHANK3. The project was competitively funded by the Leibniz Association and has been published in the journal Elife.

In the 1988 road movie "Rain Man," Dustin Hoffman played an insular autistic man in one of his signature roles, adapted from the life of the most famous savant, Kim Peek. Autism is a complex developmental brain disorder associated with peculiarities in the perception and evaluation of sensory stimuli. Autistic people find it difficult to communicate and interact socially with others, often take refuge in stereotypical behavior patterns, and sometimes have cognitive problems or insular gifts.

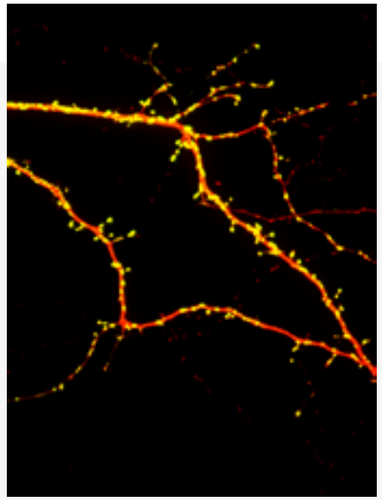
Genetic mutations may be involved in the development of autism. The gene products affected are important proteins in the brain's synapses, such as the SHANK3 molecule. SHANK3 is a scaffold protein that contains many binding sites for other proteins and acts as a kind of master organizer for the postsynaptic protein machinery: It links transmitter receptors, signaling molecules, and the cytoskeleton and is indispensable for the precise work of synapses.

What are the effects of mutations found in autistic patients on the functioning of the SHANK3 protein? Michael Bucher, a doctoral student in the research groups of Kreutz and Mikhaylova, in close collaboration with Kim's lab from the South Korean Advanced Institute of Science and Technology, has recreated the defective proteins for two of these mutations using genetic engineering and analyzed their structure. Using biophysical techniques, the research team was able to demonstrate that the mutations lead to changes in the three-dimensional protein structure that have far-reaching consequences: The mutated SHANK3 proteins enter the synapses in the nerve cells less, which disrupts synaptic function.

"We were able to see that the mutations altered SHANK3 so that it could no longer organize the order and dynamics of proteins in excitatory synapses. This gave us a molecular deciphering of why patients carrying these mutations experience disruptions in synaptic connections that could be responsible for cognitive symptoms, for example," said Michael Bucher, first author of the study. In the next step, the mutated autism risk proteins will now be studied in mice to directly analyze the effects on behavior.



Autism-related missense mutations result in the incorporation of amino acids (Middle and right panel: the amino acids proline (P68) and cysteine (C12)) that lead to a different conformation of the protein and vastly altered molecular dynamics of conformational fluctuations.



Shank proteins (left dots in the left panel) are master scaffolders of excitatory synapses.

Read more

Bucher M, Niebling S, Han Y, Molodenskiy D, Nia FH, Kreienkamp H-J, Svergun D, Kim E, Kostyukova AS, Kreutz MR, Mikhaylova M. 2021. Autism associated SHANK3 missense point mutations impact conformational fluctuations and protein turnover at synapses. eLife. 10.

Neuroplasticity

Research in NPlast is concerned with fundamental questions of neuronal cell biology. We investigate how synapses communicate with the nucleus, how activity-dependent gene expression feeds back to synaptic function and how this is related to the formation of a cellular engram. Based on our previous work we currently try to exploit principles of excitation-transcription coupling to improve cognition. In addition, we have a long-standing interest in the question how the nanoscale organization of the synapse determines functional properties in the context of learning and memory as well as in neuropsychiatric disorders like autism. In very recent work we established a compartment specific multiomics workflow that is suitable to extract information from complex lipid and protein networks involved in synaptic function and plasticity.

Synaptic function crucially relies on the constant supply and removal of membrane. The morphological complexity of neurons poses a significant challenge for neuronal protein transport since the machineries for protein synthesis and degradation are mainly localized in the cell soma. In response to this unique challenge also local microsecretory systems have evolved that appear to be adapted to the requirements of proteostasis of membrane proteins and their role in synaptic neurotransmission. In the past five years we have broadened our scope to address how local organelles and membrane trafficking serve the needs of synapses.

To achieve our goals, we use a multi-disciplinary approach with studies ranging from single molecules to in vivo animal experimentation. We also address translational aspects where we try to understand whether the processes that we investigate might be relevant for disease. To achieve these goals, we tightly collaborate with the Leibniz Group 'Dendritic Organelles and Synaptic Function' at the ZMNH in Hamburg.

» **Our research aims to bridge molecular analysis of synaptic proteins to neural circuit and engram analysis.**

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Neuromodulators bring the flow into the brain

Everyone has been in that situation - the to-do list is full, and somehow you can't really get on with any task. You're not on top of things, you are just not in the flow. Our team wants to understand how the neuromodulator norepinephrine enables us to fully concentrate on one thing and block out other impressions, learn things effectively, and be cognitively flexible.

First, we examined where exactly in the brain noradrenaline is released. The noradrenergic system is anatomically organized as a network that traverses the entire brain with a fine network of noradrenergic axons. The starting point of this network is a small nuclear area in the brainstem: the locus coeruleus. The noradrenergic axons have slight thickenings at regular intervals, called varicosities, which can secrete noradrenaline. This structure allows noradrenaline to be released anywhere in the brain, but an important question remains: How is the release of norepinephrine orchestrated towards specific areas?

Brain areas for planning give input to the locus coeruleus

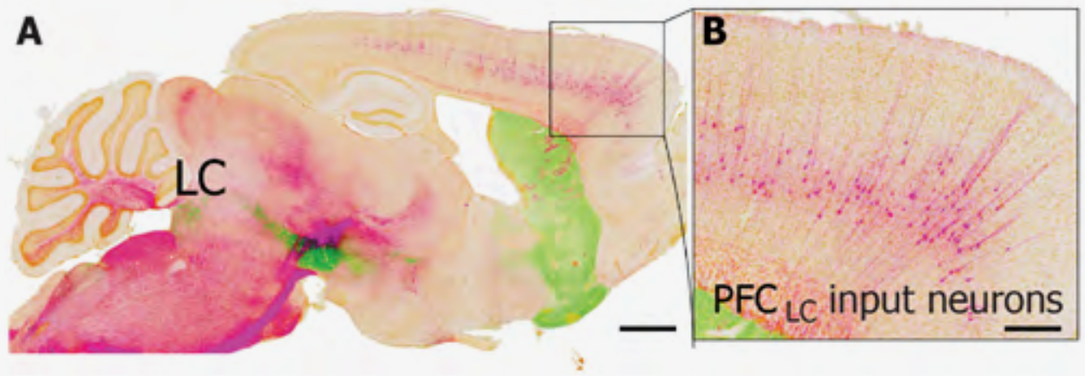
Locus coeruleus neurons have autonomic activity that allows them to discharge once or twice per second. Each discharge in the cell body also releases norepinephrine in the axons. But how specifically can individual neurons in the core area be activated to send axons to specific brain arteries, controlling the concentration of norepinephrine in those areas? Using viral tools, such as a virus specifically optimized for research that infects synapses, we can label the neurons that send information to the locus coeruleus. It turns out that predominantly neurons from the deep layers of the cortex contact the norepinephrine-producing cells. Interestingly, these neurons are mainly found in the frontal areas of the brain. These are the areas to which higher cognitive functions are attributed, such as planning strategies or merging different pieces of information into an overall picture.

Both activation and inhibition of the locus coeruleus are crucial for the flow

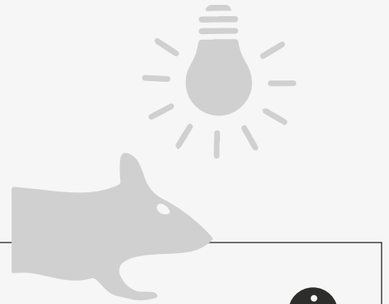
To study the function of these neurons, we used optogenetics. This involves introducing the DNA of a light-sensitive ion channel from an alga into the neurons. When exposed to blue light, the neurons discharge and an action potential is triggered with in the neuron.

Using electrophysiology, we showed that each time we shine a short pulse of light on the frontal cortex, several rapid discharges are measurable in neurons of the locus coeruleus. These discharges of 15 to 20 action potentials per second are followed by a period in which there are no discharges at all for several seconds. Following this observation, we then actually discovered inhibitory neurons scattered around the locus coeruleus that also receive input from frontal neurons (Figure 1 C). What does this mean now? Neurons from frontal, cognitively higher areas can relay information to some neurons in the locus coeruleus, which then abruptly release high concentrations of norepinephrine in specific brain areas. At the same time, inhibitory neurons are also activated, that are then curbing activity in the neurons of locus coeruleus. We believe that information arriving during phases of high norepinephrine concentration can be processed more accurately and for longer periods in cortical areas. In the subsequent phase with low levels of norepinephrine, it is more difficult for new to get processed. The cortex remains preoccupied with the previous signals.

Interestingly, during the phase of high discharges of neurons in the locus coeruleus triggered by the frontal cortex, a high concentration of norepinephrine is also released in the core area of the nucleus itself. In collaboration with the University of Magdeburg, we were able to show in a computer simulation that the release of norepinephrine from activated neurons leads directly to inhibition of neighboring neurons in the densely packed nucleus. Norepinephrine is released from activated cells, diffuses to neighboring neurons, and activates inhibitory receptors there. We now believe that the inhibited neurons send axons to other brain areas, and norepinephrine levels decreases in these areas. This temporarily creates a functional contrast that enhances and prolongs processing in some brain areas while suppressing processing in other brain areas (irrelevant to the task) - we have arrived at flow (Baral et al. 2022 BioRxiv).



Neurons from the frontal area of the brain (PFC) activate the locus coeruleus (LC) and then inhibit it again via inhibitory neurons a few seconds later. This contrast between phases of high activity and inhibition influences our attention. In A and B, a longitudinal section of a mouse brain is shown in which the neurons that conduct information to the LC are colored in pink.



Read more

Baral S, Hosseini H, More K, Braun J, Prigge M (2022) Exploring volume mediated bystander-inhibition in a neuron model of the Locus coeruleus. bioRxiv. https://doi.org/10.1101/2022.02.13.480256

Neuromodulatory Networks

Our team is researching the neuronal networks for dopamine and noradrenaline, which influence our ability to learn. These networks consist of a central nucleus and an extensive network of axons. They modulate alertness, motivation, our curiosity or our cognitive flexibility. We are less interested in HOW the brain stores information, but rather the neuronal conditions that make it possible effective storage of information. It is not only this indirect reference to learning that poses challenges us, but also that these neuromodulatory networks span the entire brain and can simultaneously influence several areas of the brain in different ways. We are meeting these challenges by developing new technologies.

Together with an international consortium, we are investigating why neuromodulatory networks in Parkinson's disease degenerate so early. Our hypothesis is that the transport of molecular waste products in the affected cells leads to overload faster than in other neurons. The network then attempts to compensate for the loss of some neurons by increasing neuronal activity, which in turn accelerates the death of the cells. We believe that the GABAergic neurons we've identified can normalise activity in the nucleus. This project is funded by the Michael J Fox Foundation and Aligne Science Against Parkinson's.

In another project, we are trying to identify opsins from South American and African chilids, which are found in deep or turbid waters. We believe that evolutionary pressures have made these opsins to be highly sensitive to light. We use these ultra-sensitive opsins to monitor the activity of neurons through transcutaneous light stimulation.

» **To idenfity and maniplulate intrinisic neuronal mechanism for effective learning will have a prounounced impact in our soceity in the upcoming 20 years.**

Dr. Matthias Prigge

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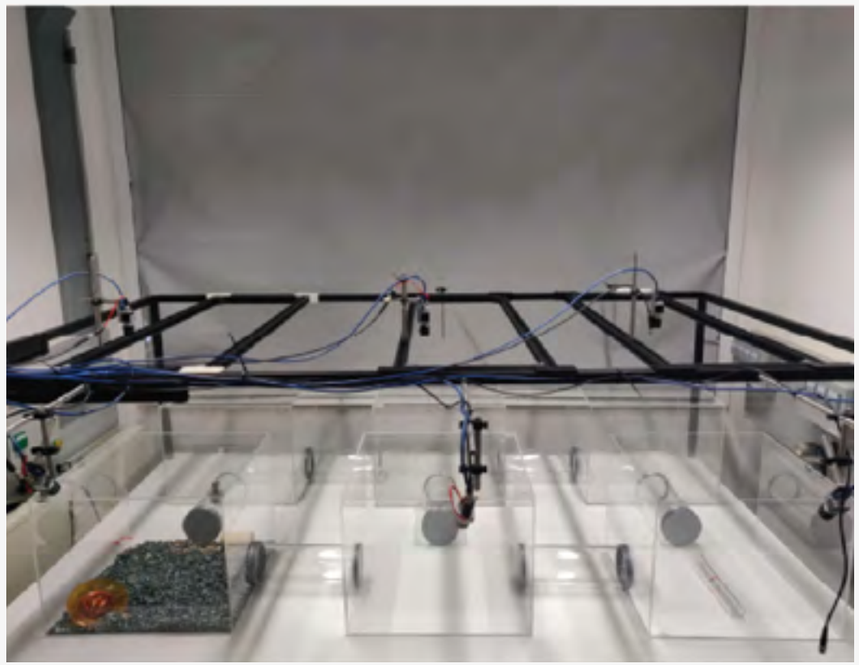
HELP! How mouse cities influence their inhabitants

“I am not ony interested in how they move, I am interested in what moves them” said Pina Bausch, a renowened German dancer. In fact, movement is related to nearly all our cognitive and emotional actions. We move to reach a specific place, receive a reward, flee from a dangerous situation, or help an individual in need (Mocellin & Mikulovic, 2021). But what is happening in our brain when we make a decision about our next move? How do these actions influence our learning and memory? And how does the environment in which we live, including stress and anxiety level, as well as availiability of resoruces, modify our decisions? These are the questions that our group attempts to answer.

Two brain regions ideally positioned to study the abovementioned questions are the septal area (including its medial and lateral subregions) and the hippocampus (including its dorsal and ventral subregions). In our ongoing work, we are monitoring cell activity in these brain regions, while mice are running on a tradmill and learning the positions of specific stimuli (motor, appetative or aversive ones). We found that specific and different brain rhythms and circuits are predicting the valence of the subsequent movement (Korvasova et al, 2021; Mikulovic et al, in preparation).

In a new research line that we started at the LIN, we aim to understand the neural mechanism underlying the “move to help”. While helping behaviour has been attributed solely to humans for a long period of time, we now know that also animals, including rodents, can help each other. And also as humans, some are more helpful than the others. But why is this the case? What is happening in our brain when we decide to help or not? Is this behaviou hard-coded in our personality, or can we learn to be good?

While still at the beginning of tackling these question, we alrady found specific cells in the brain which activity is predicting future move to help. Ongoing experiments will answer answer whether these cells are also necessary for helping behaviour to occur. In addition, in collaboration with Pavol Bauer (T-Systems Germany) and Sebastian Stober (OVGU Magdeburg), we are develping computational methods to study 3D mice pose estimation (Sarkar et al, 2021). With this method, we plan to answer how mice behaviour and interaction with others underly their motivation to help.



“Mice cities”: setups were built to study long-term social behaviour in mice (left). Identification of individual mice is possible by using different color patterns (right).

Read more

Mocellin P, Mikulovic S. 2021. The Role of the Medial Septum - Associated Networks in Controlling Locomotion and Motivation to Move. Front. Neural Circuits. https://www.frontiersin.org/articles/10.3389/fncir.2021.699798/full

Korvasová K, Ludwig F, Kaneko H, Sosulina L, Tetzlaff T, Remy S, Mikulovic S. 2021. Locomotion induced by medial septal glutamatergic neurons is linked to intrinsically generated persistent firing. BioRxiv. https://doi.org/10.1101/2021.04.23.441122

Sarkar I, Maji I, Omprakash C, Stober S, Mikulovic S, Bauer P. 2021. Evaluation of deep lift pose models for 3D rodent pose estimation based on geometrically triangulated data. CV4Animals Workshop, CVPR 2021. https://arxiv.org/abs/2106.12993

Cognition and Emotion

Our group has been launched at the LIN in January 2021. While starting in the middle of pandemic was definitely a challenging task, we are very happy and proud about everything we reached in the last years. Our group has been formed, new members came and all setups needed to study our questions of interest were built.

We are especially happy to have established a novel behavioral paradigm investigating helping behaviour in mice and built “mice cities” to study how long-term social interaction and environmental modifiers influence this type of behaviour.

To achieve this goal and answer how “mice personality” affects their social behaviour, we are using machine learning algorithms in collaboration with Pavol Bauer (senior data scientist at T Systems Germany) and Oren Forkosh (PI, Hebrew University of Jerusalem, Israel).

One of the highlights of 2021 was LINdoscope course focusing on imaging and data analysis techniques, that our group has organized together with other junior PIs at the LIN and Magdeburg. This course has attracted significant international attention and was a great success for everyone involved.

» **The best discoveries come when we are truly passionate about the questions we ask.**

Dr. Sanja Bauer Mikulovic

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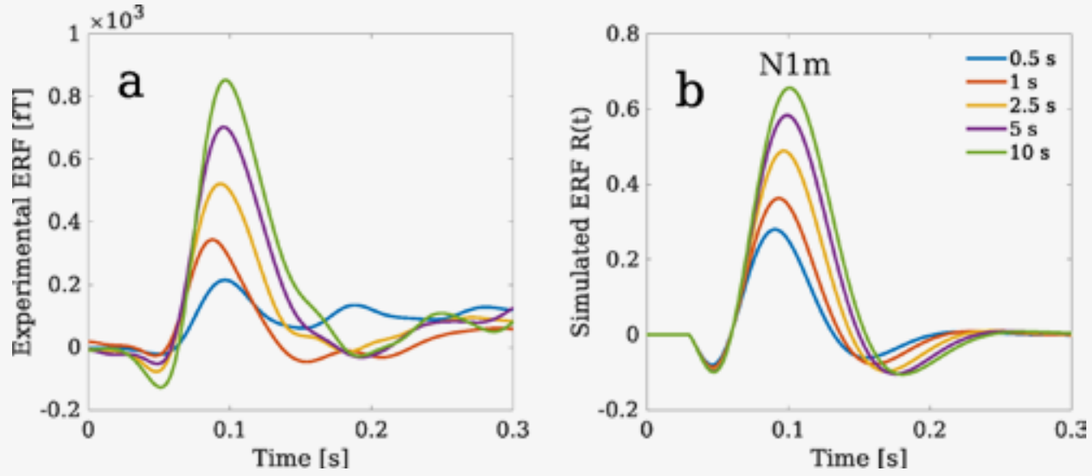
Model of the functioning of the auditory cortex

We have continued our efforts towards a deeper understanding of the general principles underlying sensory memory in auditory cortex (AC) and to further intertwine our experimental research on humans and monkeys by means of computational modelling. The auditory cortex comprises several tonotopically organised cortical fields, which differ in number and size across species, but share a general hierarchical organization: At the centre are the core fields, which receive auditory input from the subcortical auditory pathway. The activity in the core fields then propagates to a set of belt fields surrounding the core, and from the belt, the signal spreads to parabelt fields.

Our research during the reporting period focused on neuronal adaptation, a basic form of memory, which expresses itself as the attenuation of neural responses when stimuli are presented in quick succession. We hypothesize that short-term synaptic depression in conjunction with anatomical structure of AC is a potential candidate for the mechanism underlying adaptation. We examined this hypothesis by using a computational model of AC, with anatomical structure and short-term plasticity as central features. This is allowing us to integrate our results across spatial levels of AC activity.

Our modelling approach provides a fundamentally new view on AC activity. First, it suggests that the AC behaves as a set of independent oscillators, which, in mathematical terms, are called normal modes, with the waveform of the state variables being a weighted superposition of all normal modes in the system. We show that adaptation can be accounted for as modulations of these normal modes, and that repetition suppression is due to a mixture of causes, with stimulus repetition modifying both the amplitudes and the frequencies of the normal modes. In this view, adaptation results from a complete reorganisation of AC dynamics rather than a reduction of activity in discrete sources. Second, the spatio-temporal pattern of the cortically generated event-related field (ERF) represents a superposition of all the oscillating normal modes, i.e. the ERF is a system property of the entire AC, with the neural activity on all spatial levels being explicitly dependent on the core-belt-parabelt structure of the AC. Third, the inter-subject variability of ERFs in response to a repeated pure-tone stimulation is not just noise, but reflects subject-specific neural dynamics and topography of the human AC. This is seen in repetition suppression of the peak amplitude of the N1m, the most prominent ERF wave in human AC that peaks at around 100 ms after stimulus onset. Moreover, our results suggest that the latency variation of the N1m is largely related to subject-specific dynamics.

This research is not confined to the auditory cortex of humans, but is embedded in a larger framework, as the core-belt-parabelt structure of the auditory cortex is a common feature of mammals. Future experiments and modelling work may encompass the functional consequences of the wide variety in the size and organization of AC areas across species. This work will also include rodents, with an AC topology simpler than that of primates. In this context, another logical next step is to investigate to what extent adaptation is a network effect whose cross-species variations can be explained in terms of differences in the anatomical structure of the AC.



Our research identifies cross-species principles of how information is temporarily stored and temporally integrated in the auditory cortex. To do this, we use our expertise in human MEG (left) or monkey physiology and computational modelling (right) to formulate and test hypotheses about how the auditory cortex works. The simulated waveforms reproduce the main features of the experimental data very well.

Read more

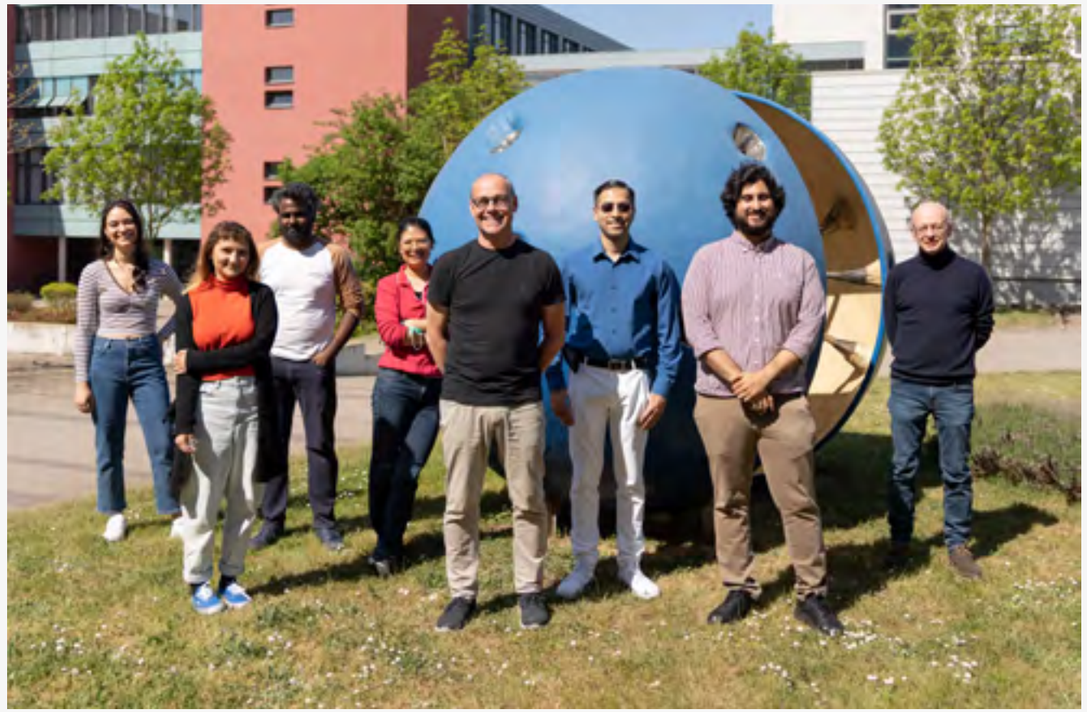
Hajizadeh A, Matysiak A, Brechmann A, König R, May PJC. 2021. Why do humans have unique auditory event-related fields? Evidence from computational modeling and MEG experiments. Psychophysiology. 58(4): Article e13769.

Hajizadeh A, Matysiak A, May PJC, König R. 2019. Explaining event-related fields by a mechanistic model encapsulating the anatomical structure of auditory cortex. Biological Cybernetics. 113(3):321-345.

Comparative Neuroscience

The Research Group Comparative Neuroscience was established in 2020 by merging the former Special Laboratories Non-Invasive Brain Imaging and Primate Neurobiology. Its focus lays in the investigation of neuronal mechanisms underlying short-term memory, drawing on its unique combination of expertise in monkey physiology, human magnetoencephalography (MEG), and computational modelling. Short-term memory is particularly important in the auditory realm, since auditory perception, cognition, and language critically depend on linking sequential sounds, most of which are only temporarily available to the listener, through time. Our work focusses on sensory memory, which automatically stores large amounts of auditory information and decays within a few seconds. It also focusses on working memory, which allows maintenance and manipulation of auditory information that was either recently acquired from the environment or retrieved from long-term memory. To elucidate the underlying neural correlates, we concentrate on the highest level of the auditory system, the auditory cortex (AC), and search for commonalities and differences between primate species.

We focus on neural adaptation as a manifestation of sensory memory, and on the processing of temporal sound patterns as a manifestation of temporal integration using sequential processing paradigms. We explore the consequences of synaptic depression in the computational model of AC we have been developing. The predictions related to memory and integration are tested via recordings of single-neuron activity and local field potentials in monkey AC and simultaneous MEG and EEG measurements in humans using several complementary experimental paradigms. Further, we test whether AC is causally related to working memory. To this end, we modify activity in the auditory cortex of monkeys by means of intracranial direct current stimulation or of dopamine antagonists and expect that these interventions change their ability to perform auditory memory tasks.



» **We combine computer simulations with experimental data obtained from the auditory cortices of humans, non-human primates and rodents. This allows us to much better formulate hypotheses about the functioning of the auditory cortex, derive predictions, and test them in experiments.**

Prof. Dr. Michael Brosch und PD Dr. Reinhard König

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How does the brain predict the consequence of an action?

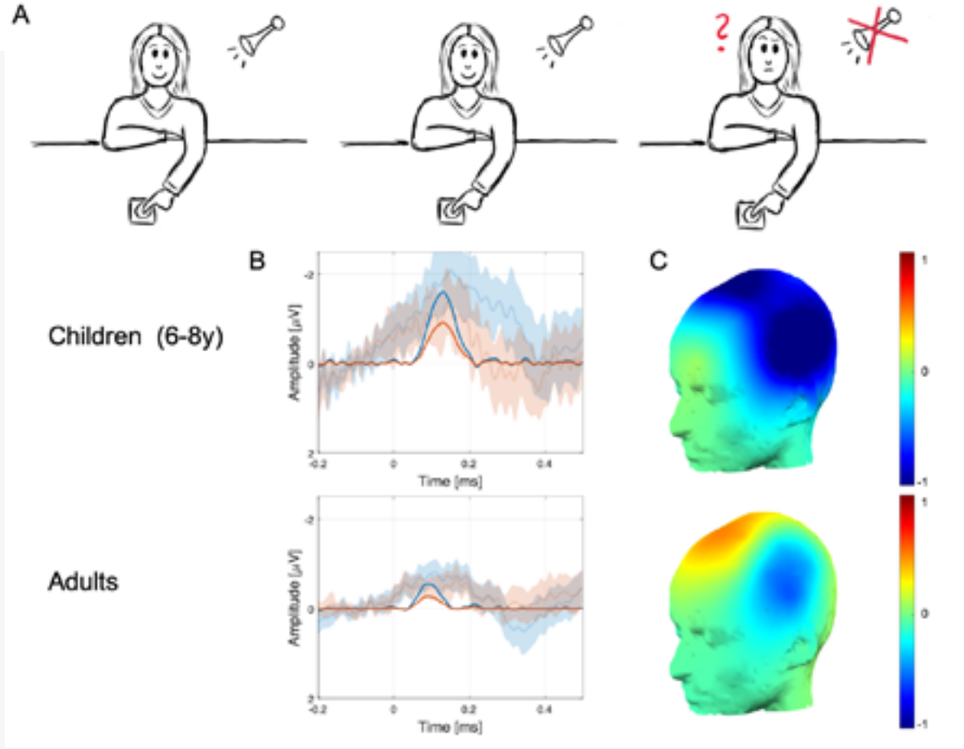
Are you familiar with the scenario in which a young child repeatedly drops a toy on the floor in order to intently listen to the result of this action? This behaviour is necessary to learn the association between actions and sensory consenquences which is a prerequisite for developing perception. If the actual sensory-action consequence does not match expectation, the brain will generate an error signal. The results of our studies support the hypothesis that these prediction errors are an important source for learning and development during childhood.

The brain perceives the external world through the sensory organs. However, the human brain does not only react to perceived stimuli from outside, but also relies on internal unconscious processes to predict what one would see, feel, hear or smell on the basis of existing knowledge of the world. These predictions make it possible for humans to perceive changes accurately and respond appropriately in often unstable environments. Occasionally a prediction is wrong and it is therefore important for the brain to recognise and correct wrong predictions.

In order to investigate these predictions more closely, a study was created in collaboration with a research team from the University of Leipzig. We asked adults to press a button in a one second rhythm whereby each button press was followed by a specific sound like the sound of a trumpet. This ensured that the brain expected a trumpet sound on each button press. At the time of the button press, it is assumed that sensory areas compare this expectation to what actually happens. Occasionally, we omitted the trumpet sound after a button press. This violation of expectation drew attention from our participants. While measuring the brain activity with EEG, it was possible to detect a change in the brain activity already 100 ms after the button was pressed. The brain region that perceived the error, in this case the auditory cortex, sent a signal to higher-level brain areas to convey that the prediction was wrong. This is how the brain is able to learn from its mistakes to improve future predictions. We were also interested in how specific this prediction mechanism is. Does the brain also form a prediction if the sound changes after each button press? In this case the brain could predict that a sound would follow on the button press, but not exactly which sound it would be. The results of our study show that the brain can also form a prediction in this more uncertain circumstance, but the prediction error is much smaller. The brain can thus form predictions (albeit less accurate) based on inconclusive evidence but assigning less weight on these predictions.

Despite the fact that prediction plays an important role in learning- and developmental- models, little is known about the underlying brain mechanisms. For this reason we asked 6-8-year old school children to perform a similar task like adults mentioned above. Again we measured brain activity after unexpected omissions and expected sounds. We wanted to know whether children could also form predictions as precise and as flexible as the adults did, despite the processing of auditory signals during middle childhood not being fully mature. Our results show clearly that children can indeed make specific and unspecific predictions as flexibly as adults do, regardless of the maturity of their auditory processing mechanism.

Our results support current theories that deem action and prediction errors as important drivers of cognitive development. These subconscious prediction processes are seen as fundamental functions of the brain. We could show that this mechanism is highly flexible and matures earlier than previously assumed.



(A) A sound followed after each button press, except occasionally the sound was omitted. (B) The omission of an expected sound resulted in an error signal in the brain, which was increased when the prediction was precise (blue line) compared to when the prediction was not precise (red line). (C) The error signal is presumably generated in the areas of the brain responsible for auditory processing (blue marked area close to the ear).

Read more

Dercksen TT, Widmann A, Schröger E, Wetzel N. 2020. Omission related brain responses reflect specific and unspecific action-effect couplings. NeuroImage. 215:116840.

Dercksen, T.T., Widmann, A., Scharf, F., & Wetzel, N. 2022. Sound omission related brain responses in children. Developmental Cognitive Neuroscience. 53, 101045.

» **Attention develops during childhood. Successful control of attention benefits many learning processes and therefore it is important for educational concepts to consider these developmental processes.**

Prof. Dr. Nicole Wetzel

Neurocognitive Development

Our vision is to foster an indepth understanding of the development of attention. The ability to focus on relevant information and to ignore everything irrelevant is crucial for learning success, which directly influences school achievements. The research group Neurocognitive Development investigates the development of attention, more specifically attention in the auditory modality. We are interested in influencing factors such as emotion and digital media and the related learning- and memory processes on the level of behaviour and the brain. We also include children that suffer from attention-related disorders.

Results from our research in 2020/21 show a significant development of auditory attention between the ages of 4 to 10 years. Children in primary school are especially sensitive to the novelty of distracting events. We could show that emotional content of distractor stimuli influences early information processing and attention processes. In a project that studied episodic memory in 8 to 9 year old children, it was possible to predict on the basis of changes in pupil dilation, how well pictures could be memorised and thus we could make predictions regarding learning success. This could potentially be used for developing appropriate learning materials. In another project, we investigated how children form predictions from their environment. Digital media increasingly influences the leisure activities and communication practises of our children. From a neurocognitive perspective, we are interested in how digital media influences attention and learning. In a current study we have shown that playing on a tablet PC has a direct effect on perception and attention.

In our German-French collaboration project (ANR-DFG, WE 5026/4-1), we study the interaction between voluntary (focusing on a task) and involuntary (being distracted) attention. Our research focus is on the influence of different activation states on the attention of healthy children and children with ADHD.

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One molecule - many functions

A regulator for the formation of synaptic contacts

The functioning of the brain depends on the correct plastic-dynamic interconnection of neurons. But how do synapses form in the young, developing nervous system? How are functioning contact points formed at very specific points from protrusions of the neurons, through which excitatory information can be processed? This process is enormously complex and still partly mysterious.

A LIN team led by Rodrigo Herrera-Molina, Eckart Gundelfinger and Constanze Seidenbecher, together with colleagues from Caltech in the USA and Magdeburg University, have been able to solve a part of the puzzle. At the future synapses, the cell surface protein neuroplastin binds to an intracellular signalling protein called TRAF6. The complex of both proteins then promotes the early formation of the excitatory synapses, and does so in a very narrow time window, which in nerve cells in culture lies exactly between days 6 and 9. If the TRAF6-neuroplastin complex is blocked experimentally during this period, the affected neurons have fewer excitatory synapses and are less neuronally active. The mechanism deciphered here could also help to better understand diseases such as schizophrenia, which are associated with lower synapse densities (Vemula et al., 2020).

A calcium switch for synapses

The neuroplastin molecule plays an important role not only in developing synapses, but also when the synapses are fully functional. It then binds in the cell membrane to a molecular calcium pump called PMCA, whose task is to quickly lower the calcium concentration inside the cell back to the initial level after activation. If the complex of pump and neuroplastin does not function properly, the selectivity of the calcium signals is lost and neuronal communication is permanently disturbed. Learning and memory abilities suffer.

Calcium ion currents can apparently be regulated with nanometre precision within synapses to precisely control the release of transmitters and the reuptake of empty vesicles. But where does such high precision come from?

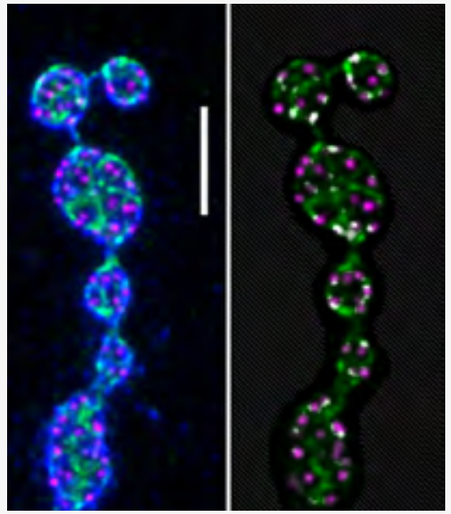
Using the example of neuromuscular synapses in fruit fly larvae, Uli Thomas and Oliver Kobler from the LIN, together with colleagues in Mainz and Berlin, have demonstrated that the PMCA pump is the key to this phenomenon. The PMCA molecular complex is located between the active zones of the synapses and separates the calcium signals for release from those for the dynamic regulation of recycling, so that both processes run parallel to each other in a confined space of only a few nanometres and can be regulated separately (Krick et al., 2021).

This mechanism could explain why mice in which neuroplastin is switched off in the neurons during the learning process no longer show associative learning, whereas in animals that lost neuroplastin only after learning, memory for the learned association fails.

An amplifier in the inner ear

Interestingly, certain mutations in the human neuroplastin gene are associated with deafness. Therefore, Dirk Montag, Rodrigo Herrera-Molina and Max Happel, together with their teams and with colleagues from the CNI laboratory, investigated in mice whether the complete absence of neuroplastin from birth or the later loss of the molecule in adulthood lead to hearing disorders. Using derivations from the brainstem of adult mice lacking neuroplastin, they were able to show that these animals are indeed deaf. With increasing age, the hair cells and spiral ganglion cells in the inner ear degenerate because the lack of neuroplastin also leads to the loss of the calcium pump PMCA and the sensitive cells perish from the disturbed calcium balance.

If neuroplastin is only switched off in adult mice after normal development, then these animals have an increased hearing threshold, i.e. they only hear particularly loud sounds. Surprisingly, a linear relationship was shown between the number of outer hair cells in the inner ear that express neuroplastin and the hearing threshold, because these cells normally amplify the acoustic signal, and their malfunction makes people hard of hearing or even deaf (Lin et al., 2021).



Molecular topography in the service of synaptic precision: At the motor neuron terminals in fruit fly larvae (blue), the positioning of PMCA/neuroplastin complexes (green) away from glutamate release sites (magenta) provides the necessary separation of the calcium-controlled processes.

Read more

Lin, X., M. G. K. Brunk, P. Yuanxiang, A. W. Curran, E. Zhang, F. Stöber, J. Goldschmidt, E. D. Gundelfinger, M. Vollmer, M. F. K. Happel, R. Herrera-Molina, D. Montag (2021b) Neuroplastin expression is essential for hearing and hair cell PMCA expression. Brain Structure and Function, online April 12 2021. doi: 10.1007/s00429-021-02269-w

Krick N, Ryglewski S, Pichler A, Bikbaev A, Götz T, Kobler O, Heine M, Thomas U, Duch C. 2021. Separation of presynaptic Cav2 and Cav1 channel function in synaptic vesicle exo- and endocytosis by the membrane anchored Ca2+ pump PMCA. Proceedings of the National Academy of Sciences of the United States of America. 118(28):Article e2106621118. https://doi.org/10.1073/pnas.2106621118

Vemula SK, Malci A, Junge L, Lehmann AC, Rama R, Hradsky J, Matute RA, Weber A, Prigge M, Naumann M, Kreutz MR, Seidenbecher CI, Gundelfinger ED, Herrera-Molina R. 2020. The Interaction of TRAF6 With Neuroplastin Promotes Spinogenesis During Early Neuronal Development. Frontiers in Cell and Developmental Biology. 8:Article 579513. https://doi.org/10.3389/fcell.2020.579513

Cooperation is what counts

Our brain consists of a right and a left hemisphere. Both hemispheres have different functions in perception and learning. One of the most important "switching stations" for processing our acoustic environment is the auditory cortex. Here, too, the tasks are distributed between the left and right hemispheres: Thus, rapid temporal changes are processed more in the left hemisphere and continuous changes in pitch more in the right. For the processing of complex stimuli such as speech and music, both hemispheres are therefore needed and they must work together. If this does not work efficiently, for example in old age or with conditions such as schizophrenia, dyslexia and tinnitus, this can lead to problems in hearing or understanding what is heard.

What are you researching?
We want to find out what happens when the cooperation of the two hemispheres is disturbed during auditory processing. To do this, we are working with Mongolian gerbils. How do these disturbances affect the animals' behaviour, how are they reflected in the activity patterns of the brain, and can they be compensated for? How can these findings be used to develop therapies for people with disturbed hemisphere interactions?

How do you go about this?
For our research, gerbils learn to perform auditory tasks. These are very similar to those used in human studies and are based on basic acoustic properties of speech and music. We then use functional magnetic resonance imaging (fMRI) to investigate how these tasks are processed throughout the mice's brains and, in particular, how the hemispheres work together in the process. In the next step, the cooperation of the hemispheres is specifically interrupted, which is not possible in humans. We then observe how the brain deals with this disruption and compensates for it through plastic changes.

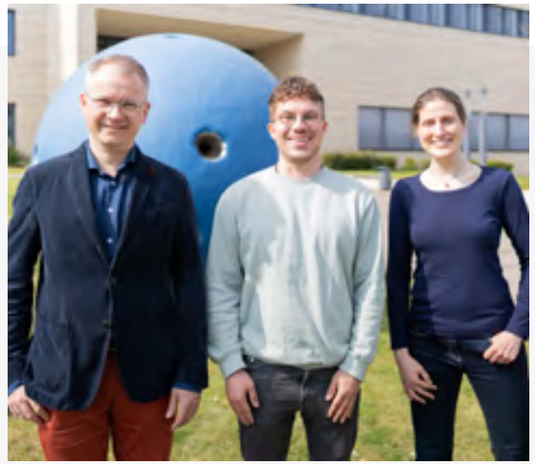
What have you found out so far?
In the Combinatorial NeuroImaging Core Facility (CNI) and other departments at the LIN, the involvement and interaction of the hemispheres in hearing has been studied for many years from different research perspectives (human/animal and basic research/clinical). We have been able to show that the left and right auditory cortex process different physical parameters of acoustic stimuli and that not only the two brain hemispheres themselves, but also their interaction are significantly involved in learning these parameters. Task difficulty and age strongly influence the involvement and cooperation of the hemispheres. Thus, in addition to peripheral hearing loss, a reduction in hemisphere interaction in older adults probably leads to the use of additional brain resources responsible for attention and memory, which probably serve to compensate for the hearing problems.

Dr. Nicole Angenstein, Prof. Dr. Eike Budinger and Annika Michalek are dealing with the cooperation of the two hemispheres of the brain during auditory processing and the consequences of the disruption of this cooperation in their joint Special Project.

Somewhere else with your mind

In everyday life we make many experiences. From this we learn how our environment is structured and how we can best react to it. However, our thoughts regularly wander - to things that are on our minds at the moment. This can be, for example, making a shopping list while we are driving.

What exactly do you want to find out?
We are investigating what exactly happens in the brain during thought digression and how the brain still manages to solve the task that is relevant at the moment: Does it intensify the selection of the desired information or does it rather increasingly try to suppress disturbing stimuli? We are particularly interested in whether it is possible to map our environmental information in the brain, to perceive it and to react to important events while our thoughts are actually somewhere else.



Dr. Stefan Dürschmid and Dr. Mandy Bartsch, together with PhD student Paul Schmid, are investigating the phenomenon of mind wandering in their Special Project.

How do you go about this?
We want to see how the brain waves of the test subjects change during mind wandering. To do this, we have test subjects solve visual search tasks on the screen for about an hour, with their thoughts sometimes more and sometimes less focused on the task, which is also tested again and again with queries. During the entire time, we measure the brain activity with the EEG, which records small current fluctuations that accompany the cognitive processes. A special feature here in Magdeburg is that with the MEG we can also measure the magnetic field that results from the brain current changes. This allows us not only to record slow frequencies, as in sleep-like states, but also to examine very high frequencies of over 80 oscillations per second, which can provide clues to the sensory processing of environmental information.

What results are there already?
There is a pretty strong hypothesis in the mind wandering literature that in moments of mind wandering, attention is completely focused inward and we decouple from information from the environment. However, in a study we published, we found that in the activity pattern, a marker for visual attentional selection is actually elevated. Therefore, we assume that the brain can even strengthen certain attentional processes when thoughts digress in order to still perform the task at hand. Furthermore, in another study, we found that even during mind wandering, the transmission of information to the early visual cortex is not impaired. This suggests that we are not directly "disconnected" from sensory environmental information. We think these results fit well with our everyday observations: Every now and then we are asked questions while thinking about something else. But we can sometimes become "time-delayed" aware of what we have been asked and then respond meaningfully to the question.

New electrodes for the brain

Brain-machine interfaces can be used to help neurologically severely damaged patients to communicate with their environment again. However, systems available so far can only read out relatively small amounts of data (one electrode = one signal), and the brain tissue can be damaged by the implantation and the relative movement between the stiff implant and the pulsating brain. Thus, the implant often has to be removed after a short time and the patient's damaged tissue becomes scarred. To solve these problems, the LIN neuroscientists Kentaroh Takagaki, Anja Oelschlegel, Zifeng Xia and Rodrigo Herrera-Molina cooperated with engineers Martin Ecke and Markus Wilke from the Faculty of Mechanical Engineering at the OVGU and developed the "Magdeburg electrode".

What is new about the "Magdeburg electrode"?
On the one hand, this system allows the signal to be tapped at different positions along an electrode at the same time. Secondly, due to the design and the material used, there is neither bleeding nor damage to the affected area of the brain and thus no inflammatory reactions or scarring in the further course: The Magdeburg electrode is almost "invisible" to the surrounding tissue.

How was this progress achieved?
The production of the electrode is interdisciplinary. Neurobiologists and physicians determine the exact positions and shapes for nano-fabrication. Material scientists then use a focused ion beam as a nanostructuring method. In this way, the electrodes can be individually adapted to the type of examination and the patient before the surgical intervention. After implantation, information can be captured directly in the brain, transmitted to the outside and recorded, at different positions along a single electrode using signal multiplexing. This makes the amount of data almost infinitely scalable.

What makes the electrode so stable?
Conventional electrodes have only low long-term stability, which is why long-term stable stimulation procedures have been difficult to achieve until now. The new electrode makes this possible for the first time, as the material used has ideal deformability in tissue and the surface design does not cause any damage. During production, the focused ion beam creates depressions in the micrometre range, which later serve as the cross-linking point of the electrode and the nerve cell in the brain. For a better connection of the neurons to the measuring positions, the electrodes are additionally coated with carbon nanotubes.

What can the electrode be used for?
In research, the electrode will help to better investigate complex processes such as learning, memory and neurodegenerative diseases, as well as the long-term effects of drugs. In addition to pure data acquisition, i.e. the reading of electrical information from the brain, the system also offers the possibility of stimulating or inhibiting individual brain areas in a targeted manner. For brain diseases such as epilepsy, this means completely new diagnostic and therapeutic possibilities, as patients who are resistant to therapy may one day be able to have the rhythm of the nerve cells corrected with permanently implanted electrodes. The underlying method of analogue signal multiplexing in the use of brain electrodes was registered as a patent, and the development team was honoured with 3rd place in the Hugo Junkers "Most Innovative Methods in Basic Research" 2021 competition.

Light cure for nerve cells
Another approach is the so-called optogenetic method, which combines light and gene therapy in the brain to stimulate or inhibit individual ensembles of nerve cells in a particularly targeted manner. In this process, light-sensitive proteins are introduced into nerve cells which, in response to a light signal, regulate the influx of ions with high precision and thus activate or inhibit the neurons.

Since the targeted use of light to regulate the activity of neurons requires an understanding of the brain's signals, additional electrodes are needed to record these signals. Conventional electrodes, however, are opaque. To get around this problem, there are ideas for solutions with novel materials, but they are expensive, difficult to process and not particularly stable. A Magdeburg research team led by Michael Lippert from the LIN and Martin Deckert from the Faculty of Mechanical Engineering at the OVGU has developed a novel foil electrode with LEDs and demonstrated its practicality. This electrode, called CortiGrid, can be used to activate superficial structures of the brain, such as brain areas that control sensory perception. The CortiGrid inventors had already been awarded the 1st place Hugo Junkers competition "Most Innovative Projects in Basic Research" in 2017. In a study published in the Journal of Neural Engineering, the scientists have now demonstrated the usability of this transparent and flexible electrode for simultaneous brain stimulation and derivation of signals.

Proven materials are manufactured a new
The Magdeburg team used proven materials for their electrodes, which are manufactured so thinly that they even surpass the properties of the novel materials - and this without worsening the long-term stability of the implants. This allows the activity of nerve cells to be measured and the same cells to be stimulated with light at the same time. "Instead of relying on complicated materials and processes, our electrodes are characterised by high practicality and low manufacturing costs," explains Marcel Brosch, lead author of the study. "This is an important aspect with rising costs in the healthcare system and increasing demand in our ageing society."

Foil electrode also useful for long-term experiments and medical use
With their work, the researchers have shown that it is possible to develop electrodes that have excellent electrical and optical properties and also provide stable signals in long-term experiments. This is particularly relevant for the planned use in humans, as the electrodes, once implanted, must function faultlessly for years. In the meantime, 15 patents have resulted from this practice-oriented research. The electrodes offer advantages especially for the field of brain-computer interfaces. The combination of transparency, durability and compatibility is an essential prerequisite for success. This further development can thus help patients after paraplegia to regain their sense of touch or blind people to perceive visual impressions again.

Microelectrode array in package with printed circuit board and connector for electrical connection

The authors of the study:
Dr. Michael Lippert (LIN), Martin Deckert (OVGU) and Marcel Brosch (LIN)

Brosch M, Deckert M, Rathi S, Takagaki K, Weidner T, Ohl FW, Schmidt B, Lippert MT. 2020. An optically transparent multi-electrode array for combined electrophysiology and optophysiology at the mesoscopic scale. Journal of Neural Engineering. DOI: 10.1088/1741-2552/aba1a4

The microscopic view

Werner Zuschratter, you were head of the microscopy service area at the institute from 1992. How did a few microscopes become an imaging centre?

→ **Werner Zuschratter:** The cornerstone for Magdeburg as a renowned imaging site was laid back in the early 1990s, when we recognized that for a comprehensive neurobiological understanding of learning, memory and brain plasticity modern imaging techniques at all levels of brain organization will be of utmost importance. We invested into high-end microscopic and macroscopic imaging technology, and soon realized that the growing number of devices, the larger amounts of data and the associated higher demands on data management and image analysis required more staff.

To join forces, to improve the work opportunities for users and to professionalize our service, André Brechmann, our former director Henning Scheich and me secured DFG funds for a Combinatorial NeuroImaging Core Facility (CNI) in 2012, which enables access to cutting edge infrastructure and to promote collaborative research projects across different size scales and species, and which is also accessible to external scientists. To this end, CNI might be regarded as a pioneer of an overarching collaborative imaging community in Magdeburg.

Let's take a look back at your professional career, Mr. Zuschratter. How have microscopy techniques changed over the past decades?

→ **Werner Zuschratter:** When I came to the institute in 1992 there was a great spirit of optimism among all its members. With the introduction of genetically encoded dyes and the discovery of numerous synaptic constituents in the Department of Molecular Biology, there was a need to investigate interactions between synaptic proteins and use the possibilities of confocal and live cell imaging for their dynamic observation. However, various limitations quickly became apparent. These were, on the one hand, the limited spatial resolution, which did not allow conclusions about interactions of two synaptic proteins drawn from co-localisation of their labels. On the other hand, the limited acquisition speed of confocal microscopes did not allow recording of fast movements, e. g. of small vesicles. Moreover, we found that irradiation with high light intensities, as used in confocal and 2-photon microscopy, harms living cells and tissues after a short time.

Together with your team, you developed an ultra-high resolution research camera. What was your motivation?

→ **Werner Zuschratter:** For the reasons mentioned above, we have been trying to achieve higher resolution by using correlative light- and electron microscopy approaches and by means of Förster resonance energy transfer (FRET) to investigate interactions of proteins in cells. In this respect, we started researching imaging detectors with high temporal resolution and extreme sensitivity as part of EU funded projects. Our activities eventually led to the installation of two super-resolution STED microscopes and several BMBF grants to develop an ultra-sensitive, time-resolving research camera based on the principle of single photon counting. The latter was patented, received several research awards and finally led to the spin-off Photonscore GmbH, which now markets the research camera under the name “LINCam”.

Hongbo Jia, you have already gained experience as a laboratory manager in China and in Munich. What particularly appealed to you about the new task here in Magdeburg?

→ **Hongbo Jia:** For me this was a unique chance in the sense that there is perhaps nowhere else in the world a unified institutional core facility that offers the full functional spectra of imaging instruments and services from high-resolution cellular and tissue microscopy to whole-brain human imaging. This is of course, realizable only with multiple peoples’ expertise together as a whole, which, by philosophy attributed to Aristotle, is greater than the sum of its parts.

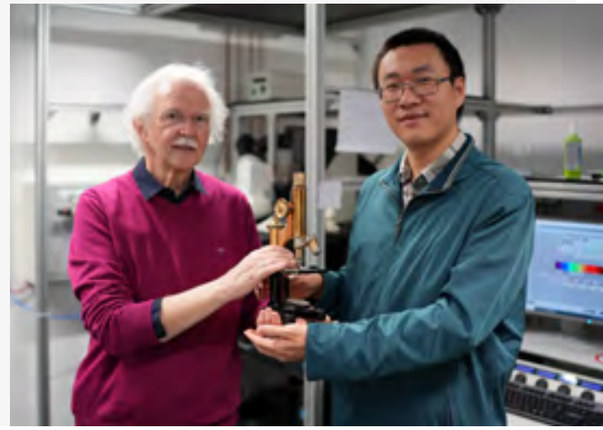
I think my personal spectrum of technical expertise fits well in the team by leading the microscopy section while my colleague André Brechmann leads the macroscopy section, together with a broad range of other colleagues, each specialized in one of the imaging techniques. I am happy that I could take over the task as microscopy team leader from Werner Zuschratter who is leaving the team leadership with a fine record, with many achievements, which have profoundly transformed the microscopy service unit to the benefit of its users.

What are new projects and challenges in the future?

→ **Hongbo Jia:** The CNI is a very good concept, and I believe that in the upcoming years there could be good science output achieved by a genuine combination of the full spectrum of the imaging techniques. This will involve not only members of the CNI but also members of the research departments of LIN. In other words, the newly reformed CNI is a miniaturized projection of the entire LIN such that a selected subset of people converges on a few highly interlinked scientific questions with one core – neurobiological mechanisms of learning and memory, and makes use of all the available imaging instruments and expertise to tackle those most challenging questions in concurrent brain research, thus significantly contributing to the understanding of learning and memory-associated brain processes. And this not only for people from just Magdeburg or Germany but also worldwide.

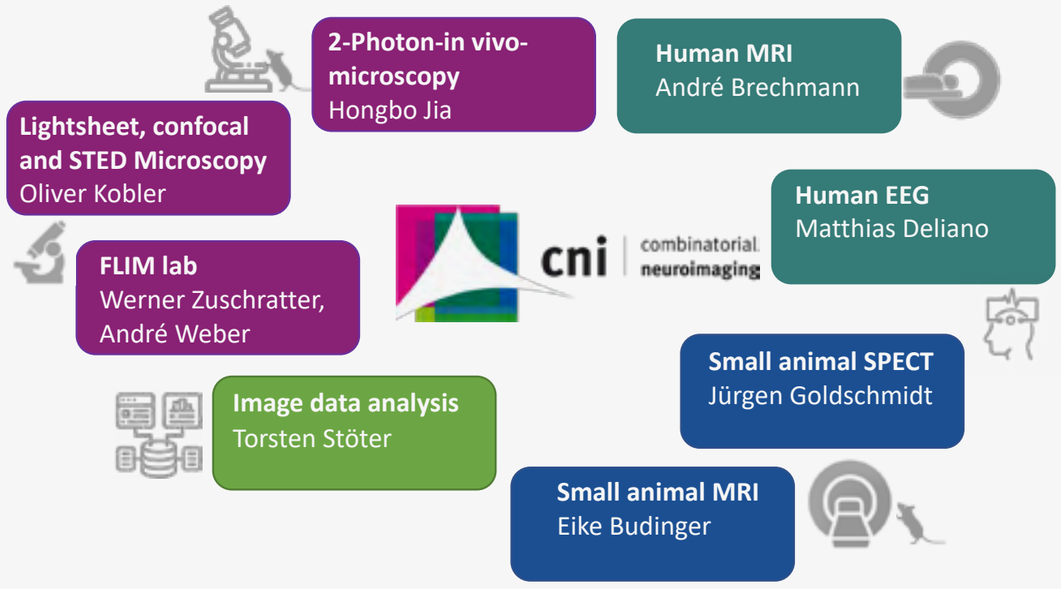
→ **Werner Zuschratter:** In general, I see the safe and responsible handling of data as the greatest challenge for the future. The amount of data, the complexity of the methods and the computer-based evaluation procedures have increased enormously in the past 30 years. This means that entire networks of neurons in the brains of mice can now be observed, analysed with artificial intelligence-based algorithms and modulated or manipulated with optical methods. Therefore, the neurosciences in general and especially the scientists who use and further develop these methods have a great responsibility for ensuring that the findings are used for the benefit of society, but not abused by autocratic governments for mind control and manipulation of people's free will.

All in all, I look back gratefully on 30 years of good cooperation in my team, with the scientists of the research groups and departments, the colleagues in administration, workshop and animal house. I'm also a bit proud having been involved in setting up the core facility CNI. After the recent excellent evaluation CNI is well positioned for future challenges. Hence, I wish the team every success in their work.



Combinatorial NeuroImaging Core Facility

The CNI Core Facility hosts and provides access to a broad range of imaging techniques for high resolution microscopy as well as animal and human brain imaging for bridging the gaps between molecular, cellular, and systems level neuroscience research across species. CNI staff members also perform own research projects to ensure robust state-of-the-art imaging technology, remove technological barriers and facilitate LIN-projects on learning and memory.



Team

Heads
Dr. André Brechmann (Coordinator for systemic imaging)
Dr. Hongbo Jia (Coordinator for microscopic imaging, from 01/2022)
Dr. Werner Zuschrater (Coordinator for microscopic imaging, until bis 12/2022)

Group leaders
Dr. Nicole Angenstein
Prof. Dr. Eike Budinger
Dr. Matthias Deliano
Dr. Jürgen Goldschmidt
Dr. Rodrigo Herrera-Molina

Postdocs & expert staff members
Dr. Heidi Faber-Zuschratter
Dr. Oliver Kolber
Dr. Jörg Stadler
Torsten Stöter
André Weber
Patricia Wenk
Dr. Susann Wolff

Doctoral Students
Fahmida Akter
Rituparna Bhattarcharjee
Anna Groppe
Marcel Lommerzheim
Jing Ma
Annika Michalek
Norman Peitek
Peggy Seidel

Diploma and Master Students
Franziska Bischoff
Lisa-Marie Goncalves
Tobias Gottschall
Philipp Wittkopf
Annika Zacher

Students, guests and trainees
Frank Angenstein (DZNE Magdeburg)
Ana Belén de Landeta (Universität Buenos Aires)
Lukas Hessel
Jan-Richard Sprigade
Nastaran Takmil
Emma Luisa Wille

Technicians and lab service
Renate Blobel-Lüer
Andreas Fügner
Anke Michalsky
Holger Reim
Gabriele Schöps
Janet Stallmann
Sybille Tschorn

CONGRATULATIONS

Doctoral theses

Dr. Francesca Abela (2020)
Role of the auditory cortex during learning of frequency modulated sounds

Dr. Fahmida Akter (2020)
Effects of Chronic Taurine Supplementation on a Rodent Cognitive Learning task

Dr. Armand Blondiaux (2021)
Modulation of the Brain's Extracellular Matrix in Mouse Models of Epilepsy

Dr. Michael Brunk (2020)
Dopaminergic influence on cortical processing in rodents by optogenetic stimulation of the ventral tegmental area

Dr. Eneko Pina Fernandez (2021)
The Role of Piccolo and Bassoon in the Regulation of Voltage-Gated Calcium at Presynaptic Neurotransmitter Release Sites

Dr. med. Julius Heil (2021)
Der Einfluss von Einzelnukleotid-Polymorphismen verschiedener Gedächtnis- und Krankheits-assoziierter Gene auf das Volumen des Hippocampus und seine Input- und Output-Regionen

Dr. Hendrik Griep (2021)
Die Rolle des Pulvinars bei der Verarbeitung von Distraktoren und visueller Suche

Dr. Haydée Guadalupe García-Lázaro (2020)
Neural mechanisms of global attention- and reward-related selection in human visual cortex

Dr. Solveig Jandke (2020)
Untersuchung des Zusammenhangs von hypertensiver Arteriopathie und zerebraler Amyloidangiopathie im Modell der spontan hypertensiven stroke-prone Ratte

Dr. med. Lennart Junge (2021)
The regulation of the expression of PMCA isoforms by neuroplastin has an impact on the calcium clearance in cultured hippocampal neurons

Dr. Oliver Kobler (2020)
Struktur und Dynamik der neuromuskulären Synapse von Drososhila melanogaster: Untersuchungen am Dlg-Gerüstkomplex mittes hochauflösender Lichtmikroskopie und 3D/4D-Bildanalysen

Dr. Xiao Lin (2021)
Significance of Neuroplastin and its paralog Basigin for Plasma membrane-associated Ca^{2}+ ATPases in the central and peripheral neurvous system

Dr. Ayse Malci (2021)
Participation of PMCA-Neuroplastin complexes in neuronal Ca^{2}+ regulation, signaling and plasticity

Dr. Alice Weiglein (2020)
Behavioral and optogenetic analyses of reinforcement processing in larval Drosophila

Dr. Maria-Marina Zempeltzi (2021)
Task rule and choice are reflected by layer-specific processing in rodent auditory cortical microcircuits, Development of long-term chronical current source density in auditory cortex in awake, behaving Mongolian gerbils

Master theses

Sümeryra Aksit (2021)
Cortical circuit proscessing of FM-Tones
during auditory learning and task change

Fatima Amin (2021)
A pharmacological approach for studying dopaminergic mechanisms of punishment and relief learning in adult Drosophila melanogaster

Mohammed Istaque Amin (2021)
Attentional Modulation of Spinal
Responses to Median Nerve Stimulation

Anastasia Chrysidou (2020)
The effect of age on rapid spatial
coding of tactile body maps

Lisa-Marie Goncalves (2021)
Auswirkungen regelmäßiger sportlicher Betätigung auf die Struktur und kognitiven Leistungen des Gehirns untersucht mittels Magenetresonanztomographie am Rattenmodell

Johanna Kneidinger (2021)
Differences in auditory distraction
during L1 and L2 reading

Felix Werner Georg Kuhn (2021)
Investigating forward enhancement and
forward inhibition in auditory cortex
using computational modeling

Sabina Nowakowska (2021)
Prefrontal cortical circuit activity during
reversal learning in freely-moving Mongolian gerbils

Charitha Omprakash (2020)
Does movement result in
enhanced perceptual precision?

Parthiban Saravanakumar (2021)
Exploratiory attentional resource allocation by the anterior prefrontal cortex in a rodent foraging model

Paul Rocco Schmid (2021)
Mind Wandering: Aufmerksamkeitseffekte
anhand der C1-Komponente des EEG

Harini Srinivasan (2021)
Regulation of calcium extrusion by Neuroplastin-PMCA in glutamatergic neurons

Igor Fabian Tellez Ceja (2020)
Impact of stimulus features on BCI performance induced by lateralized attention-based EEG signals

Sindram Volkmer (2021)
Analysis of developmental
processes and experimental moderators

Alina Zacher (2021)
Anatomy of neurotransmitter-specific connections between the auditory cortex and mid- and hindbrain in Mongolian gerbils

Bachelor theses

Patricia Gottschalk (2021)
Scheidungskinder - Psychische Auswirkungen von Scheidungen und Trennungen auf Kinder

Lukas Hessel (2021)
Impact of MR-scanner noise on brain activation patterns in acoustically stimulated Mongolian Gerbil (Meriones unguiculatus) - a CBF SPECT-imaging study

Celine Jakel (2020)
The effects of visual imagery on the representation of verbal information in memory. How does visual imagery influence the memory of verbal descriptions?

Anna Schmitz (2021)
Subjektive Theorien von ErzieherInnen und Grundschul- LehrerInnen zu Stand und Förderung der Aufmerksamkeit und Konzentrationsfähigkeit bei Vorschulkindern

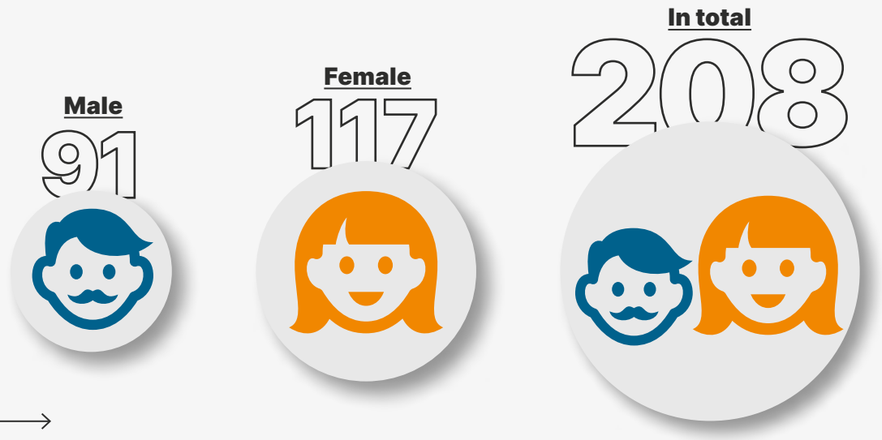
Marie-Christin Schulz (2020)
Elektromagnetische Untersuchungen
zur raumzeitlichen Dynamik von
Farbunterschiedsdiskrimination in
humanen visuellen Kortex

Maximilian Schulze (2020)
Statistische Analyse der Zusammenhänge zwischen grundlegenden auditiven Verarbeitungsfähigkeiten

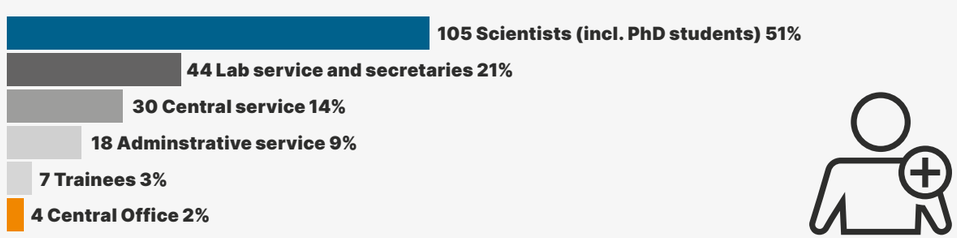
Michael Thane (2021)
Visual Analysis of Drosophila Larval Locomotion
Quantification

Emma Luisa Wille (2021)
Statistische Analyse von Verhaltensdaten - aufgenommen während auditorischem Training im MRT von jüngeren und älteren Erwachsenen

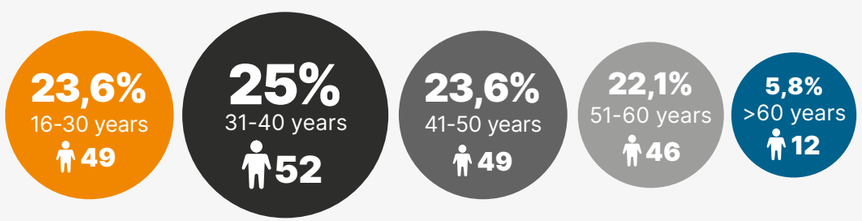
Gender distribution



Work areas



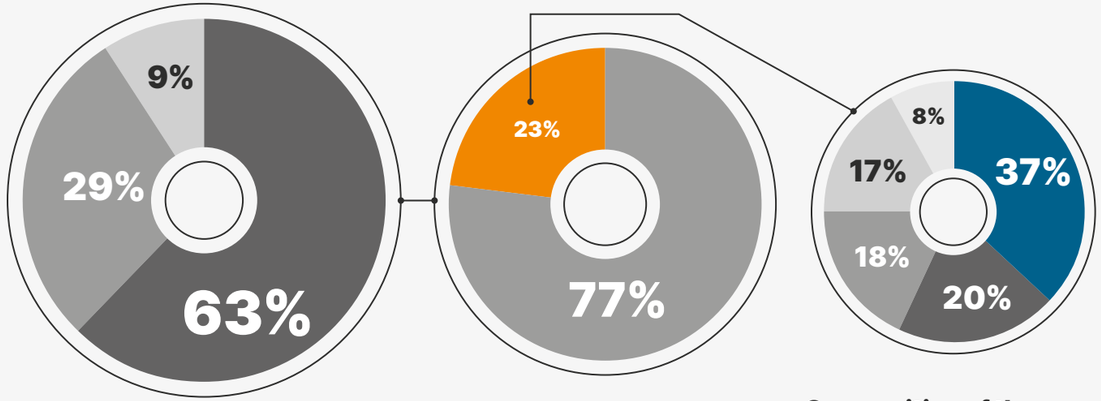
Age of employees



International

Albania 1, Bangladesh 5, Brazil 2, Chile 2, China 3, Colombia 3, Cuba 1, Cyprus 1, Egypt 1, France 3, Hungary 1, India 8, Italy 4, Iran 4, Japan 3, Lebanon 1, Nepal 1, Netherlands 2, Nigeria 1, Pakistan 1, Poland 2, Russia 3, Spain 1, Sweden 1, Tajikistan 1, Taiwan 3, Tunisia 1, Turkey 3, Ukraine 1, United Kingdom 1, USA 2, Zypern 1

20,5 Mio. Euro Budget in 2021



Expenditure

63% Staff costs
29% Material and operating expenses
9% Investments

Expenditure

77% Institutional Budgets
23% Third-party funds

Composition of the third-party funds

37% German Research Foundation
20% Federal government and State
18% Leibniz Association
17% Others
8% European Union

Interview with Dr. Sarah Czerney

In the science system, there are still way more male than female professors, although roughly the same number of men and women finish a PhD. What could be the reasons from your point of view?

→ Yes, that's puzzling, isn't it? This phenomenon, also called "leaky pipeline", persists, despite intensive efforts for more equal opportunities and despite the increasing establishment and professionalisation of gender equality work in science. That this is due to the women and their life choices themselves and that they voluntarily decide to leave science – which one often hears – falls short as an explanation, however. The reasons are much more complex: unconscious gender biases, male definitions of success and excellence, networks that are still strongly male-dominated, the unequal distribution of childcare and household chores as well as caring for relatives, family-unfriendly work cultures also sexism and sexualised harassment and violence play a role. As a result of the pandemic, these inequalities will probably get worse because women will be further disadvantaged by the increase in care work load. In addition, the ideal type of scientist is still male-dominated in most people's minds. Ultimately, also men and all those who do not conform to this image, for example because they want to be active fathers or simply have a life on the side, suffer from this.

In the FEM POWER project, you work with others for more equal opportunities. Where do you see concrete points for improvement?

The most important point is not to focus only on women, but to include everyone and especially consider the systematics of barriers. The phrase "Don't fix women, fix the system" sums it up well. That is why, on the one hand, we offer concrete support for female scientists, for example through coaching, workshops on career-relevant skills, through networking and empowerment,

and on the other hand, we also address the responsibility of managers in decision-making positions. At the LIN, we established a compulsory workshop on gender-sensitive leadership for the predominantly male management a year ago. Another focus of our work is to raise awareness of structural inequalities among all employees, for example through a regular newsletter, lectures, panel discussions and other events. Last year, for example, we showed the film "Picture a Scientist" with a panel discussion on the topic of "How male is science?". The response and the exchange were constructive and profitable for all.

> **Overall, my work is always about equal opportunities being an issue for everyone, and together we can achieve a lot.**
>
> Dr. Sarah Czerney

What successes have there been in recent years in the area of equal opportunities at the LIN?

For me, a great success is that I have the impression that most people are now aware of the issue of equal opportunities and are dealing with it. This awareness work is the basis for a common path. The other day, a colleague approached me and said that because of the campaign against sexual harassment that we had at the LIN, he had started to think about it and would now rather let go of some of the sayings that he would otherwise have made. Another colleague told me that in retrospect he had noticed that at a conference he had helped organise, only male speakers were invited and that he would like to do things differently in the future. It's great to work together to make the LIN more equal.

Another success is the establishment of an Equal Opportunities Commission at the LIN, in which colleagues from all employee groups, from trainees to the scientific director, exchange views and receive further training on equal opportunities issues. We have also created structures and counselling services to protect against discrimination and sexual harassment in the workplace. For the female scientists at the LIN, I initiated a monthly networking meeting, which is now established and very well received. Especially in times of the pandemic, the participants find these meetings very empowering.

And I organise the lecture series "Gender and Neuroscience", which is very successful and attracts an ever larger audience from all over Germany. In short, the issues of equal opportunities and gender are simply here to stay.

How do you personally manage to reconcile work and family life?

I would put the question differently: Is it generally possible to reconcile both? In my experience, this works if, firstly, the care work in the family is distributed fairly and is not exclusively or mostly on the woman's shoulders, and secondly, if working cultures – also in academia – change in such a way that it is possible to have a healthy life and to take care of oneself and others in addition to work.

You co-edited a book on motherhood and science and the (in)compatibility of motherhood and scientific activity. And you also co-founded the Network for Motherhood and Science. What topics do you discuss there?

Basically, it's about the question of whether and how motherhood and science are compatible. Of course, this has become even more explosive under pandemic conditions, as studies already show that female scientists who have small children are disadvantaged by school and day-care closures to a much greater extent than fathers and childless people. That is why our follow-up book is about motherhood and science in the Pandemic and the (in)compatibility of children, care and Covid-19. In our books, we make visible the experiences of very diverse mothers and non-mothers in science. Because of the overwhelming response we founded the network. Our focus is on networking, exchange and mutual empowerment, for example in regular online meetings and in local groups that have been founded all over Germany.

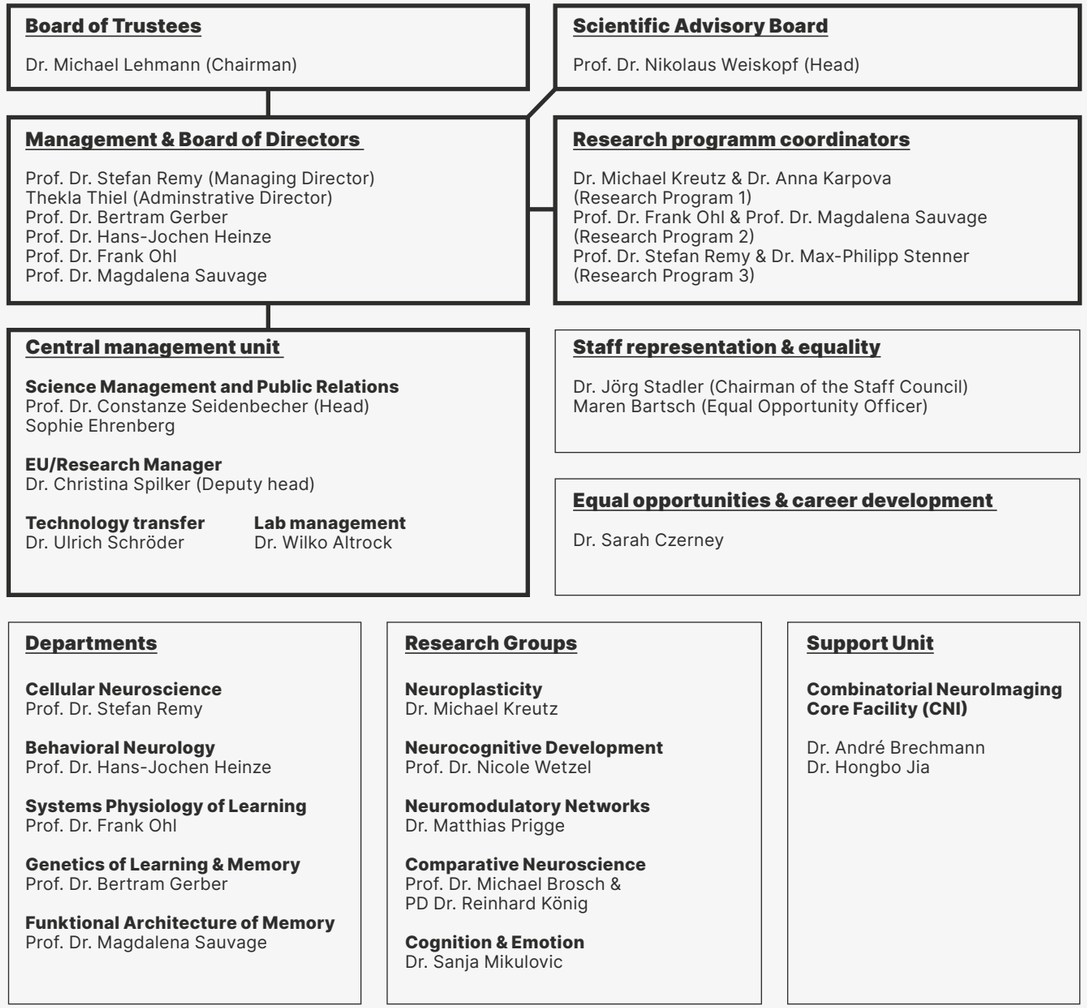
» Our claim: Enabling science - for each other and with each other, no matter how great the challenges are.

Thekla Thiel, Head of adminstrative service

→ The colleagues from the administration support the scientific departments and groups in hiring new team members, they keep an eye on the budgets and help with the procurement of getting equipment or working materials. In addition, the Central management unit offers services for laboratory management, technology transfer and European funding as well as the scientific library.

→ The colleagues in the technical area take care of everything concerning the building and the laboratory equipment and ensure cleanliness and order in the building. The staff members in research technology built behavioural test apparatus and entire mouse cities out of plexiglas, and the extensive conversion of biochemical labs into behavioural and imaging areas and the expansion of the research data infrastructure were the main tasks of the facility management and IT service.

→ Dr Judith Kaufhold's team makes sure that the animals at the LIN are doing well - from breeding and species-appropriate husbandry to the veterinary care of the four-legged experiment participants. The animals' well-being and their trust in the animal care staff are essential for the success of the neurobiological experiments.



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