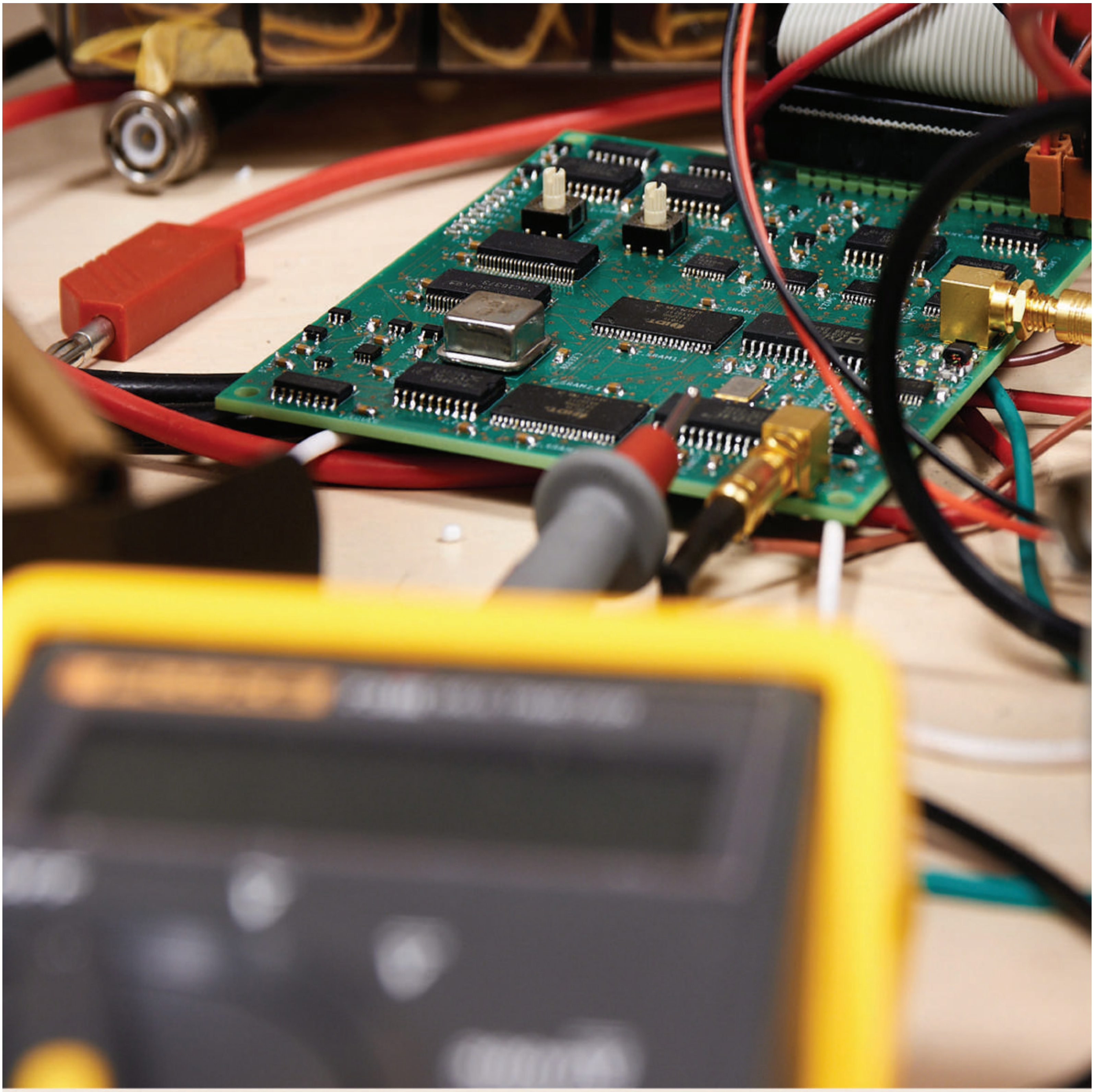

HIGHLIGHTS

ERWIN L. HAHN INSTITUTE FOR MAGNETIC RESONANCE IMAGING

2022

ERWIN L. HAHN INSTITUTE FOR MAGNETIC RESONANCE IMAGING

Erwin L. Hahn Institute for Magnetic Resonance Imaging

HIGHLIGHTS 2022

Annual Report

ERWIN L. HAHN INSTITUTE FOR MAGNETIC RESONANCE IMAGING


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Preface

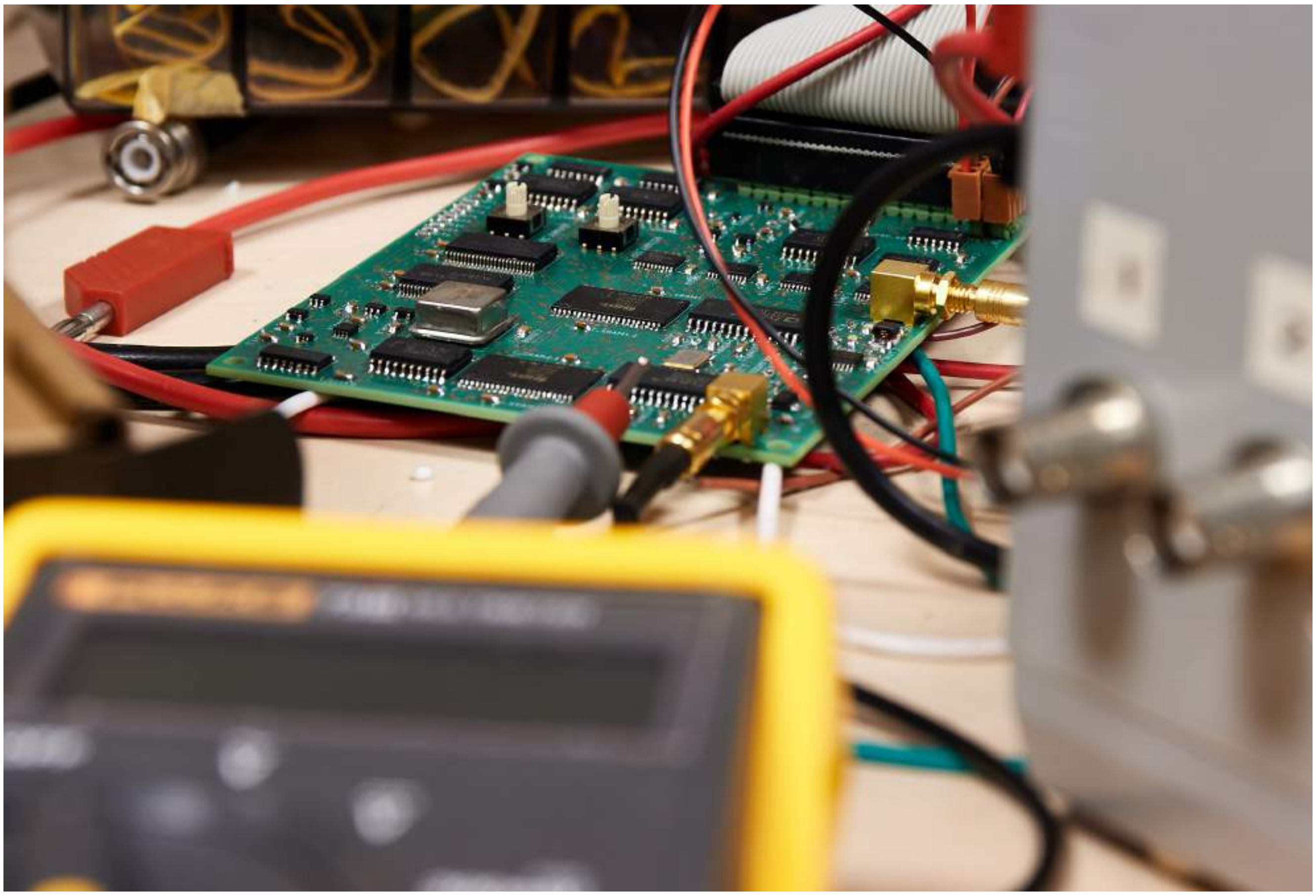
2022 was the year in which the COVID-19 pandemic loosened its grip on our lives and allowed us by the end of the year to have returned to something like normal life. When I attended the International Society for Magnetic Resonance in Medicine (ISMRM) ultra-high-field workshop in Lisbon in April, there was already a strong feeling of renewing contact with your scientific network, and at the annual ISMRM Meeting the level of activity was almost feverish. This meant that come 19th October we could enjoy our annual Erwin L. Hahn lecture in person at the Oktogon (also with a large on-line attendance). The main lecture was given by Floris de Lange from the Donders Institute of the Radboud University in Nijmegen and covered his pioneering work on laminar fMRI. This is a topic where the ELH has played a leading role for many years and remains the subject of current and future research activities. An innovation at this year's lecture was the first award of the International ELH prizes for the categories of both 'brain' and 'body'. These were awarded to Evgeniya Kirilina of the Max Planck Institute for Cognitive and Brain Sciences in Leipzig, and Christoph Aigner of the Physikalisch-Technische Bundesanstalt in Berlin respectively. The Young Scientists Award for outstanding work at the ELH went to Markus May for his dissertation "7 Tesla Ultra-High-field MRI in the Head and Neck using an Integrated 64-Channel receive-16-channel transmit-Coil". This year the ELH lecture will take place on 25th October with Andrew Webb (Leiden University) as guest speaker.

This year's ELH Highlights follows the format of recent years in offering a concise snapshot of our activities. Our traditional strengths in hardware development are reflected in the first two reports on a multinuclear array and an integrated array for proton imaging both for the body. Switching to the brain, you can read about work on identifying the neural mechanisms of addictions, how the cerebellum is important for mechanisms of fear, and the interaction between pain and cognitive processing. We round off with another important theme, that of applying laminar fMRI to the hippocampus, something that will require methodological developments in laminar fMRI, which are to be found in the final report.

I hope that you will find this report informative and hope to see many of our readers at the Erwin L. Hahn Lecture in October!

David Norris
Essen, May 2023

Jennifer Schulz, Ivo Maatman, Carlijn Tenbergen, Sjaak van Asten,
Markus May, Oliver Kraff, Thomas Meurs and Tom Scheenen



First use of a multinuclear body array coil at the 7T Terra system

Tom Scheenen's research is focused on the development of in vivo magnetic resonance imaging and spectroscopy for oncological applications.

Due to the high signal-to-noise ratio, ultra-high field is an excellent candidate for imaging small anatomical structures such as pelvic lymph nodes inside the body, which in combination with USPIO nanoparticles can aid in nodal staging of different types of cancer. Accurate staging of metastasised disease is essential for the choice of treatment, and if present, suspicious nodes detected with USPIO-enhanced MRI can guide treatment of these nodes. This provides a handle towards treatment with curative intent of so-called oligo-metastatic disease: if the first few metastases can be detected, they can be incorporated in various treatment plans.

In the European (EFRO) project "Metabolic Imaging for Robotic guided interventions (MI-Robot)", the research group collaborates with two Dutch companies, Tesla Dynamic Coils (TDC) and Soteria Medical, to develop innovative hardware and software techniques focusing on the research question.

In this context, a multinuclear body array coil has been built by TDC and has successfully been installed at the 7T Terra system in Essen (Fig. 1). It has initially been designed to image safely and with high precision the lower abdomen (prostate surrounding pelvic tissues), but can also be used for imaging the upper abdomen and thorax or for cardiac applications. The coil holds 8Tx/Rx 1H antennas for parallel transmit proton imaging. This is combined with a 4Tx/(4+24)Rx 31P coil array to also perform non-invasive metabolic imaging investigating 31P-metabolites in the region of interest.

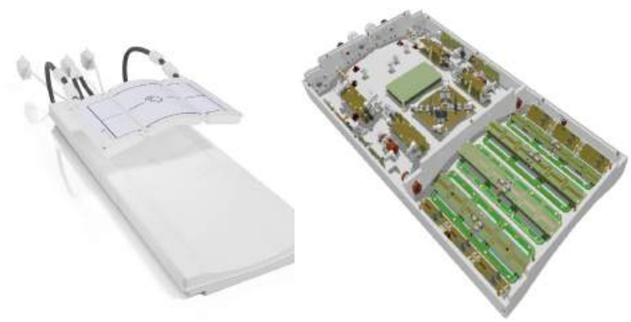


Figure 1. The new design RF coil for 1H imaging and 31P spectroscopy of the body at the ISMRM 2022 in London, UK.

To ensure high image quality, advanced software development was concurrently performed. Therefore, several MR-imaging and spectroscopy sequences were installed and tested to image safely and qualitatively while maintaining patient comfort.

An example in figure 2 shows the group's software based (TIAMO) approach minimizing B1-related signal dropouts leading to uniform and high-quality high

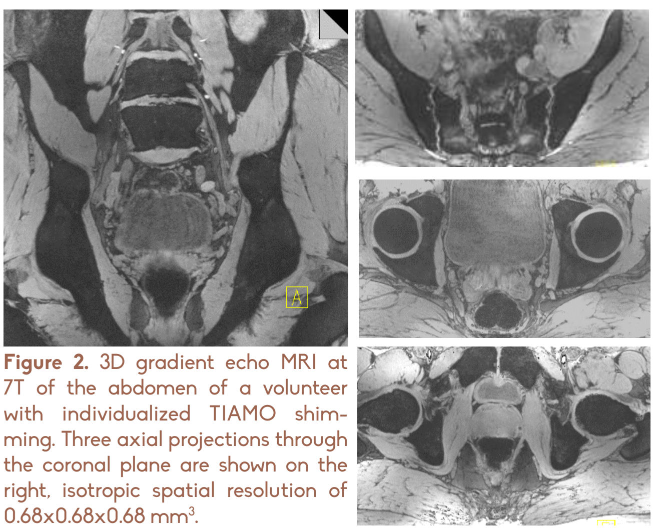


Figure 2. 3D gradient echo MRI at 7T of the abdomen of a volunteer with individualized TIAMO shimming. Three axial projections through the coronal plane are shown on the right, isotropic spatial resolution of 0.68x0.68x0.68 mm^3.

resolution large FOV images of the pelvic region which can be used for diagnostic purposes of tumors in this region. The advances in improved B1-shimming have been developed together with the group of Sebastian Schmitter from the Physikalisch-Technische Bundesanstalt, Berlin and can easily be transferred to other applications and other 7T Terra sites.

In this context and in combination with the built coil, the team also developed a preliminary protocol for free-breathing abdominal MRI. Here, motion-corrected radial MRI techniques were used to create homogeneous images of the upper abdomen at high spatial resolutions (Fig. 3).

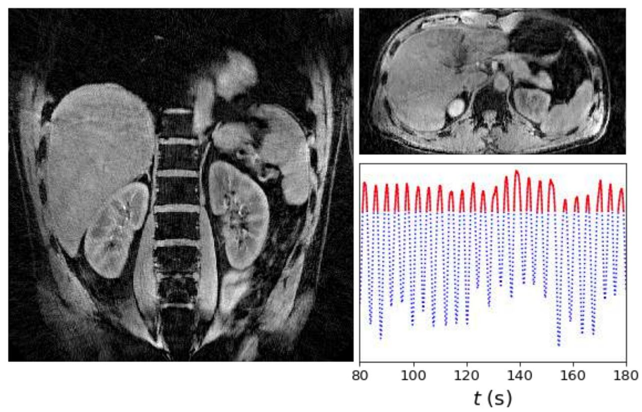


Figure 3. Reconstruction of motion-detected 3D radial MRI stack-of-stars data in coronal and transversal views with TIAMO of a free-breathing volunteer. These images provide sharp depiction of the diaphragm and adrenal glands. Part of the detected respiratory signal is plotted versus time. Red indicates the time windows in the exhale state which were used for reconstruction, while time points along the blue dotted lines were discarded.

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Florian Fiedler, Harald Quick and Mark Ladd

The ELH-DKFZ collaboration on 7T Body MRI

Despite the re-enablement of body MRI on the ELH Terra system with local transmit arrays, a long-held goal of the ELH PIs has been to demonstrate a body transmit coil integrated into a 7T system, similar to the built-in RF body coils available on 1.5T and 3T systems. A first generation of such a system was demonstrated on the Terra predecessor at ELH. Due to the high-performance gradient coil of the Terra system that limits space under the covers, this work is now being pursued as part of a collaboration with the German Cancer Research Center (DKFZ) in Heidelberg. Although the transmit efficiency of such a built-in RF coil is lower than that of an RF transmit array placed directly on the patient, simulation and experimental work has shown that excellent image uniformity can still be obtained while complying with all safety regulations if a high number of independent transmit channels is available to drive a multi-channel array. In 2021 and 2022 the focus of this collaboration has been on the numerical simulation and evaluation of the imaging performance of integrated RF coils for body MRI at 7T.

Clinical Imaging Performance at 7T with Integrated Transmit Arrays for Body Imaging

Integrated RF transmit antennas, with the elements placed in the gap between bore liner and gradient coil, provide several intrinsic advantages. The number of antenna elements can be higher compared to local arrays placed closely to the subject, thus providing higher degrees of freedom for pulse optimisations to reduce inhomogeneities caused by wave effects inherent when imaging larger FOVs, and the larger distance to the subject avoids SAR hotspots directly beneath the elements. Additionally, integrated RF arrays can provide a clinical workflow with improved patient comfort, because there is no need to reposition the transmit coil with each new imaging region, and heavy or bulky elements on the subject can be avoided. Also, more space in the bore is available for the use of additional equipment, such as dedicated receive arrays, X-nuclei antennas, fMRI equipment, or MR-guided interventions.

However, there are also several concerns regarding remote antennas: the elements will couple less with the body of the subject due to the larger distance; thus, mutual coupling between the elements increases, which can lead to a need for complex decoupling strategies. Further, the larger distance to the subject leads to higher RF power demands per channel (lower transmit efficiency), and increased overlap in B1+ maps between elements could result in reduced encoding capabilities per element.

The integrated body array the scientists are pursuing, originally developed at the ELH as part of the EU-funded ERC project MRexcite, consists of 32 microstrip antennas placed in three interleaved rings around the bore liner covering a length of 55 cm in the longitudinal direction. The position of the elements was previously evaluated in an extensive simulation study showing favorable results for arrays with interleaved rings (Fig. 1). In a current study, the simulated imaging performance was compared to a clinical RF transmit system at 3T (Fig. 2). A 45 cm-long birdcage, excited at 2 ports offset by 90°, was used as the comparison baseline at 3T. All simulations were performed with anatomical body models.

Despite the expected higher SAR at 7T, the array shows favorable results regarding SAR efficiency ((B1+)/√SAR) due to the high channel count and the ability to distribute SAR to different body areas with pulse optimisations. In contrast, the power efficiency ((B1+)/√P) is lower compared to the 3T coil, which is due to higher losses in the transmit path and can be compensated by stronger power amplifiers on each channel (the current MRexcite system provides 2 kW of peak RF power per channel). The results furthermore show that despite a large volume of the subject being exposed, the constraining aspect is still the local SAR limit, which is reached before whole-body or partial-body SAR limits.

The imaging performance was evaluated in transverse and coronal slices, encompassing the body without arms. Such large volumes of interest are requested by physicians for general diagnostic body imaging and place high demands on imaging performance. Smaller ROIs (e.g. heart, kidneys, or prostate) are less demanding and generally achieve higher homogeneity. With a simple B1-shim (optimisation of channel amplitude and phase), the array already outperforms the 3T coil in coronal slices, but shows residual inhomogeneities in transverse slices. With more sophisticated optimisations that include multiple RF pulses and k-space optimisation (e.g. spokes, kT-points), the array is able to achieve imaging performance comparable to or better than the 3T coil. However, a higher SAR or a lower duty cycle is necessary in both cases to achieve similar performance, which can prolong scan times. Figure 1 shows the B1+ field

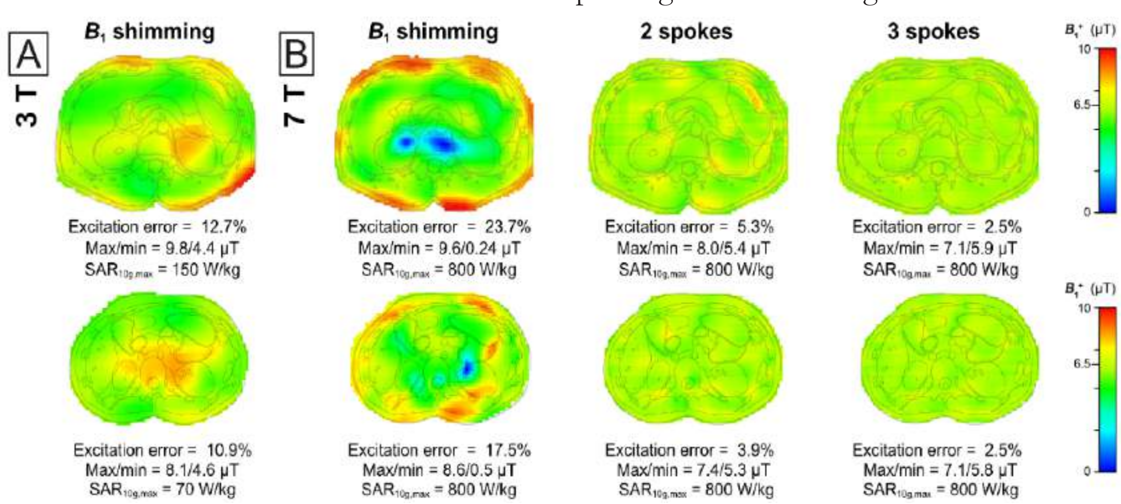

Figure 1. B1+ field distributions optimised in a central transverse slice. Top: male, bottom: female body model. Target magnitude of the B1+ field was 6.5 µT. At 7T the maximum local SAR was 800 W/kg, implying a maximum duty cycle of 1.25% to comply with the local SAR limit of 10 W/kg.

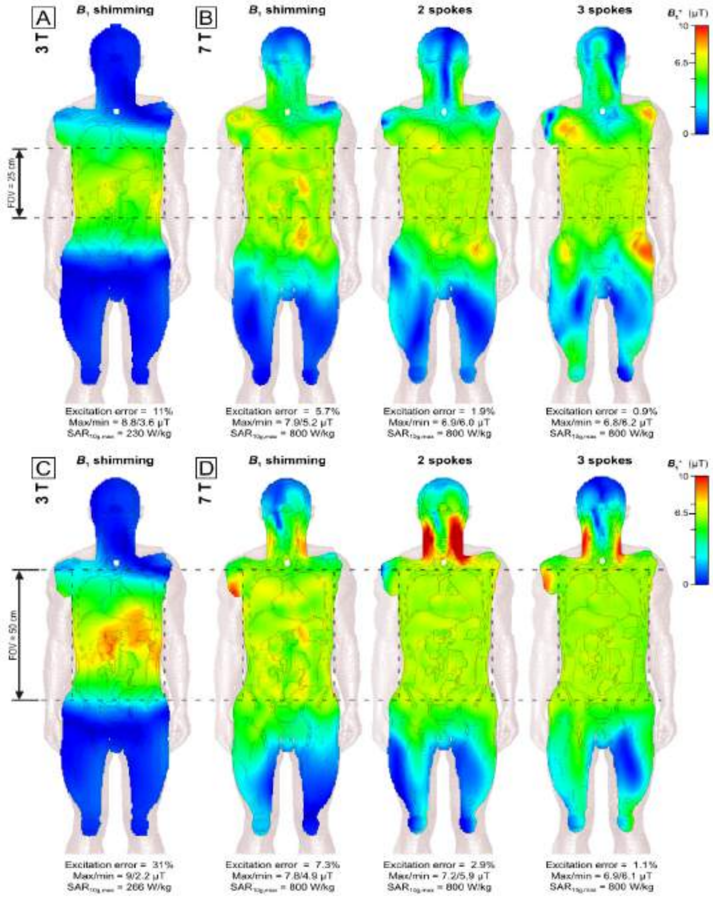

Figure 2. B1+ field distributions optimised in 25 cm coronal slices in the male body model. Target magnitude of the B1+ field was 6.5 µT. At 7T the maximum local SAR was 800 W/kg, implying a maximum duty cycle of 1.25% to comply with the local SAR limit of 10 W/kg.

distributions optimised in a central transverse slice, figure 2 in a 25 cm long coronal slice. The target magnitude of the B1+ field was 6.5 µT. For each case, the excitation error (NRMSE), the maximum and minimum B1+ amplitude, and maximum local SAR are shown.

In the future, the transmit array will be extended with a dedicated 32-channel receive array placed locally on the subject to increase SNR, similar to the standard clinical workflow at lower field strengths.

International German Ultrahigh Field Imaging (GUFI) Meeting at ISMRM 2022 in London

In 2021, DFG funding for the GUFI project connecting all UHF MRI sites in Germany (German Ultrahigh Field Imaging, www.mr-gufi.de) came to an end after 8 years of DFG support. But this does not mean that the GUFI activities came to a halt. At the final DFG-sponsored GUFI Meeting in November 2021 in Magdeburg (see ELH Highlights 2021), it was agreed that the established GUFI structures, trainings, and meetings should be actively pursued and maintained beyond the DFG funding. Further, all partners agreed to actively seek suitable funding opportunities to support and expand future GUFI activities, including the perspective to support the establishment of a 14T human MRI in Germany.

At the ISMRM 2022 meeting in London, UK in May, Mark Ladd (DKFZ, Heidelberg), Harald Quick (ELH, Essen), and Oliver Speck (OVGU, Magdeburg) organized an on-site GUFI meeting with invited international UHF MRI partners and European partner networks. Representatives of Siemens Healthcare also attended the event. The focus of this GUFI meeting was a discussion of UHF MRI beyond 7T field strength. Nicolas Boulant and Alexandre Vignaud from ISEULT (Paris, FR) reported about the current status of their 11.7T human MRI, a system that has been in planning for more than 15 years and is now gaining shape: the magnet is on-site and able to deliver 11.7T, and has produced first test images of fruits.

The presentation from France was followed by Richard Bowtell (Nottingham, UK), who presented the current status of establishing a human brain-only 11.7T system in the UK. Shortly after the meeting in London, funding for this system in the amount of £29.1 million was announced. Mark Ladd concluded the update on European UHF activities with a report on the continued activities in Germany to acquire funding for a 14T human whole-body MRI system.

The meeting continued with updates from individual GUFI working groups (pTx coil safety and testing, RF coil safety, implant safety, MR safety training, GUFI homepage), and further activities of the working groups were planned for 2023. The meeting concluded with a group picture (Fig. 3).

Figure 3. Group picture of participants at the 2022 GUFI & Friends Meeting at the ISMRM 2022 **in London, UK.**

1. Fiedler TM, Orzada S, Flöser M, Rietsch SHG, Quick HH, Ladd ME, Bitz AK (2021). Performance analysis of integrated RF microstrip transmit antenna arrays with high channel count for body imaging at 7 T. *NMR Biomed* 34(7):e4515.
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Stephanie Antons, Kjell Büsche and Matthias Brand

Identifying the neural mechanisms of the development and maintenance of behavioural addictions

In the recent version of the International Classification of Diseases (ICD-11; World Health Organization 2022) a new group of disorders called "disorders due to addictive behaviours" has been included under the category of behavioural addictions as a second category besides substance-use disorders. Gambling disorder and gaming disorder have been listed in the ICD-11 as specific behavioural addictions. Further problematic behaviours such as the use of pornography, buying/shopping, and the use of social network sites are considered as potential addictive behaviours, however, evidence on the biopsychological mechanisms involved in the development and maintenance that would warrant their classification as behavioural addiction is still scarce.

Within three completed projects (Antons & Brand 2020, Brand et al. 2016, Trotzke et al. 2021) and one ongoing project (part of the DFG-research group FOR2974; Brand et al. 2021) carried out at the ELH, the research group around Matthias Brand focuses on the identification of neural mechanisms involved in the development and maintenance of behavioural addictions.

Core mechanisms of the development and maintenance of behavioural addictions that are in the focus of these projects are cue-reactivity, craving, and inhibitory control (see Brand 2022). The interactions between these mechanisms and how they contribute to behavioural addictions are summarized within the Interaction of Person-Affect-Cognition-Execution (I-PACE) model (Brand et al. 2019). Relevant neural pathways that contribute to the development and maintenance of behavioural addictions have been highlighted by Brand (2022). In early stages of the disorder it comes to an increased processing via the "feels better", a pathway including the nucleus accumbens and the ventromedial prefrontal cortex. In later stages, when the behaviour is executed although experiencing negative consequence due to the behaviour, the processing gradually switches to the "must do" pathway including the striatum (caudate nucleus and putamen) and dorsomedial prefrontal cortex. In addition, decreased inhibitory control is associated with impairments of control processes of the dorsomedial prefrontal cortex.

These hypothesized pathways have been the focus of the three completed projects. It has been shown for pornography use disorder that individuals with higher symptom severity show an increased cue-reactivity and responding towards preferred sexual images (compared to non-preferred) within the ventral striatum (Brand et al. 2016). Similar results have been found for buying-shopping disorder during cue-reactivity (Trotzke et al. 2021), indicating an increased activity in the dorsal striatum during shopping-cue exposure in individuals with buying shopping disorder compared to controls. In addition, activity in the ventral striatum was associated with symptoms of buying-shopping disorder in affected individuals, but not in control participants.

Furthermore, the insula has been identified as an important region modulating inhibitory control performance during cue-reactivity (Antons & Brand 2020). Indicating that diminished control over the addictive behaviour presumably results from the interaction between "feels better", "must do", "can't stop" pathways and additional pathways that moderate the interaction between these structures. The ongoing project aims to add to these results by identifying neural correlates of cue-reactivity in gaming disorder and pornography use disorder. One focus will be to identify specific neural correlates of different stages of the disorder by investigating differences between regular users, risky users and pathological users.

With a focus on the neural correlates of cue-reactivity, craving and inhibitory control in three different types of behavioural addictions (pornography use disorder, buying-shopping disorder, gaming disorder), the work of the group contributes to a better understanding of core mechanisms involved in the development and maintenance of behavioural addictions.

1. Antons S, Brand M (2020). Inhibitory control and problematic Internet-pornography use – The important balancing role of the insula. *Journal of Behavioral Addictions* 9(1):58-70.
2. Brand M (2022). Can internet use become addictive? *Science* 376(6595):798-799.
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4. Brand M, Snagowski J, Laier C, Maderwald S (2016). Ventral striatum activity when watching preferred pornographic pictures is correlated with symptoms of Internet pornography addiction. *Neuroimage* 129:224-232.
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7. World Health Organization (2022). *International statistical classification of diseases and related health problems* (11th Revision), 02/2022.

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Dagmar Timmann

A journey to understand the contribution of the cerebellum to extinction learning

The team's overarching aim is to get a fuller understanding of the contribution of the human cerebellum to learning and memory of fear, an important emotion for survival. The cerebellum is well known to contribute to associative learning in the motor, cognitive and emotional domain. Surprisingly little is known about its contribution to extinction. A major aim of current studies is to show that the cerebellum has to be included in the network underlying extinction of learned fear responses.

Extinction processes likely involve erasure of memories, but there is ample evidence that at least part of the original memory remains. In a recent study performed in collaboration with colleagues from the Ruhr University in Bochum (Christian Merz, Nicolas Diekmann, Sen Cheng), the scientists asked the question whether memory persists within the cerebellum following extinction training (Batsikadze et al. 2022). The renewal effect, that is the reoccurrence of the extinguished fear memory during recall in a context different from the extinction context, constitutes one of the phenomena indicating that memory of extinguished learned fear responses is not fully erased during extinction training. A fear conditioning 7T fMRI study in a group of young and healthy participants was performed. On day 1, fear acquisition training was performed in context A and extinction training in context B. On day 2, recall was tested in contexts A and B. Fitting skin conductance responses data, a deep neural network model was trained to predict the correct shock value for a given stimulus and context. Event-related fMRI analysis with model-derived prediction values as parametric modulations showed significant effects on activation of the posterolateral cerebellum (lobules VI and Crus I) during recall. Since the prediction values differ based on stimulus (CS+ and CS-) and context during recall, data provide support that the cerebellum is involved in context-related recall of learned fear associations. Thus, part of the original memory likely remains within the cerebellum following extinction training.

In ongoing studies the research group wants to get a more mechanistic understanding about the proposed contribution of the cerebellum to extinction learning. In a previous study the observation was made that fMRI activation of the cerebellum was most marked during the unexpected omission of the unconditioned stimulus (US) in unreinforced CS+ trials during fear acquisition in healthy human participants (Ernst et al. 2019). An unreinforced CS+ trial can be considered as a very first extinction trial. Furthermore, the unexpected omission of an aversive stimulus can be considered rewarding. Therefore, the scientists propose that cerebellar fMRI activation during the unexpected omission of an aversive stimulus reflects processing of reward prediction error, which drives extinction learning.

Timmann's research group is in the process to perform four 7T fMRI experiments, including studies in patients with cerebellar disease and studies using dopaminergic drugs, to test the hypothesis that the cerebellum is involved in processing reward prediction error in extinction learning, and that this involvement is conveyed via the connection between the cerebellum and ventral tegmental area (VTA). In addition to skin conductance response recordings which were successfully realised in the 7T scanner in now three experiments, pupillometry using an eye tracker system was implemented, to get additional trial-by-trial measures of conditioning. The much improved gradient strength of the new Terra 7T MRI system at the ELH will allow performing fMRI studies at the level of the VTA. After successfully performing two 2-day 7T fMRI experiments in the past that allowed for consolidation of extinction learning, the paradigms will be expanded to a 3-day design allowing for consolidation of both the fear and extinction memory trace. Data collection of the first experiment, which will be performed in 50 young and healthy participants, has started in summer of 2022, and finished in spring 2023.

The experiments will allow a fuller understanding of how the cerebellum contributes to fear extinction learning in humans. The group's work is funded by the Marie Skłodowska-Curie Innovative Training Network (ITN): Cerebellum and emotional networks (CEN) and the CRC 1280 Extinction learning (TP A05; PIs Timmann and Quick). Dagmar Timmann is Deputy Network Coordinator of the ITN CEN, and Deputy Speaker of the CRC 1280.

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2. Ernst TM, Brol AE, Gratz M, Ritter C, Bingel U, Schlamann M, Maderwald S, Quick HH, Merz CJ, Timmann D (2019). The cerebellum is involved in processing of predictions and prediction errors in a fear conditioning paradigm. *Elife* 8:e46831.

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Pain and cognitive processes

Ulrike Bingel and her research group focus on the interaction between pain and cognitive processes. They have a longstanding expertise in investigating the CNS mechanisms underlying nociception, pain, and pain modulation in health and disease. In their research, they use behavioural paradigms, pharmacological modulations, as well as functional and structural brain imaging. Being particularly intrigued by the reciprocal effects of pain and cognition, they have a strong focus on translational questions such as the role of expectations and prior experiences on analgesic treatment outcomes. Their interdisciplinary research group comprises neurologists, neuroscientists, psychologists, biologists, and computer scientists and is based at the Department of Neurology at the University Medicine Essen.

In 2022 the scientists were finally able to resume their research activities after – as for many research groups – the COVID-19 pandemic had substantially slowed down experimental research activities since spring 2020. Currently, Ulrike Bingel and her team are in the mid of the first funding period of the transregional CRC 289 "Treatment Expectation" (www.treatment-expectation.de) that has been funded by the DFG since 2020. The consortium lead by Ulrike Bingel focuses on the mechanisms underlying expectations on health and treatment outcomes and explores how expectations can be systematically used to improve health care. The consortium involves many projects using brain imaging and the central scientific project Z03 co-lead by Tamas Spisak (https://pni-lab.github.io) has started to develop a unique research infrastructure for harmonising and sharing brain imaging data across sites and projects. This will provide a unique basis for pooled and meta-analytic approaches as will also benefit future collaborative engagement of the ELH. Such "mega-analyses" of several hundred datasets of the placebo imaging consortium (https://github.com/placebo-imaging-consortium) have already fostered novel discoveries regarding the mechanisms of placebo analgesia, such as the contribution of the cerebellum, as published in Nature Communication in 2021 (Zunhammer et al. 2021). The cerebellum provides an ideal target to be followed up with high field neuroimaging in a joint endeavor with the group by Dagmar Timmann, a world leading expert in this field. Dagmar Timmann is thus nominated as a new PI in the CRC Treatment Expectation in the next funding period. The joint work in the placebo imaging consortium has also fostered a recent joint "matters arising" publication with Tamas Spisak and Tor Wager in Nature (Spisak et al. 2020). In this publication we outline chances and challenges of multivariate whole-brain wide association studies and importantly, how these challenges can be overcome.

Further, the project A11 in the CRC 1280 Extinction Learning (https://sfb1280.ruhr-uni-bochum.de) has been funded for the next funding period. In this project Ulrike Bingel will continue to investigate the mechanisms underlying pain-related learning and how this might contribute to the development and maintenance of chronic pain.

The CRC 1280 and CRC 289 represent core pillars of the joint initiative for a cluster of excellence between the UDE and the RUB. The initiative "Re-Think" lead by Onur Güntürkün with co-speakers Nikolai Axmacher and Ulrike Bingel aims to investigate the neural foundation of future oriented cognitions. The ELH also represents a crucially important infrastructure in this exciting joint endeavor. The stage 1 application (Vorantrag) of this proposal will be submitted by the end of May 2023 and evaluated by an international grants committee until spring 2024.

Last but not least several exciting projects have been initiated. Together with Peter Koopmans, Ulrike Bingel will pioneer layer-specific MRI in pain processing and top-down modulations of pain. Together with David Norris and colleagues, they will explore the contribution of resting state activity of the spinal cord for an individual's pain sensitivity in health and chronic pain states, a project that perfectly builds upon their previous work on cerebral resting state networks and pain sensitivity in healthy volounteers.

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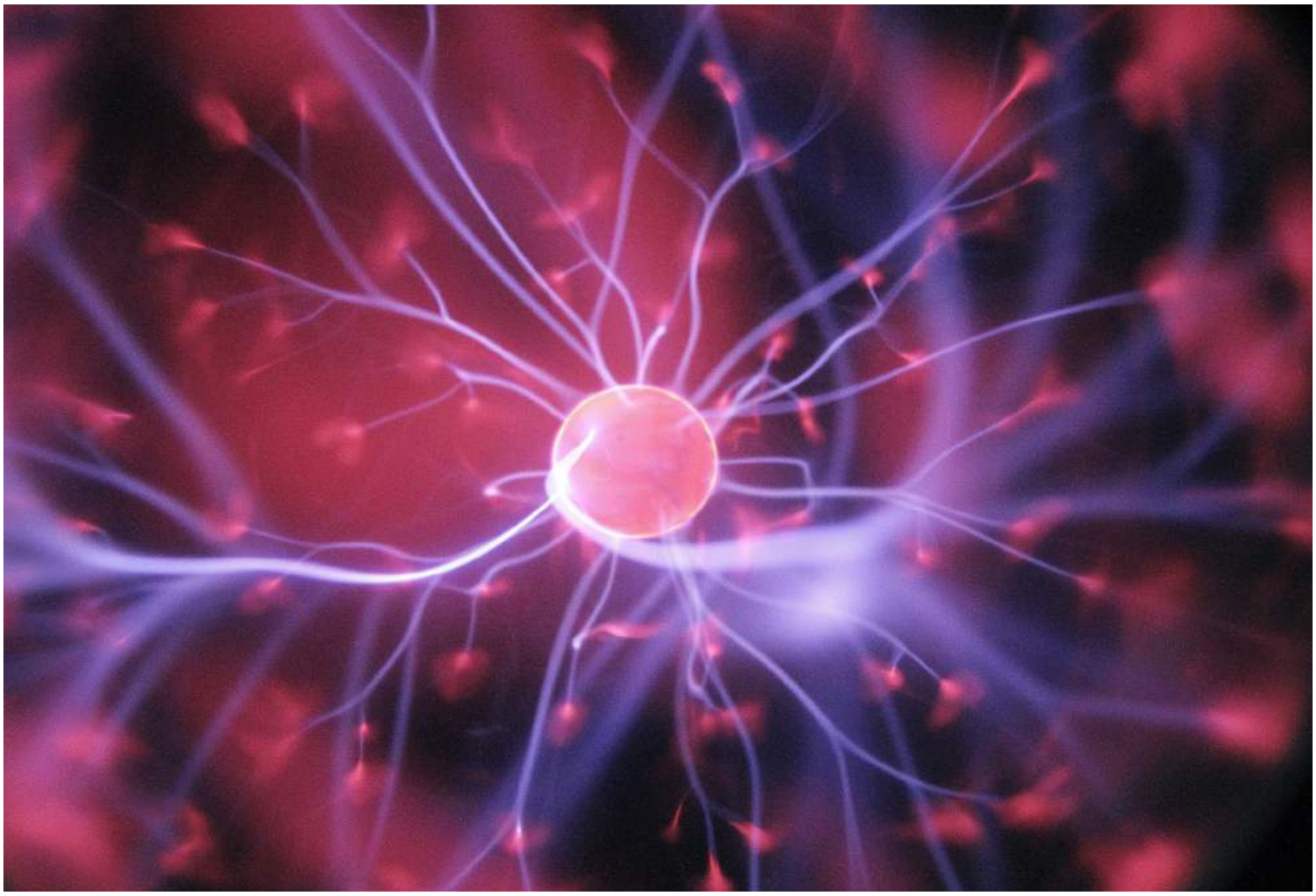
David Stawarczyk and Nikolai Axmacher



Unlocking the laminar organization of the medial temporal lobe structures

Volitionally controlled or active learning has become an important topic in education, psychology, and neuroscience. Previous studies by Axmacher's group and others indicate improved memory performance following active learning. This beneficial effect is thought to be due to the modulation of attention, motivation and cognitive control requiring the activation of fronto-parietal network and the hippocampus. Despite its central role in coordination of the volitional learning, it remains unclear how actively learned memories are processed across the hippocampal laminae. Moreover, little is known about the impact of active learning on grid-cell like representations in the entorhinal cortex playing a major role in spatial navigation.

In the group's current project at ELH, submillimeter fMRI at 7T in combination with a VR-based video game consisting of six interleaved active and passive blocks is leveraged to study the laminar profile of the hippocampus and neighboring regions at an unprecedented detail. During the active blocks, the participants freely explore the content of sixteen boxes that are randomly distributed across a virtual arena, whereas in the passive condition they are exposed to the movie of the free navigation of a previous participant. Specifically, the aim is to I) assess BOLD signal fluctuations in grey matter layers of distinct subfields of the hippocampus between active and passive learning conditions, II) to determine which layers in the entorhinal cortex support grid-like representations and whether those representations differ between active vs passive blocks, and III) to determine functional connectivity between different hippocampal and entorhinal cortex layers in active and passive conditions.

The anticipated findings of this study will advance the understanding of how volition influences mnemonic processing in the human brain. Concomitantly, the researchers are analyzing a laminar fMRI dataset that was acquired at ELH over the last two years. Forty-one healthy young adults underwent structural and functional MRI at two sessions, performing a first-person spatial navigation video game. The aim of this study was to examine grid-like representations in the entorhinal cortex at fine spatial resolution. The data is now preprocessed using an in-house developed pipeline that makes use of tools implemented in ANTS, FSL and SPM packages. Given that the entorhinal cortex is one of the earliest regions affected by Alzheimer's disease pathology, the findings of this study will not only provide detailed and fine-grained insights on navigation-related brain circuits but also may serve as a biomarker for early diagnosis of the disease with potential implications for future therapeutic approaches.

Mechanisms of fear generalization during fear acquisition and extinction: A 7T fMRI study

Intrusive memories are involuntary recall events of past experiences. While they occur frequently during daily life, intrusive memories of past traumatic events are a hallmark symptom of post-traumatic stress disorder (PTSD) leading to important distress in patients.

Past work from Axmacher's lab has suggested that intrusive memories could occur because of a higher generalisation of the neural representation of traumatic events, i.e. the neural representations of traumatic memories are more similar between each other compared to neutral events. If neural representations of traumatic events are less specific, they could be more likely triggered by neutral cues associated to them. In their experiment, the team aims to test this hypothesis by studying the neural representations of trauma-analogue events (short movie clips showing violent or distressing scenes) in a fear acquisition and extinction context using submillimeter fMRI at 7T.

The aims are the following: I) test for fear generalization using univariate and multivariate (e.g. Representational Similarity Analysis) techniques to understand what distinguishes the neural representations of traumatic and neutral movies, as well as the difference between neutral cues associated to traumatic movies and cues associated to other neutral movies; II) determine which factors (e.g. degree of generalisation of neural representations) predict the likelihood that a given event (traumatic movie) will result in an intrusive memory; III) unveil how neocortical and limbic regions of the fear learning network interact at the laminar level to process the neural representations of neutral and traumatic events during the different phases of fear learning and extinction.

The research group will also conduct a pattern separation paradigm using neutral and emotionally negative stimuli. Pattern separation is a computational process supported by the dentate gyrus subfield of the hippocampus, which is responsible for assigning non-overlapping neural representations to similar memories during memory encoding. Impaired pattern separation entails a lesser memory specificity which could accompany increased neural generalisation. Therefore, impaired pattern separation could be a mechanism contributing to the increased frequency of intrusive memories in PTSD patients. The team aims to test the relationship between pattern separation and fear generalisation by exploring if variation of neural activity or similarity during pattern separation encoding relates to fear generalsation and/or to the frequency of intrusive memories.

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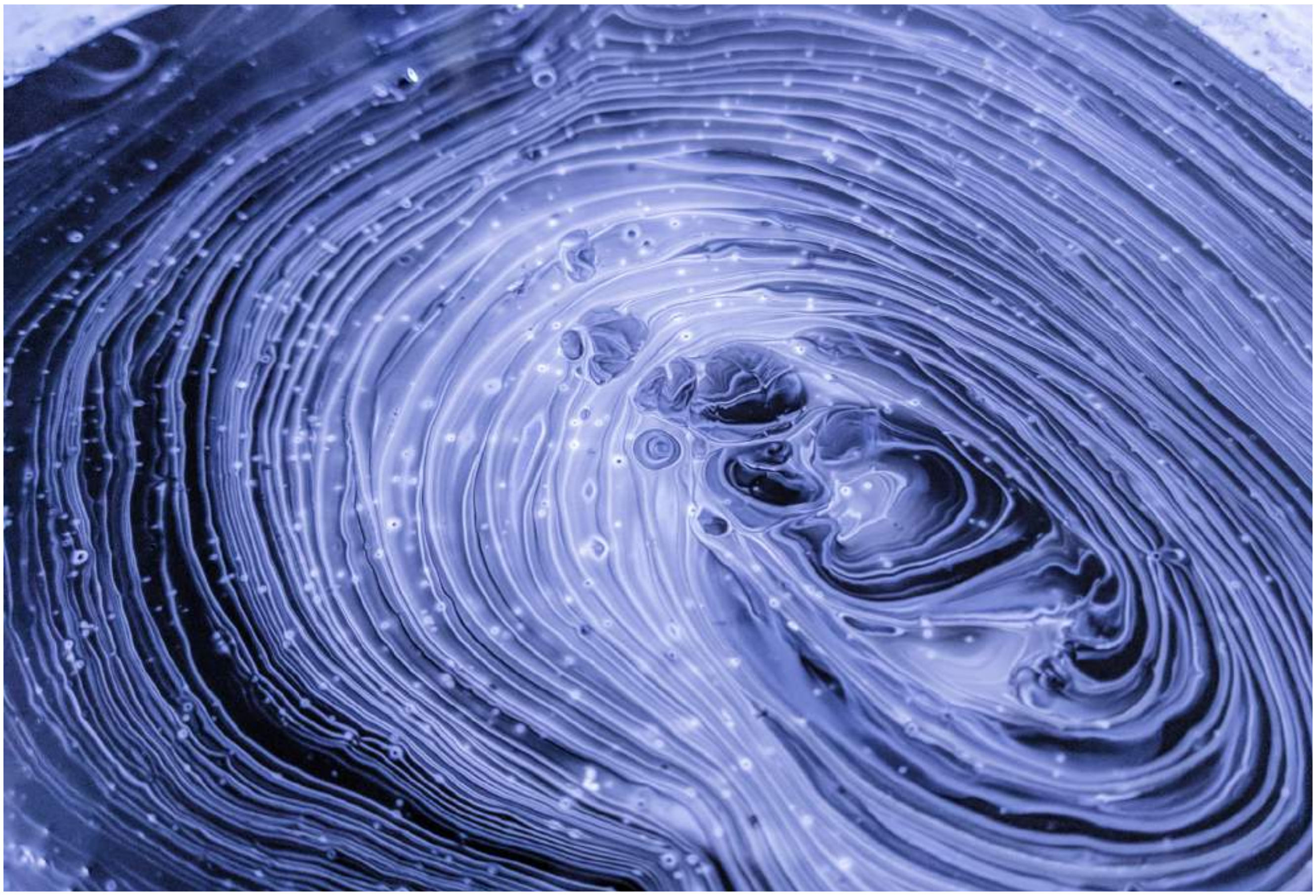

fMRI of cortical layers

Combining laminar fMRI with EEG

Understanding how the brain is organised is imperative for understanding how the brain functions in health and disease. Not only the knowledge of the presence of certain connections is of interest, but also the directionality of information flow within and between brain areas. Laminar fMRI is currently the only modality which promises to probe the direction of connections non-invasively in humans while, at the same time offering a spatial resolution high enough to elucidate local functions.

To better understand how the signals measured with laminar fMRI can be used to infer connectivity, it is important to link them to well-known connectivity measures like electroencephalography (EEG) frequency responses. In a recently published work, Norris's group investigated how neural oscillations measured with EEG relate to laminar level coupling between regions in the visual cortex in a visual demanding task. In earlier work it was observed that gamma band oscillations correlate negatively to superficial layer fMRI activity, while beta oscillations correlate negatively with deep layer activity and alpha negatively with both deep and superficial layer activity. When the neural oscillations in these frequency bands were related to coupling between layers of visual brain regions (Fig. 1B, D), the team observed that beta oscillations correlate negatively between deep layers of different brain regions in visual cortex, and between deep-to-middle and middle-to-superficial layers within brain regions in early visual cortex.

Contrary to beta oscillations, alpha oscillations were observed to correlate positively with coupling between deep and superficial layers within brain regions, while no relation was observed for the gamma band. These results provide the first evidence that neural oscillations measured by EEG reflect not only laminar-specific neural activity but also changes in laminar-specific connectivity within and between

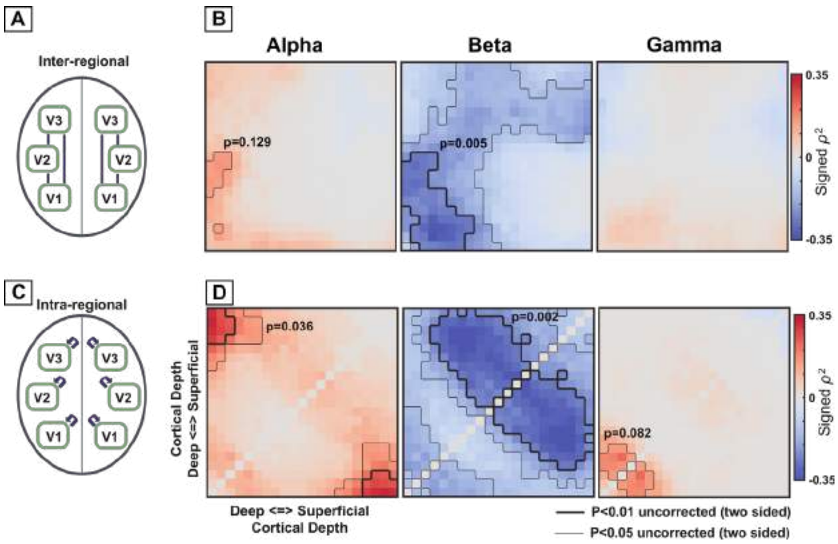

Figure 1. Relation between EEG power and inter-regional and intra-regional fMRI connectivity. The top row shows the results for inter-regional, the bottom row for intra-regional connectivity, respectively. (A) and (C) illustrates for each row the connections over which connectivity was averaged. Panels (B) and (D) show the relation between attention effect in EEG power for the indicated frequency bands and laminar fMRI connectivity.

brain regions. As such, they provide a neurophysiological basis for investigating laminar level connectivity with fMRI.

Laminar fMRI of the Hippocampus

Using ultrahigh fields (UHF), laminar fMRI has so far been established and validated in mostly sensory areas of the neocortex. Moving to more inferior regions like the hippocampus poses additional challenges for UHF laminar fMRI. First, B0 and B1 inhomogeneities are more severe at the hippocampus, resulting in the necessity for careful parameter fine tuning of GRE-BOLD 3D-EPI to achieve acceptable image quality (Fig. 2A). Second, the hippocampus' location renders it a challenging candidate to be measured with a non-BOLD laminar fMRI contrast named vascular space occupancy (VASO). The idea behind VASO laminar fMRI is that the change in cerebral blood volume (CBV) associated with functional activity is more co-located to the microvascular blood compartment, i.e. capillaries, small arterioles and venules, which are physically closer to the neurons. Typically, sensitization of the functional contrast toward changes in CBV in VASO is achieved by means of acquiring the signal at a time point where blood magnetisation, inverted by a non-selective RF pulse, passes the zero-crossing during T1-relaxation. The resulting nulled-blood image is corrected for extravascular BOLD effects, inevitably emerging during EPI readouts, by acquiring a volume without blood-nulling in an interleaved fashion. As VASO is a negative functional contrast, it is strongly affected by inflow effects which result in a positive signal change upon activation, counteracting the VASO contrast. The inflow effects depend on the arterial arrival time at the region of interest, and are considerably shorter at the hippocampus compared to regions of the neocortex. The sensitivity toward these inflow effects and the reduced temporal resolution makes VASO challenging for laminar fMRI of the hippocampus. In the current project funded by MERCUR, the researchers tackle these challenges using the increased coverage and parallel transmission (pTx) capability of multi-transmit radiofrequency (RF) hardware available with the Siemens 7T Terra system. Preliminary results (Fig. 2B, C) demonstrate the image quality of non-optimised (Fig. 2B) and optimized (Fig. 2C) 3D GRE-EPI readouts at short TE, forming the backbone for VASO fMRI of the hippocampus at the ELH.

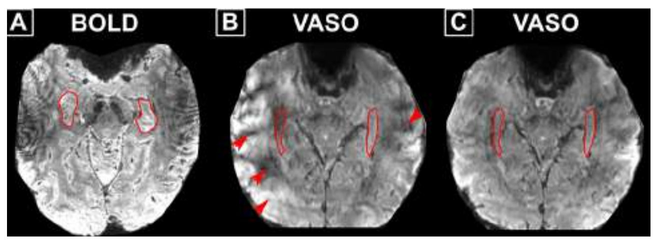

Figure 2. Image quality for laminar fMRI of the hippocampus. All images (average over 10 volumes) were acquired with a 3D GRE-EPI sequence optimized for the individual functional contrast. (A) BOLD image (0.8 mm isotropic resolution, TE/temporal resolution = 22/2000 ms, 27.2 mm z-coverage). (B) VASO EPI readout with non-optimized parameters (0.9 mm isotropic resolution, TE/temporal resolution = 13.7/2140 ms, 16.2 mm z-coverage, 1-2-1 water excitation). Note the strong B0-related image artifacts (red arrows in B). (C) Parameter optimization (TE/temporal resolution = 14.4/2180 ms, 1-1 water excitation) results in improved image quality. The hippocampus is highlighted as red contours in each image, respectively.

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2022 IN SHORT

More than 400 scanned test subjects

350 people from around the world joined the Erwin L. Hahn Lecture & Workshop via live stream

The most viewed tweet was: "In Germany development of MRI started in 1978. The first patient was a paprika." (@ELH_Institute)

David Norris's abstract "Phase encoded NMR flow imaging" (1984) was selected amongst the most important ISMRM publications to date. (*Walking with the ISMRM in the Footprints of our MR History*)

First ever International Erwin L. Hahn Awards

ISMRM Participation 2022 in London, UK

Kincses B, Forkmann K, Schmidt K, Bingel U, Spisak T: Resting-state functional connectivity predicts subsequent pain-related threat learning. *Session: Quality Assessment & Data Harmonization I*; e-poster.

Koopmans P: The Higher, the Better: Acquisition & Analysis at Ultra-High Field. *Session: Acquisition & Analysis in Context: Imaging at Different Field Strengths*; e-poster.

Kraff O, Deuschl C, Dodel R, Evers J, Nietert A, Verheyen A, Quick HH: Evaluation of brain volumetric changes and alterations in T1 relaxation times in American football players using 7 Tesla MRI. *Session: Quantitative Neuroimaging: Clinical & Translational Studies II*; e-poster.

Pfaffenrot V, Koopmans P: Laminar fMRI with MT-prepared multi-echo 3D FLASH. *Session: High-Resolution fMRI*; e-poster.

Spisak T, Kincses B, Kotikalapudi R, Zunhammer M, Schlitt F, Schmidt-Wilcke T, Kincses ZT, Bingel U: Predictive modelling and center effects: towards a robust functional connectivity-based neuromarker of pain sensitivity. *Session: Resting-State Functional Connectivity Methods*; e-poster.

Spronk T, Kraff O, Schaefers G, Quick HH: Numerical approach to quantify MR imaging artifacts at metallic orthopedic implants at 1.5T, 3T, and 7T. *Session: Novel Image Reconstruction Techniques I*; pitch.

Schulz J, Kraff O, Quick HH, Scheenen T: A Software-based TIAMO approach to enable high resolution large FOV body imaging at 7T ultra-high field. *Session: New (RF) Devices & High-Field MR II*; e-poster.

Dissertations 2022

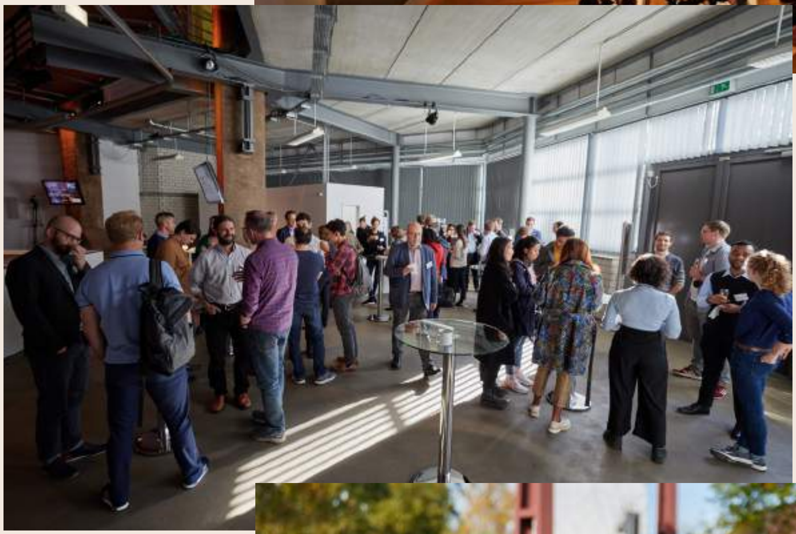
Viktor Pfaffenrot: Laminar fMRI of long-range connections: Methods and contrast mechanisms. (PhD Thesis)

Rutger CH Stijns: Organ preservation in rectal cancer and improvements in the primary staging and response assessment. (PhD Thesis)

Nassim Tayari: Combined acquisition and data processing strategies for optimized MR spectroscopic imaging of the prostate. (PhD Thesis)

Annika Verheyen: Analyse von repetitiven quantitativen 7 Tesla MRT-Daten von American Football Spielerinnen in Deutschland. (B.Sc. Thesis)

Erwin L. Hahn Workshop & Lecture 2022



Top:
View of the OKTOGON from the gallery.

Middle:
Coffee break.

Bottom:
Harald Quick, Keyspeaker Floris de Lange, Matthias Brand, David Norris (left to right)

Top:
Evgeniya Kirilina receives the first International Erwin L. Hahn Award for her outstanding scientific work.

Middle:
Christoph Aigner receives the first International Erwin L. Hahn Award for his outstanding scientific work.

Bottom:
View from the back.

Current Grants

R. Cools, D. Norris
NWO: **Unravelling dopamine's role as gatekeeper of prefrontal cortex** (2022-2027)

Using high-resolution fMRI, neuronal effects of the dopamine drugs methylphenidate and sulpiride will be measured on a submillimetre scale in the cortical layers to better understand how dopamine affects the working memory and to decipher the mechanisms what information from the working memory guides action and attention.

O. Güntürkün, U. Bingel, M. Brand
MERCUR: **ReThink** (2022-2026)

ReThink is a research alliance of scientists from the University of Duisburg-Essen and Ruhr University Bochum connecting research areas from neuroscience, through psychology, through philosophy of mind and cognition.

N. Axmacher, D. Norris
MERCUR: **Unlocking the function of the hippocampus with laminar fMRI** (2022-2024)

In this project measurement methods to advance laminar - i.e. cell layer-specific - imaging of the hippocampus are to be developed. The goal is to map the neuronal processes in the human hippocampus and their importance for memory and navigation.

D. Klomp, H.H. Quick, T.W. Scheenen
EU: **Non-ionizing Metabolic Imaging for predicting the effect of and guiding Therapeutic Interventions (MITI)** (2022-2024)

The goal of MITI, coordinated by the University Medical Center Utrecht, is to broaden and mature the metabolic imaging technology towards commercialisation as well as to validate the technology in several clinical use cases: liver metastases, lung tumours, (drug discovery in) heart disease, and muscle disorders via the expert university hospitals.

D. Timmann-Braun
EU: **Marie-Skłodowska-Curie Innovative Training Network: Cerebellum and emotional networks (CEN)** (2021-2025)

This consortium brings together researchers from across Europe and will address the contribution of the cerebellum in the control of emotions, in particular fear and anxiety. Timmann's group is one of seven European sites. Two PhD students will work on the project with a focus on cerebellar 7T fMRI.

D. Timmann-Braun, H.H. Quick
DFG: CRC 1280 - A05. **The contribution of the cerebellum to extinction: intrinsic mechanisms and cerebello-cerebral interactions** (2021-2025)

The project A05 is part of the Collaborative Research Center 1280 "Extinction learning". It aims to study the contribution of the cerebellum to extinction learning in humans using 7T fMRI.

N. Axmacher, D. Timmann-Braun, R. Kumsta
DFG: CRC 1280 - F02. **Focus Group Neuroimaging and Genetics** (2021-2025)

The project F02 is part of the Collaborative Research Center 1280 "Extinction learning". Metaanalyses of resting state and DTI data acquired at 3T and 7T by projects in the CRC will be performed. One focus will be on the cerebellum.

T. Scheenen
EFRO: **MI-Robot** (2021-2023)

This grant focuses on the development of metabolic imaging for robotic MR guided interventions.

D. Timmann-Braun
EU: **Spinocerebellar ataxias: Advanced imaging with ultra-high field MRI (SCAIFIELD)**(2021-2024)

The "Experimental Neurology" research group of Dagmar Timmann is one of the recruiting centers for an international research project on ultra-high-field MRI.

S.B. Shah, S. Maderwald, O. Kraff, S. Orzada, K. Ferenz, H.H. Quick
University Medicine Essen: **IFORES: Impact and long-term compatibility of Perfluorocarbon-based albumin capsules on regenerative capacity of small animals model, after high blood loss** (2021-2022)

In this project long-term pre-clinical data will be collected in a rat model; and 7T MRI with a dual-tuned $^{19}F/^{1}H$ rodent RF coil will be used to detect Perfluorocarbon-based albumin signals in the body and organs of the rats.

U. Bingel
DFG: **CRC/TRR 289 Treatment Expectation** (2020-2024)

The researchers and clinicians involved in "Treatment Expectation" (Collaborative Research Centre/Transregio 289) aim to unlock the neurobiological and psychological mechanisms behind treatment expectation effects.

N. Axmacher
DFG: **CRC1280 - A02. Neural mechanisms of context generalization** (2021-2025)

The project A02 is part of the CRC 1280 „Extinction learning". The researchers investigate how context generalisation is controlled by neural activity in core regions of the extinction network.

N. Axmacher, E. Genç
DFG: **CRC 1280 - A03. Functional role and dynamic change of extinction network connectivity** (2021-2025)

The project A03 is part of the CRC 1280 „Extinction learning". The researchers study how progress in fear extinction alters functional fMRI connectivity within the extinction network.

M. Brand
DFG: **FOR 2974 - Affective and cognitive mechanisms of specific Internet-use disorders (ACSID)** (2020-2024)

The aim of the research unit is to contribute to a better understanding of the fundamental affective and cognitive mechanisms, which are involved in the development and the maintenance of predominantly online addictive behaviours, namely pathological gaming, pornography use, buying-shopping, and social-networks use.

T.W. Scheenen, J.J. Fütterer, F. Witjes, M. Sedelaar, M. Maas, J.O. Barentsz, D.W.J. Klomp, H.H. Quick
Radboudumc: **A personalized image-based assessment of metastatic potential of prostate cancer** (2018-2021)

In this grant the assessment of the aggressiveness of localised prostate cancer is correlated and validated with early detection of the first metastases of the disease.

M.E. Ladd, H.H. Quick, O. Speck
DFG: **German ultra-high field imaging (GUFI), Core Facility** (2016-2021)

Aim of this project is to maintain and expand a nationwide network of UHF-MRI sites.

Publications on 7T

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Frass-Kriegl R, Broche LM, Ginefri JC, Ladd ME, Roat S, Sarracanie M, Winkler SAS, Laistler E (2022). Editorial: Innovations in MR hardware from ultra-low to ultra-high field. *Frontiers in Physics* 10:1015289. DOI: 10.3389/fphy.2022.1015289

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Schilham MGM, Rijpkema M, Scheenen TWJ, Hermsen R, Barentsz JO, Sedelaar JPM, Kusters-Vandevelde H, Kerkmeijer LGW, Somford DM, Gotthardt M (2022). How Advanced Imaging Will Guide Therapeutic Strategies for Patients with Newly Diagnosed Prostate Cancer in the Years to Come. *European Urology* 82(6):578-580. DOI: 10.1016/j.eururo.2022.09.005.

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Personnel & Organisational Structure at the ELH

Managing Director/PI
Prof. Dr. David G. Norris

Directors/PIs
Prof. Dr. Matthias Brand
Prof. Dr. Harald H. Quick

PIs
Prof. Dr. Nikolai Axmacher
Prof. Dr. Ulrike Bingel
Prof. Dr. Onur Güntürkün
Prof. Dr. Mark E. Ladd
Prof. Dr. Tom W.J. Scheenen
Prof. Dr. Dagmar Timmann

Administrative Director
Dr. Franziska Günther

Staff Scientists
Dr. Oliver Kraff
Dr. Stefan Maderwald

Technician
Kim Jotzo

Radiographer
Daniel Osenberg

Public Relations
Stefanie Zurek

Scientists

MSc. Shahrokh Abbasi-rad
Dr. Khazar Ahmadi
Dr. Stephanie Antons
Dr. Mareike Bacha-Trams
Dr. Giorgi Batsikadze
Dr. Antoine Bouyeure
MSc. Kjell Büsche
MSc. Alice Doubliez
Dr. Friedrich Erdlenbruch
Dr. Thomas Ernst
Dr. Carlos A. Gomes
Dr. Marcel Gratz
Dr. Balint Kincses
Evgenij Knorr
Dr. Tijmen Koëter
Dr. Magnus Liebherr
Dr. Maike Lindemann
Dr. Markus May
Dr. Silke M. Müller
MSc. Enzo Nio
Dr. Stephan Orzada
Patrick Pais Pereira
Dr. Mykola Petrenko
Dr. Viktor Pfaffenrot
Dr. René Scheeringa
Dr. Jennifer Schulz
MSc. Daniel Sharoh
MSc. Tobias Spronk
Dr. David Stawarczyk
MSc. Carlijn Tenbergen
Dr. Jan-Willem Thielen
Dr. Andreas Thieme

Students

Yasmin Abdelnaby
Lena Grunwald
Carolin Hensel
Jana Hupe
Jana Theisejans
Annika Verheyen
Miriam Weirauch

New in 2022

Yasmin Abdelnaby
Mareike Bacha-Trams
Antoine Bouyeure
Lena Grunwald
Kim Jotzo
Daniel Osenberg
Mykola Petrenko
Miriam Weirauch

Left in 2022

Shahrokh Abbasi-rad
René Scheeringa


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