HIGHLIGHTS

2021

ERWIN L. HAHN INSTITUTE FOR MAGNETIC RESONANCE IMAGING

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Erwin L. Hahn Institute for Magnetic Resonance Imaging

HIGHLIGHTS 2021

Annual Report

ERWIN L. HAHN INSTITUTE FOR MAGNETIC RESONANCE IMAGING


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Preface

The first part of 2021 was spent in the grip of the COVID-19 pandemic, but as vaccination programmes were implemented the year ended with a gradual return to normality. The most prominent indication of returning scientific life was the Erwin L Hahn Lecture albeit in hybrid format. Cancellation of the 2020 Lecture meant that the programme was carried over and updated and we were fortunate to have a majority of presentations in person, including an excellent keynote lecture given by Oliver Speck. You can enjoy some of the photos from this event on pages 28 and 29 of this report.

Our new Terra system has been designed by Siemens to give optimal performance for brain imaging, and this has posed some challenges for the groups that have traditionally been focused on body-MRI at 7T. The first two articles in this report documents the collaborative work being undertaken by the Erwin L. Hahn Institute together with other 7T sites to improve body imaging in general (page 6) and the assessment of prostate cancer in particular (page 10). We are also working on new developments in the field of laminar fMRI as documented in the report of the Emmy Noether research group on the fMRI of cortical layers (page 12) and performing interleaved BOLD imaging and proton spectroscopy (page 14).

With regard to applications in neuroimaging and neuroscience the Erwin L. Hahn Institute is proud to be playing a key role in the special research area (CRC) on Extinction Learning, which features a strong collaborative element between Essen and Bochum (page 16). We are also happy to welcome the first two contributions from Bochum (pages 18 and 20) dedicated to Memory and Learning in the first instance, and the diagnosis of Alzheimer's Disease in the second. Continuing the theme of applying modern neuroimaging techniques to socially relevant problems this years report is completed with an article on the Erwin L. Hahn Institute 's long-standing work in internet-based disorders, and the interaction between pain and cognitive processes.

As time goes by, we are seeing the burden of COVID-19 reduce and scanner usage increase. All being well we intend to hold the Erwin L Hahn Lecture online this year, so please mark your calendar for Wednesday 19th October!

David Norris,
Essen, March 2022

Harald Quick, Mark Ladd

Tuning up the Terra – (re)Enabling Brain & Body MRI at 7T

With the advent of the DFG-funded new 7-Tesla (7T) MRI system (MAGNETOM Terra, Siemens Healthcare GmbH) at the ELH in 2020, a new era has begun for the ultrahigh field (UHF) research activities at the ELH[1]. While the Terra MRI system provides powerful hardware, new software, and more operational stability while consuming significantly less of the expensive helium for cooling of the superconducting magnet when compared to the former 7T system at the ELH, UHF MRI still faces fundamental challenges when considering Brain & Body MRI.

The background is that 7T MRI systems show general differences to the clinical MRI scanners operating at 1.5 Tesla or 3 Tesla magnetic field strength. The clinical MRI systems feature a built-in radiofrequency (RF) transmit antenna (coil) to excite the hydrogen atoms in the human body at the resonance frequency. Additional local RF receiver coils are then placed along and on top of the patient's body to receive the weak MRI RF signals emitted from within the body. This configuration with a large built-in body transmit RF coil and with local receiver RF coils allows for routine clinical MRI exams from "head to toe". At 7T this is fundamentally different.

The wavelength of the RF excitation pulses is significantly shorter at UHF, which inherently leads to strong signal inhomogeneities and signal voids in the resulting MR images, and is also associated with safety issues. A well-known remedy and necessity to overcome this physical challenge is to develop our own hardware strategies for multi-channel RF excitation and to build local multi-channel RF transmit/receive array coils to enable localized 7T MRI in virtually all regions of the human body.

While working with the previous 7T MRI system at the ELH (2006-2020), this has been a major task of the PI groups at the ELH. The proposed hardware developments, methods developments, and pioneering body imaging applications have placed the ELH among the world-leading sites performing not only neuro (f)MRI of the brain but also body imaging at 7T. With the new Terra system and its new parallel transmit (pTx) RF architecture, however, some of the previous hardware developments and RF coils for body imaging have to be reconsidered. As was expected, a simple plug & play of the formerly developed RF coils with the new Terra system does not work.

Therefore, the three ELH PI groups of Harald Quick, Mark Ladd and Tom Scheenen, that all have a focus on 7T hardware development and body imaging applications, have joined forces to "tune up the Terra" to re-enable 7T body imaging at the ELH. First steps along this path included reconnection of already existing prototype 8/32-channel RF body coils[2] to the pTx system of the Terra (Fig. 1). This required hardware and also significant software adaptations to integrate further methods to homogenize the RF signals (e.g. the TIAMO method). Further multi-channel RF array coils for 7T MRI are already planned and under construction. RF coil development for UHF MRI generally encompasses the following steps: electromagnetic simulations, building and decoupling of the individual RF elements, assembling the RF array, bench measurements (RF lab), phantom measurements (MRI system), safety evaluation (simulations and measurements), and determination of the maximum RF power that can be used while staying within the allowed safety limits.

Only after successful finalization of this cascade can MRI on human subjects be conducted. During each MRI exam using the new RF coils, real-time monitoring of the RF power deposition on all RF channels has to be performed while scanning. To support funding of this ongoing work and the development of further Terra-specific RF coils (e.g. body arrays and a head/neck array), several grant applications have been submitted in 2021. If accepted for funding, these RF coil-focused projects will support all ELH PI groups in their 7T Brain and Body UHF MRI research activities.

Classic & New: The ELH-DKFZ cooperation 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

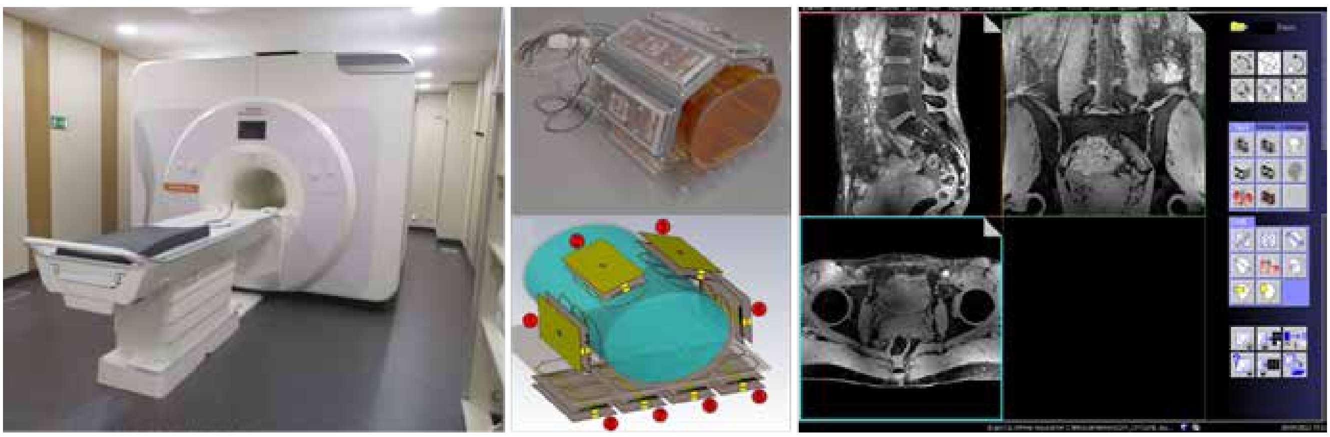

Figure 1. By interfacing an existing self-developed 8-channel transmit/32-channel receive RF array (middle: physical coil top and computer simulation model bottom)[2] to the new Terra 7T MRI system at the ELH (left). First images of the female pelvis (right) have been successfully acquired, thereby re-enabling important scientific investigations into the potential of 7T for clinical applications in the abdomen and pelvis.

Figure 2. The self-developed 32-channel integrated body coil mounted on the bore liner of the classic 7T at the DKFZ (bottom). The coil is driven by a self-developed pTx system[8] with 32 RF amplifiers, each with 2 kW peak power (top left). First images in two different subjects (top middle and right) demonstrate large field-of-view imaging capability.

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 channels is available[3,4]. A remaining challenge is the capability to monitor the RF signals on all of these channels in real time to ensure safe scanning; in the past year, we made several contributions to compressing the amount of data that has to be monitored[5-7]. In 2021, the second generation of a 32-channel integrated body coil and self-developed 32-channel pTx system were put into operation for the first time in Heidelberg on their Classic 7T system (Fig. 2). Ongoing studies are expected to show that such an integrated transmit system can enable full-body imaging at 7T following the same clinical workflow utilized at 1.5T and 3T.

German Ultrahigh Field Imaging (GUFI) Network

In 2021 DFG funding for the GUFI project connecting all UHF MRI sites in Germany (https://mr-gufi.de/) came to an end after 8 years of DFG support (1st funding period 2013-2016, 2nd from 2017-2021). The GUFI network was initiated in 2013 by Mark Ladd (DKFZ, Heidelberg), Oliver Speck (OVGU, Magdeburg), and David Norris (ELH, Essen). For the 2nd funding period (2016-2021) Harald Quick (ELH, Essen) joined as PI. The GUFI network over the years has connected all German UHF sites (7T and 9.4T sites, alphabetical order: Berlin, Bonn, Erlangen, Essen, Freiburg, Heidelberg, Jülich, Leipzig, Magdeburg, Tübingen, Würzburg). The network was expanded to GUFI & Friends to include also Maastricht, the Netherlands and Vienna, Austria, and GUFI also exchanges experience with further UHF sites around the globe including sites in Europe, the United States, Israel, and Australia. In emulation of the GUFI model, further national UHF communities have been founded in other European countries (UK7 in the UK and FUIN in France).

From the start the interaction between the UHF sites in the GUFI network has been very active and productive. Yearly meetings have been held at ISMRM as well as at one of the GUFI sites. Online safety training has been developed, and information on the safe examination of subjects with various implants shared. Importantly, the development of common phantoms (test objects) and quality assurance measurements at all GUFI MRI systems has ensured that all systems can operate at consistent optimum quality.

In 2021, an important joint study established the reproducibility and comparability of various quantitative MRI methods across sites, laying the groundwork for future multi-center UHF studies[9].

After postponement in 2020 and 2021 due to the restrictions of the COVID-19 pandemic, the long-awaited next GUFI meeting was finally held

Figure 3. Participants at the 2021 GUFI Meeting in Magdeburg.

in November 2021 in Magdeburg. This was a great opportunity for all participants to see each other again in person (Fig. 3). It was agreed that the established GUFI structures, trainings, and meetings will 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 14-Tesla human MRI in Germany.

Contact

Prof. Dr.
Harald Quick

Tel.: +49 201 723 84541
E-Mail:
harald.quick@uni-due.de

Contact

Prof. Dr.
Mark Ladd

Tel.: +49 6221 42 2550
E-Mail:
mark.ladd@
dkfz-heidelberg.de

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Jennifer Schulz, Carlijn Tenbergen, Sjaak van Asten, Tom Scheenen

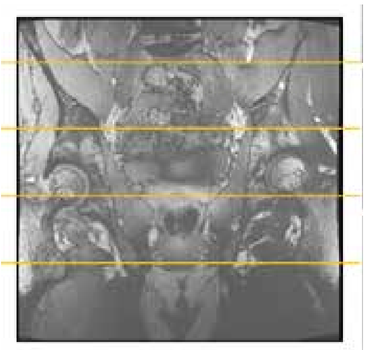
Assessment and diagnosis of prostate cancer and its metastatic potential at 7T

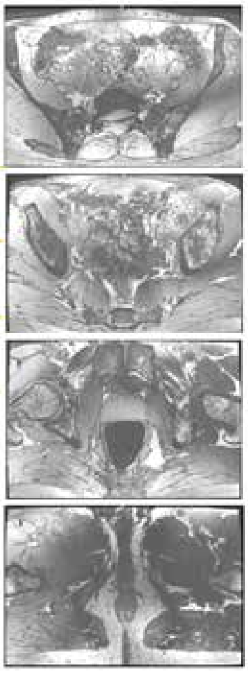
Getting precise diagnosis of the lymph node status in prostate cancer is crucial for the determination of its treatment plan. The European (EFRO) project "Metablic Imaging for Robotic MR guided interventions (MI-Robot)" is focusing on this research question. In a collaboration with Dutch companies Tesla Dynamic Coils and Soteria Medical, expertise from industry and scientific research is combined to develop innovative hardware and software techniques.

To improve the assessment of the aggressiveness and the metastatic potential of local tumors, the MI-robot project will make use of the advantages that come along with the new 7T Terra Siemens system.

On the hardware side, a multinuclear body array coil is currently under development which will be able to safely examine the lower abdomen of patients and volunteers with high precision in and around the prostate region. This new coil will not only be capable of carrying out standard proton imaging, but can (due to the combination of an 8Tx/32Rx ^{1}H body array with a 4Tx/12Rx ^{31}P coil array) also perform non-invasive metabolic imaging. A prototype of the body array has already been designed by Tesla Dynamic Coils and could successfully be installed at the TERRA in Essen. The new combined-coil prototype is expected to be operational this spring.

At the same time, advanced software development is necessary to obtain high quality images at ultra-high field. New software version specific MR-imaging and spectroscopy sequences need to be programmed, installed and tested to ensure that examinations can be performed smoothly, safely, and with reliable quality. The results of the combined examination together with the new software will improve the assessment





Large field of view excitation of a 3D volume in a healthy volunteer with the adapted TIAMO technique for the 7T Terra system. In coronal view 4 positions are depicted with orange lines with the corresponding axial images through the 3D dataset on the right.
Different axial views through the 3D dataset. Isotropic resolution of 0.68 x 0.68 x 0.68 mm^3. Notice signal within the bones at this short TE.

of the aggressiveness of prostate tumors and their metastatic potential.

In parallel, an MRI-compatible robot is being developed by Soteria Medical. The robot will be able to steer a needle guidewire inside the human body. After a first patient examination with the body array coil described above, MR images will be assessed by an uro-radiologist. In a second examination, the robot can be used to retrieve MR-guided robotic biopsies of suspicious regional lymph nodes and determine their pathology. The wire guidance needs to be live supervised by continuous imaging methods which will ensure maximal precision. The anatomical and metabolic imaging information of the first extensive 7T MRI/MRS examination will after medical examination be used to “guide” the needle to the target position.

The result is an innovative technique with hardware and software components which can also be transferred to other MRI systems. As the body array and the MI-robot are designed to be handled separately of each other, one will be able to transfer each individual system to other medical applications apart from this oncological focus. Furthermore, diagnosis and biopsy are not necessarily performed at the same MRI system which will give more flexibility in the planning of patient treatment.

The first spin-off project of the new hardware above has already been approved in the Horizon2020 project MITI: Non-ionizing Metabolic Imaging for predicting the effect of and guiding Therapeutic Interventions. In a collaboration with the universities of Cambridge, Utrecht, Nijmegen, Essen, and Pisa, saturation transfer techniques in ^{31}P spectroscopic imaging will be explored at the 7T Terra system in Essen with the new multi-nuclear coil array from Tesla DC.

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Contact

Prof. Dr.
Tom Scheenen

Tel.: +31 24 3614545
E-Mail:
tom.scheenen@
radboudumc.nl

Peter Koopmans

DFG Emmy Noether research group: fMRI of Cortical Layers

Our research group aims to develop fMRI methodology to investigate brain functioning at a very fine scale in order to help solving a question that arises from conventional functional neuroimaging where we study processes in the brain at a 'regional' scale. Through decades and decades of research, neuroscientists have managed to identify many unique areas in the brain. For instance, there are regions that are primarily involved in processing of emotions, pain sensation, movement of limbs, visual perception, and many more of course. Seldom does a particular process involve a single brain area, usually it is an entire network of brain areas that together execute whatever is needed. To fully understand these processes, we would like to be able to track the information stream: What triggers the process? Which areas are involved immediately after this trigger? If there is a "supervisory" brain area involved, where in the network does it send its feedback information to? It would be very interesting to be able to directly measure these steps but unfortunately with current neuroimaging techniques this is very hard.

Using resting state fMRI and diffusion imaging we can see which areas are connected, either functionally or structurally respectively. But apart from providing evidence whether or not a connection is present, it does not tell us in which direction the information would be flowing at any given time. Attempts have been made to deduct this information from temporal aspects of the fMRI signal, but as the intrinsic temporal resolution of the BOLD signal is rather poor (most information limited to timescales on the order of seconds) this is extremely hard. Using layer fMRI we hope to leveraging spatial aspects of the signal: from animal work it is known that the cortex consist of histologically distinct layers, and that these layers have different functions in terms of input, output,

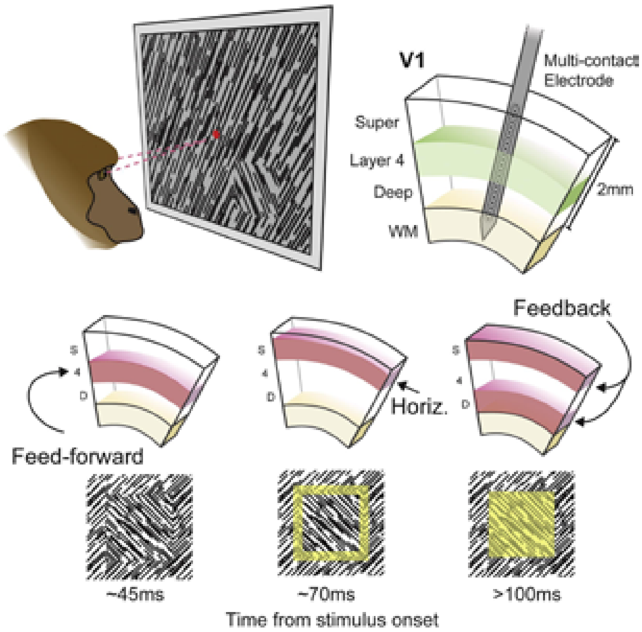

Figure 1. Cortical layers have different functions. In this example, information from the retina enters primary visual cortex in the middle layer (feedforward, bottom left panel), it is then processed locally and sent to the next region in the hierarchy from its superficial layers (output; middle bottom panel), and finally, when feedback is received from these higher-up regions, it arrives in the deep and superficial layers (bottom right panel).
Image taken from: Self MW, et al.; Curr. Biology 2013, pg 2121-2129

and feedback processing (Fig. 1).

One of the main challenges in high-resolution fMRI is that fMRI techniques do not measure neuronal signals directly, but through the effect that neuronal activity has on the local vasculature. Upon activation local blood volume and blood flow increase as well as the blood oxygenation levels. The main challenge in terms of methods development is to find techniques that are sensitive to activity-related changes in only the tiniest blood vessels (which physically are very close to the activated neurons that cause the vascular effects) and not as sensitive to large blood vessels that are remote from the site of neuronal activity. Those large vessels can result in us measuring signal changes in different layers than that the actual activity is taking place in, which of course makes it a lot harder to infer directionality based on layer information. Our latest work involves a sequence that is sensitive to blood volume changes. Blood volume changes are interesting as the small capillary vessels are known to drive this effect (as opposed to the large veins which barely change in volume). An example can be seen in Figure 2, where at a short echo time, the proposed MT-prep method shows much more activity inside the cortex than the standard BOLD measurement which predominantly shows activity in the draining veins outside the cortex. At the ELH, we hope to further develop this MT-prep method as a tool for efficient high-resolution fMRI.

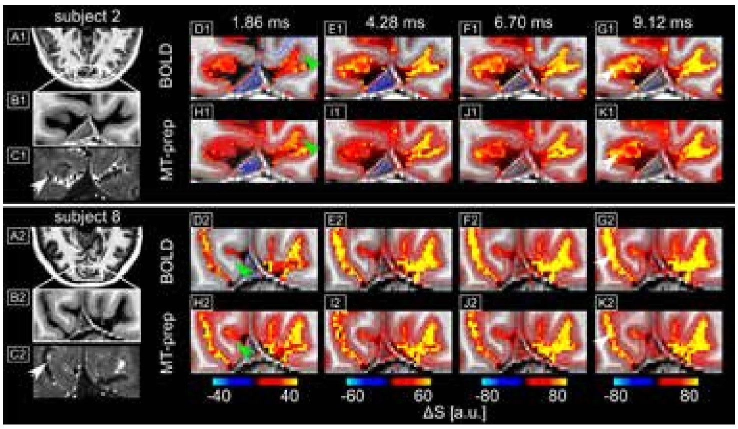

Figure 2. Comparison between MT-prep and BOLD activation maps in two subjects. Whereas at these early echo times, the BOLD response barely shows any activity inside the cortex but only inside the large pial vessels, the MT-prep data nicely shows intracortical activation (e.g. green arrows). At much later echo times (not shown here), both methods show extensive activation in and outside the cortex, both driven by extravascular effects of large veins that are of less interest. For optimal specificity, future developments will therefore be focused on MT-prep methods in combination with efficient short echo time acquisitions (e.g. spiral-out sequences).
Image taken from: Pfaffenrot et al. (submitted)

Contact

Dr.
Peter Koopmans

Tel.: +49 201 183 6089
E-Mail:
peter.koopmans@
uni-due.de

Shahrokh Abbasi-Rad, David Norris

Interleaved BOLD imaging and proton spectroscopy

In 2021 progress was again hindered by the impact of the COVID-19 pandemic. Our main experimental endeavour was to establish an interleaved BOLD imaging and proton spectroscopy experiment. This was achieved by Shahrokh Abbasi-Rad in collaboration with the lab of Andre van de Kouwe (MGH) and will be used in a large study in 2022 examining the excitatory/inhibitory imbalance in autism spectrum disorder led by Jill Naaijen.

The experiment comprises of a 3D-EPI sequence which can be used to measure BOLD activation and a single voxel (PRESS) spectroscopy experiment which can measure both glutamate and gamma-ammino-butyric acid (GABA), which are the main excitatory and inhibitory neurotransmitters in the brain respectively. Figure 1 schematically represents the pulse sequence that has been implemented for this study.

In terms of grant funding, we will be actively involved in several projects involving laminar fMRI in the coming years. In an exciting new project funded by MERCUR (Mercator Research Center Ruhr) together with Nikolai Axmacher (RUB) we shall use laminar fMRI to examine the function of the human hippocampus in memory and navigation.

As the hippocampus has a different histological and vascular structure as compared to the isocortex there are also many methodological and biophysical challenges to be resolved in order to obtain interpretable data. We have also obtained funding from the Dutch Science Foundation (NWO, Cools and Norris) for "Unravelling Dopamine's role as Gatekeeper of Prefrontal Cortex", which contains a substantial amount of laminar fMRI to be performed at the Erwin L. Hahn Institute.

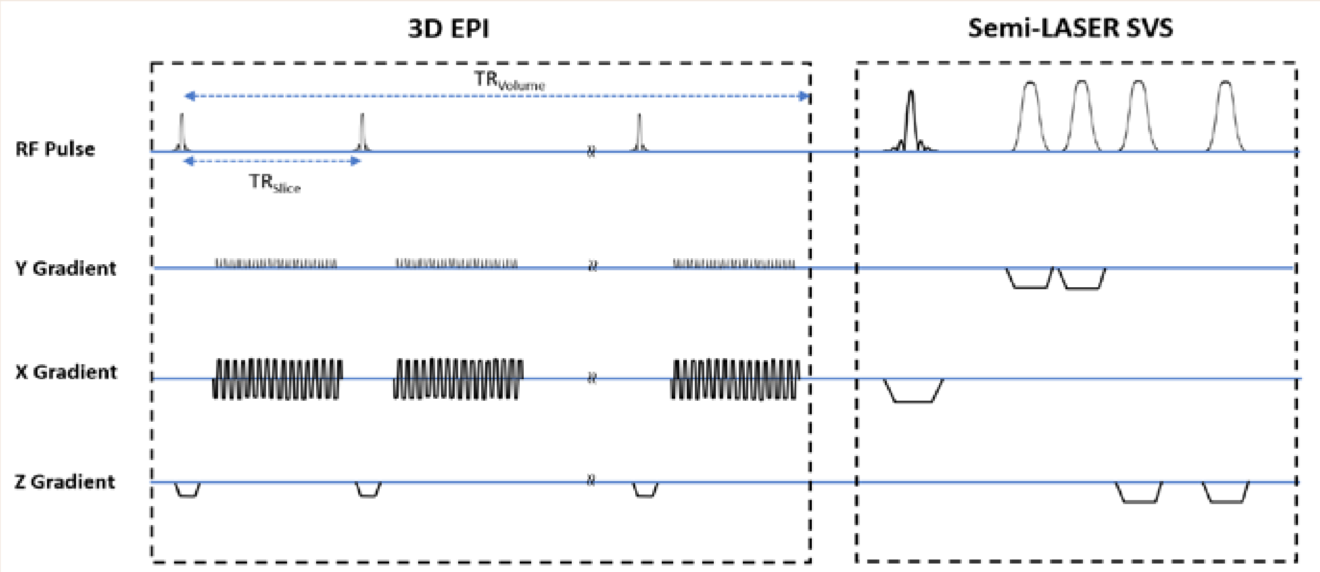

Figure 1. One average (TR) of the combined fMRI-MRS pulse sequence, which consits of a 3D echo-planar-Imaging sequence to measure BOLD followed by a short echo semi-localization by adiabatic selective refocussing (semi-LASER) sequence for single-voxel spectroscopy to measure Glutamate and GABA. Semi-LASER was used to minimize the chemical shift displacement at ultra-high field. The crusher and spoiler gradients are not shown for simplicity.

Contact

Prof. Dr.
David Norris

Tel.: +31 24 3610649
E-Mail:
d.norris@donders.ru.nl

Dagmar Timmann

Cerebellum and emotion memory – the cerebellum's role in extinction of learned fear responses

The human cerebellum is well known for its contribution to motor learning, and disorders in motor learning have been related to motor performance deficits in patients with cerebellar disease. The cerebellum is likely also involved in learning and memory processes in the cognitive and emotional domains, but this has been studied in much less detail. Our 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. To provide further evidence that the human cerebellum contributes to the different phases of fear learning we are performing fear conditioning studies in healthy human participants, including pharmacological interventions, and in patients with cerebellar degeneration in the 7T MRI scanner.

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 our current studies is to show that the cerebellum has to be included in the network underlying extinction of learned fear responses. We want to get a more mechanistic understanding about the proposed contribution of the cerebellum to extinction learning. In a previous study we made the observation 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[1]. An unreinforced CS+ trial can be considered as a very first extinction trial. We propose that cerebellar fMRI activation during the unexpected omission of an aversive stimulus reflects processing of reward prediction error, which drives extinction learning.

There is recent evidence that the role of the cerebellum goes beyond processing of sensory prediction error (a well-accepted concept of cerebellar functioning[2]), but also includes processing of reward prediction errors (a very new concept of cerebellar functioning[3]). Reward prediction errors are thought to be at the core of extinction learning, and there is exciting new evidence that the cerebellum receives reward signals[4] on the one hand, and is connected with the mesolimbic dopaminergic system, in particular the ventral tegmental area (VTA), on the other hand[5].

We are currently planning 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 VTA.

The unpredicted omission of the aversive US is thought to be rewarding. Therefore, cerebellar activation should be equally present related to the unpredicted presentation of reward in appetitive conditioning paradigms. To test this hypothesis we will compare cerebellar activations in reversal learning paradigms of differential fear and appetitive conditioning in the 7T MR scanner.

We will take advantage of the new MAGNETOM Terra 7T MRI system (Siemens Healthcare GmbH, Erlangen) at the Erwin L. Hahn Institute (ELH), a system with much improved gradient strength compared to the previous Siemens MAGNETOM 7T system. This will allow us to perform 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, we will expand our paradigms to a 3-day design allowing for consolidation of both the fear and extinction memory trace. In addition to skin conductance (SCR) recordings which were successfully realized in the 7T scanner in now three experiments, we want to implement pupillometry, to get additional trial-by-trial measures of conditioning. An eye tracker system is available at the new MAGNETOM Terra 7T MRI system.

Our experiments will allow a fuller understanding of the interactions between the cerebellum and the known fear acquisition and extinction networks. Furthermore, close collaboration between the MRI sites in the CRC 1280 and ITN will allow a comprehensive understanding of changes in emotional networks not only in cerebellar disease, but also neurodevelopmental and anxiety disorders, an important prerequisite to develop future treatments.

Our work is funded by the Marie-Skłodowska-Curie Innovative Training Network (ITN): Cerebellum and emotional networks (CEN) and the Collaborative Research Center CRC 1280 "Extinction learning" (subproject 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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Contact

Prof. Dr.
Dagmar Timmann

Tel.: +49 201 723 2180
E-Mail:
dagmar.timmann-braun@
uni-due.de

Memory and Learning

On January 26/27, 2021, the CRC 1280 "Extinction learning" was positively evaluated and subsequently approved by the DFG in May 2021. This CRC studies the mechanisms of extinction as a form of learning that involves both forgetting as well as a new learning process that is different and far more complex than the initial learning event. Extinguished responses do not simply disappear but can return under diverse conditions – potentially turning them into invasive components of psychopathological conditions.

Despite its relevance, the behavioral, the neural, and the clinical aspects of extinction are by far not understood. Using psychological, neurobiological, clinical, and computational approaches, the CRC 1280 aims to study the neural, behavioral, ontogenetic, and clinical mechanisms of extinction in various species, including humans. It consists of 18 projects and is funded with over 13 million Euro for the 2021-2025 period.

In April 2021 the ERC Advanced Grant "AVIAN MIND: Inquiries into a different kind of mind" was accepted as one of 8% of submitted proposals. Here the aim is to gain deeper insights into executive cognition, memory, and consciousness in pigeons by testing the hypothesis that despite major macroscopic differences, the pallial cognitive network of birds is highly similar to that of mammals while their memory systems differ. The funding of over 2.2 million Euro started on January 2022.

The Ruhr University Bochum (RUB) and the University Duisburg-Essen (UDE) plan to apply for a joint Cluster of Excellence with name THINK@Ruhr of which Onur Güntürkün was elected as speaker. Here, the neuroscientific and cognitive expertise of both universities will be combined to develop a novel view on how cognitive processes and aspects of mind are generated in brains. To this end, the rectorates of RUB and UDE forwarded the application for initial support the initial activities of THINK@Ruhr to

MERCUR (Mercator Research Center Ruhr). MERCUR decided to support this initiative as the only application without any cuts with 2 million Euro.

The Research Center "One Health" is one out of four centers that will be funded by the state NRW for the three universities of the Ruhr. It was conceived by the rectorate of UDE by including the research areas molecular biology, cancer research, water ecology, and cognitive neuroscience. Together with three further PIs, Onur Güntürkün interacted with the National Research Council as well as the UDE to incrementally shape this application until it was finally funded by the NRW Ministry of Culture & Research. Two well-funded W3 professorships ("the predictive brain" and "the adaptive brain") will be established in 2022/23 that are both planned to establish strong interests to conduct a part of their research at ELH.

Onur Güntürkün is associated with the ELH-project of Erhan Genç and Nikolai Axmacher in the CRC 1280 ("Functional role and dynamic change of extinction network connectivity").

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2. Rook, N.; Tuff, J.M.; Packheiser, J.; Güntürkün, O.; Beste, C. (2021) A hierarchical processing unit for multi-component behavior in the avian brain. *IScience* 24, 103195.
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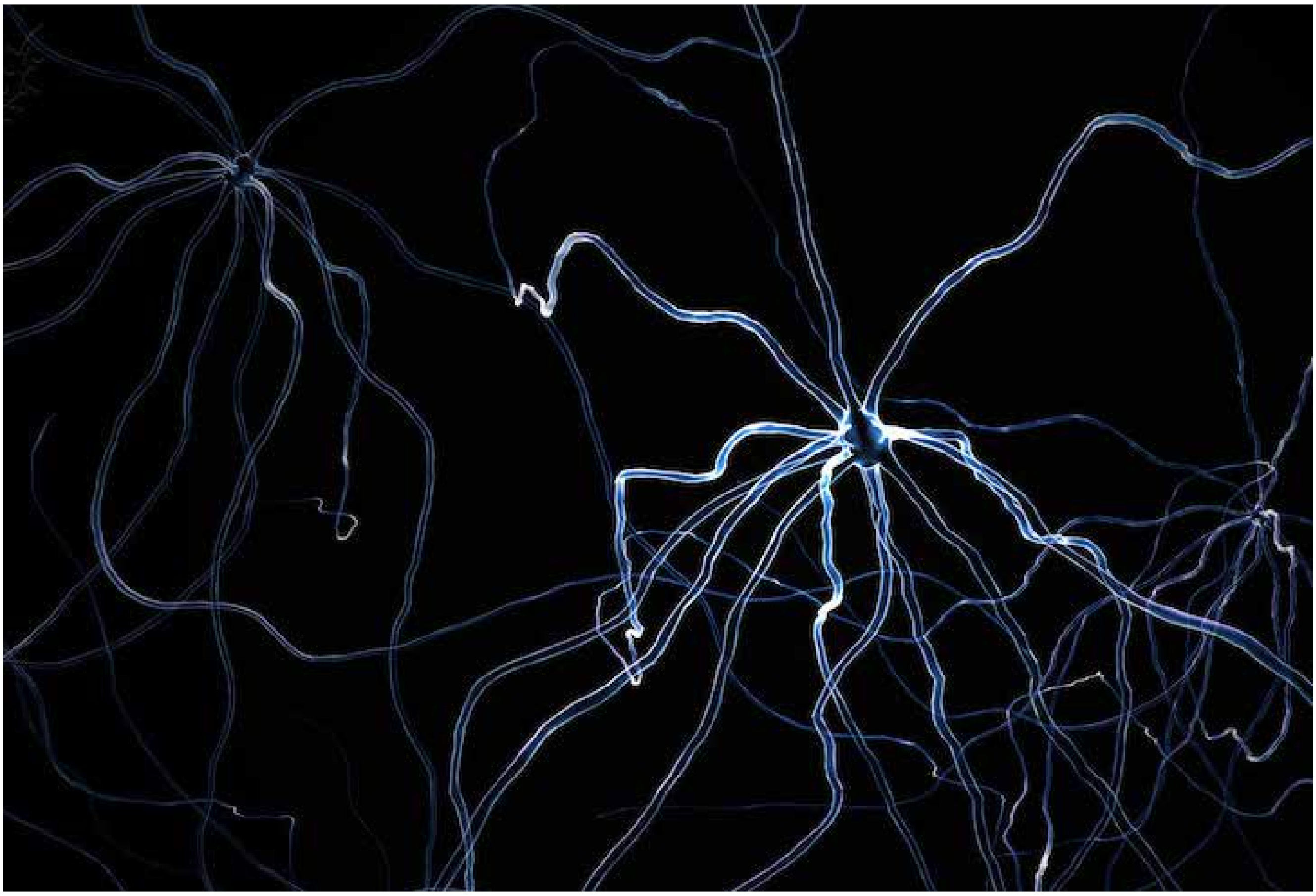
Contact

Prof. Dr.
Onur Güntürkün

Tel.: +49 234 32 28213
E-Mail:
onur.guentuerkuen@
ruhr-uni-bochum.de

David Stawarczyk, Nikolai Axmacher



New early diagnostic approaches to Alzheimer's disease

Grid cell-like representations are a kind of brain activity that appears when we are moving in space according to a 60-degree grid. These grid cell-like representations are located in a part of the brain named the entorhinal cortex that is among the first area to be affected by Alzheimer's disease. We have recently demonstrated that these Grid cell-like representations are disrupted in genetic Alzheimer's disease risk carriers at young age (less than 30 years old), which suggests that they might be a biomarker for early disease processes.

In our current project at ELH we plan to use the submillimeter resolution of 7T functional magnetic resonance imaging in combination with a first-person spatial navigation video game to examine grid cell-like representations at a finer spatial scale than in our previous works. We aim to determine which cortical layers of the entorhinal cortex support these representations, which will give us critical information about their functional relevance among the various brain regions involved in supporting spatial navigation, and we hope to pave the way for novel early diagnostic approaches to Alzheimer's disease.

Traumatic events are often recalled as intrusive memories, which are involuntary, spontaneous, and vivid reminiscences of past events. Intrusive memories of a traumatic event usually dissipate after a period of time in the general population. However, patients with post-traumatic stress disorder (PTSD) have long-lasting intrusive memories, which can induce significant distress. We recently developed a new version of a paradigm designed to study intrusive memories by presenting healthy subjects with neutral or aversive movie scenes. Aversive movie scenes act as trauma-analogue events and can later give rise to intrusive memories. Using this paradigm on the 3T scanner, we showed that the neural representations of trauma-analogue movie scenes differed from those of neutral movie scenes. This suggests that specific properties of the neural representations of trauma-analogue events may be related to the subsequent formation of intrusive memories.

In our current project at ELH, we will further test this hypothesis by using ultra-high resolution fMRI to investigate whether changes in the neural representations of aversive movie scenes and of neutral movie scenes that precede them predict the subsequent occurrence of intrusive memories. We hope to provide a better understanding of the neural mechanisms of trauma, which may inform therapeutic approaches for PTSD patients.

We have also developed a registration and distortion correction pipeline that is highly optimized for laminar data. This pipeline mostly makes use of tools from the ANTs package, although it also incorporates functions from other neuroimaging software packages, such as SPM and FSL.

In short, our pipeline initially creates the necessary masks and average images that will be used for the registration/distortion correction. Inter-volume motion for both EPI and opposite phase-encoding (PE) images are estimated with an in-house function that computes templates for both types of images. The opposite PE template is registered (rigidly) to the mean functional template and the resulting files are then passed to the ANTs SyN algorithm for subsequent distortion correction. All transformations and distortion warps are saved for later reslicing.

After motion and distortion estimation, inter-run registration (i.e. aligning different functional runs) is performed using another in-house script. This script takes the template of a specific functional run and implicitly aligns it to a reference template within the same session. In addition, the templates belonging to runs acquired on different days will be aligned to the first run of the first day, so that every single run is aligned to the first run of the first day.

Next, the anatomical workflow will be run, which cleans up the MP2RAGE image and generates the appropriate mask and tissue files. Functional-to-anatomical registration then takes place by utilizing the boundary-based registration algorithm implemented in FSL.

Finally, reslicing is performed by using an in-house script that applies a series of ANTs functions. All the transformations and distortion warps generated in the steps above will be applied in one instance during this step. As such, the data are interpolated only once during the whole preprocessing.

For ease of use, we have created a fully automatic script as well as a companion "HowTo" document, detailing the steps described above, both of which will be made publicly available.

Contact

Prof. Dr.
Nikolai Axmacher

Tel.: +49 234 32 22674
E-Mail:
nikolai.axmacher@rub.de

Stephanie Antons, Kjell Büsche, Matthias Brand

Neural correlates of cue-reactivity in gaming disorder and pornography use disorder

With the approval of the transregional Research Unit FOR2974, "Affective and cognitive mechanisms of specific Internet-use disorders (ACSID)", supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, Nr 411232260), our working group started the preparations at the ELH for the implementation of the research project 4 "Cue reactivity in gaming disorder and pornography-use disorder: Behavioral and neural correlates and effects of acute stress".

The project consists of two parts. The first part, which will be conducted in the laboratory of the Ruhr University Bochum (Martin Diers, Lukas Mallon, and Oliver Wolf), will focus on behavioral and neuroendocrinological effects of acute stress on cue reactivity in gaming disorder and pornography use disorder. Participants who are eligible and willing to participate in an additional part that includes fMRI will be invited to ELH for the second part of the study. The goal of this second part is to identify the neural correlates of cue reactivity in gaming disorder and pornography use disorder and the differences in neural activities between regular, risky, and pathological users. A total of 170 participants will be studied with fMRI as part of this project.

Preparations began with a pilot project application in May 2021 aimed at identifying the most appropriate sequence parameters leading to high quality data for functional whole brain images in an event-related design. Together with Viktor Pfaffenrot and Stefan Maderwald (both ELH), different sequences and parameters for both structural and functional images were systematically tested on the new Siemens MAGNETOM Terra 7-Tesla MRI system. Based on signal-to-noise estimates, the decision was made to use MP2RAGE (TR = 6000 ms, TE = 2.11 ms, FOV = 240 mm, slice thickness = 0.6 mm) and 3-D EPI (TR = 1630 ms, TE = 23 ms, FOV = 210 mm, slice thickness = 1.50 mm). In parallel, the data preprocessing pipeline was optimized and the cue reactivity paradigm was programmed for the functional imaging part. In June 2021, the full project proposal was approved. The first real scans with project participants have been successful, and we look forward to performing the further scans at ELH over the next two years as part of this research project.

Contact

Prof. Dr.
Matthias Brand

Tel.: +49 203 379 2541
E-Mail:
matthias.brand@uni-due.de

The interaction between 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.

As has been true for many of us, the COVID-19 pandemic has substantially slowed down our experimental research activities since spring 2020. However, 2021 has been very successful in securing grant support at the group and faculty level which will lay the foundation for exiting avenues of research at the ELH.

In July 2020 the transregional CRC 289 "Treatment Expectation" (www.treatment-expectation.de) has been funded by the DFG. The consortium lead by Ulrike Bingel will focus on the mechanisms underlying expectations on health and treatment outcomes and explore 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 harmonizing 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[2]. The cerebellum provides an ideal target to be followed up with high field neuroimaging in a joint endeavor with the group by Dagmar Timmann (see page 16), a world leading expert in this field. A grant grant proposal to cover this exiting avenue of research is currently being prepared.

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.

Under the leadership of Ulrike Bingel, the Medical Faculty and University Medicine Essen have secured funding for the Advanced Clinician Scientist program UMEA2 which will – together with the established (junior) Clinician Scientist program UMEA (https://www.uni-due.de/med/umea/) – provide a unique structural framework to support Clinician Scientists who have completed their clinical training to found their own and independent research groups and pursue both a career in medicine and science. Only eight medical faculties in Germany have been selected by the BMBF to receive this prestigious and competitive funding scheme and Bingel's team is delighted to consolidate and expand the superb structural conditions to support our excellent clinician scientists. The ELH is an important hub in the excellent research infrastructure of the UDE and the Research Alliance Ruhr.

Last but not least several exciting projects to be performed at the ELH in 2021 have been initiated. Together with Peter Koopmanns (see page 12), 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 volunteers.

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2. Zunhammer, M.; Spisák, T.; Wager, T.D.; Bingel, U.; The Placebo Imaging Consortium (2021) Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nature communications* 12, 1391.

Contact

Prof. Dr.
Ulrike Bingel

Tel.: +49 201 723 2446
E-Mail:
ulrike.bingel@uk-essen.de

2021 IN SHORT

First Hybrid "Erwin L. Hahn Workshop & Lecture"

We are now on Twitter! (@ELH_Institute)

Total of 10 PI-Groups from three universities

188 test subject scans with the new 7T MRI system

Nikolai Axmacher and his PI group join the ELH

ISMRM Participation 2021
(online event)

Fortuin, A.; van Asten, S.; Veltien, A.; Philips, B.; Hambrock, T.; Orzada, S.; Quick, H.H.; Barentsz, J.; Maas, M.; Scheenen, T.: The power of field strength: a direct comparison of USPIO-enhanced MRI at 3 and 7T to detect suspicious lymph nodes in patients with prostate cancer.
Session: Cancer: Contract Agents & MRS; talk.

Kraff, O.: Member of the ISMRM Working Group on Best Practices for Safety Testing of Experimental RF Hardware.

Guye, M.; Ladd, M.E.: MR Physics for Clinicians: Hardware, Fields & Contrast Agents.
Session Number: WD-01; organizers of the course.

Orzada, S.; Fiedler, T.M.; Quick, H.H.; Ladd, M.E.: A local SAR compression algorithm with improved compression, speed and flexibility.
Session: SAR & RF Heating; digital poster.

Spronk, T.; Kraff, O.; Schaefers, G.; Quick, H.H.: Development and evaluation of a numerical simulation approach to predict metal artifacts from passive implants in MRI.
Session: Artifcats & corrections related to the system & sample; digital poster.

Invited Talks & Workshops 2021

Timmann, D.: Imaging of the cerebellar nuclei in humans.
Workshop: *Terra incognita: Diving into the subcortex.* Amsterdam 1-3 March, 2021.

Dissertations 2021

Deuermeier, N.: Evaluierung einer 8-Kanal Sende-/32-Kanal Empfangsspule zur Kopfbildgebung am 7 Tesla MRT. (B.Sc. Thesis)

Ernst, T.: On the importance of the cerebellum for emotional control using the example of acquisition and extinction of conditioned fear responses. (PhD Thesis)

Haupt, D.: System Performance Assessment and Quality Assurance at a Newly Installed 7 Tesla Magnetic Resonance System. (B.Sc. Thesis)

Lauth, A.: Messung der T2*-Relaxationszeit des Liquors in Ruhe und bei Aktivität in der laminaren funktionellen Magnetresonanztomographie. (B.Sc. Thesis)

Noureddine, Y.: Charakterisierung der hochfrequenz-induzierten Erwärmung passiver Implantate während MRT-Untersuchungen bei 7 Tesla am Beispiel von intrakraniellen Aneurysma-Clips. (PhD Thesis)

Erwin L. Hahn Workshop & Lecture 2021

Top:
Harald H. Quick

Left:
Jennifer Schulz

Right:
Karsten Wrede

Bottom:
Keynote Speaker
Oliver Speck

Top:
Keynote Speaker
Oliver Speck

Middle:
Bixia Chen

Bottom:
Thomas Ernst (left)
receives the ELH Award
for Young Scientists

Current Grants

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-Braun'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: **The contribution of the cerebellum to extinction: intrinsic mechanisms and cerebello-cerebral interactions. A05 of CRC 1280** (2021-2025)

The project 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: **Focus Group Neuroimaging and Genetics. F02 of CRC 1280** (2021-2025)

The project 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: **JPND-SCAIFIELD-2021, Associated recruitment center** (2021-2024)

The aim of SCAIFIELD is to perform advanced brain imaging with ultra-high field MRI in patients with spinocerebellar ataxias (SCA). Timmann is head of the ataxia clinic at the Essen University Hospital and will recruit SCA patients who will be scanned with SCAIFIELD protocols at the ELH.

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**

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.

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

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 behaviors, 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 localized prostate cancer is correlated and validated with early detection of the first metastases of the disease.

N. Axmacher, D. Timmann-Braun, H.H. Quick
DFG: **Focus group Neuroimaging: Extinction network connectivity across learning paradigms. F01 of CRC 1280** (2017-2021)

In this joined project between PIs of the Ruhr University Bochum and University Hospital Essen, metaanalyses will be performed of fMRI data acquired in CRC 1280. The main aim is to systematically investigate structural and functional extinction network connectivity across different learning paradigms and subject populations.

P. Koopmans
DFG Emmy Noether Programme – Independent Junior Research Group:
Functional Magnetic Resonance Imaging of cortical layers to measure directionality of information flow in brain networks for pain (2016-2021)

Koopmans' proposal focuses on the development of a high-resolution fMRI technique to improve understanding of how the brain processes pain.

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

Fiedler, T.M.; Orzada, S.; Flöser, M.; Schmidt, S.; Stelter, J.K.; Wittrich, M.; Quick, H.H.; Bitz, A.K.; Ladd, M.E. (2021) Performance and safety assessment of an integrated transmit array for body imaging at 7 T under consideration of specific absorption rate, tissue temperature, and thermal dose. *NMR in Biomedicine* e4656.

Fiedler, T.M.; Orzada, S.; Flöser, M.; Rietsch, S.H.G.; Quick, H.H.; Ladd, M.E.; Bitz, A.K. (2021) Performance analysis of integrated RF microstrip transmit antenna arrays with high channel count for body imaging at 7T. *NMR in Biomedicine* e4515.

Markuerkiaga, I.; Marques, J.P.; Bains, L.J.; Norris, D.G. (2021) An in-vivo study of BOLD laminar responses as a function of echo time and static magnetic field strength. S*cientific Reports* 11, 1862.

Norris, D.G.; Webb, A. (2021) This house proposes that low field and high field MRI are by destiny worst enemies, and can never be the best of friends! *Magnetic Resonance Materials in Physics, Biology and Medicine* 34, 475-477.

Orzada, S.; Fiedler, T.M.; Quick, H.H.; Ladd, M.E. (2021) Post-processing algorithms for specific absorption rate compression. *Magnetic Resonance in Medicine* 86, 2853-2861.

Orzada, S.; Fiedler, T.M.; Quick, H.H.; Ladd, M.E. (2021) Local SAR compression algorithm with improved compression, speed, and flexibility. *Magnetic Resonance in Medicine* 86, 561-568.

Pfaffenrot, V.; Voelker, M.N.; Kashyap, S.; Koopmans, P.J. (2021) Laminar fMRI using T2-prepared multi-echo FLASH. *NeuroImage* 236, 118163.

Scheenen, T.W.J.; Zamecnik, P. (2021) The Role of Magnetic Resonance Imaging in (Future) Cancer Staging: Note the Nodes. *Investigative Radiology* 56, 42-49.

Spronk, T.; Kraff, O.; Kreutner, J.; Schaefers, G.; Quick, H.H. (2021) Development and evaluation of a numerical simulation approach to predict metal artifacts from passive implants in MRI. *Magnetic Resonance Materials in Physics, Biology and Medicine.*

Trotzke, P.; Starcke, K.; Pedersen, A.; Brand, M. (2021) Dorsal and ventral striatum activity in individuals with buying-shopping disorder during cue-exposure: A functional magnetic resonance imaging study. *Addiction biology* e13073.

Voelker, M.N.; Kraff, O.; Goerke, S.; Laun, F.B.; Hanspach, J.; Pine, K.J.; Ehses, P.; Zaiss, M.; Liebert, A.; Straub, S.; Eckstein, K.; Robinson, S.; Nagel, A.N.; Stefanescu, M.R.; Wollrab, A.; Klix, S.; Felder, J.; Hock, M.; Bosch, D.; Weiskopf, N. (2021) The traveling heads 2.0: Multicenter reproducibility of quantitative imaging methods at 7 Tesla. *NeuroImage* 232, 117910.

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. Ulrike Bingel
Prof. Dr. Dr. h.c. Onur Güntürkün
Prof. Dr. Tom W.J. Scheenen

Associated PIs
Prof. Dr. Nikolai Axmacher
Dr. Peter J. Koopmans
Prof. Dr. Mark E. Ladd
Prof. Dr. Dagmar Timmann

Administrative Director
Dr. Franziska Günther

Staff Scientist
Dr. Oliver Kraff
Dr. Stefan Maderwald

Public Relations
Stefanie Zurek

Scientists

MSc. Shahrokh Abbasi-rad
Dr. Stephanie Antons
Dr. Giorgi Batsikadze
MSc. Kjell Büsche
Dr. med. Cornelius Deuschl
MSc. Alice Doubliez
Dr. Thomas Ernst
Dr. rer. nat. Marcel Gratz
Dr. med. Tijmen Koëter
Dr. Bernhard Müller
Dr. Silke M. Müller
MSc. Enzo Nio
Dr. Stephan Orzada
MSc. Viktor Pfaffenrot
Dr. René Scheeringa
Dr. Jennifer Schulz
MSc. Daniel Sharoh
MSc. Tobias Spronk
Dr. Emma Sprooten
Dr. David Stawarczyk
MSc. Carlijn Tenbergen
Prof. Dr. med. Indira Tendolkar
Dr. med. Andreas Thieme
Dr. Jan-Willem Thielen

Students

Niklas Deuermeier
Dennis Haupt
Anna Lauth
Daniel Leinweber
Annika Verheyen
Philippe Zeidan

New in 2021

Nikolai Axmacher
Franziska Günther
Annika Verheyen

Left in 2021

Mahmoud Bagheri
Niklas Deuermeier
Dennis Haupt
Anna Lauth
Daniel Leinweber
Philippe Zeidan

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Erwin L. Hahn Institute
UNESCO World Heritage Zollverein
Building C84
Kokereiallee 7
45141 Essen

Tel.: +49 201 183 6070
E-Mail: elh@uni-due.de

https://hahn-institute.de

Universität Duisburg-Essen – Open-Minded

Ruhr-Universität Bochum – RUB

Universität Duisburg-Essen – Ingenieurwissenschaften

UMC St Radboud

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Universitätsklinikum Essen

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