Research Report
2017–2019
Preface

The Max Planck Institute for Human Cognitive and Brain Sciences has continued its pursuit of excellent and internationally renowned research and development in the past three years (2017 to 2019). The Institute currently houses four full departments, eight research groups, and three methods and development units. Around 380 staff members contribute to the lively buzzing atmosphere, the cutting-edge science, and the daily multicultural exchange.

As always, the Institute continues to develop. The youngest of our departments, the new Department of Psychology headed by Christian Doeller, has settled in and is rapidly growing. Christian Doeller joined the Institute, as its latest director, from Trondheim and Donders in 2018. He brings with him a prestigious ERC Consolidator grant as well as several large-scale EU-wide collaborative projects. The Department of Neurophysics headed by Nikolaus Weiskopf has made substantial progress on their ERC Consolidator grant held in collaboration with UCL in London. Angela D. Friederici’s Department of Neuropsychology continues their involvement in a large-scale international priority programme funded by the DFG and have recently secured a new ERC Starting Grant. The Department of Neurology, under the tutelage of Arno Villringer, secured several new large-scale project grants on obesity and neural rehabilitation and started the follow-up of the LIFE population health study together with Leipzig University on 10,000 subjects. 12 of Arno Villringer’s former group members have achieved faculty positions in the last three years.

Of course, development means change. In December 2018, Professor Tania Singer, former director of the Department of Social Neuroscience, left the Institute and started a new Research Group on Social Neuroscience in Berlin. Four of our independent research group leaders have left the Institute for new positions in capital cities across Europe. Stefanie Höhl, who formerly headed the Max Planck Research Group “Early Social Cognition”, has moved to Vienna to take up a full professorship position. Daniel Margulies, former leader of the Max Planck Research Group “Neuroanatomy and Connectivity”, accepted a Chargé de Recherche position in Paris, France. Katharina von Kriegstein’s research group came to an end in 2017. She moved to Dresden for a full professorship position. The Otto Hahn group of Daniela Sammler wrapped up in summer 2019. Daniela now holds a senior researcher position at the Institute.

At the same time, six new research groups have been established in the reporting period. Gesa Hartwigsen and her “Cognition and Plasticity” Research Group started as one of the first recipients of the Lise Meitner Excellence Programme—designed to recruit and promote exceptionally qualified female scientists. The Max Planck Research Group “Pain Perception” is headed by Falk Eippert who joined us from Oxford (UK). The Max Planck Research Group “Language Cycles” is headed by Lars Meyer, the Research Group “Stress and Family Health” is led by Veronika Engert. Martin Hebart recently joined the Institute, from the NIH in Bethesda (USA), to start the Max Planck Research Group “Vision and Computational Cognition”. Finally, the Minerva Fast Track Group “Milestones of Early Cognitive Development” is led by Charlotte Grosse Wiesmann, who moved to Leipzig from Copenhagen, Denmark.

There have also been advances and changes for the Institute’s students. The International Max Planck Research School on Neuroscience of Communication (NeuroCom) has continued its success in both recruiting promising new doctoral students and seeing the “old” cohorts to completion. During the reporting period, the number of doctoral students pursuing their degree within the programme has doubled.

In addition to the IMPRS NeuroCom, the Institute now also houses the Max Planck School of Cognition, a brand-new, interdisciplinary, highly competitive doctoral programme involving numerous prestigious German universities and research organisations.

We hope you will enjoy reading this report, which contains up-to-date scientific and administrative information about our Institute and world-class research.
Preface

Scientific Members and Boards

The Institute

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Arno Villringer

Department of Neuropsychology: Neurocognition of Language
Angela D. Friederici

Department of Neurophysics: Non-invasive Imaging of the Anatomical and Functional Micro-Organisation of the Human Brain
Nikolaus Weiskopf

Department of Psychology: Space for Cognition
Christian Doeller

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<td>Director, Department of Neurology</td>
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### Emeriti

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<td>Professor Dr Tania Singer</td>
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The Max Planck Institute for Human Cognitive and Brain Sciences at Stephanstrasse in Leipzig was established on 1 January 2004 by a merger between the former Leipzig Max Planck Institute of Cognitive NeuroScience and the Munich-based Max Planck Institute for Psychological Research. The decision to merge both centres of expertise into one followed the development of psychological, neuroscientific, and neurological research increasingly being conducted closely together. The creation of the centre in Leipzig also established exceptional conditions for interdisciplinary behavioural and neurobiological research into human cognition.

The Institute currently consists of four departments: Neuropsychology, Neurology, Neurophysics, and Psychology. The Institute presently hosts a number of research groups, amongst them four Max Planck Research Groups: “Adaptive Memory” (Roland Benoit), “Language Cycles” (Lars Meyer), “Pain Perception” (Falk Eippert), and “Vision and Computational Neuroscience” (Martin Hebart, whose group only just started its research). The Institute also hosts a Lise Meitner Research Group, “Cognition and Plasticity” (Gesa Hartwigsen), a Minerva Research Group, “EGG (Emotion and neuroimaGinG) Lab” (Julia Sacher), a Minerva Fast Track Group, “Milestones of Early Cognitive Development” (Charlotte Grosse Wiesmann, whose group only just started its research), and the Research Group “Stress and Family Health” (Veronika Engert). Three methods and development groups facilitate scientists’ access to the Institute’s state-of-the-art technical equipment while also conducting research into the methodology of high-resolution and digital-resource methods: “Nuclear Magnetic Resonance”, “Brain Networks”, and “Databases and IT”.

Research foci

The general agenda of the MPI CBS is the investigation of the neural bases of human cognitive functions. These are explored by combined assessment of cognition, behaviour, and emotion, and by using neuroscientific tools such as magnetic resonance imaging (MRI), magneto-encephalography (MEG), electro-encephalography (EEG), noninvasive optical imaging, and various transcranial stimulation techniques. Positron emission tomography (PET) is performed in collaboration with the University Hospital Leipzig, based upon a joint grant. Besides these neurophysiological tools, the integration of genetic, autonomic, and other biological markers (e.g. hormones, neuropeptides) has become increasingly important in the Institute’s research.

The Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig provides an exciting framework for these topical and appealing theoretical domains, with the full gamut of cognitive and neuroscientific methodology available under one roof. A defining characteristic of the Institute—and at the same time a basic principle of our research approach—is the dovetailing of research and technical development. The state-of-the-art technical equipment of the Institute both accentuates Leipzig’s long-standing tradition in psychological research and, additionally, contributes to cutting-edge research within relevant areas. Modern imaging techniques are increasingly being used in traditional psychological approaches. The Institute utilises and, most importantly, improves these techniques. Hosting the entire spectrum of techniques and approaches that are established within human cognitive science and neurosciences, our Institute offers ideal conditions for its own and guest researchers.

Cooperation agreements and collaborations

There has been a long-standing collaboration with Leipzig University. The first cooperation agreement between the Max Planck Society and Leipzig University, involving the (then) Max Planck Institute of Cognitive NeuroScience and Leipzig University, goes back to September 1994. In December 2006/January 2007, the Max Planck Society signed a cooperation agreement with Leipzig University and the University Hospital Leipzig with regard to the Max Planck Institute for Human Cognitive and Brain Sciences. The purpose of this agreement is to maintain and promote cooperation between the University, the Hospital, and the MPI in the field of cognitive neurology. Above all, this co-
The operation is implemented through: 1) the management of the Clinic of Cognitive Neurology as part of the hospital by a director of the Max Planck Institute who is also appointed by the University; 2) the exchange of scientific information and experience; 3) the undertaking of joint research projects and cooperation in individual research ventures; 4) the teaching and fostering of junior scientists; and 5) the mutual use of facilities. A new cooperation agreement between all Leipzig Max Planck Institutes and Leipzig University, further extending and strengthening existing collaborations, has just been signed.

In 2010, a collaboration agreement with the Institute of Cognitive Neuroscience (ICN) at UCL, UK, was signed, establishing a partnership between the ICN and the International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity (IMPRS NeuroCom). The agreement includes collaborations in the organisation and running of the annual IMPRS summer school and student exchange programmes, as well as collaborations between the ICN and the MPI CBS. IMPRS NeuroCom is an interdisciplinary PhD programme originally initiated by the Max Planck Institute for Human Cognitive and Brain Sciences. It is based at the Institute and Leipzig University, and also involves the Max Planck Institute for Evolutionary Anthropology, Leipzig, and the Institute of Cognitive Neuroscience at UCL, UK.

MPI CBS proudly houses the brand-new Max Planck School of Cognition (MPS Cog), a collaborative, interdisciplinary and customised doctoral programme that offers exceedingly bright doctoral candidates the tools to gain a superior grasp on the different methods and approaches used in the rapidly evolving field of cognition. The programme, in which all directors are involved and that is headed by Arno Villringer, is characterised by the passion to better understand both human cognition and "mental phenomena" potentially occurring in non-biological systems and agents (artificial intelligence). MPS Cog bundles the best cognition researchers from different universities and scientific organisations in a unique setting, also involving international experts in the field like Patrick Haggard at ICN, UCL.

All departments hold long-standing collaborations in the form of joint teaching and supervision projects with German and international universities and university hospitals, as well as with non-university research institutions like Helmholtz, Fraunhofer, or Wellcome Trust. Further collaborative links exist in the shape of joint supervision and assessment of doctoral students between the Max Planck Institute for Human Cognitive and Brain Sciences and several international graduate programmes like the Berlin School of Mind and Brain at Humboldt University Berlin.
Language is a uniquely human capacity. Although human and non-human animals share a number of perceptual and cognitive abilities, only humans possess the ability to combine words into phrases and sentences.

The human language ability is supported by a fronto-temporal network of brain regions connected by white matter fibre tracts. In earlier studies, we were able to specify this network in the adult brain with respect to the function of its grey matter subparts, its white matter connectivity, as well as its functional connectivity. In particular, we found that BA 44 in the inferior frontal cortex is the hub for building structural hierarchies, which is at the core of human language. This region crucially interacts with the posterior temporal cortex during sentence comprehension. We showed that the dorsal white matter fibre tract connecting BA 44 to the posterior temporal cortex is crucial for the ability to process syntactically complex sentences, evidenced by the finding that the maturation of this fibre tract during development predicts children’s ability to comprehend such sentences. These data lead to the conclusion that particular grey and white matter structures in the human brain support the unique capacity to process syntax—the core of any natural language.

In 2017, I published a book entitled Language in our Brain (MIT Press), which, based on our own data and those in the literature, proposed a model of the neural language network, specifying its functional and structural parameters in the adult brain. Moreover, a developmental model of the neural language network was put forward, describing the neurobiology of language development as a shift from bottom-up processes supported by the temporal cortex to a specialisation of semantic and syntactic aspects of language processing in the left inferior frontal cortex. It is argued that this neural network for the uniquely human capacity of language follows a predetermined neurobiological programme with sensitive periods of neural plasticity.
In order to shed further light on the specificity of human syntax and its underlying brain structure, two novel empirical approaches were taken. The first approach focussed on the domain-specificity of language, and the second approach aimed at uncovering the species-specificity of language. The theoretical argument for this research strategy was formulated in a recent paper (Friederici, 2018, Phil Trans R Soc B). Our empirical data gathered over the past few years strongly suggest that the language network is domain-specific and, moreover, species-specific.

**Domain-specificity.** We investigated the domain-specificity of the language network by comparing the neural language network to neural networks of several non-language domains, which have been proposed to contain structural hierarchies similar to language. These domains are music, mathematics, and action. For none of these non-language domains did we find a direct overlap with the language network, neither with respect to the neuro-functional nor the neurostructural anatomy. Thus, building syntactic hierarchies in language is specific. It depends on BA 44 and its dorsal connection to the temporal cortex, fully matured in the adult human brain, but not well developed in the newborn prelinguistic human infant (Perani et al., 2011, PNAS, 108, 16056–16061). This dorsal fibre tract remains plastic through childhood, thereby allowing its formation by language input (Skeide et al., 2016, Cereb Cortex, 26, 2127–2139). With its plasticity it stands in clear contrast to three other fibre tracts connecting the frontal and temporal cortices, which are already considerably mature and well myelinated at birth.

**Species-specificity.** The second approach that we used to learn about the specificity of this uniquely human capacity focussed on the comparison of the language-related neural network in human and in non-human primates. It had been shown that non-human primates can learn auditory sequences following simple rule-based sequences (AB)n, but not the more complex A’B’n rule-based sequences that lead to hierarchical dependencies, whereas humans learn both grammar types easily. In an fMRI study with adult humans, we demonstrated that the simple grammar activated the frontal operculum, a phylogenetically older cortex than Broca’s area, whereas the more complex phrase structure grammar activated left Broca’s area, in particular BA 44 (Friederici et al., 2006, PNAS, 103, 2458–2463). Related white matter probabilistic analyses indicated that the frontal operculum is connected to the temporal cortex by a ventral pathway, while BA 44, relevant for hierarchical syntax, is connected to the temporal cortex via a dorsal pathway. The dorsal pathway to BA 44 is weak in non-human primates (see 1.2.7) and not yet well developed in prelinguistic infants, that is, in those who are incapable of syntax (Perani et al., 2011). These data suggest that the ability to process hierarchically structured sequences in language as well as its neural bases develops late in phylogeny and ontogeny.
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1.1 Functional Neuroanatomy of the Language Network
Over the past few years, we have specified various aspects of the fronto-temporal language network in human adults and, moreover, investigated its domain-specificity. The ability to combine elements into hierarchies is a basic mechanism of language, called Merge in linguistic theory. In a previous meta-analysis, we demonstrated that Broca’s area is the crucial region supporting this operation. A recent functional MRI study showed that Broca’s subregions BA 44 and BA 45 hold responsibility for different phrase types (1.1.1). Using a TMS–EEG setting to investigate the temporal dynamics during sentence processing, we found that the inferior frontal cortex is active earlier than the superior temporal cortex (1.1.2). We furthermore examined the neural dynamics of hierarchical phrase structure building in Chinese, finding that network modulations emerged from BA 44 to the posterior temporal cortex and involved BA 45 once lexico-semantic aspects came into play (1.1.3). A functional MRI study on the role of prosody during sentence comprehension revealed a left hemispheric activation in the inferior frontal gyrus whenever intonation was crucial for syntactic processing (1.1.4). These data clearly confirm the primacy of BA 44 in the left hemisphere in syntactic processing during sentence comprehension.

Investigating hierarchy processing in different non-language domains, we found that hierarchical processing in music revealed activation in the right inferior frontal gyrus, suggesting domain-selective neural populations for music compared to language (1.1.5). Within the domain of mathematics, we observed that the dorsal white matter fibre tracts and cortico-thalamic tracts varied in streamline density as a function of mathematical expertise (1.1.6). For the domain of action, a meta-analysis revealed that there is an involvement of posterior BA 44 for action compared to language, which recruits anterior BA 44 (1.1.7). Together, these data suggest that the neural network supporting hierarchical processes within the language domain differs from that in non-language domains.
When processing connected speech, our linguistic combinatorial capacity must be flexible enough to make sense out of infinite word combinations from the linguistic environment. Linguistic combination is however not an all-with-all process: words do not randomly combine but are constrained by syntactic rules based on word-category relationships. How different word combinations are recognised by the human brain, depending on the word category entering the computation, remains largely unknown, although this is the necessary condition for the combinatorial unboundedness to apply. Here we applied multi-voxel pattern analysis (MVPA) to functional magnetic resonance imaging data of healthy subjects, actively listening to simple, two-word, phrasal contexts in German. The phrases we used consisted of a noun (boat), which could either form a noun phrase (NP) with another content word, i.e. as the adjective blue in blue boat, or form a determiner phrase (DP) with a function word, i.e. the determiner this in this boat. We found that neural populations classifying simple phrasal combinations in Broca’s area, a high-order structure-building hub of the linguistic system in the inferior frontal gyrus (IFG), are not uniformly distributed, but rather sensitive to structurally distinct sub-regions within the area, depending on the word categories forming the phrase. Namely, the information patterns for the NP adjective-noun combination were localised in the anterior part (BA 45), given the additional semantic specificity of the adjective, whereas the DP determiner-noun combination was localised in its posterior part (BA 44), as a function of specific syntactic load. Our findings provide preliminary evidence for neuronal reliance on word-category relationships when building linguistic structures. They support the hypothesis that language faculty must consist of some neural computation capturing universal combinatorial power on one side, and particular categorical restrictions on the other.

Contributions of left frontal and temporal cortex to sentence comprehension: Evidence from simultaneous TMS-EEG

Sentence comprehension requires the rapid analysis of semantic and syntactic information. These processes are supported by a left hemispheric dominant frontotemporal network, including the left posterior inferior frontal gyrus (pIFG, BA 44) and posterior superior temporal gyrus/sulcus (pSTG/STS). Previous electroencephalography (EEG) studies have associated semantic expectancy within a sentence with a modulation of the N400 and syntactic gender violations with increases in the LAN and P600. Here, we combined focal perturbations of neural activity by means of short bursts of transcranial magnetic stimulation (TMS) with simultaneous EEG recordings to probe the functional relevance of pIFG (BA 44) and pSTG/STS for sentence comprehension. We applied 10 Hz TMS bursts of three pulses at verb onset during auditory presentation of short sentences. Verb-based semantic expe-
tancy and article-based syntactic gender requirement were manipulated for the final noun of the sentence. We did not find any TMS effect at the noun. However, TMS had a short-lasting impact at the mid-sentence verb that differed for the two stimulation sites. Specifically, TMS over pIFG (BA 44) elicited a frontal positivity in the first 200 ms post verb onset, whereas TMS over pSTG/STS was limited to a parietal negativity at 200–400 ms post verb onset. This indicates that during verb processing in sentential context, frontal brain areas play an earlier role than temporal areas in predicting the upcoming noun. The short-lived perturbation effects at the mid-sentence verb suggest a high degree of online compensation within the language system, since the sentence processing of the final noun was unaffected.

Universal neural basis of structure building evidenced by network modulations emerging from Broca’s area

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The basic steps in constructing language involve binding words of different categories into a hierarchical structures. To what extent these steps are universal or differ across languages is an open issue. Here we examine the neural dynamics of phrase-structure building in Chinese—a language that, in contrast to other languages, heavily depends on contextual semantic information. We used functional magnetic resonance imaging and dynamic causal modelling to identify the relevant brain regions and their dynamic relations. Language stimuli consisted of syntax-driving determiners, semantic-embedded classifiers, and nonverbal symbols making up two-component sequences manipulated by the factors structure (phrase/list) and number of words (2-word/1-word). Processing phrases compared with word lists elicited greater activation in the anterior part of Broca’s area, Brodmann area (BA) 45, and the left posterior superior/middle temporal gyri (pSTG/pMTG), while processing two words against one word led to stronger involvement of the left BA 45, BA 44, and insula. Differential network modulations emerging from subparts of Broca’s area revealed that phrasal construction, in particular, highly modulated the direct connection from BA 44 to left pMTG, suggesting BA 44’s primary role in phrase-structure building. Conversely, the involvement of BA 45 rather appears sensitive to the reliance on lexico-semantic information in Chinese. Against the background of previous findings from other languages, the present results indicate that phrase-structure building has a universal neural basis within the left fronto-temporal network. Moreover, they provide evidence demonstrating that the structure-building network may be modulated by language-specific characteristics.
Intonation guides sentence processing in the left inferior frontal gyrus

van der Burght, C. L., Goucha, T., Friederici, A. D., Kreitewolf, J., & Hartwigsen, G.

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Speech prosody, the variation in sentence melody and rhythm, plays a crucial role in sentence comprehension. Specifically, changes in intonational pitch along a sentence can affect our understanding of who did what to whom. To date, it remains unclear how the brain processes this particular use of intonation and which brain regions are involved. In particular, one central matter of debate concerns the lateralisation of intonation processing.

To study the role of intonation in sentence comprehension, we designed a functional magnetic resonance imaging experiment in which participants listened to spoken sentences. Critically, the interpretation of these sentences depended on either intonational or grammatical cues. Our results showed stronger functional activity in the left inferior frontal gyrus (IFG) when the intonational cue was crucial for sentence comprehension compared to when it was not. When a grammatical cue was instead crucial for sentence comprehension, we found involvement of an overlapping region in the left IFG, as well as in a posterior temporal region. A further analysis revealed that the lateralisation of intonation processing depends on its role in syntactic processing: Activity in the IFG was lateralised to the left hemisphere when intonation was the only source of information to comprehend the sentence. In contrast, activity in the IFG was right-lateralised when intonation did not contribute to sentence comprehension. Together, these results emphasise the key role of the left IFG in sentence comprehension, showing the importance of this region when intonation establishes sentence structure. Furthermore, our results provide evidence for the theory that the lateralisation of prosodic processing is modulated by its linguistic role.

Figure 1.1.3 In (A), the activation clusters in warm colours show significant effects of STRUCTURE (greater for phrase than for list condition), and the clusters in cool colours show significant effects of WORDS (greater for 2-word than for 1-word condition). The peak coordinates of the left BA 44, BA 45, and pMTG were used for volumes-of-interest specification in the DCM analysis. (B) Modulations of the winning family had driving inputs on both the left BA 44 and BA 45. The phrase conditions had greater modulation effects on the connection from left BA 44 to left pMTG as compared with the list conditions (*p < .05).

Figure 1.1.4 Lateralisation analysis showing functional contrasts of interest compared to their left–right flipped equivalent. (A) Lateralised functional activity evoked by processing of sentence structure guided by a prosodic cue. (B) Lateralised functional activity evoked by processing a sentence structure in which the prosodic cue is superfluous. All comparisons are thresholded on the cluster level at p < .05, FWE-corrected. BL stands for baseline.
Functional Neuroanatomy of the Language Network

The right inferior frontal gyrus processes nested non-local dependencies in music

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Complex auditory sequences known as music have often been described as hierarchically structured. This permits the existence of non-local dependencies, which relate elements of a sequence beyond their temporal sequential order. Previous studies in music have reported differential activity in the inferior frontal gyrus (IFG) when comparing regular and irregular chord transitions based on theories in Western tonal harmony. However, it is unclear if the observed activity reflects the interpretation of hierarchical structure as the effects are confounded by local irregularity. Using functional magnetic resonance imaging, we found that violations to non-local dependencies in nested sequences of three-tone musical motifs, in musicians, elicited increased activity in the right IFG. This is in contrast to similar studies in language, which typically report the left IFG in processing grammatical syntax. Effects of increasing auditory working memory demands are, moreover, reflected by distributed activity in frontal and parietal regions. Our study therefore demonstrates the role of the right IFG in processing non-local dependencies in music, and suggests that hierarchical processing in different cognitive domains relies on similar mechanisms that are subserved by domain-selective neuronal subpopulations.

Mathematical expertise modulates the architecture of dorsal and cortico-thalamic white matter tracts


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The white matter brain structures for language have been specified to involve dorsal and ventral pathways, with the dorsal pathway identified to be crucial for the syntactic expertise. Here, we analysed the white matter brain structure of mathematicians versus non-mathematicians using probabilistic tractography. Having mathematicians and non-mathematicians as participant groups enabled us to directly compare profiles of structural connectivity arising from individual levels of expertise in mathematics. Tracking from functional seed regions activated during the processing of complex arithmetic formulas revealed an involvement of various fibre bundles such as the infe-
Prior fronto-occipital fascicle, arcuate fasciculus/superior longitudinal fasciculus (AF/SLF), cross-hemispheric connections of frontal lobe areas through the corpus callosum, and cortico-subcortical connectivity via the bilateral thalamic radiation. With the aim of investigating expertise-dependent structural connectivity, the streamline density was correlated with the level of expertise, defined by automaticity of processing complex mathematics. The results showed that structural integrity of the AF/SLF was higher in individuals with higher automaticity, while stronger cortico-thalamic connectivity was associated with lower levels of automaticity. Therefore, we suggest that expertise in the domain of mathematics is reflected in plastic changes of the brain’s white matter structure, possibly reflecting a general principle of cognitive expertise.

1.1.7 The topographical organisation of motor processing: An ALE meta-analysis on six action domains and the relevance of Broca’s region

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Action as a cognitive domain has repeatedly been discussed to involve left Broca’s area. Action, however, is a cover term used to refer to a large set of motor processes differing in domain-specificities (e.g. execution or observation). Here we review neuroimaging evidence on action processing (N = 416; Subjects = 5912) using quantitative activation likelihood estimation (ALE) and meta-analytic connectivity modelling (MACM) approaches to delineate the functional specificities of six domains: (1) action execution, (2) action imitation, (3) motor imagery, (4) action observation, (5) motor learning, and (6) motor preparation.
observation, (5) motor learning, and (6) motor preparation. Our results show distinct functional patterns for the different domains with convergence in posterior BA 44 (pBA 44) for execution, imitation, and imagery processing. The functional connectivity network seeding in the motor-based localised cluster of pBA 44 differs from the connectivity network seeding in the (language-related) anterior BA 44, suggesting that these two networks subserve distinct cognitive functions. We propose that the motor-related network encompassing pBA 44 is recruited in specific action domains requiring a mental representation of the action itself.

Figure 1.1.7.2 Overview of significant clusters resulting from the MACM analysis. Two co-activation patterns were obtained from different subregions centred within BA 44, one anterior (aBA 44) and one posterior (pBA 44). Co-activation patterns resulting from aBA 44 are contrasted with patterns co-activated by pBA 44 (blue); co-activation patterns resulting from pBA 44 are contrasted with patterns co-activated by aBA 44 (red). Coordinates are in the MNI space.
1.2 Ontogeny and Phylogenesis of the Language Network
The brain's structure matures as language abilities develop. It is an open question how grey and white matter changes correlate within the language network during development. Investigating this interrelationship, we found a high overlap of measures of the cortical surface area and the ongoing myelination of white matter connections (1.2.1). The investigation of the relation between cortical changes within the language network and language behaviour revealed that increased covariance of cortical thickness between left frontal and temporal regions within the language network was associated with advanced syntactic processing abilities (1.2.2).

As a precursor of syntactic processing, the processing of non-adjacent dependencies in auditory sequences has been considered as mandatory. We investigated the processing of non-adjacent dependencies in children aged 2 and 3 years, as during this age period the prefrontal cortex matures quite dramatically. When testing syllable sequences and tone sequences using near-infrared spectroscopy (NIRS), we observed a difference between the two domains. For linguistic sequences, but not for tone sequences, we found increased activation in two-year-olds, suggesting an early domain-specific sensitivity to language (1.2.3).

Clear age-related periods of cognitive processes have also been claimed for a non-language domain, namely Theory-of-Mind (ToM). The respective experimental tasks are either explicit (involving verbal instruction) or implicit (no verbal instruction). Two-year-old children can solve the latter, but not the former task raising the question of the relation between ToM and language. Our structural brain data show that implicit and explicit ToM tasks involve different non-language cortical regions suggesting different underlying processes for implicit and explicit ToM, which are both unrelated to language (1.2.4).

Language acquisition builds on various aspects. Learning sequences and words is one aspect. Another aspect is recollection, that is, the ability to remember what has been learnt. In a series of studies we investigated these two aspects, measuring learning in one session and recollection in a second session, which was conducted after a nap. In sequence learning studies on word learning we showed that sleep enhances the formation of word meanings in young infants (1.2.5) and even helps children to generalise semantic knowledge in memory (1.2.6).

Lastly, we investigated the evolution of the neurobiological basis of the language network and attempted to specify the particular brain structures that enable human language. Preliminary data again point towards a special role of the dorsal pathway targeting BA 44 (1.2.7).
The concurrence of cortical surface area expansion and white matter myelination in human brain development

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The human brain undergoes dramatic structural changes during childhood that co-occur with behavioural development. These age-related changes are documented for the brain’s grey matter and white matter. However, their interrelation is largely unknown. In this study, we investigated age-related effects in cortical thickness (CT) and cortical surface area (SA) as parts of the grey matter volume as well as age effects in T1 relaxation times in the white matter. Data from N = 170 children between the ages of 3 and 7 years contributed to the sample. The general pattern of correlations between age and white matter properties was widespread, suggesting ongoing myelination with the strongest effects in the superior longitudinal fascicle, inferior longitudinal fascicle, inferior fronto-occipital fascicle, and corona radiata. Tracing the connections that contribute to the significant age effects, back to the cortex, allowed us to obtain a more reliable representation of the cortical regions whose connections display the decrease in T1 values with increasing age. This analysis revealed the strong involvement of frontal, temporal, and parietal associative cortices, together with the medial wall and the precuneus. The correlation between SA increase and age showed a similar pattern. We found a high spatial overlap of age-related correlations between SA and T1 relaxation times of the corresponding white matter connections, but no such relation between SA and CT. The results indicate that during childhood the developmental expansion of the cortical surface is closely associated with an age-related increase of white matter fibre connections terminating at the cortical surface.

1.2.1

The emergence of long-range language network structural covariance and language abilities

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Language skills increase as the brain matures. Language processing, especially the comprehension of syntactically complex sentences, is supported by a brain network involving functional interactions between left inferior frontal and left temporal regions in the adult brain, with reduced functional interactions in children. Here, we examined the grey matter covariance of the cortical thickness network relevant for syntactic processing in relation to language abilities in preschool children (i.e. 5-year-olds) and analysed the developmental changes of the cortical thickness covariance cross-sectionally by comparing preschool children, school age children, and adults. In addition, to demonstrate the agreement of cortical thickness covariance and white matter connectivity, tractography analyses were performed. Covariance of language-relevant seeds in preschoolers was strongest in contralateral homologous regions. However, a more adult-like significant cortical thickness covariance between left frontal and left temporal regions was observed in preschoolers with advanced syntactic language abilities. By compar-
ing the three age groups, we were able to show that the cortical thickness covariance pattern from the language-associated seeds develops progressively, from restricted brain regions in preschoolers to widely-distributed regions in adults. In addition, our results suggest that the cortical thickness covariance difference of the left inferior frontal gyrus to superior temporal gyrus/sulcus between preschoolers and adults is accompanied by distinctions in the white matter tracts linking these two areas, with more mature white matter in the arcuate fasciculus in adults compared to preschoolers. These findings provide anatomical evidence of developmental changes in language, both from the perspective of grey matter structure covariation within the language network and white matter maturity as the anatomical substrate for the structural covariance.

Figure 1.2.2 Developmental differences in cortical thickness covariance maps seeding from the left inferior frontal gyrus (IFG) across age groups. (A) Cortical thickness covariance maps seeding from the left IFG (depicted in grey) in school-age children (top) and adults (bottom). (B) Developmental differences of the cortical thickness covariance seeding from the left IFG across the three age groups. Significant differences were observed in the left temporal regions (p = 0.006) and right precentral gyrus (p = 0.043, FWE-corrected). (C) Covariance of the left IFG seed and left temporal regions as target (peak value adjusted for model) for all three age groups (t (48) = 4.45, r = 0.54, p < 0.001, for adults, in black; t (47) = 1.98, r = 0.28, p = 0.053, for school age children, in blue; t (60) = −1.56, r = −0.20, p = 0.125, for preschool children, in red).

Linguistic and non-linguistic non-adjacent dependency learning in early development

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Non-adjacent dependencies (NADs) are important building blocks for the hierarchical structure of language, and extracting them from the input is a fundamental part of language acquisition. Event-related potential (ERP) studies revealed that 4-month-old infants can learn NADs by merely listening, while adults need an active task. Moreover, inhibition of the adult prefrontal cortex led to infant-like ERP patterns in NAD processing. Recent evidence suggests a developmental shift from implicit NAD learning in infants to more controlled NAD learning after the age of two years. This shift might potentially be caused by prefrontal cortex development. The present study aimed to specify which brain regions are involved in this developmental shift and whether this shift extends to NAD learning in the non-linguistic domain. In two experiments, 2- and 3-year-old German-learning children were familiarised with either Italian sentences or tone sequences containing NADs and subsequently tested with NAD violations (incorrect) while functional near-infrared spectroscopy data were recorded. Results showed increased hemodynamic responses related to the detection of linguistic NAD violations in the left temporal and inferior frontal regions in 2-year-old children, but no increased responses in 3-year-olds. A different developmental trajectory was found for non-linguistic NADs, where 3-year-old, but not 2-year-old, children showed evidence of the detection of non-linguistic NAD violations although in different brain regions. These results point to distinct mechanisms underlying NAD learning in the linguistic and non-linguistic domain.
1.2.4 Implicit and explicit Theory-of-Mind are dissociated in development

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Figure 1.2.4 Distinct and independent brain regions were associated with success on the explicit (blue) and the implicit ToM tasks (red/orange). While the explicit ToM tasks were related to cortical thickness and surface area in the classical ToM network (precuneus, posterior temporal and temporo-parietal regions in blue), the implicit ToM task was related with the supramarginal gyrus and dorsal precuneus (in red/orange).
Human interaction crucially relies on our ability to infer what other people know and think. Known as Theory of Mind (ToM), this ability has long been argued to be uniquely human and emerge around the age of 4 years. This developmental dogma was based on traditional explicit ToM tasks in which children were explicitly asked where another person with a false belief about the location of an object would search for this object. Recently, however, this dogma has radically been questioned by a set of non-verbal implicit ToM tests passed by infants younger than 2 years of age. These findings have caused one of the most controversial debates of current developmental psychology: How do infants in their second year of life solve these implicit tasks, and why do they only pass the traditional explicit ToM tasks several years later in development? To address this, we related 3- and 4-year-olds’ performance on implicit and explicit ToM tasks with each other, as well as with markers of cortical brain structure measured with MRI. This showed that while different explicit ToM tasks were strongly correlated with each other, there was no relation between implicit and explicit ToM tasks. This dissociation was confirmed on the neural level. Explicit ToM performance was supported by cortical surface area and thickness of the precuneus and temporoparietal junction, classically involved in ToM in adults, whereas implicit ToM performance was supported by the cortical structure of the supramarginal gyrus, involved in action observation and visual perspective taking. These findings show that implicit and explicit ToM are supported by different brain structures suggesting the involvement of different cognitive processes. While mature adult-like ToM reasoning emerges around the age of 4 years, as measured by the traditional explicit ToM tasks, non-verbal ToM tasks seem to rely on a different earlier-developing cognitive process.

The sleeping infant brain anticipates development

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Earlier studies have shown that from the age of 3 months, infants learn relations between objects and co-occurring words. These very first representations of object–word pairings in infant memory are considered as non-symbolic protowords, comprising specific visual–auditory associations that can already be formed in the first months of life. Genuine words that refer to semantic long-term memory have not been evidenced before the age of 9 months. Sleep is known to facilitate the reorganisation of memories, but its impact on the perceptual-to-semantic trend in early development is unknown. Here, we explored the formation of word meanings in 6- to 8-month-old infants and its reorganisation during the course of sleep. Infants were exposed to new words as labels for new object categories. In the memory test about an hour later, generalisation to novel category exemplars was tested. In infants who took a short nap during the retention period, a brain response similar to 3-month-olds was observed, indicating generalisations based on early developing perceptual-associative memory. In the infants who napped longer, a semantic priming effect revealed the formation of genuine words. The perceptual-to-semantic shift in memory was related

Figure 1.2.5 Category–word pairing effects during learning and memory testing. The infant ERPs in response to words paired with novel category exemplars. Following standard analyses of the N400 priming effect, we calculated all memory effects as the difference between unprimed and primed conditions (i.e. inconsistent–consistent and incorrect–correct); negativity is plotted upward. (A) Late negativity in the memory test of the short-nap group, indicating the presence of less developed perceptual-associative memory for the category–word pairings. (B) N400 cluster in the memory test of the long-nap group, indicating the presence of more-developed lexical-semantic memory.
to the duration of sleep stage 2 and to locally increased sleep spindle activity (not depicted here). Subsequent to the massed presentation of several labelled category exemplars, it was found that sleep enabled 6- to 8-month-olds to generalise across individual exemplars and to create a long-term memory representation.

1.2.6 Sleep-dependent memory formation in infants: New episodic memories are protected from generalised semantic memories

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Any experienced event may be encoded and retained in detail as part of our episodic memory and may contribute to generalised knowledge stored in semantic memory. The beginnings of this declarative memory formation are poorly understood, and even less is known about the interrelation between episodic and semantic memories during their early stages. Here, we show that the formation of episodic memories in 14- to 17-month-olds depends on timely sleep after an infant’s waking exposure to novel events. Our data reveal that semantic processing is suppressed for the newly stored detailed events, even though lexical-semantic memories are available for simi-

Figure 1.2.6 The N400 semantic memory effect and the FTMR episodic memory effect. ERP responses to correct (black lines) and incorrect (grey lines) object–word pairs in the whole trial interval, time-locked to word onset. Negativity is plotted upward. The parieto-occipital (PO) region includes mid-parieto-occipital, left parietal, and right parietal ROIs and was calculated as the mean of the ERP amplitudes at the electrode sites P8, P2, P4, CP5, CP6, P7, P8, O1, and O2. The left fronto-temporal ROI (LFT) involves F7 and T7. Voltage maps represent the spatial distributions of the ERP differences between incorrectly paired and correctly paired words in the temporal range between 400 and 800 ms post word onset. (A) N400 semantic context effect to pairings with old objects in the wake group (t29 = –3.632, P = .001, d = –.663) and missing episodic context effect (t29 = .238, P = .814). Source data are provided as a Source Data file.
lar events that were not experienced before the nap. This selective inhibition of semantic processing may protect precise episodic memories from interference with generalised semantic memories. It enables infants to temporarily overcome strong attractors in semantic memory.

**Evolution and development of language-related pathways in great apes**

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The ability to generate language by using words and syntactic rules is a uniquely human trait. Today we know that the human language ability is built on a network of dorsal and ventral fibre pathways connecting the language-specific brain areas in the inferior frontal and temporal lobe. The ontogenetic change of this language network through human development has been characterised by essential features such as maturation and lengthening of the dorsal path (Perani et al. 2011, PNAS, 108, 16056–16061). However, the phylogenetic emergence of this unique language network remains unresolved. This is partially due to the unavailability of brain data from close evolutionary relatives as well as the lack of behavioural and structural data from wild apes.

In a collaborative project with the Max Planck Institute for Evolutionary Anthropology, Leipzig, we are closing this gap by extending our research on the development of the human language network to the phylogenetic dimension. To understand the evolution of the language network, we investigate the connectivity of homologous brain areas of our closest evolutionary relative, the chimpanzee. We scan the brains of wild and habituated chimpanzees that died at different ages from a natural death in African national parks, sanctuaries, or European zoos. We use diffusion-weighted MRI (dMRI) to investigate the structural connectivity of the brain’s white matter, employing highly specialised MRI technology to obtain ultra-high-resolution dMRI data of the fixated post mortem brains. The dorsal and ventral pathways are reconstructed using whole-brain diffusion fibre tractography.

Our first data, from a newborn and an adult chimpanzee, show the developmental status of the homologous language network in the chimpanzees compared to averaged data in humans (see Figure 1.2.7). We were able to construct both the dorsal and the ventral pathways from our high quality dMRI data. This clearly showed a strengthening of the dorsal pathway during development in the chimpanzee, which is comparable to the human ontogeny (Perani et al. 2011, PNAS, 108, 16056–16061). However, the dorsal connection, which is crucial for human development of syntactic abilities, does not show the same shape and endpoints in the adult chimpanzee as in the human brain. Our data allow the reconstruction of the development of the precursors of the language network at an unprecedented level of detail, thereby contributing to our understanding of the evolution of the unique human ability to process language.

**Figure 1.2.7** The two dimensions of language network development (only left hemisphere displayed). The figure shows the reconstruction of language-related dorsal fibre tracts targeting BA 6 (yellow) and targeting BA 44 (blue) and ventral fibre tract (green) in humans across development and the homologue of newborn and adult chimpanzees (top row, adapted from Perani et al. 2011, PNAS, 108, 16056–16061).
Congresses, Workshops, and Symposia

2017

2018
- Friederici, A. D. (November). Mental Structures and Sequences: Evolutionary solutions from birds to primates. Symposium. 48th Annual Meeting of the Society for Neuroscience. San Diego, CA, USA. (Chair together with Christopher I. Petkov)

2019
- Skoide, M. A. (September) Symposium: Developmental learning disorders – from genes and brains to cognitive profiles, Biannual meeting of the Developmental and Educational Psychology Section of the German Psychological Society, Leipzig, Germany.

Degrees

Habilitation Theses
2018
- Sammler, D. The Melodic Mind: Neural bases of intonation in speech and music. Leipzig University, Germany.
- Skoide, M. A. The brain basis of developmental dyslexia. Humboldt University Berlin, Germany.

PhD Theses
2017
- Goucha, T. Conciliating language differences with universal competence in brain structure and function. Humboldt University Berlin, Germany.
- Grosse Wiesmann, C. The emergence of theory of mind: Cognitive and neural basis of false belief understanding in preschool age. Leipzig University, Germany.
- Xiao, Y. Resting-state functional connectivity in the brain and its relation to language development in preschool children. Leipzig University, Germany.

2018
- Vavatzanidis, N. From syllables to words: Language perception and language acquisition of young children with cochlear implants. Leipzig University, Germany.
- Vissiennon, K. The functional organization of syntactic processing in three- and six-year-old children. Leipzig University, Germany.

2019
- Beese, C. The effects of neurocognitive aging on sentence processing. Leipzig University, Germany.
- Kroczek, L. The impact of speaker information on language processing. Leipzig University, Germany.
Appointments

2018
- Männel, C. Guest Professorship, Stand-in for (W3) Professorship "Psycholinguistics", University of Potsdam, Germany.

2019
- Hartwigsen, G. Lise Meitner Research Group Leader (W2 position), Max Planck Society, Germany.
- Männel, C. W2 Research Group Leader "Early language acquisition", Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.
- Männel, C. W2 Professorship "Early language acquisition", Charité University Medicine Berlin, Germany.

Awards

2017
- Friederici, A. D. Plaque of Appreciation at the Wall of Honor Event of DIGIST, South Korea.
- Männel, C. SNL Post-Doctoral Abstract Merit Award, Society for the Neurobiology of Language (SNL), Baltimore, USA.
- Skoide, M. A. Advancement Award for groundbreaking research in the field of Cognitive Neuropsychology. German Society for Neuropsychology, Germany.

2018
- Cheung, V. Science Slam Winner. 7th Visions-in-Science Conference, Berlin, Germany.
- Eichner, C. Summa Cum Laude Award. International Society for Magnetic Resonance in Medicine, USA.
- Friederici, A. D. Wilhelm Wundt Medal of the German Society of Psychology.
- Friederici, A. D. Order of Merit of the State of Saxony.

2019
- Cheung, V. Community Grant. International Society for Music Information Retrieval, Delft, NL.
- Friederici, A. D. Elected Honorary Member of the Linguistic Society of America (LSA), USA.
- Friederici, A. D. The Justine and Yves Sergent Award, Montréal (Québec), Canada.
- Govaart, G. Open Innovation in Science Award of the Einstein Center for Neurosciences Berlin, Germany for a crowdsourcing project on speaker variability, together with Claudia Männel & Angela D. Friederici.
- Paul, M. SIPS Travel Award. Society for the Improvement of Psychological Science (SIPS), Rotterdam, NL.
- Skoide, M. A. ERC Starting Grant. European Research Council (ERC), Brussels, Belgium.

Publications

Books and Book Chapters


Journal Articles


Index of Published Figures

Figure 1
- Figure 1 (B) and (D) adapted from Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., & Behrens, T.E.J. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. Nature Neuroscience, 11(4), 426–428.
- Figure 1 (C) adapted from Friederici, A.D. & Gierhan, S.M.E. (2013). The language network. Current Opinion in Neurobiology, 23(2), 250–254.
- Figure 1.1.2 Figure adapted from Kroczek, L.O.H, Gunter, T.C., Ryaso, A.U., Friederici, A.D., & Hartwigsen, G. (2019). Contributions of left frontal and temporal cortex to sentence comprehension: Evidence from simultaneous TMS-EEG. Cortex, 175, 86–98.
- Figure 1.1.3 Figure adapted from Wu, C.-Y., Zaccarelli, E., & Friederici, A.D. (2019). Universal neural basis of structure building evidenced by network modulations emerging from Broca’s area: The case of Chinese. Human Brain Mapping, 40(6), 1705–1717.
- Figure 1.1.4 Figure adapted from van der Burght, C.L., Goucha, T., Friederici, A.D., Kreitewolf, J., & Hartwigsen, G. (2019). Intraon guided sentence processing in the left inferior frontal gyrus. Cortex, 117, 122–134.
- Figure 1.1.5 Figure adapted from Cheung, V.K.M., Meyer, L., Friederici, A.D., & Koelsch, S. (2018). The right inferior frontal gyrus processes nested non-local dependencies in music. Scientific Reports, 8:3822. doi:10.1038/s41598-018-22144-9


Figure 1.2.1 Caiefero, R., Brauer, J., Anwander, A. & Friederici, A.D. (2019). The concurrence of cortical surface area expansion and white matter myelination in human brain development. Cerebral Cortex, 29(2), 827–837.


Figure 1.2.5 Figure adapted from Friedrich, M., Wilhelm, I., Mölle, M., Born, J., & Friederici, A.D. (2017). The sleeping infant brain anticipates development. Current Biology, 27(15), 2374–2380.

Professor Dr Arno Villringer
Director
The overarching mission of our department is to prevent and treat stroke. To this end, we investigate neural mechanisms underlying:

(i) the development of vascular risk factors (obesity, hypertension) and their neural impact, closely connected and overlapping with the second topic

(ii) neurobehaviour and neurocognition of stroke and dementia (brain lesion)

(iii) behavioural and cognitive recovery from stroke (rehabilitation).

Paralleling these research areas, our translational goals are the development of interventional strategies to prevent the development of risk factors, to stop risk factor-dependent processes leading to stroke and dementia, and to improve recovery from stroke. This can be conceived as a cycle in which each research theme closely hinges on the other themes.

Risk Factors Brain Lesion Rehabilitation

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Research Approach

We perform our studies exclusively with human subjects, either in large population-based cohorts of thousands, in smaller groups of healthy young and old subjects (e.g., for studies on heart-brain interaction), in highly selected subjects (e.g., with obesity or at risk for hypertension), and in very well characterised cohorts of patients with stroke or dementia. Studies take place in the "lab", but also – increasingly – in more naturalistic settings to improve ecological validity. The selection and characterisation of specific patient cohorts is
constitutively aided by the Clinic for Cognitive Neurology and a tight co-operation with ‘external’ clinical institutions (University Hospital Leipzig, Charité Hospital Berlin).

A central theme across all our research areas are brain-body interactions. These are crucial to understand the vicious cycles in the generation of risk factors (e.g., the relationship between cardiac output, blood pressure, and neural activity), and the pathogenesis of brain damage (e.g., the relationship between visceral fat, chronic inflammation, and white matter lesions in the brain). Brain-body interactions are also central to understanding and supporting recovery after brain lesions (e.g., when using a brain-computer interface coupled with peripheral stimulation for motor recovery).

Our research methodology involves behavioural and cognitive assessments and non-invasive methods to assess neural structures and function (magnetic resonance imaging (MRI), magneto-encephalography (MEG), electroencephalography (EEG), near-infrared spectroscopy (NIRS)). Given our focus on brain-body interactions, techniques to assess bodily function are used such as metabolic parameters in blood and saliva, MRI of visceral fat, ECG, blood pressure, and a robotic exoskeleton device to monitor body movements. In addition to these “diagnostic” approaches, for interventional studies, we use devices to induce neuromodulation including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (TDCS), transcranial alternate current stimulation (TACS), transcranial focused ultrasound stimulation (tFUS), and Brain Computer Interfaces (BCI).

Research Quality, Open Science

The department actively addresses issues which are known to impair research quality. The symposium Mind the Brain organised by members of our department (Isabelle Bareither, Felix Hasler, Daniel Margulies, Arno Villringer) in 2014 served as a wake-up call for activities in the department. Soon thereafter, in 2015, a research quality group was established in our department. This group has stimulated and pushed forward many useful developments for the department. Standard operating procedures (SOP) were established for most of the equipment used in the department. Statistical education of junior (and senior) scientists was improved by additional courses and training. The department was pushed towards an open science approach, for example by making databases publicly available (Babayan et al. Sci Data 2019, Mendes et al. Sci Data 2019). Quality and reproducibility of studies will be further supported by pre-registrations on internet-based sites (all studies have already been pre-registered locally for many years). Finally, the group has produced a handbook for the department, which is particularly helpful for newcomers.

An Institute-wide open science initiative (CBS-Open Science) has been founded with a kick-off meeting in May 2019 co-organised by several members of the department (Blazej Baczkowski, Lieneke Janssen, Maria Paerisch, Lina Schaare, Cornelia van Scherpenberg). A two-day symposium on research quality in November 2019, Doing Good – Scientific Practice under Review, has also been co-organised by a department member (Cornelia van Scherpenberg).

Local Research Setting

The major part of our research takes place at the Max Planck Institute. However, our research approach involving – among others – large human cohorts and patients requires close collaboration with other groups and departments within the Institute (neuroimaging, behavioural tasks, and paradigms) and groups at local universities, particularly Leipzig University, but also universities in Berlin, Halle, and Potsdam.

Most importantly, we interact closely with our partner-institution, the (Day-) Clinic for Cognitive Neurology at the University Hospital Leipzig (about 100m walking distance from the Max Planck Institute) where patients with brain lesions are diagnosed and treated. The Clinic for Cognitive Neurology offers an interface open to all researchers at the Max Planck Institute. Clinical care and therapy for patients with acquired brain lesions is warranted by a highly interdisciplinary team, covering all aspects of neurologic, neuropsychological, and neuropsychiatric deficit expertise, neuropsychology plus the therapeutic fields of speech and language therapy, orthoptics, physio-, ergo- and social therapy, as well as counselling. This
offers a unique platform to perform research on the underpinnings of cognitive impairment, forming the basis for the development of novel interventions and a highly interdisciplinary therapeutic range focusing on all relevant neuropsychological domains.

Beyond the established therapy schemes the clinic explores and develops novel strategies to help patients minimise their deficits and the burden of stroke and other diseases leading to the acquired brain lesion. A project on virtual reality, a study using tDCS as a support for an intensified naming training, robots, and participation in a nation-wide speech and language therapy (SLT)-study are a few examples of the clinic's engagement.

In the past three years, a total of 19 studies in a total of 270 patients have been performed with (former) patients of the Clinic by researchers (of all departments) at the MPI.

Clinicians at the Day Clinic hold leading roles in German clinical neuroscience networks: Hellmuth Obrig is the head of the German Aphasia Society, Matthias Schroeter is the neuroimaging expert in the frontotemporal dementia network in Germany and Europe, Angelika Thöne-Otto is in the steering committee of the German Neuro-psychological Society, Arno Villringer is the coordinator of the German competence network Stroke and was co-chair of this year's meeting of the German Society for Neurorehabilitation.

### Grants:
During the last three years, the department and its members have been part of several large project grants such as the Collaborative Research Center "Obesity mechanisms", the Leipzig Research Centre for Civilisation Diseases (LIFE), and the Integrated Research and Treatment Center (IFB) AdiposityDiseases, together with Leipzig University. The NeuroCure Cluster and the Berlin School of Mind and Brain are both large-scale projects within the German Excellence Initiative (together with Humboldt University and Charité University Medicine Berlin). Furthermore, in a project grant together with the Charité, the Heinrich Hertz Institute of the Fraunhofer Society, the Clinic for Cognitive Neurology at Leipzig University, and our Department at the MPI, we have been developing virtual reality methods for clinical diagnostics and rehabilitation (VReha) funded by the German Ministry of Research. The department is also involved in the Max Planck UCL Centre for Computational Psychiatry and Ageing Research, of which Arno Villringer is member of the Coordination Committee.

### Cooperations:
There is a plentitude of national and international co-operations; an overview is given in the Status Report of our Institute. Long-term co-operations exist with researchers in Montreal (Chris Steele, Claudine Gauthier, Christine Tardif), Harvard Medical School (Bruce Rosen), University of Haifa (Hadas Okon-Singer; Smadar Ovadia-Caro), Institut du Cerveau et de la Moelle épinière, Paris (Daniel Margulies), and Stanford University (Audrey Fan).

In the past year, we have started new co-operations in the area of obesity and diabetes with a research group at the National Autonomous University of Mexico (UNAM) in Mexico City (Carlos A. Aguilar-Salinas, focusing on a genetic disposition for diabetes type 2, which is highly prevalent in Mexico), and the Institute for Cognitive Neuroscience, National Research University Higher School of Economics, Moscow, Russia (Maria Nazarova, Vadim Nikulin) focusing on transcranial stimulation to improve rehabilitation in patients after stroke, and a group at Hebrew University, Jerusalem (Mona Soreq) working on epigenetics of hypertension and obesity.

### Graduate Schools:
We are part of several graduate school programmes in Berlin and Leipzig, such as the International Max Planck Research School NeuroCom at our Institute, the DFG-funded Berlin School of Mind and Brain at Humboldt University Berlin, the International Max Planck Research School on the Life Course at the MPI for Human Development, Berlin, the new International Max Planck Research School on Computational Methods in Psychiatry and Ageing Research (Comp2PsyCh), and the newly founded (DFG-funded) Research Training Group on Extrospection: External Access to Higher Cognitive Processes at Humboldt University Berlin. Arno Villringer is the lead PI – and now spokesperson – of a major new Germany-wide initiative for graduate education: the Max Planck School of Cognition (MPS Cog). In a highly competitive process, MPS Cog was selected as one of three national Max Planck Schools funded by the German Ministry of Education and Research and the Max Planck Society. MPS Cog combines 11 Max Planck Institutes, 14 German universities, University College London, Institutes of the Helmholtz Association, and a Fraunhofer Institute (see separate report below in this report).

### Scientific conferences
Are important means of science communication. Besides participation at major conferenc-
Plasticity

es, e.g., OHBM (Organization for Human Brain Mapping) and SFN (Society for Neuroscience), the department regularly organises several symposia and conferences. There are two conference series organised every year by us: the MindBrainBody Symposium (between 2017 and 2019 the 5th, 6th, and 7th installations took place), and the Stroke Prevention Symposium (8th, 9th, and 10th). Furthermore, in 2019, the yearly meeting of the German Aphasia Society (GAB) took place in Leipzig (organised by Hellmuth Obrig). In December 2019, the annual meeting of the German Society for Neurorehabilitation with more than 900 participants took place in Leipzig (Conference Chairs: Caroline Renner, Arno Villringer).

Careers

A central mission of our department concerns the promotion of personal development and professional careers of all department members. Between 2017 and 2019, 12 former department members and former doctoral students and postdocs of Arno Villringer’s group advanced to faculty positions and professorships: Annette Horstmann (Helsinki University, Finland), Chris Steele (Concordia University, Montreal, Canada), Smadar Ovadia-Caro (University of Haifa, Israel), Claudia Männel (Charité University Medicine Berlin, Germany), Daniel Margulies (Institut du Cerveau et de la Moelle épinière, Paris, France), Isabel Garcia-Garcia (Barcelona, Spain), Yating Lv (Hangzhou Normal University, China), Lorenz Deserno (University of Würzburg, Germany), Petra Ritter and Christian Nolte (Charité University Medicine Berlin, Germany), Georg Häusler (University of Würzburg, Germany), and Susanne Wegener (University of Zürich, Switzerland). The department has further developed career trajectories to promote outstanding female scientists, such as Julia Sacher, leader of the Minerva Research Group “Emotion Neuroimaging Lab”, and Veronica Witte, leader of the Department Group “Aging & Obesity”, in a tenure-track process with Leipzig University.

Publications

It is probably fair to say that our department has some relevant impact on the brain imaging and neurovascular literature given that – in the last three years – we published a total of 59 papers in the field of brain imaging, blood flow and metabolism in leading journals: i.e., *NeuroImage* (33), *NeuroImage Clinical* (9), *Human Brain Mapping* (9), *Journal of Cerebral Blood Flow and Metabolism* (7), and *Stroke* (1). Further studies appeared in leading journals such as *Lancet, eLife, Brain* (2), *Annals of Neurology* (2), *JAMA Network Open, Neurology* (4), *Nature Neuroscience, Nature Communications* (2), *Journal of Neuroscience* (3), *Trends in Cognitive Sciences, Cerebral Cortex* (3), *EMBO Molecular Medicine, Nat Rev Neurosci, PLOS Comput Biol* (2), and *Nat Hum Behaviour*. As part of large consortia, there are further publications in *Nature Genetics* and *Nature Communications*. Highlighting these publications does in no way imply that we are not fully convinced of the scientific value of all the other papers; the entire publication record of the last three years is given at the end of this department’s report.

On the following pages – structured along the three major research areas Risk Factors, Brain Lesions, and Rehabilitation – some research results obtained in the last three years by members of our department are described.
List of Employees

Research Group Leaders

Professor Dr Vadim Nikulin
PD Dr Julia Sacher (Minerva Research Group—reports independently, see pp. 175)

Group Leaders

Professor Dr Tom Fritz
Dr Michael Gaebler (11)
Professor Dr Annette Horstmann (17, 48)
(in cooperation with Leipzig University)
Professor Dr Jane Neumann (17, 48) (*)
Professor Dr Hellmuth Obirg
(in cooperation with Leipzig University)
Professor Dr Matthias L. Schroeter (74) (*)
(in cooperation with Leipzig University)
PD Dr Bernhard Sehm
PD Dr Veronika Witte (48)

Personal and Scientific Assistants

Cornelia Ketscher
Birgit Mittag
Dr Anahit Babayan
Silke Friedrich (30)
(in cooperation with Leipzig University)
Dr Natacha Mendes (**)
Susan Prejawa (17, 48)
(in cooperation with Leipzig University)

Senior Researchers and Postdocs

Mehmet Mert Akbal (11) (*)
Dr Pierre-Louis Bazin
(in cooperation with the University of Amsterdam, NL)
Alejandro Galvez-Pol (*)
Dr Leneke Janssen
(in cooperation with Leipzig University)
Dr Judy Kipping
(in cooperation with Leipzig University)
Dr Tilmann A. Klein (*)
(in cooperation with University of Magdeburg)
Dr Jan Mehnert (*)
(in cooperation with Leipzig University)
Dr Claudia Maennel (**)
(in cooperation with Leipzig University)
Dr Leonie Lampe (11, 22) (*)
(in cooperation with Leipzig University)
Mauricio J. D. Martins, PhD (*)
(in cooperation with Leipzig University)
Dr Till Nierhaus
Dr Martin Panitz (*)
(in cooperation with Charité University Medicine Berlin)
Dr Smadar Ovadia-Caro (*)
Dr Maryna Polyakova (11) (PhD since 04/2019)
Dr Gesa Schaadt (**)
Dr Melanie Schreiner (*)
(in cooperation with Leipzig University)
Dr Ami Tsuchida (22)
(in cooperation with Leipzig University)
Dr Johanne Tromp (11) (*)

Technical and Administrative Assistants

Alyson Dawn Buchenau (49) (*)
Eric Busch (*)
Anne-Kathrin Franz
Dirk Gummel (11) (*)
Bettina Johst
Dr Ulika Lachmann (**) 
Ramona Menger
Maria-Josephine Paerisch (*)
Kirsten Scharr (49) (*)
Ulrike Scharrer
Sylvia Stasch
Annett Wiedemann

Clinic for Cognitive Neurology, University Hospital Leipzig

Professor Dr Hellmuth Obirg

Dr Sabine Herzig
Dr Annerose Engel
Dr Frank Regenbrecht
Professor Dr Dr Matthias L. Schroeter
Dr Angelika Thöne-Otto
Juliane Weicker
Dr Christopher Weise
PhD Students

Ismet Zeynep Akbal
Esra Al
Franziska Albrecht (11, 74) (*) (PhD since 10/2019)
Blazej Baczkowski (11)
Tommaso Ballarini (11, 30, 74) (*)
Dr Claudia Barth (*) (PhD since 01/2017)
Seyma Bayrak (**) (PhD since 10/2017)
Julia Belger (30)
Frauke Beyer (48) (in cooperation with Leipzig University)
Dr Roberta Bianco (*) (PhD since 06/2017)
Dr Sandrine Bisenius (74) (*) (PhD since 10/2017)
Maria Bloechl (30)
Elena Cesnaire
Nadene Dermody (*) (in cooperation with Leipzig University)
Miray Erbey (16)
Dr Norman Forschack (*) (PhD since 07/2019)
Magdalena Gippert
Dr Claudia Grellmann (17) (*) (PhD since 05/2017)
Khosrov Alexander Grigoryan
Dr Johanna Grosse Rueschkamp (16) (*) (PhD since 07/2019)
Martin Grund
Katarzyna Gugnowska (94)
Dr Christopher Gundlach (30) (*) (PhD since 05/2017)
Dr Samyogita Hardikar (**) (PhD since 04/2019)
Hendrik Hartmann (30, 48) (in cooperation with Leipzig University)
Nadine Herzog (30)
Simon Hofmann (30)
Dr Maike Hoff (*) (PhD since 12/2017)
Nicole Hudl (23) (*) (PhD since 12/2019)
Dr Sebastian Huhn (23) (*) (PhD since 01/2019)
Fivos Iliopoulos (67) (*)
Mina Jamshidi Idaji
Anna-Thekla Jaeger (née Schmidt) (23)
Benjamin Kalloch
Dr Elisabeth Kaminski (47) (PhD since 11/2017)
Dimitra-Maria Kandia (83)
Rouven Kenville
Dr Ahmed Abdelrahim Khalil (67) (*) (PhD since 09/2018) (in cooperation with Charité University Medicine Berlin)
Dr Shahrzad Kharabian Masouleh (*) (PhD since 05/2019)
Felix Klotzsche (11)
Natalie Kohler
Carina Denise Krause (30)
Jana Kube (17) (in cooperation with Leipzig University)
Dr Saurabh Kumar (48) (*) (PhD since 11/2017)
Deniz Kumral
Dr Jana Kynast (11, 23) (*) (PhD since 05/2019)
Mark Lauckner (**) (PhD since 12/2017)
Dr Nico Lehmnam (75) (*) (PhD since 10/2018)
Carolin Lewis (née Maier) (49) (in cooperation with Leipzig University)
Dr David Mathar (17) (*) (PhD since 10/2018)
Tom Maudrich
Evelyn Medawar (16)
Marie-Theres Meemken (17) (in cooperation with Leipzig University)
Dr Nora Mehl (23) (*) (PhD since 05/2019)
Eoin Molloy (49)
Dr Filip Morys (17) (*) (PhD since 05/2019)
Toni Muffel (55) (in cooperation with Leipzig University)
Madeleine Ordnung (23)
Katja Paul (76) (in cooperation with University of Groningen, NL)
Maria Poessel (48) (in cooperation with Leipzig University)
Dr Sven Preusser (*) (PhD since 05/2019)
Janis Reinelt (48) (*)
Dr Viola Rjosk (48) (*) (PhD since 01/2018)
Josefin Roebbig
Firat Sansal (16) (*)
Lina Schaare (49)
Lydia Schneider (85)
Dr Anne Schrimpf (23) (*) (PhD since 10/2017)
Pei-Cheng Shih
Tilmann Stephani
Ronja Thieleking (14)
Hsing-Fen Tu (83)
Marie Uhlig
Cornelia van Scherpenberg (16)
Maria Waltmann (30)
Juliane Weicker (30)
Kathleen Wiencke (48) (in cooperation with Leipzig University)
Dr Luise Woost (80) (*) (PhD since 02/2019)
Juani Zhang (67)
Dr Rui Zhang (30) (*) (PhD since 04/2019)
Georgy Zarubin (30)
Rachel Zsido (11)
## MD Students (in cooperation with Leipzig University)

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Nathalie Beinhölzl</td>
<td>Student</td>
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<tr>
<td>Josef Bormann</td>
<td>Student</td>
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<tr>
<td>Nora Breuer</td>
<td>Student</td>
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<tr>
<td>Dr Marian Ciupek (*)</td>
<td>(MD since 06/2017)</td>
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<tr>
<td>Luise Claß</td>
<td>Student</td>
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<tr>
<td>Lina Eisenberg</td>
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<tr>
<td>Martin Federbusch</td>
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<tr>
<td>Maria Felber</td>
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<tr>
<td>Leila Gajieva</td>
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<tr>
<td>Johanna Girbardt</td>
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<td>Annegret Glathe</td>
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<tr>
<td>Linda Grassner</td>
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<tr>
<td>Agnes Groba (*)</td>
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<tr>
<td>Jana Grothe</td>
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<tr>
<td>Felicitas Grundeis (*)</td>
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<tr>
<td>Johanna Halfpaap</td>
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<tr>
<td>Annika Hedrich</td>
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<tr>
<td>Matthias Heinrich</td>
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<tr>
<td>Dr Sabine Herzig (*)</td>
<td>(MD since 03/2018)</td>
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<tr>
<td>Paula Hillebrand</td>
<td>Student</td>
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<tr>
<td>Dr Martin Huss (*)</td>
<td>(MD since 08/2018)</td>
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<tr>
<td>Emmy Kaspar (*)</td>
<td>Student</td>
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<tr>
<td>Dr Lucas Kastner (*)</td>
<td>(MD since 08/2018)</td>
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<tr>
<td>Alexis Klengel</td>
<td>Student</td>
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<tr>
<td>Julian Malte Klingebiel (*)</td>
<td>Student</td>
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<td>(in cooperation with Leipzig University)</td>
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</table>

## Research Associates

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Lorenz Deserno</td>
<td>Research Associate</td>
<td>Psychiatry and Ageing Research, Max Planck UCL Centre for Computational Psychiatry, London, UK</td>
</tr>
<tr>
<td>Professor Dr Bogdan Draganski (*)</td>
<td>Research Associate</td>
<td>Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Switzerland</td>
</tr>
<tr>
<td>Professor Dr Hans-J. Heinze (*)</td>
<td>Research Associate</td>
<td>Department of Neurology, University Medical Center Magdeburg, Germany</td>
</tr>
<tr>
<td>Professor Andreas Melzer</td>
<td>Research Associate</td>
<td>Innovation Center Computer Assisted Surgery (ICCAS), Leipzig University, Germany</td>
</tr>
<tr>
<td>Professor Dr Hellmuth Obrig</td>
<td>Research Associate</td>
<td>Clinic of Cognitive Neurology, University Hospital Leipzig, Germany</td>
</tr>
<tr>
<td>PD Dr Burkhard Pleger</td>
<td>Research Associate</td>
<td>Department of Neurology, BG University Hospital Bergmannsheil, Bochum, Germany</td>
</tr>
<tr>
<td>Professor Patrick Ragert</td>
<td>Research Associate</td>
<td>Institute for General Kinesiology and Exercise Sciences, Faculty of Sport Science, Leipzig University, Germany</td>
</tr>
<tr>
<td>Professor Dr Florian Schlagenhauf</td>
<td>Research Associate</td>
<td>Department of Psychiatry and Psychotherapy (CCM), Charité University Medicine Berlin, Germany</td>
</tr>
<tr>
<td>Christopher Steele, PhD</td>
<td>Research Associate</td>
<td>Department of Psychology, Concordia University, Montreal, Canada</td>
</tr>
</tbody>
</table>
Guest Researchers

Samuel H. Cosper (*) Institute of Cognitive Sciences, University of Osnabrück
Bruno Dampney, PhD (*) University of NSW, Australia
Sencer Melih Deniz Bogazici University, Turkey
Dr Christopher Gundlach Leipzig University, Germany
Dr Lydia Hellrung University Hospital Zuerich, Switzerland
Luca Iemi HSE University Moscow, Russia
Itamar Jalon Tel Aviv University, Israel
Dr Jakob Kaminski Charité University Medicine Berlin, Germany
Dr Elisabeth Kaminski Leipzig University, Germany
Dr Esther Kuehn German Center for Neurodegenerative Diseases Magdeburg, Germany
Dorottya Lantos (*) Goldsmiths University of London, UK
Dr Keyvan Mahjoory (*) Institute for Biomagnetism and Biosignalanalysis, Westfalian Wilhelms University of Muenster, Germany
Mauricio J. D. Martins, PhD Département d’Etudes Cognitives, Ecole Normale Supérieure de Paris (ENS), France
Nobuaki Mizuguchi Keio University, Japan
Pawel Motyka (*) University of Warsaw, Poland
Maria Nazarova, PhD (*) HSE University Moscow, Russia
Dr Birgit Nierula (**) IDIBAPS Barcelona, Spain
Pavel Novikov (*) HSE University Moscow, Russia
Dr Smadar Ovadia-Caro University of Haifa, Israel
Dr Andrea M. F. Reiter Technical University of Dresden, Germany
Maria Richter University of Potsdam, Germany
Dr Maria Herrojo Ruiz (*) Goldsmiths University London, UK
Dr Oliva Rossella Department of General Psychology, University of Padua, Italy
Dr Michael Rullmann Leipzig University, Germany
Dr Haiko Schloegl Leipzig University, Germany
Dr Zsuzsika Sjoerds (*) University of Leiden, NL
Christine Tardif, PhD (*) McGill University, Montreal, Canada
Dr Birol Taskin Charité University Medicine Berlin, Germany
Denis Volk, PhD (*) NRU Moscow, Russia

Former Researchers and Postdocs

Mehmet Mert Akbal Cognitive artist and researcher, Berlin
Dr Tilmann A. Klein Institute for Psychology, Otto v. Guericke University Magdeburg, Germany
Dr Leonie Lampe AICURA medical GmbH, Leipzig, Germany
Mauricio J. D. Martins, PhD Département d’Etudes Cognitives, Ecole Normale Supérieure de Paris (ENS), France
Dr Jan Mehnert Systemic Neuroscience, University Medical Center Hamburg-Eppendorf (UKE), Germany
Professor Dr Jane Neumann Biosignal and Biodata analysis, Ernst Abbé University of Applied Sciences, Jena, Germany
Dr Smadar Ovadia-Caro University of Haifa, Israel
### Former PhD Students

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and Department</th>
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<tbody>
<tr>
<td>Franziska Albrecht</td>
<td>Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Stockholm, Sweden</td>
</tr>
<tr>
<td>Tommaso Ballarini</td>
<td>German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany</td>
</tr>
<tr>
<td>Dr Claudia Barth</td>
<td>Institute of Clinical Medicine, University of Oslo, Norway</td>
</tr>
<tr>
<td>Dr Roberta Bianco</td>
<td>Ear Institute, University College London (UCL), UK</td>
</tr>
<tr>
<td>Dr Norman Forschack</td>
<td>Experimental Psychology and Methods, Leipzig University, Germany</td>
</tr>
<tr>
<td>Dr Claudia Grellmann</td>
<td>Analyst in industry</td>
</tr>
<tr>
<td>Dr Christopher Gundlach</td>
<td>Experimental Psychology and Methods, Leipzig University, Germany</td>
</tr>
<tr>
<td>Dr Samyogita Hardikar</td>
<td>Max Planck School of Cognition, Max Planck Society, Germany</td>
</tr>
<tr>
<td>Dr Sebastian Huhn</td>
<td>Department of Molecular Systems Biology, Helmholtz-Centre for Environmental Research (UFZ), Leipzig, Germany</td>
</tr>
<tr>
<td>Dr Elisabeth Kaminski</td>
<td>Faculty of Sport Sciences, Leipzig University, Germany</td>
</tr>
<tr>
<td>Dr Shahrizad Kharabian Masouleh</td>
<td>Institute of Neuroscience and Medicine, Brain and Behaviour, Research Center Juelich, Germany</td>
</tr>
<tr>
<td>Dr Saurabh Kumar</td>
<td>Systemic Neuroscience, University Medical Center Hamburg-Eppendorf (UKE), Germany</td>
</tr>
<tr>
<td>Dr Jana Kynast</td>
<td>Neurological Rehabilitation Centre Bennewitz (NRZ), Germany</td>
</tr>
<tr>
<td>Dr Nico Lehmann</td>
<td>Sport Sciences, Institute for Psychology, Otto v. Guericke University Magdeburg, Germany</td>
</tr>
<tr>
<td>Dr David Mathar</td>
<td>Faculty of Human Sciences, University of Cologne, Germany</td>
</tr>
<tr>
<td>Dr Nora Mehl</td>
<td>Institute of Clinical Psychology and Psychotherapy, Technical University Dresden, Germany</td>
</tr>
<tr>
<td>Dr Filip Morys</td>
<td>Montréal Neurological Institute, McGill University, Canada</td>
</tr>
<tr>
<td>Dr Sven Preusser</td>
<td>Institut für Hochschulforschung, Martin Luther University Halle-Wittenberg, Germany</td>
</tr>
<tr>
<td>Janis Reinelt</td>
<td>AICURA medical GmbH, Leipzig, Germany</td>
</tr>
<tr>
<td>Dr Viola Rjosk</td>
<td>Clinic right of the ISAR Clinic for Neurology, Munich, Germany</td>
</tr>
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A central hypothesis of our work is that an imbalance of mind-body interaction underlies the development of obesity and hypertension. Psychological/cognitive factors continuously interact with metabolic and vascular factors and – in vicious cycles – they mutually adjust. With time (years, decades), early functional and reversible alterations progress towards – often irreversible – structural damage both in the nervous system (e.g., white matter lesions, brain atrophy, small strokes) and in the body (e.g., arteriosclerosis, diabetes, kidney damage). Stroke and dementia are endpoints (among others such as myocardial infarction) of these long-term developments.

Together with researchers at Leipzig University, we have established a strong research focus on brain-body interactions, especially regarding obesity (integrated research center obesity, collaborative project grant on "obesity mechanisms" and a recently founded Helmholtz institute). A large cohort of subjects (the LIFE study, n=10000) has been investigated thoroughly. As will be outlined subsequently, we study brain-body interactions underlying obesity, i.e., the relationship between metabolic factors, BMI, visceral fat, etc. and cognitive/emotional/neural factors and the progression towards brain damage. Regarding hypertension, we study the mutual interaction between brain/behaviour and the cardiovascular system, particularly the heart, as well as the progression towards brain damage.
Neurocognition of obesity development

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The O'BRAIN group has studied cognitive/behavioural alterations in relation to eating behaviour in lean, overweight, and obese subjects to identify potential modifiable drivers of obesity development. We have shown that obese subjects fail to learn from negative prediction errors (Mathar et al., 2017a, Mathar et al., 2017b) as illustrated in Figure 2.1.1. We also identified alterations of psychological factors that may facilitate unhealthy eating behaviour such as impulsivity (Rosella et al., 2019), flexibility (Meemken et al., 2018), incidental priming (Morys et al., 2018), reinforcement learning (Kube et al., 2018), and attention bias (Mehl et al., 2017) in adults and children with obesity. Several pilot studies have aimed at exploring the intervention potential of retraining automatic action tendencies and using cognitive bias modification (Mehl et al., 2018, Mehl et al., 2019). General approach and avoidance behaviour are related to hemispheric asymmetries as captured by resting state EEG and fMRI, but seem to be unrelated to eating behaviour or weight status (Morys et al., in press). Further, we showed that amygdala activity during food processing, as well as food liking, is modulated by emotional context, independent of weight status (García-García et al., in press), and used fMRI neurofeedback to modulate amygdala activity (Hellrung et al., 2018). In sum, many of the behavioural aspects can be linked to alterations in dopamine, a neurotransmitter involved in motion, motivation, and reward.

Obesity also has a strong societal/social component. We have therefore studied how bodily reactions (heart rate) and emotions during social interactions are influenced.

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**Figure 2.1.1**

A. Learning rate for obesity vs lean and obese subjects. B. Response switches as a function of response consistency beta (model). C. % correct responses vs positive PE. D. % correct responses vs negative PE. E. % correct responses vs positive PE. F. % correct responses vs negative PE.
by obesity (Schrimpf et al., 2017). We demonstrate that these factors are modulated by different societal influences when comparing societies allegedly having a more positive ‘image’ of obesity (Samoa) with a western society in which obesity is often stigmatised (Schrimpf et al., 2019).

2.1.2 Impact of obesity on brain and behaviour in a population-based cohort

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To assess how overeating and obesity (and associated metabolic changes) affect brain structure and function, in cooperation with Leipzig University, we have been acquiring and analysing data of the population-based LIFE-Adult study (n ~ 2600, aged 18-82 years), a uniquely rich dataset comprising genetic, metabolic, behavioural and advanced (neuro)imaging protocols. Applying multivariate statistics and replication in independent samples, we were able to provide evidence that a higher body mass index (BMI) is associated with reduced functional connectivity in the default mode network, a finding that may reflect a predisposition to Alzheimer’s Disease (AD) (Beyer et al., 2017). In addition, a higher BMI and higher waist-to-hip ratio were linked to grey and white matter structural alterations across multiple brain regions, which correlated with subtle differences in executive functions and memory performance (Beyer et al., 2019a; 2019b, Kharabian et al., 2018; Zhang et al., 2018). Using a novel in-house-developed segmentation technique on high-resolution fluid attenuated inversion recovery (FLAIR) images of 1280 participants, whole-brain analyses provided the first evidence that visceral fat accumulation uniquely predicts lesion load in the deep white matter (Lampe et al., 2019). Moreover, structural equation modeling suggested that visceral obesity contributes to deep white matter hyperintensities (WMH) through elevated pro-inflammatory cytokines, i.e. interleukin-6, measured in blood (Figure 2.1.2). This hints toward a pathomechanistic link between obesity, inflammation, and deep WMH.

Future longitudinal studies, including the ongoing six-year-follow up assessment of the LIFE-Adult study (currently at n ~ 600), are needed to confirm these hypotheses. While the spatial distribution of white matter lesions is indicative of specific impairments in certain cognitive domains (Lampe et al., 2018), potential genetic underpinnings of this regional inhomogeneity remain unclear. We therefore joined the NeuroCHARGE consortium in a meta-genome wide association study (GWAS) on periventricular vs. deep white matter lesions (n = 26,654; Nyquist et al., Stroke, in revision). We identified genetic loci previously implicated in vascular as well as astrocytic and neuronal function, particularly for deep WMH. Upcoming RNA sequencing in the LIFE-cohort, which we pursue in cooperation with the Soreq-lab (Hebrew University, Jerusalem) will now offer the opportunity to disentangle the (epi)genetic mechanisms of obesity.

Figure 2.1.2 Visceral obesity, measured using waist-to-hip ratio (WHR), is related to deep white matter hyperintensities (WMH, red brain colour) via systemic low-grade inflammation (interleukin-6 (IL-6), measured in blood). Blue brain colour indicates regional associations of WMH with higher systolic blood pressure. Figure modified from Lampe et al., 2019.
We have previously shown how blood pressure regulation is influenced by emotion-related brain areas (Okon-Singer et al., 2014, J Neurosci, 34(12), 4251–9). A key control element of cardiovascular function is the heartbeat and thus, in a series of studies, the MindBodyEmotion group has investigated the bidirectional information flow between the brain and the heart and its links to emotions, stress, but also perception and action. During each cardiac cycle, when the ventricles contract and eject blood into the arteries (i.e., systole), stretch-sensitive baroreceptors signal blood pressure changes to the lower brainstem and further to subcortical (e.g., amygdala and thalamus) and cortical regions (e.g., anterior cingulate cortex and insula). These higher-level brain structures, in turn, adapt autonomic (i.e., sympathetic and parasympathetic) activity to situational demands via efferences to brainstem nuclei, adrenal glands, and the heart (Critchley and Harrison, 2013, Neuron, 77(4), 624–38). While heart-brain interaction is – obviously – bidirectional, our studies can be discussed along the main directions of the said interaction.

**Brain to heart:** By analysing temporal variations in the interval between consecutive heartbeats, heart rate variability (HRV) can quantify parasympathetic cardio-regulation – during tasks and at rest. HRV during the socio-emotional cyberball task was found to differ between lean and obese participants (Schrimpf et al., 2017). By repeating this “travelling” experiment in American Samoa, where body weight is less stigmatised than in Germany, we found that HRV was modulated by culture (Schrimpf et al., 2019). In a different study, HRV decreased after acute psychosocial stress (the Trier Social Stress Test), and this decrease was associated with stress-related changes in thalamic connectivity, as measured using resting state functional MRI (Reinelt et al., 2019). Focussing on brain-heart interactions over the lifespan, we found age-dependent associations between resting HRV and (1) resting-state functional connectivity along the cortical midline (Kumral et al., 2019) as well as (2) orbitofrontal cortical thickness (Koenig et al., submitted), which may contribute/link to age-associated decreases in HRV function.

**Heart to brain:** Not only do mental and situational (e.g., socio-emotional) processes influence the heart rate and its variability, but spontaneous activity in the heart also influences the processing of signals in the environment. We found two heartbeat-related effects on perception. The first is linked to the timing of a stimulus within the heartbeat cycle: near-threshold somatosensory stimuli at the index finger are more likely to be perceived when they are presented during later (i.e., diastole) compared to earlier phases (i.e., systole) of the cardiac cycle (Al et al., submitted; Motyka et al., 2019). The second is linked to the amplitude of the so called “heartbeat-evoked potential” (HEP), which is assumed to be the central representation of the heartbeat. Higher HEP amplitudes were associated with lower detection rates and lower amplitudes in the somatosensory-evoked potential (Figure 2.1.3 and Al et al., submitted). Interestingly, the cardiac phase not only modulates perception but also action. In Kunzendorf et al., 2019, we found that participants preferentially pressed a button, which prompted briefly presented pictures they had to memorise, during cardiac systole.

![Figure 2.1.3](image-url)  
Figure 2.1.3 Left and Middle: Near-threshold somatosensory stimuli at the finger are more likely to be detected during diastole (blue) than during systole (red), and they increase later components (i.e., P300) of the somatosensory evoked potential (SEP) over somatosensory electrodes (C4). Right: Higher heartbeat-evoked potential (HEP) amplitudes over somatosensory electrodes were associated with lower detection rates. Modified from Al et al. (Al et al., submitted).
Thus, the coupling between activity in the heart and the brain goes along with emotions and stress as well as with perception and action. Currently, we are studying alterations of these interactions in subjects with different stages of hypertension and heart disease. It has already been suggested that the modulation of HEP amplitude during interoceptive tasks differs between normotensive subjects and those with early stage hypertensive disease (Yoris et al., 2018, Hum Brain Mapp, 39(4), 1563–81). We have recently pre-processed EEG with ECGs in more than 3000 subjects of the LIFE study. Based on these subjects, we will assess how the HEP amplitude is associated with blood pressure levels and specifically stages of hypertension, anti-hypertensive medication, HRV, as well as alterations of brain morphology and functional connectivity.

Potential drivers of a vicious neuro-behavioural-blood pressure cycle in hypertension are assumed beneficial effects of elevated blood pressure. For example, it has been reported that higher blood pressure is associated with elevated pain threshold and emotional dampening (especially for negative emotions). A large survey of German teenagers (n=7688) has reported better well-being and lower distress in those with elevated blood pressure (Berendes et al. Psychosom Med 2013 75:422-8). Another study in adults has suggested that high blood pressure is associated with lower rates of depression and better well-being (Herrmann-Lingen et al. Psychosom Med. 2018 80:468-74). Since the latter study was on a clinical sample, it may not be representative for the general population. We are currently addressing these relationships in data of the UK Biobank (n > 500,000). Our results confirm the reduced prevalence of depressive symptoms and higher levels of well-being with increasing blood pressure (Schaare et al., in preparation). The diagnosis of hypertension itself, however, is negatively associated with well-being. In another study, we are testing (and our preliminary results seem to confirm) the emotional dampening hypothesis by exposing subjects to pictures of different emotional valence (Erbey et al., in preparation).

Regarding the impact of blood pressure levels on brain structure, our study on 423 young subjects (19–40 years) has provided quite provocative results, i.e., by showing that in young subjects with elevated blood pressure (>120/80mmHg) but below the level of hypertension, reductions of brain volume are seen in comparison to subjects with lower blood pressure (Schaare et al., 2019). These findings may have implications for the definition of an optimal blood pressure.
Next steps: Longitudinal and intervention studies

While many of our studies (regarding both risk factors) are cross-sectional and correlational, we are now entering the phase of longitudinal and interventional studies, based on which we are hoping for conclusions about prediction and causation. The large LiFE cohort study is now in the 7-year follow-up phase (by the time of this writing, we have a follow-up in more than 600 subjects).

Also, we have now been starting (or will in the near future) several intervention studies. We are investigating the impact of high-sugar/high fat diets on the dopaminergic system. We hypothesise that the impact on dopaminergic neurotransmission will be similar to those observed in subjects with obesity and that this is mediated by chronic low-grade inflammation. In another study, we are assessing the impact of prebiotics on food-related brain activity and behaviour which we hypothesise to be mediated by changes in the gut microbiome and subsequent pathways, such as short chain fatty acids metabolites. Complementing these “bottom-up” interventions, we will assess the effect of transcranial direct current stimulation (tDCS) on eating behaviour, and blood pressure, and the effect of executive control training, which we have shown to improve emotion regulation (Cohen et al., 2016, NeuroImage, 125, 1022–1031), on blood pressure regulation. Methodologically, the development of non-invasive deep brain stimulation using low-intensity ultrasound is promising as the basis for a next round of intervention studies targeting obesity and hypertension.

Conceptually, the department collaborates with the Minerva Research Group "Emotion Neuroimaging Lab" to study (cross-sectionally and longitudinally) sex differences in mind-body interactions and to develop sex-specific strategies to improve prevention and treatment of obesity and hypertension.
We attempt to understand the underlying pathophysiology of different forms of brain damage, and its impact on brain organisation, cognition, and behaviour. This research can be grouped into three closely interacting research lines focusing on (i) local and distant effects of acute ischemic lesions (in cooperation with the Center for Stroke Research Berlin (CSB)), on (ii) neuroimaging biomarkers of (impaired) cognitive function, and on (iii) neuroimaging and biochemical (CSF, serum) biomarkers of dementia & neurodegeneration.
Brain Lesion

Neuroimaging of acute and subacute ischemic brain damage

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We validated the resting-state based perfusion assessment method (Khalil et al., 2017, Ni et al., 2017), which we inaugurated (Lv et al., 2013, Ann Neurol, 73(1), 136–40), by comparing it to established dynamic susceptibility-based perfusion measurements. We furthermore demonstrated how it allows the identification of reperfusion online (Khalil et al., 2018). In order to reduce imaging time as much as possible, we tried to find the optimal balance between image-quality and SNR versus scan length (Tanritanir et al., submitted). We show that adequate SNR for lesion detection can be achieved at a measurement time of only 2 min (Tanritanir et al., submitted). We have also further validated the MR-based assessment of oxygen extraction fraction based on quantitative susceptibility mapping (QSM) in patients with acute stroke (Fan et al., 2019).

We know that the impact of an acute lesion goes beyond the focal damage, and we have previously shown that areas connected to the site of a lesion are more affected than other areas (Ovadia-Caro et al., 2013, J Cereb Blood Flow Metab, 33(8), 1279–85; Ovadia-Caro et al., 2014, Stroke, 45(9), 2818–24). Clearly, this is not a yes/no distinction, but rather more/less. Recent functional connectivity studies have now overcome the subdivision of the brain into separated networks, but rather define gradients of connectivity as a new metric to map the brain (Margulies et al., 2016, PNAS, 113(44), 12574–9, Huntenburg et al., 2018). We were now able to show that this view on brain architecture also provides a meaningful new framework to understand the local/distal consequences of focal lesions (Bayrak et al., 2019).

We are currently trying to bridge the gap between acute lesion mapping and long-term functional outcome. In one study, we have prospectively recruited 120 patients with acute stroke affecting predominately the somatosensory system (no or little motor symptoms) and followed them

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Figure 2.2.1.1 Lesion location across patients shown in anatomical space as well as along connectivity gradients. (A) Anatomical lesion distribution in individual stroke patients (n=28) projected onto an MNI brain. Red-to-yellow colour bar indicates the probability of a voxel to be lesioned across patients. (B) Location of lesions projected onto the first three connectivity gradients. The three connectivity gradients represent a low-dimensional description of the whole-brain connectivity matrix obtained using healthy controls data (n=28). Corresponding spatial maps of each connectivity gradient are projected on a brain surface mesh near respective axes. Colours represent positive (red) and negative (dark blue) embedding values, in accordance with values along the axes. Along each gradient voxels that share similar connectivity patterns are situated close to one another and have similar embedding values. Grey scatter plots depict a two-dimensional connectivity space created as a combination of any two given gradients. Lesion location along each gradient is projected onto the two-dimensional space. Red-to-yellow colour bars indicate the probability of a voxel to be lesioned across patients, as an alternative approach to anatomical lesion mapping. Lesioned voxels are mostly clustered around the edges of the connectivity gradients such that they affect sensorimotor areas and areas associated with ventral and dorsal attention.
Plasticity up for one year (behaviorally, MRI) specifically regarding the development of chronic poststroke pain (CPSP). 20 patients developed pain, and we are currently identifying predictive factors for pain development. We also contribute to a prospective study on “1000 stroke patients” at Charité Hospital, Berlin.

Neuroimaging determinants (biomarkers) of (impaired) cognitive function

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We have identified and validated several markers of intact (or disturbed) cognitive function and (brain) health. Many of these biomarkers are based on MRI findings, which reflect neural activity and cognition only indirectly. Interestingly, in recent years, significant progress in EEG data analysis has been achieved which allows similar questions to be addressed with electrophysiological signals that directly represent the underlying neural function (see below).

**2.2.2 Neuroimaging determinants (biomarkers) of (impaired) cognitive function**

BOLD variability, EEG variability, EEG alpha power, EEG long-range temporal correlations: A number of studies in recent years have proposed BOLD signal variability (both in task-based as well as resting-state fMRI) as a marker of overall brain health (Grady and Garrett, 2018, NeuroImage, 169, 510–23). BOLD variability is known to decrease with age but also in mental disorders (Armbruster-Genc et al., 2016, J Neurosci, 36(14), 3976–87, Garrett et al., 2013, Cereb Cortex, 23(3), 684–93). However, given the indirect relationship between BOLD and underlying neural activity,
A neural ability and cognition is truly based on variability, which depends crucially on intact neurovascular coupling, and is not clear whether the relationship between BOLD variability (8–12 Hz) and cognitive performance is reflected by EEG alpha power at rest. We therefore assessed EEG variability across different age groups and compared it to BOLD variability acquired in the same subjects. The interesting result was that both measures (EEG variability, BOLD variability at rest) were affected by age, but in this well-powered study of 189 subjects, there was almost no significant correlation between the two types of variability (Kumral et al., 2019a). In addition to EEG variability (i.e. the standard deviation of the signal over time), alpha power and long-range-temporal correlations (LRTC) are highly promising biomarkers. The presence of LRTC shows that there is a slowly decaying memory in the temporal signatures of neuronal activity. Moreover, LRTC indicates that neuronal networks operate at the critical state (a state describing a balance between excitation and inhibition), which is thought to be optimal for the functioning of the neuronal networks in the brain, where dynamic range, information capacity, and transmission are maximised (Shew and Plenz, Neuroscientist, 2013; 19: 88-100).

We recently found differential relations between EEG alpha power and LRTC to the results of cognitive assessment. In brief, our findings suggest that alpha power at rest relates to tasks that employ sustained inhibitory control, while LRTC might reflect the capacity of neuronal networks to perform tasks that require phasic attention and quick adaptation to changing task demands (Mahjoory et al. Neuroimage 2019; Figures 2.2.2.1 and 2.2.2.2). These findings are potentially of relevance for research in dementia e.g., they might be used for the identification of people at risk for developing cognitive impairments.

White matter lesions (WML) are a well-known marker of progressive brain damage associated with risk factors, but their relationship to specific cognitive functions has been difficult to establish. In several studies, we have established a relation between WML, their location, and specific cognitive domains (Kynast et al. J Cereb Blood Flow Metab 2018, Lampe et al. J Cereb Blood Flow Metab 2019) and also their differential relationship to different risk factors, specifically BMI (Lampe et al. Ann Neurol 2019). More generally, we have also shown that variations in fractional anisotropy (FA) of white matter – another potential marker of damage – relates to cognition (Zhang et al. Neuroimage 2018).

Changes in grey matter have mostly been analysed with voxel based morphometry or measurements of cortical thickness by us as well as other groups. Recently, we identified grey matter structural brain networks that are affected by vascular risk factors and aging and which underlie variations in different cognitive domains. Most no-

Figure 2.2.2.1 Spearman correlation shows a significant relationship between attention-span scores and resting-state power in alpha oscillations (8–12 Hz). (A) Sensor space results indicated that higher alpha power at rest was associated with increased attention-span (CVLT-II) score. Significant correlations at p < 0.05 are marked as bold channels and are circled for p < 0.01. (B) Across subjects scatter plot of the relationship between the power and the task score is shown for the electrode Fz. (C) Colour-coded correlation-coefficient values at source space are plotted on the cortical surface.

Figure 2.2.2.2 Spearman correlation shows a significant relationship between working memory performance and LRTC in resting-state alpha oscillations (8–12 Hz). (A) Negative correlations in sensor space are plotted on the cortical surface. (B) Significance at p < 0.05 is marked as bold channels and are circled for p < 0.01. (B) Scatter plot across subjects of the most significant correlation at the electrode FC2, v indicates LRTC. (C) Colour-coded correlation-coefficient values at source space are plotted on the cortical surface.
tably we reported that a network of multimodal regions that correlated with memory performance was affected by visceral fat (VAT) content (Kharabian-Masouleh et al. J Cereb Blood Flow Metab 2018). For this network we furthermore showed – in cooperation with the EGG group of Julia Sacher – that estradiol concentration was associated with a reduction in the negative association of VAT with this network’s covariance in women (Zsido et al., 2019).

While the above-mentioned findings are all based on hypothesis-driven studies, we also looked into machine-learning based approaches. The brain age prediction that we established did not only correlate well with chronological age, but – importantly – we found that deviations of the predicted age from the cognitive age captured cognitive impairment (Liem et al., 2017, already cited more than 100 times). In the next step, in cooperation with the Machine Learning group at TU-Berlin and the Fraunhofer Institute (Hofmann et al., in preparation), we are using semi-automated Spectral Relevance Analysis (Lapuschkin et al., 2019, Nat Comm, 10(1), 1096) to characterise the behaviour of nonlinear learning machines in order to identify – without a priori hypotheses – the imaging features on which these predictions are based on. Mechanisms of brain lesions and their impact on brain function and cognition/behaviour continues to be a major subject of our research. With several studies in the past three years, we have continued to study brain lesions from the acute to the chronic phase.

### 2.2.3 Dementia (Phenotyping with imaging, serum, and CSF biomarkers)

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Neurodegenerative diseases are widespread and society is confronted with an increasing prevalence in the future. The most important challenges are early recognition and treatment. We have been developing statistical approaches to utilise biomarker information from multimodal imaging, serum, and cerebrospinal fluid to predict diagnosis, differential diagnosis, and treatment efficacy in these diseases. Diseases cover a wide spectrum ranging from dementia syndromes such as Alzheimer’s disease, behavioural variants & frontotemporal dementia, and language variants such as primary progressive aphasias to motor syndromes such as Parkinson’s disease and its atypical variants corticobasal syndrome and progressive supranuclear palsy.

To address these challenges we start from “big data mining” approaches including meta-analyses and multi-centric cohort data. Here, we have validated disease-specificity of imaging criteria by conducting quantitative and systematic anatomical likelihood estimate (ALE) and seed-based d mapping (SDM) meta-analyses. These meta-analyses identify the neural correlates of the aforementioned neurodegenerative diseases and reveal disease-specificity of the imaging criteria (Albrecht et al., 2017, Albrecht et al., 2019a, Albrecht et al., 2019b; Bisenius et al., 2016, Europ J Neurol, 23, 704–12; Schroeter et al., 2009, NeuroImage, 47, 1196–206; Schroeter et al., 2014, Cortex, 57, 22–37; Schroeter et al., 2015, J Neurol Neurosurg Psychiatry, 86, 700–1). In the next step, we have “personalised” these data by validating their specificity for single patients in multi-centric cohort data. Here, we showed that multimodal imaging approaches are reliable biomarkers to predict the diagnosis, differential diagnosis, and symptoms in individual patients with high accuracy (Bisenius et al., 2017; Meyer et al., 2017; Mueller et al., 2017). Figure 2.2.3 illustrates that MRI combined with machine learning was able to predict corticobasal syndrome and a peculiar clinical syndrome, i.e. alien hand syndrome, where persons perceive their own hand / foot...
as alien (Albrecht et al., 2019). In Parkinson's disease, therapy efficacy of levodopa can be predicted based on MRI (see again Figure 2.2.3; Ballarini et al., 2019), a decisive step towards personalised therapy optimisation with biomarkers. Finally, we used molecular biomarker data from cerebrospinal fluid and serum, in particular neurofilaments, to predict disease course and imaging changes in these diseases (Lehmer et al., 2017; Steinacker et al., 2017; Steinacker et al., 2018). We focused on genetic disease cases such as c9orf27 mutation carriers (Diehl-Schmidt et al., 2019).

Figure 2.2.3  (A) Regions predicting corticobasal syndrome (CBS) in comparison with healthy controls (HC) and CBS with alien limb syndrome (CBS-AL) in comparison with CBS without alien limb syndrome (CBS-O) in structural MRI. (B) Higher age and brain regions predict treatment response to levodopa in Parkinson's with structural MRI in multivariate analysis. Univariate analysis also reveals atrophy in this brain region (overlap yellow).
Sensorimotor Function, Learning, and Plasticity: 
In Healthy Aging and Rehabilitation after Stroke

This research line is motivated by the translational goal of improving rehabilitation after focal lesions (stroke) but also counteracting functional decline in aging. There is a focus on the sensorimotor system. We perform (i) basic studies on somatosensory processing, (ii) sensorimotor performance and motor learning and their alteration during aging and after focal lesions, and we are (iii) developing and validating interventions to improve sensorimotor function.
Somatosensory processing (also general method development to understand cortical processing and excitability noninvasively)

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A long-term research interest of our group has been the noninvasive mapping of somatosensory (and motor) function (since the work of Kurth et al., 1998, Neuroreport, 9(2), 207–12). In collaboration with the Dept of Neurophysics and the University of Magdeburg, we were able to parcellate the homuncular organisation of the sensorimotor cortex (Area 3b and 4) based only on structural T1-maps (i.e. reflecting myelin concentration). This parcellation is possible due to the new finding (for humans) that there are myelin-based borders (septa) between major body parts (e.g., hand-face) (Kühn et al., 2017). In the same collaboration we furthermore showed that functional mapping of the cortical representation of individual fingers, in primary somatosensory cortex, can be achieved even without actually touching/stimulating the finger but by passively observing that the respective finger is touched. In other words, we have provided evidence for “foreign source maps” in early sensory cortices in the healthy human brain (Kühn et al., 2018).

Beyond the mapping of cortical representations, we are employing noninvasive neuroimaging approaches (EEG, fMRI, MEG) to understand cortical processing related to sensory input. A focus has been on the functional significance of background alpha rhythms. Many research groups have investigated whether (mostly spontaneous) modulations of the background alpha are associated with alterations in perception and evoked activities. Regarding the perception of subsequent stimuli, we provided strong arguments for a causal role of background alpha by showing that transcranial alternating current stimulation (TACS) over the sensorimotor cortex not only modulated the alpha rhythm (Gundlach et al., 2017) and decreased selectively local BOLD activity (Gundlach et al., in revision), but also was associated with cyclic alterations of somatosensory perception (Gundlach et al., 2016, Brain Stimul, 9, 712–9). Results regarding the background alpha rhythm influence on evoked brain activity (evoked potentials) have been quite controversial. Some studies show effects of background alpha on early potentials, while others show effects on late evoked potentials (e.g., our own studies by Becker et al., 2008, Neuroimage, 39, 707–16; Becker et al., 2011, J Neurosci, 31, 11016–27). In a recent study (Iemi et al., 2019), we now show that this controversy can be resolved by considering the non-sinusoidal nature of the alpha rhythm which, does not integrate to zero over time, but rather is associated with a DC-like offset (baseline-shift). In combination with the amplitude modulation of oscillations, this leads to the generation of evoked responses. The fundamental aspect of such a baseline-shift mechanism is due to its applicability to virtually all sensory, motor, and cognitive tasks where there is a modulation of neuronal oscillations. Our results (for the visual system) show that with higher alpha rhythm strength early EP-components are suppressed (via functional inhibition) while later components (after 0.4s) were actually enhanced due to this novel baseline-shift mechanism. For the somatosensory system, we recently tested whether the alpha-related inhibitory effect on the earliest cortical SEP component (S20) can be confirmed, and indeed we were able to show this effect (Stephani et al, submitted). Here we provided a neurophysiological explanation for the paradoxical increase of evoked responses associated with the stronger inhibitory cortical state due to the presence of pronounced alpha oscillations. Moreover, in the same study we showed that trial-to-trial variability of N20, reflecting EPSPs, follows power-law temporal dynamics. This in turn provides a parsimonious explanation for the functional benefits of neuronal variability in S1, due to the presence of critical dynamics (explained above in Abstract 2.2.2).

Given the influence of background alpha rhythms on cortical processing, we feel that it is quite exciting using subliminal stimulation. Alpha rhythms can actually be up- or down regulated depending on the pattern of stimulation (single stimuli versus trains) (Forschack et al., 2017, Ilipooulus et al., submitted). That is, we have identified a way to manipulate cortical excitability completely noninvasively.

Currently, our work on cortical somatosensory processing is establishing an exciting link to our research on brain-heart-interaction (see first paragraph). It seems that the somatosensory cortex plays a major role in this interaction and is the site of the heartbeat evoked potential (Al et al., in revision).
2.3.2 Motor performance and learning

Ragert, P.¹,², & Sehm, B.¹,³
¹ Neuroplasticity and Motor Recovery Group, Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
² Faculty of Sport Science, Leipzig University, Germany
³ Clinic of Neurology, University Hospital Halle, Germany

Predictors of sensorimotor learning: We continued to investigate factors that can predict interindividual differences in motor learning. We showed that grey matter volume in the right orbitofrontal cortex was related to the subjects’ initial level of proficiency and their ability to improve performance during practice of a complex motor task (Lehmann et al., 2019). In this study, baseline fractional anisotropy (FA) in commissural prefrontal fibre pathways also showed a strong trend to predict motor learning. Analogously, we showed that fibre bundle cross section, a measure of structural connectivity between right lateral PFC and left striatum, predicted learning associated functional connectivity changes in a complex whole-body serial reaction time task (Mizuguchi et al., 2019).

Motor coordination in aging and stroke patients: The use of a robotic device in an augmented-reality environment enables us to deploy ecologically valid tasks that represent important aspects of sensorimotor control including visually guided reaching, proprioception, and bilateral coordination. By adopting a classical bimanual coordination task in the setting of a robotic device in an augmented-reality environment we were able to differentiate central control mechanisms of bimanual coordination in healthy humans (Shih et al., 2019) and investigate oscillatory mechanisms underlying a functional decline of bilateral coordination in aging (Figure 2.3.2; Shih et al., in prep).

2.3.3 Recursive hierarchical embedding: Neural implementations in the motor, musical, and visual domains

Martins, M. J. D.¹
¹ Recursion and Hierarchies Group, Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

The human ability to generate complex hierarchical structures in language, vision, music, and action is thought to be implemented by a Recursive Hierarchical Embedding (RHE) capacity. In this research program, we characterised the neural underpinnings of RHE, and compared their instantiation across domains. Hinging on our previous work in the visual domain, we tested well-trained participants in the motor and music domains, and contrasted the application of a recursive rule, which generates new hierarchical levels, with an iterative rule, which adds elements within a fixed hierarchical level without generating new levels. These experiments show that different brain networks support the representation or RHE in different domains (Right Superior Temporal Gyrus in music...
Rehabilitation

Figure 2.3.3.1  Brain activations during the application of a Recursive Rule in the motor domain. Application of the Recursive rule yielded stronger activations compared to both Iteration and Repetition (no rule) in a bilateral network known to be involved in motor planning and imagery, including sensorimotor and premotor cortices, cerebellum and lateral occipital cortex (Martins et al. Hum Brain Mapp 2019).

Figure 2.3.3.2  Lesion-behaviour analyses. A drift diffusion analysis with the RHE rule generates a drift rate \( v' \) (uncorr.) and boundary separation \( a' \) (uncorr.) value per participant. IFG lesions were associated with lower \( a' \), meaning that participants collected less information before reaching a decision, and lesions in the MTG and STG were associated with lower drift rate, meaning that these patients collected information slower.

**Interventions to improve sensorimotor function after stroke**

Sehm, B.\(^{1,2}\), & Nikulin, V.\(^{3,4}\)

1 Neuroplasticity and Motor Recovery Group, Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Clinic of Neurology, University Hospital Halle, Germany
3 Neural Interactions and Dynamics Group, Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
4 Centre for Cognition and Decision Making, Institute for Cognitive Neuroscience, National Research University Higher School of Economics, Moscow, Russia

We are testing different interventional approaches to improve sensorimotor function and motor learning both in healthy people and in patients after stroke. Our aim is to improve the patients’ behavioural deficits, delineate mechanisms that underly recovery, and identify reliable biomarkers for treatment planning and patient stratification. In collaboration with our Russian colleagues (Nazarova et al., submitted) we have shown recently that fractional anisotropy in the internal capsule and the presence of motor evoked potentials to TMS are equally important markers of poor recovery. In interventional studies we assess the modulatory potential of non-invasive brain stimulation and augmented-reality training on sensorimotor functions in healthy young and elderly individuals and stroke patients. Recently, we tested a short-term high-intensity visuomotor coordination training programme of the paretic arm in chronic stroke patients. The setting was a robotic device coupled to an exo-skeleton, which on the one hand prevented compensatory movements and on the other, allows the assessment of alterations in behaviour accurately. Our study showed significant behavioural gains both in objective kinematic parameters as well as in daily activity tasks of the arm. Using fMRI before and after training in relation to kinematic improvements we furthermore...
Figure 2.3.4 (A left) Example of the reaching results from a representative patient. (B right) Group results from the reaching test. A lower value indicates a faster and more accurate performance during the reaching. **p< 0.01, *p< 0.05. (B left) Activation map during the elbow movement (movement execution period contrast to rest period). (B middle) Activations in frontal motor network before training positively predict the training outcome (improvement in reaching performance).Cluster corrected threshold p < 0.05. (B right) Training-induced change in laterality index (between the two motor cortices) is correlated with the behavioural improvement (improvement in reaching performance). (C) Simulation on MNI standard brain to illustrate the different electrical field distributions and electrode montages for the two tDCS setups. Anodes always positioned over ipsilesional motor cortices (M1). (D left) Both setups induce complex performance changes across all parameters, as assessed with paired t-tests. More positive effects in reaching tasks, negative effects in Position Matching (proprioception) and Ball on Bar Tasks (bilateral coordination) with both setups, respectively. Overall, bilateral tDCS exhibits a more favourable outcome pattern. (D right) Statistical significance was assessed through permutation-testing for all parameters (50% of data randomly switched, 5000 iterations)
showed specific neuroplastic functional brain network alterations related to the behavioural improvements (Figure 2.3.4, A and B; Shih et al., submitted) that serve as targets for non-invasive brain stimulation in subsequent studies. Another study investigated the modulatory potential of transcranial direct current stimulation (tDCS). We demonstrate that tDCS differentially affects proprioception in young and elderly participants as assessed with an arm position matching task using the robotic device (Muffel et al., 2019). In stroke patients, we found that tDCS induces complex behavioural changes on paretic arm function across different sensorimotor tasks and suggest that functional increases go hand in hand with decreases (Figure 2.3.4, C and D; Muffel et al., submitted).

Optimising rehabilitation success with music

Fritz, T. 1, 2
1 Music and Brain Plasticity Group, Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Institute for Psychoacoustics and Electronic Music (IPEM), Ghent University, Belgium

In clinical practise music is often used to increase motivation to engage in physical activity, which is known to amplify rehabilitation success, e.g. through an increase of brain plasticity through enhanced BDNF levels. In recent years we have tested the hypothesis that physical exercise can improve through music, beyond making it less tedious. We have observed that systematically combining exercise and music-making positively influences parameters relevant to rehabilitation success, including learning success (with respect to both motor and cognitive parameters), endurance, and perception of exertion (Fritz et al., PNAS 2013;110:17784-9), physical pain (Fritz et al. Front Psychol 2018), mood (Fritz et al. Front Psychol 2013;4:921), and social integration (Fritz et al. Front Hum Neurosci 2015;9:300). To maximise musical arousal in a therapeutic setting, we have devised a method that effectively increases arousal while making music. Participants can play music with movements that are perceived as particularly exhausting physically, and/or with respect to motor control, using music-feedback technology we call Jymmin™. Musical arousal is a concept that is central to how we believe musical effects can be optimised for patients in stroke rehabilitation. Stimuli evoking stronger emotional responses are often more likely to also evoke stronger neural plasticity, e.g. resulting in more vivid memories of emotional experiences.

We have begun to investigate neural mechanisms of musical arousal, applying PET-MRI to better understand its underlying neuro-chemistry, for example with respect to the multi-faceted role of the dopaminergic system (Figure 2.3.5.1). We have found evidence that not only the D2-receptor system is involved in mediating the response to music, but also musical-arousal-related activity of the D1-receptor system.

We are currently implementing the Jymmin™ intervention in a multitude of clinics in Germany and Switzerland. In a recent pilot experiment with patients doing unilateral hand training after stroke we observed that patients were more motivated performing a two week hand training with music feedback compared to therapy as usual plus passively listening to music. Figure 2.3.5.2 also depicts that all participants perceived the music feedback intervention as more aesthetically pleasing, and that 11 of the 12 participants showed a stronger increase in their action research arm test values (ARAT) after two weeks of music feedback training.

Figure 2.3.5.1 Distribution of striatal BP_{ND} from PET scans using the D1-sensitive tracer [11C]SCH 23390 for neutral emotion scans (left), scans with pleasant and unpleasant music stimulus (middle) and scans with and without musical stimulus (right; indicating effects of musical arousal irrespective of valence). The individual differences between both corresponding scans are plotted in-between with the P value of the corresponding paired t test shown above.
Figure 2.3.5.2 Histograms depicting the results of a 2-week musical-feedback training.

- **Action Research Arm Test**
  - Difference in total ARAT score between musical-agency condition and non-musical-agency condition

- **Motivation**
  - Difference in motivation between musical-agency condition and non-musical-agency condition

- **Aesthetic appreciation**
  - Difference in aesthetic appreciation of music between musical-agency condition and non-musical-agency condition
Congresses, Workshops, and Symposia

2017


- Villringer, A., Lachmann, U., & Babayan, A. (March). 5th Mind, Brain, and Body Symposium. Mind-Brain Institute at Berlin School of Mind and Brain, Humboldt University Berlin, Germany.


- Klotzsche, F. (September): Influences of cardiac cycle on perceived distances to threatful and harmless objects - A study in immersive virtual reality. Hands-on workshop. Central Kolleg, supported by the CENTRAL Network (https://www.projekte.hu-berlin.de/de/central/centralkollegs/).


2018


- Klotzsche, F. (September): Influences of cardiac cycle on perceived distances to threatful and harmless objects - A study in immersive virtual reality. Hands-on workshop. Central Kolleg, supported by the CENTRAL Network (https://www.projekte.hu-berlin.de/de/central/centralkollegs/).


- Klotzsche, F. (December): Influences of cardiac cycle on perceived distances to threatful and harmless objects - A study in immersive virtual reality. Hands-on workshop. Central Kolleg, supported by the CENTRAL Network (https://www.projekte.hu-berlin.de/de/central/centralkollegs/).

2019


• Schroeter, M. L., & Koutsouleris, N. (June). Predicting diagnosis & treatment in neuropsychiatric disorders with pattern recognition algorithms. Symposium. World Federation of Societies of Biological Psychiatry (WFSBP), 14th World Congress of Biological Psychiatry, Vancouver, Canada.

• Villringer, A., & Krieghoff, V. (June). Summer School. IMPRS NeuroCom, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.


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Degrees

Habilitation Theses

2019

• Witte, V. Einfluss von Adipositas, Ernährung und Stoffwechseländerungen auf die Gehirnstruktur und -funktion. [Influence of obesity, nutrition and metabolic changes on brain structure and function]. Leipzig University, Germany.

PhD Theses

2017

• Barth, C. Exploring structural and functional brain dynamics across the menstrual cycle. Leipzig University, Germany.

• Bianco, R. Principles of action planning in music production: Evidence from fMRI and EEG studies. Leipzig University, Germany.

• Bisenius, S. Validation of diagnostic imaging criteria for primary progressive aphasia. Leipzig University, Germany.

• Grellmann, C. Combining brain imaging and genetic data using fast and efficient multivariate correlation analysis. Leipzig University, Germany.

• Gundlach, C. Modulation neuronaler Oszillationen durch transkraniale Wechselstromstimulation und deren Einfluss auf die Somatosensoren. [Modulation of neuronal oscillations by transcranial alternating current stimulation and its influence on somatosensory]. Leipzig University, Germany.

• Hoff, M. Motorische Plastizität über die Lebensspanne – Untersuchungen zur Reduktion altersbedingter feinmotorischer Defizite durch motorisches Lernen und nicht-invasiver Hirnstimulation. [Motor plasticity over the lifespan - Investigations on the reduction of age-related motor deficits through motor learning and non-invasive brain stimulation]. Leipzig University, Germany.

• Kaminski, E. Augmenting dynamic balance performance by transcranial direct current stimulation. Leipzig University, Germany.

• Kumar, S. A. EEG study on the differences between lean and obese individuals during regulation of food desire. Leipzig University, Germany.

• Lehmann, N. Hirnstrukturelle Korrelate der Steigerung motorischer Lernprozesse durch eine neuromodulatorische Voraktivierung. [Brain structural correlates of the enhancement of motor learning processes by neuromodulatory pre-activation]. Leipzig University, Germany.

• Radenbach, C. Stress und modellbasiertes Entscheidungsverhalten: [Stress and model-based decision-making behavior]. Leipzig University, Germany.

• Schrimpf, A. Weight-related stigmatization and its impact on behavioral adaptations, affect, and parasympathetic activity during social information processing – a cross-cultural comparison. Leipzig University, Germany.

2018

• Khalil, A. A. A. Improved assessment of hypoperfusion, blood-brain barrier disruption, and ischemic cellular damage in stroke patients using magnetic resonance imaging. Charité University Medicine Berlin, Germany.

• Mathar, D. Obesity is associated with insufficient behavioral adaptation. Leipzig University, Germany.

• Rjosk, V. Augmenting motor performance with mirror visual feedback (MVF): Underlying mechanisms and neural correlates. Leipzig University, Germany.
### MD Theses

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<tr>
<td>2017</td>
<td>Cliqupek, M. Untersuchung zur Auswirkung von Musik unterschiedlicher Valenz auf den Blutdruck und die Wahrnehmung bei schwangeren und nicht-schwangeren Frauen. [Study on the effect of music of different valences on blood pressure and perception in pregnant and non-pregnant women]</td>
<td>Leipzig University, Germany.</td>
<td>Study of the effect of music of different valences on blood pressure and perception in pregnant and non-pregnant women.</td>
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<td>2018</td>
<td>Herzig, S. Depression und Fatigue bei Patienten mit chronischer Hepatitis C. [Depression and fatigue in patients with chronic hepatitis C]</td>
<td>Leipzig University, Germany.</td>
<td>Study of depression and fatigue in patients with chronic hepatitis C.</td>
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<td></td>
<td>Mühlberg, C. Der Einfluss der Faktoren Geschlecht und Adipositas auf die inhibitorische Kontrolle. [The influence of gender and obesity factors on inhibitory control]</td>
<td></td>
<td>Study of the influence of gender and obesity factors on inhibitory control.</td>
</tr>
<tr>
<td>2019</td>
<td>Grundeis, F. The influence of non-invasive prefrontal/frontal brain stimulation on food reappraisal abilities and calorie consumption in obese females.</td>
<td>Leipzig University, Germany.</td>
<td>Study of the influence of non-invasive prefrontal/frontal brain stimulation on food reappraisal abilities and calorie consumption.</td>
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<td></td>
<td>Morys, F. Characterising and altering maladaptive behaviours and tendencies in obesity.</td>
<td>Leipzig University, Germany.</td>
<td>Study of characterising and altering maladaptive behaviours and tendencies in obesity.</td>
</tr>
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<td></td>
<td>Polyakova, M. Searching for pathomechanisms of late life minor depression – a combined MRI, biomarker and meta-analysis study.</td>
<td>Leipzig University, Germany.</td>
<td>Study of searching for pathomechanisms of late life minor depression.</td>
</tr>
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<td></td>
<td>Preusser, S. Der ventral kortikale Verarbeitungspfad der Berührwahrnehmung. [The ventral cortical processing pathway of touch perception]</td>
<td></td>
<td>Study of the ventral cortical processing pathway of touch perception.</td>
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<td></td>
<td>Zhang, R. Obesity, brain microstructure, and cognition in aging.</td>
<td>Leipzig University, Germany.</td>
<td>Study of obesity, brain microstructure, and cognition in aging.</td>
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### Other Publications

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<tr>
<td></td>
<td>Simmank, J. Biasing reward-based decision-making in obesity.</td>
<td>Leipzig University, Germany.</td>
<td>Study of biasing reward-based decision-making in obesity.</td>
</tr>
</tbody>
</table>

### Further Reading

- Forschack, N., Conscious and unconscious somatosensory perception and its modulation by attention. Leipzig University, Germany.
- Hardikar, S. Taste perception in obesity. Leipzig University, Germany.
- Huhne, S. The impact of nutrition on hippocampal function – Results of a literature review and a randomized controlled trial. Leipzig University, Germany.
- Kynast, J. What makes us social? Investigating mindreading from the eyes in adulthood. Leipzig University, Germany.
- Mehl, N. About self-regulation and automatic behavior in the context of obesity. Leipzig University, Germany.
- Grundeis, F. The influence of non-invasive prefrontal/frontal brain stimulation on food reappraisal abilities and calorie consumption in obese females. Leipzig University, Germany.
Appointments

2019

- Horstmann, A. Professorship, University of Helsinki, Finland.
- Maennel, C. Guest-Professorship, Stand-in W3 Professorship. University of Potsdam, Germany.
- Maennel, C. W2 Professorship, Charité University Medicine Berlin, Germany.
- Witte, V. W2 Professorship (declined), University of Greifswald, Germany.

Awards

2017

- Maennel, C. SNL Post-Doctoral Abstract Merit Award. Society for the Neurobiology of Language (SNL), Baltimore, USA.
- Mehl, N. Best Poster Prize. 33rd Annual Conference of the German Obesity Society, Potsdam, Germany.
- Mehl, N. New Investigator Travel Award. 25th Annual Meeting of the Society for the Study of Ingestive Behavior, Montreal, Canada.
- Morys, F. Best Poster Prize. 33rd Annual Conference of the German Obesity Society, Potsdam, Germany.
- Muffel, T. Best Poster Award. MindBrainBody Symposium, Berlin School of Mind & Brain, Germany.
- Schroeter, M. L. Travel stipend. European Congress of Radiology (ECR), Vienna, Austria (together with Leonie Lampe).
- Schroeter, M. L. Poster Award. 24th International Symposium about Current Issues and Controversies in Psychiatry – Crisis in Psychiatry?, Barcelona, Spain (together with Maryna Polyakova).

2018

- Bisenuis, S. Promotionspreis der Medizinischen Fakultät [Best Dissertation Award of the Faculty of Medicine]. Leipzig University, Germany.
- Heinrich, M. Deutschlandstipendium. Leipzig University, Germany.
- Hofmann, S. Research Talent grant. Dutch Research Council, NL.
- Schroeter, M. L. Leibniz Travel Grant. Research Academy Leipzig for ICFTD Meeting Sydney (together with Franziska Albrecht et al.).

2019

- Barth, C. Best Poster Presentation Award. 32nd Annual Meeting European College of Neuropsychopharmacology (ECNP), Copenhagen, Denmark.
- Heinrich, M. Deutschlandstipendium. Leipzig University, Germany.
- Muffel, T. Best Teaching Award. Free University of Berlin, Department of Education & Psychology, Berlin, Germany.
- Schroeter, M. L. Travel Grant. Alzheimer Research Initiative for WFSBP Congress Vancouver (together with Franziska Albrecht et al.).
- Schroeter, M. L. Leibniz Travel Grant. Research Academy Leipzig for WFSBP Congress Vancouver (together with Franziska Albrecht et al.).
- Shih, P.-C. Trainee Professional Development Award. Society of Neuroscience (SfN), Chicago, USA.
Publications

Books and Book Chapters


Journal Articles


Zsido, R. G. Best Poster Presentation Award. 8th IMPRS NeuroCom Summer School. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.


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Hoefle, S., Engel, A., Basilio, R., Alluri, V., Toiviainen, P., Cagy, M.,
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Lost in translation?: On the need for convergence in animal and
human studies on the role of dopamine in diet-induced obesity.
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in neuronal excitability bias subjective perception rather than

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Plasticity


Plasticity


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Figure 2.1.2

Figure 2.1.3

Figure 2.2.1.1

Figure 2.2.1.2

Figure 2.2.2.1

Figure 2.2.2.2

Figure 2.2.3


Figure 2.3.2

Figure 2.3.3.1

Figure 2.3.3.2
Our long term research agenda is to develop and apply non-invasive magnetic resonance imaging (MRI) methods to reliably characterise the detailed anatomical and functional micro-organisation of the human brain.

Understanding the normal and diseased human brain crucially depends on reliable knowledge of its anatomical microstructure and functional micro-organisation (e.g., cortical layers, columns, and stripes; Figure 3). To date, the micro-organisation can only be determined using invasive methods, such as post-mortem histology or invasive electrophysiology. This limits neuroscience, clinical research, and diagnosis.

The non-invasive characterisation of the micro-organisation and its changes in health and disease poses significant challenges. Several orders of magnitude of spatial scale need to be spanned and the multitude of different anatomical and physiological structures need to be captured and integrated (Figure 3).

Thus, unprecedented spatial resolution, minimal artifact levels, and high tissue specificity must be achieved. To address these extraordinary methodological challenges, we pursue an integrated interdisciplinary approach consisting of:

1. MR physics developments
2. Biophysical modelling and data analysis
3. Neuroscientific applications and validation

The successful development of in-vivo histology using MRI (hMRI) of the anatomical and fMRI of the functional micro-organisation hold great potential for research and clinical applications. For the first time, investigations of the struc-
ture-function relationship and plasticity at the microstructural level would become feasible in the human brain on a large scale. This will allow for an improved understanding of how brain structure determines function and functional demands affect structure. Microstructure imaging is expected to provide sensitive biomarkers of nervous system changes due to trauma or neurodegeneration, providing important early biomarkers in personalised medicine and clinical trials.

Over the last three years and after crucial start-up work, the research in the Department of Neurophysics has focused more on in-vivo applications of the recently developed methods for microstructure and functional imaging. The cortex in general and visual cortex in particular were early targets of our research into microstructure and its relation to function (e.g., 3.1.4, 3.1.5, 3.3.1, 3.3.2). The development and application of advanced histological approaches for validation and reference data generation has continued (e.g., 3.2.2, 3.3.3). Developments in the field of MR physics have continued improving resolution and data quality, enabling robust data acquisition at ultra-high resolution (e.g., 800µm resolution in diffusion and functional MRI, 3.1.1, 3.1.4; and <500µm resolution in quantitative multi-parameter mapping, 3.1.3).

Figure 3. Examples of neocortical organisation on the macroscopic (A–C), mesoscopic (D–G), and microscopic (H–J) scales, spanning five orders of magnitude in resolution and various structural features. (A) Cytoarchitectonic parcellation, (B) myeloarchitectonic parcellation, (C) recent in-vivo cortical parcellation based on combining structural and functional MRI. The neocortex can be subdivided into six distinct layers based on cytoarchitecture (D, left) or myeloarchitecture (D, right). Mesoscopic ontogenetic columns (columns of increased neuron cell body density and decreased myelin density) are indicated by arrows in (D). (E) High resolution T2*-weighted MR image showing distinct cortical layers. Functional units are also found on the mesoscopic scale. Examples of these functional cortical columns are (F) ocular dominance and (G) orientation preference columns in human visual cortex. On the microscopic scale, neuronal cell bodies, myelinated fibres, and glial cells are important constituents of the cortex. (H) Microscopy shows neuronal cell bodies, myelinated fibres and astroglia. (I) Myelin sheath around axonal fibres imaged using electron microscopy. (J) Iron localised in oligodendrocytes and myelinated fibres. Reprinted from Edwards et al. (2018, NeuroImage, 182, 184-206), which also provides a comprehensive list of references for the different subfigures.
Non-invasive Imaging of the Anatomical and Functional Micro-Organisation of the Human Brain

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3.1 MR Physics Developments
MR Physics developments focused on the 7T and 3T Connectom MRI platforms (300mT/m high performance gradient system, which is one of three worldwide), since they offer superior contrast/signal-to-noise ratio (CNR/SNR). Several studies combined the strength of 7T MRI in high resolution functional and anatomical imaging with the strength of the Connectom MRI in diffusion weighted imaging (DWI). For example, the combination of 7T fMRI-based retinotopy with Connectom DWI tractography allowed for functional specificity of U-fibers in the visual system (3.3.2). The ultra-high resolution DWI became possible by careful integration of advanced pulse sequences with the latest hardware developments such as flexible radio-frequency (RF) surface coils and magnetic field cameras (3.1.1, 3.3.2). To make the imaging methods more widely accessible, we have implemented quantitative multi-parameter mapping techniques on various scanner platforms from two different vendors using generally available product pulse sequences (3.1.2). In a travelling heads study a high comparability across clinical sites and time points is demonstrated, which enables the use of multi-parameter mapping in the international clinical NISCI trial on treatment of spinal cord injury (https://nisci-2020.eu/). Developments and investigations into functional MRI methods at 7T allow for routinely capturing the micro-organisation of columns and stripes in the visual cortex (3.1.4, 3.1.5). Anatomical imaging benefited from navigator based corrections, optical prospective motion correction and deep learning-based denoising approaches making it possible to routinely scan with 500 µm resolution at 7T (3.1.3).
High-resolution diffusion weighted imaging with spiral readout and field monitoring on a 300mT/m Connectom MRI scanner

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Mapping of intracortical diffusion and subcortical U-fibres requires ultra-high-resolution diffusion-weighted imaging (DWI) combined with high b-values. To achieve the necessary signal-to-noise and image quality, we developed DWI with spiral readout, field monitoring (Skope Magnetic Resonance Technologies AG, Zurich, Switzerland), and generalised image reconstruction using a high gradient 300 mT/m Connectom MRI scanner (Siemens Healthineers, Erlangen, Germany; Figure 3.1.1.1). An echo time (TE) of 32 ms was achieved at 0.8 mm isotropic resolution for b-values up to 2000 s/mm². The use of magnetic field probes (Barmet et al., 2008 Magn Reson Med, 60, 187–197) and static ∆B₀ maps combined with generalised SENSE reconstruction (Skope-I) corrected dynamic field distortion up to third-order spatial spherical-harmonics and static field distortion. A significant reduction in blurring and increase in sharpness of the white-matter and grey-matter boundary were observed in the images reconstructed with monitored third order trajectories compared to the first order correction (Figure 3.1.1.2). The ultra-high resolution DWI enabled investigation of intra-cortical diffusion and thin U-fibres (Figure 3.1.1.3). The high performance of the DWI spiral acquisition approach offers great potential for future high-resolution diffusion studies, even for challenging applications such as intracortical diffusion measurements and U-fibre mapping.

Figure 3.1.1.1  (A) Stejskal-Tanner diffusion imaging sequence with spiral readout. (B) Integration of field monitoring setup including RF front-end and probes.

Figure 3.1.1.2 Reconstructed images with 0.8 mm isotropic resolution for b = 0 s/mm², single direction diffusion weighted data (b = 1000 s/mm²) and directionally-encoded fractional anisotropy (FA) and coloured FA (cFA) with multi-shell (b = 1000, 2000 s/mm²) DWI data for monitored first- and third-order readout trajectories with ∆B₀ off-resonance correction. For third-order monitored trajectories, blurring is reduced (arrows) and finer anatomical details are visible (e.g. in the frontal lobes, dashed circles), compared to only first-order. Diffusion weighted data were acquired with 60 diffusion directions per shell (with 20 interleaved b = 0 s/mm²).
Development and validation of Multi-Parameter Mapping (MPM) for the NISCI multi-centre clinical trial

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Embedded as a sub-study within the clinical trial NISCI (Nogo inhibition in spinal cord injury; www.nisci-2020.eu), we employed whole brain quantitative imaging at 3Tesla as a new biomarker for de- and regeneration. The quantitative MRI technique of multi-parameter mapping (MPM; Weiskopf et al., 2013, Frontiers in Neuroscience, 7, 1–11) was adapted to the possibilities at clinical sites with vendor sequences as well as reduced resolution (1mm isotropic resolution) and scanning time to fit in a session <25 min. To evaluate the protocol setup for consistency between and within sites (test-retest) we performed a travelling heads study with five healthy subjects across six sites, involving different scanner hard- and software (Figure 3.1.2.1). For processing the data we used the hMRI-toolbox (www.hmri.info) for quantitative MRI data, which is developed by the MPI CBS and an international consortium (Tabelow et al., 2019, NeuroImage, 194, 191–210).

For quantitative maps (Magnetization Transfer saturation [MT], Proton Density [PD], longitudinal [R1] and effective transverse relaxation times [R2*]) the intra-site coefficient of variation (CoV) was between 4% and 8% for maps of MT, R1, and PD, whereas it was higher for R2* with up to
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15% (Figure 3.1.2.2). The inter-site CoV varied between 5% and 12% for maps of MT, R1, and PD, whereas it was higher for R2* with up to 18% (Figure 3.1.2.2). The inter-site bias varied between 2% and 5% for MT, R1, and PD, whereas it was higher for R2* (up to 7%, Figure 3.1.2.2). However, longitudinal studies of spinal cord injury showed that effect sizes are in the range of 17–20% for R1, and 14% for MT (Grabher et al., 2015, Ann Neurol, 78, 751–761) 1 year after injury compared to healthy controls. Thus, we expect to reliably detect injury related changes and potentially significant treatment effects in the NISCI trial, using the optimised and validated MRI protocols and post-processing methods.

Reducing the level of artifacts in quantitative parametric maps at 3T and 7T

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Multi-parametric quantitative MRI measures different MR parameters and offers the potential to characterise human brain microstructure. An efficient implementation of this concept, the multi-parameter mapping (MPM) protocol, uses 3 differently weighted multi-echo 3D-FLASH volumes to simultaneously quantify R1, R2*, proton density (PD) and magnetization transfer (MT) (Weiskopf et al., 2013, Front Neurosci, 7, 95). However, MRI artifacts are propagated into the quantitative maps and obfuscate meaningful physical values. To improve the reliability of the generated MPMs, rigid head motion and B0-fluctuation were measured during acquisition at 7T and corrected in a prospective or post-processing approach. Optical prospective motion correction (Kineticor, HI) was used to track head movement. It has been previously shown to reduce the level of motion related artifacts in the parametric maps (Callaghan et al., 2015, Front Neurosci, 9, 97). By monitoring the magnetic field fluctuations with free induction decay (FID) navigators and performing phase correction during image reconstruction, dynamic field changes due to respiration were addressed, effectively decreasing the level of regional patchiness and blurring (Figure 3.1.3.1).

To correct artifacts of unknown origin, we employed general function approximators in the form of CARE-Net/U-Net like feed forward neural networks (Weigert et al., 2018, Nat Methods, 15, 1090–1097 / Ronneberger et al., 2015, MICCAI 2015, 234–241). One specific example is ringing artifacts of unknown origin, appearing in maps acquired at 3T (Figure 3.1.3.2A). Training labels were generated by averaging multiple acquisitions showing the ripples in different locations, which yielded mostly artifact free images. The trained model was used to correct the weighted multi-echo images before MPM computation. Corrected images showed reduced artifact, while changes to unaffected regions of the image were minimised (Figure 3.1.3.2B). This approach preserves image features considerably better than other options to address the specific artifact, like Gaussian blurring or removing k-space lines.

Figure 3.1.3.1 Artifact reduction in 500µm resolution R1 maps due to navigator correction (bottom row) and optical prospective motion correction (PMC, right column). Dynamic B0-fluctuation correction using FID navigators results in increased R1 homogeneity in white matter by reducing patchy hyper-/hypo-intensities (red arrows). Blurring of the grey-white matter boundaries (yellow arrows) caused by motion is reduced in motion-corrected maps.

Figure 3.1.3.2 Artifact reduction using a neural network: Exemplary slice of corrupted T1 weighted input image (first echo) with ringing artifacts in the frontal areas (A), corrected output from neural network (B) and variance map showing model intrinsic uncertainty of the corrected image (C).
Using these different methods we were able to substantially reduce the severity of the most pronounced artifacts in the quantitative maps. We showed qualitative improvement of parametric maps by reducing the blurring and ringing coming from rigid head motion. B0-fluctuation correction resulted in a decrease in variance of dorsal white matter voxels of ~5% (in R1, R2*, PD map). The neural network was able to reduce the artifact in a test dataset by 12 dB while preserving artifact free image areas (multi scale structural similarity (MS-SSIM) in artifact free ROIs over all contrasts 0.89).

Reliable 3D mapping of ocular dominance columns in humans using GE-EPI at 7T

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Ocular dominance columns (ODCs) in primary visual cortex (V1) are a prominent example of the modular organisation of cells in certain mammalian brains. With the development of ultra-high field (UHF) functional MRI (fMRI), the mapping of neural dynamics at the spatial scale of cortical layers (Polimeni et al., 2010, Neuroimage 52, 4, 1334–1346) and columns (Yacoub et al., 2007, Neuroimage 37, 4, 1161–1177) became possible. Combined with sophisticated analysis techniques for parcellating and contouring the cortex we were able to robustly image the three-dimensional structure of ocular dominance columns in human visual cortex. In order to do so, we acquired functional data at 7T with 1.0 mm and 0.8 mm isotropic resolution in a single subject in 4 separate scanning sessions. ODCs were localised using a differential paradigm with visual stimulation of either the left or right eye by moving sparse random dot stereograms viewed through anaglyph goggles (Nasr et al., 2016, J Neurosci 36, 6, 1841–1857). Activation maps (t-score, left eye > right eye) were sampled on the reconstructed surface mesh of the participant’s cortex at different cortical depths. V1 was delineated using a separate retinotopy scan. The V1 surface was cut out, flattened, and regridded onto a cartesian representation (Figure 3.1.4.1), which allows for an easy visualisation of the ODCs across the cortex (Figure 3.1.4.2). Both figures show that we were able to robustly map ODCs in each session. The apparent broadening of the columns towards the pial surface can be explained by the well-known sensitivity of GE-EPI acquisitions to large draining veins. This demonstration of functionally-based visualisation of fine structures with high resolution can help to quantify the cortical depth dependent vascular blurring typically seen in fMRI. Recently, we collected data from a larger cohort using GE-EPI, SE-EPI, and SS-SI VASO (Huber et al., 2017, Neuron 96, 6, 1253–1263). This data set will allow us to compare these different high-resolution fMRI approaches regarding their sensitivity to the brain macrovasculature across cortical depth.
Mapping colour-selective stripes in human V2 using GE-EPI and SE-EPI at 7T

Hänelt, D.1, Trampel, R., Nasr, S., Polimeni, J., Tootell, R., Sereno, M., & Weiskopf, N.

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The extrastriate secondary visual area (V2) is known to have a unique modular organisation (thin, thick, and pale stripes; Figure 3.1.5.1), which functionally segregates features of the visual input signal. For example, thin stripes are selectively activated by colour content, which was exploited to map these structures for the first time in the living human brain using high-resolution fMRI at 7T (Nasr et al., 2016, J Neurosci 36, 6, 1841–1857). We replicated these results in one volunteer multiple times on different days using the same paradigm and GE-EPI protocol with nominal isotropic 1 mm resolution. Additionally, we extended this work by showing the same activation pattern using SE-EPI. Figure 3.1.5.2 shows thresholded t-maps (colour > no colour) for different sessions acquired on different days with GE-EPI and SE-EPI, respectively. As expected, the colour-selective thin stripes radiate outward from the V1/V2 border and run in parallel through V2. The exact location of the V1/V2 border (white line) was determined by a separate retinotopy scan. The expected stripe pattern can be robustly seen in all sessions. It is already known that the stripe architecture can be seen histologically not only using cytochrome oxidase staining methods (Figure 3.1.5.1) but also with myelin stains (Horton et al., 1997, Cereb Cortex 7, 2, 166–177). As MRI is inherently sensitive to myelin, studying the structure-function relationships of fine structures in human visual cortex is possible in vivo using ultra-high field strength of 7T. Therefore, we are running a study to investigate this relationship using fMRI and qMRI (MPM protocol, Weiskopf et al., 2013, Front Neurosci 7, 95) to acquire further knowledge about the microstructure-function interdependencies in the living human brain.

Figure 3.1.5.1 Flat-mounted section from the lateral surface of squirrel monkey cortex stained with cytochrome oxidase. Anterior in the brain is toward the left and dorsal is toward the top. The semicircular region of the right is central V1. To the left, the stripe topography in V2 can be identified as a band of parallel stripes. Figure and caption taken from Tootell et al. (1983, Science, 220, 4598, 737–739), black line: 5 mm.

Figure 3.1.5.2 Thresholded activation maps (colour > no colour) show the colour-selective stripes in V2 on the left hemispheres of one participant. As expected the stripes are radiating outerwards from the V1/V2 border and run in parallel through V2. (A)-(B) show estimates in single GE-EPI sessions, which demonstrates scan-rescan reliability. (C)-(D) show the average over two GE- and SE-EPI sessions, respectively.
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Biophysical Modelling and Data Analysis
The development of unified biophysical models is central for the success of non-invasive imaging of the brain’s micro-organisation. They effectively integrate and leverage the wide range of contrasts (e.g., diffusion, relaxometry, magnetisation transfer contrasts) for inferring the underlying microstructure from MRI, even when the microstructural features are smaller than the nominal voxel size (Figure 3.2). Generative models of MR contrast predict the contrast in MR images from the underlying known microstructure. Gleaning microstructure information from MRI requires the inversion of these models, which is frequently ill-posed. To constrain the problem and improve its conditioning, the models include a priori known aspects of structural and functional micro-organisation, e.g., layers, tangential and radial fibres in the cortex (Figure 3.2). Moreover, the use of multiple contrasts improves the micro-organisation estimates from MRI, since they provide different perspectives of the underlying microstructure and improve the conditioning of the notoriously difficult model inference. An example for a generative model based on first principles is the description of neuromelanin-iron induced contrast in the substantia nigra (3.2.1). Another example, which is based on a data-driven model, is the description of myelination-related contrast in the cortex by a spectrum of histological stains and MALDI (3.2.2). The integration of multiple contrasts is exemplified by the work on IR-DWI (3.2.3), which integrates measurements of longitudinal relaxation with diffusion. Potential issues of using post-mortem tissue for informing biophysical modelling are highlighted by fundamental changes in the contrast drivers in the locus coerules due to formalin fixation (3.2.4).

The different unified biophysical models require accurate mesoscopic and macroscopic anatomical information combined with the multi-contrast MRI data. Thus, the biophysical modelling is combined with developments in the field of image and data processing, which allow for high quality registration and segmentation of ultra-high resolution datasets. An example is the development of the hMRI-toolbox (www.hMRI.info), which is an open-source toolbox for quantitative MRI and hMRI analysis and developed by an international network of developers.
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Figure 3.2 From standard MRI to in-vivo histology using MRI (hMRI). (A) MRI offers a multitude of contrasts that can be weighted towards particular MRI parameters, for example, proton density (PD), magnetisation transfer (MT) rate, longitudinal and transverse relaxation time \(T_1\) and \(T_2\) and susceptibility effects as visible in the phase MR signal. (B) Quantitative MRI (qMRI) uses physical models to calculate quantitative parameter maps that depend nontrivially on the underlying tissue microstructure. (C) hMRI uses biophysical models to convert MRI or qMRI data to specific biological metrics such as myelin density, iron density, fibre orientation or g-ratio. This even allows for studying microstructural features that are smaller than the nominal voxel size by providing aggregate measures of them. (D) Ultimately, hMRI may provide a detailed microstructural description of the brain, here, for example, the myeloarchitectural description of the cortical sheet (reprinted from Weiskopf et al., 2015, Curr. Opin. Neurol., 28, 313–322).
A biophysical model of iron-induced transverse MRI relaxation in nigrosome 1: Toward an early biomarker of Parkinson's Disease

Brammerloh, M. 1,2, Kirilina, E. 1,3, Weigelt, I. 4, Lange, C. 1,2, Reinert, T. 1,2, Jahnkuhn, S. 2, Jäger, C. 1, Pine, K. 1, Gavrilidis, F. 1, Trampel, R. 1, Reimer, E. 1, Morawski, M. 1, Arendt, T. 4, & Weiskopf, N. 1,2

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In Parkinson’s disease, the depletion of iron-rich dopaminergic neurons in nigrosome 1 in substantia nigra precedes the first motor symptoms by almost two decades. Methods capable of monitoring this neuronal depletion at an early disease stage are highly desired for diagnosis and treatment monitoring.

MRI is particularly suited for this task, since it is sensitive to iron accumulated in the neuromelanin of dopaminergic neurons (Figure 3.2.1.1). However, the mechanisms of MRI contrast in substantia nigra are unknown, hindering the development of specific biomarkers. We elucidate the mechanisms of iron-induced transverse relaxation in nigrosome 1 by combining quantitative 3D iron histology, quantitative MRI on post-mortem human brain tissue, and biophysical modelling.

We developed a comprehensive biophysical model accounting for the chemical form of iron binding and the heterogeneous iron distribution at the cellular scale. This model was informed with 3D quantitative iron concentration maps of nigrosome 1 obtained from combining Proton-Induced X-ray Emission microscopy (PIXE) with classical iron stains. We showed that iron in dopaminergic neurons is the dominant source of effective transverse relaxation rate R2*. We determined the proper theoretical relaxation regime describing R2*, which was found to be close to static dephasing (Figure 3.2.1.2). In this regime, R2* is analytically linked to the total iron content in dopaminergic neurons, i.e., the product of neuronal density and mean cellular iron concentration (Yablonskiy & Haacke, 1994, Magn Reson Med, 32, 6, 749–763). Our...
model’s predictions were shown to be accurate by comparing them to relaxation rates acquired at 7 T on a specimen before and after chemical iron extraction.

For the first time, we achieved a mechanistic model of iron-induced MR contrast in substantia nigra derived from first principles and based on iron microstructure quantification. This knowledge paves the road toward novel, specific biomarkers for Parkinson’s disease.

## 3.2.2 Different characteristics of cortical and white matter myelin: A challenge for MRI myelin biomarkers

Myelin, the fatty axon-insulating substance in the brain, is composed of a large variety of lipids, proteins, and trapped water. It is the main source of contrast in magnetic resonance images (MRI) of the human brain. All MRI parameters, including longitudinal and transverse relaxation rates (R1, R2, R2*), proton density (PD), magnetization transfer and magnetic susceptibility are sensitive to tissue myelination due to different biophysical mechanisms (Edwards et al., Neuroimage 2018). Therefore, quantitative MR parameters used as myelination biomarkers may provide unique in vivo information on brain development, cortical myeloarchitecture, plasticity, and neurodegeneration (Edwards et al., Neuroimage 2018, Natu et al., PNAS, 2019). However, the mechanisms underlying the sensitivity of MRI parameters to tissue myelination are only partly understood and quantitative comparisons between MRI metrics and tissue myelination are limited to a few studies. Moreover, specificity and sensitivity of R1, R2*, and PD to myelin composition are only starting to be explored in more detail (Filo et al., 2019, Nature Commun, 2019, 10, 3403). Validation of MRI-based myelin biomarkers is difficult due to the lack of methods for histological myelin quantification. Classical histological and immunohistochemistry stains provide only qualitative information on myelin distribution and reflect only some of the various myelin components. Recently developed advanced methods for lipid quantification promise to overcome this limitation.

Here, we systematically explored several methods for myelin quantification for the validation of MRI myelin biomarkers. To this end, we combined quantitative MRI in post mortem human brain tissue samples with histological and immunohistochemical myelin stains and lipid imaging with matrix-assisted laser desorption/ionisation mass spectrometry (MALDI-MSI).

We demonstrated that different histological stains for myelin detection provide similar, but distinct information on tissue myelination, particularly in the cortex (Figure 3.2.2.1). Therefore, the assessment of cortical myelin mapping requires the use of multiple stains and is, even in this case, not comprehensive. We showed that lipid composition of tissue varies across different cortical layers and white matter pathways, potentially reflecting differences in myelin structure (Figure 3.2.2.2). We suggested that a principal component analysis of MALDI-MSI lipid maps can be used to obtain a histological myelin biomarker for the validation of quantitative MRI parameters (Figure 3.2.2.3). Our results demonstrated that MALDI-MSI is a powerful tool for validation and development of myelin MR markers and that differences in lipid composition of the cortex and in white matter pathways need to be taken into account when interpreting MRI-based maps of brain myelination.

![Figure 3.2.2.1 Selectivity of histological myelin markers and myelin-sensitive quantitative MRI parameters obtained on post-mortem human brain tissue blocks, containing the primary visual cortex. Optical images (A) and optical density maps (B) of histological stains are presented for Luxol Fast Blue stain (top), Silver impregnation fibre stain (middle) and immunohistochemistry with a myelin-basic-protein (MBP) antibody (bottom). Quantitative maps of MR parameters, including longitudinal relaxation rate R1 (top), proton density (PD) map (middle), and effective transverse relaxation rate R2* (bottom), were obtained on the same tissue block. High contrast between white and grey matter was observed for all detection methods and MRI parameters. However, different patterns of myelination were observed in the cortex with different histological stains and MRI parameters.](image-url)
Exploring diffusion properties in grey matter using inversion recovery diffusion weighted imaging

Movahedian Attar, F.1, Dhital, B.1,4, Kirilina, E.1,2, Kiselev, V.3, Edwards, L. J.1, & Weiskopf, N.1,4

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We aimed to identify different microstructural components of the grey matter by their different relativity (T1) and diffusivity properties. Inversion recovery diffusion weighted imaging (De Santis et al., 2016, Magn Reson Med, 75, 1, 372–380) was used to investigate this compartmentalisation.

The diffusion tensor derived fractional anisotropy (FA) and mean diffusivity (MD) were obtained using b=0, 500, 1300 s/mm² at multiple inversion times (TI). While the TI independent MD and FA do not provide any evidence of multiple compartments in white matter, their observed TI dependence reveals multicompartment structure in grey matter (Figure 3.2.3.1).
We hypothesised that this finding could be explained by compartmentalisation at three different spatial scales. Cortex is organised into intra- and extra-axonal compartments on a microscopic scale; on a mesoscopic scale the effects could be described in terms of myelin-proximal and myelin-distal water (cells and fibres) due to myelin’s efficient relaxation and water hinderance properties; and on a macroscopic scale it is organised into cortical laminae and areas (Figure 3.2.3.2). To disentangle these contributions we are going to measure the microscopic FA (µFA, Szczepankiewicz et al., 2015, Neuroimage, 104, 241–252) and investigate the dependence on the spatial resolution and the abundance of myelin on the macroscopic scale.

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**Figure 3.2.3.1** Multi-TI diffusion weighted imaging experiment conducted with $b=0$, 500 and 1300 s/mm$^2$ showed TI-dependent grey matter and TI-independent white matter diffusion properties. (top) Signal for $b=0$ s/mm$^2$ variation at various TI. White and grey matter signals were suppressed at TI~500 ms and TI~900 ms, respectively. (bottom) Real and simulated ($S=S_0(1-2e^{-TI/T_1})$) $b=0$ s/mm$^2$ signal, FA and MD variation with TI. Grey matter MD and FA differ at short and long TI whereas white matter MD and FA are constant with TI. The diffusion tensor was estimated using $b=500$ and 1300 s/mm$^2$. Plots are shown for a candidate axial slice in the brain. The highlighted regions in red indicate TI for which diffusion tensor estimates were unreliable due to low signal.

**Figure 3.2.3.2** The observed TI-dependent grey matter property may be explained by compartmentalisation at different spatial scales. The microscopic scale (adapted from Liewald et al., 2014, Biol. Cybern., 108, 541–557) where intra- and extra-axonal compartments dominate, the mesoscopic scale (adapted from Morawski et al., 2018, Neuroimage, 182, 417–428) where the water proximal (fibres) and distal (cells) to the fibres dominates and/or macroscopic scale (adapted from Vogt & Vogt, 1919, J Psychol Neurol, 25, 275–462) where the cortical layers dominate. To investigate each possibility, experiments at various spatial resolutions and dedicated acquisition and modelling are planned.
Iron-induced MR contrast in human Locus Coeruleus: A cautionary tale of misleading Post Mortem MRI results

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7 Department of Anatomy and Embryology, Maastricht University, NL
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The locus coeruleus (LC), a small nucleus in the pons, is affected in early stages of several tauopathies and synucleinopathies, including Alzheimer’s disease (AD). MRI provides highly promising in-vivo biomarkers of LC integrity, for early AD diagnosis and monitoring of potential treatments (Hammerer et al., PNAS, 2018). LC visualisation and quantification utilise MR contrasts driven by the pigment and metal chelate neuromelanin that is stored in noradrenergic neurons in LC. The mechanisms of neuromelanin-induced MRI contrasts are puzzling and no mechanistic link between MRI parameters and tissue microstructure in LC has been established yet.

We combine high-resolution post-mortem MRI, histology/immunocytochemistry, ion-beam microscopy, and electron paramagnetic resonance (EPR) for a comprehensive description of the contrast mechanisms in LC. As part of these studies, we demonstrate that the main source of MR contrast in formalin fixed LC is paramagnetic iron accumulated in NM-containing neurons. However, we show that MR contrast in LC drastically changes during the first six months of tissue fixation. We assign these changes to iron being scavenged by NM and the change of its paramagnetic state. These results have major consequences for MRI of the locus coeruleus, demonstrating a fundamental change rather than the commonly known gradual changes in contrast due to formalin fixation.

Since the in-vivo and post-mortem MRI cannot readily be compared, histological validation studies and developing AD biomarkers based on the LC are complicated and some previously published results should be re-interpreted.
3.3 Neuroscientific Applications and Validation
The non-invasive imaging of brain micro-organisation offers possibilities for a broad range of neuroscientific studies. At the same time the newly developed imaging methods and biophysical models require careful validation. This section provides examples of different in-vivo and post-mortem studies pursuing these goals.

A novel combination of ultra-high resolution quantitative multi-parameter mapping at 7T with gene expression and cytoarchitectonic atlases is used for validating cortical layer information in MRI (3.3.1). This combination promises new ways to study the specific connectivity between the cortex and subcortical areas and its changes in disease. The study on U-fibres in the visual cortex and their relation to the functional retinotopic organisation is an example of a multi-modal in-vivo validation of the microstructure imaging approaches (3.3.2).

Advanced histology techniques are developed as part of the post-mortem validation. For example, semi-thin and electron microscopy acquisition and analysis methods are developed and applied to characterising the microstructure of the white matter (3.3.3), which will help us validate models of diffusion contrast in white matter and of crossing fibres. The novel opportunities of whole brain microstructure imaging were also exploited for comprehensive post-mortem imaging of entire human brains and hominoid brains (3.3.4) as part of the Evolution of Brain Connectivity project in collaboration with the Department of Neuropsychology, MPI for Evolutionary Anthropology (Leipzig), Paul Flechsig Institute of Brain Research (Leipzig University), and Robert Koch Institute (Berlin).
Validation of quantitative 7T MRI across cortical depths using cytoarchitectonics, gene expression, and connectomics

McColgan, P.1,2, Helbling, S.1, Vaculciakova, L.1, Pine, K. J.1, Wagstyl, K.3, Edwards L. J.1, Movahedian Attar, F.1, Papoutsi, M.2, Wei, Y.4, van den Heuvel, M. P.4, Tabrizi, S. J.2, Rees, G.3, & Weiskopf, N.1,5

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Quantitative MRI (qMRI) is sensitive to micro-structural properties of brain tissue such as myelination and iron concentration (Stüber et al. 2014, Neuroimage, 93, 95–106; Callaghan et al. 2015, Magn Reson Med, 73, 1309–1314) and has been demonstrated to be predictive of functional brain measures (Helbling et al., 2015, Neuroimage, 108, 377–385). Ultra-high field MRI has the potential to push qMRI-based in vivo histology of the human cortex to reach even laminar resolution (Trampel et al., 2019, Neuroimage). Here we have validated cortical layer-specificity for quantitative maps from a 7T multi-parametric mapping (MPM) 500μm whole brain protocol.
The sensitivity of layer-specific measures of effective transverse relaxation rate ($R^2*$) and longitudinal relaxation rate ($R_1$) was characterised by relating $R^2*$ and $R_1$ to cortical cytoarchitecture provided by the von Economo and Big Brain post-mortem histology atlases (Scholtens et al., 2018, Neuroimage 170, 249–256; Amunts et al., 2013, Science 340, 1472–1475). We also investigated the relationship between 7T MPMs and layer-specific gene expression using the Allen Human Brain atlas (Hawrylycz et al., 2012, Nature 489, 391–399), and linked MPM cortical depth measures with anatomical white matter connections using high fidelity diffusion tractography from a 300mT/m Connectom MRI system (Siemens Healthineers, Erlangen, Germany). We showed that the $R^2*$ across cortical depths is highly correlated with layer-specific cell numbers and cell staining intensities. While these correlations were significant for $R^2*$ measures across multiple cortical depths, we note that this low laminar specificity may at least partly be attributed to the presence of high cross correlations between layers for both von Economo and Big Brain data (i.e., most likely high covariance of biological origin). Gene enrichment analysis (Arnatkeviciute et al., 2019, Neuroimage 189, 353–367) demonstrated significant correlations between $R^2*$ across cortical depths and layer-specific genes. Furthermore, diffusion tractography based white matter connectivity measures were highly correlated with grey matter $R_1$ and $R^2*$ across cortical depths. These findings demonstrate the potential of combining 7T MPMs, gene expression, and white matter connections to provide an anatomically precise framework for elucidating layer-specific neural communication pathways in a whole-brain fashion.

U-fibre connectivity mapping using sub-millimetre resolution diffusion MRI tractography

Movahedian Attar, F.1, Kirilina, E.1,2, Hänelt, D.1, Pine, K. J.1, Trampel, R.1, Edwards, L. J.1, & Weiskopf, N.1,3
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Short cortico-cortical association fibres (U-fibres) are white matter fibres that run directly below the cortical grey matter in the superficial white matter and connect nearby cortical areas (Meynert 1885, Schüz & Braitenberg, 2002). U-fibres have demonstrated involvement in brain development, function, and pathology but are underrep-

Figure 3.3.2.1 Combination of sub-millimetre resolution diffusion weighted imaging and functional retinotopy help validate U-fibre mapping in the human brain in-vivo. (A–C) High quality fibre orientation distribution function estimates at 0.8 mm isotropic resolution using a multi-fibre estimation model capable of disentangling crossing fibres and partial volume effects (Tournier et al., 2004, Neuroimage, 23, 3, 1176–1185; Dhollander et al., 2016, ISMRM, Lisbon, Portugal). High quality virtual dissection of (D) optic radiation tract was obtained and agreed with early histology (E, adapted from Sachs, 1892, Georg Thieme Verlag, Leipzig) for (F) short fibres. (G) Segmentation of V1 and V2 was performed using 7T functional retinotopy (Serenou et al. 1995, Science, 268, 889–893) and (H) each area was further subdivided into three sub-areas as shown on the inflated brain surface. (I) The sub-divisions of V1 and V2 were transformed to the volumetric diffusion weighted image space and used to obtain connectivity between the different V1 and V2 sub-areas. In this context, retinotopic and non-retinotopic connectivity were defined as connections between corresponding V1 and V2 sub-areas (1-1, 2-2, etc.) and non-corresponding V1 and V2 sub-areas (1-2, 3-6, etc.), respectively. ANOVA: anterior, posterior, right, left, inferior, superior.
Measuring axon diameter, axon density, g-ratio, myelin thickness, and myelin density in human white matter tracts using light and electron microscopy

Morozova, M.1,2, Mordhorst, L.1, Rusch, H.1, Tabarin, T.3, Jäger, C.1, Anwander, A.1, Mohammadi, S.1,3, Morawski, M.1,2, & Geyer, S.1

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Recent advances in magnetic resonance imaging (MRI)-based biophysical models facilitate the estimation of different white matter (WM) properties in-vivo. The goal of the interdisciplinary DFG-funded SPP 2041 project is to develop a computational framework that uses this kind of microstructural information to resolve kissing and crossing fibres in diffusion MRI based tractography and minimises false positive connections. However, it is first necessary to validate the quantification of MRI-derived WM properties, such as axonal diameter and density, g-ratio (i.e. the ratio of the inner to outer fibre diameter) of individual axons, myelin thickness, and myelin density in human brain tissue. We use ultra-high resolution histology to characterise these microstructural properties in WM tracts in order to improve reference data for the interpretation of structural MRI findings. MRI-scanned post-mortem tissue samples from a variety of WM structures, such as the optic chiasm, the corticospinal tract, and the corpus callosum are processed to obtain semi- (500nm) and ultra-thin (50nm) sections. Light microscopy of semi-thin sections, and especially electron microscopy of ultra-thin sections are restricted by a very small field of view. To overcome this limitation, we optimised our pipeline for entire cross-sections of
human tissue samples in semi-thin sections and a large field of view in ultra-thin sections. For a comprehensive description of tract properties we use high-resolution light microscopy images (resolution: 250 nm) of cross-sections of entire tracts (~10 mm²; Figure 3.3.3.1). Parts of these light microscopy images (111x111 µm) were manually segmented by M.M. and T.T. into three structural compartments, i.e. axonal cytoplasm, myelin, and background to train a deep-learning algorithm (Figure 3.3.3.2). Axon density and diameter, g-ratio, myelin thickness, and myelin density can then be derived from these images. The trained deep-learning algorithm will be able to compute these microstructural parameters for the entire cross-sections of tracts. To evaluate the quality of automatic segmentation of light microscopic images we use adjacent ultra-thin sections processed for electron microscopy. Microscopical analysis and quantification of human brain WM properties within our project will improve the understanding of MRI contrasts. The combination of the acquired MRI data and histological measurements from the same samples will provide unique insight into the microstructural composition of human brain WM tracts and help to understand which are the most meaningful properties to disentangle complex fibre compositions.

Evolution of cortical myelination in hominoids

Lipp, I. 1, Kirilina, E. 1, 2, Jäger, C. 1, Morawski, M. 3, Jauch, A. 1, Pine, K. 1, Edwards, L. J. 1, Eichner, C. 1, Anwander, A. 1, Friederici, A. D. 1, Wittig, R. 4, Crockford, C. 4, & Weiskopf, N. 1, 5

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Comparing brain ontogeny across hominoid species provides important insights into the evolution of human cognition and behaviour. However, developmental studies on cortical brain maturation in great apes are rare and mostly rely on captive primates. The captive environment may not fully promote brain plasticity, and primates raised in captivity do not express their typical entire behavioural repertoire. In this unique collaborative project, we study cortical myelination in whole post-mortem brains of wild and captive chimpanzees and other great apes at different developmental stages, by combining ultra-high resolution quantitative magnetic resonance imaging with histology.
In the pilot phase of the project, we studied the brains of six chimpanzees that have died from natural causes (between 3 weeks and 32 years old). The tissue was collected and formalin-fixed within hours after death. The high tissue quality enabled myelin-sensitive MRI multi-parameter mapping at high field strength with 300 μm isotropic resolution. The combination of whole-brain coverage and ultra-high resolution allowed characterisation of myeloarchitecture across the entire brain. Whole-brain MRI measures were validated by various histological methods in selected brain regions (Figure 3.3.4.1).

We have established MRI-based mapping of myeloarchitecture in great apes at unprecedented resolution, providing a unique resource for comparative neuroscience research. Combined with white matter connectomics and behavioural characterisation of the same individuals (conducted by our collaborators at the Department of Neuropsychology and MPI EVA), these data will open new doors for a better understanding of the functional neuroanatomy underlying human-specific traits.

Figure 3.3.4.1 qMRI maps of two wild chimpanzees at different developmental stages. Various quantitative MR parameters (R1, R2*, PD and MT saturation) were acquired in a human 7 Tesla MRI scanner (Siemens Healthineers, Erlangen, Germany) with ultra-high 300μm isotropic resolution. Sagittal slices of the longitudinal relaxation rate (R1) are shown for two chimpanzees – a 3 week old and a 6 year old. Early myelination (EM) in white matter in the chimpanzee newborn is clearly visible in qMRI (R1) and the myelin histology stain (anti-myelin basic protein antibody). In the 6 year old chimpanzee, the myeloarchitectonically distinct primary and secondary visual areas (V1 and V2) are clearly visible in qMRI (R2*) and the myelin histology stain (anti-myelin basic protein antibody).
Appendix

Congresses, Workshops, and Symposia

2017

2018

2019

Degrees

PhD Theses
2018
- Streicher, M. Application of phase imaging at high filed MR thermometry at 7 Tesla. Leipzig University, Germany.

Appointments

2019
- Scherf, N. Group Leader, Institute for Medical Informatics and Biometry, Faculty of Medicine Carl Gustav Carus, Technical University of Dresden, Germany.
Awards

2018

- Brammerloch, M., International Society for Magnetic Resonance in Medicine Magna Cum Laude Merit Award. ISMRM, USA
- Brammerloch, M. International Society for Magnetic Resonance in Medicine Quantitative MR Study Group trainee research awards: Second Place. ISMRM, USA

2019

- Brammerloch, M. International Society for Magnetic Resonance in Medicine Summa Cum Laude Merit Award. ISMRM, USA

Publications

Books and Book Chapters


Journal Articles

- Kirilina, E. Sign Up! Careerbuilding. Max Planck Society and European Academy for Women in Politics and Economics Berlin, Munich/Berlin, Germany

Awards

2018

- Brammerloch, M., International Society for Magnetic Resonance in Medicine Magna Cum Laude Merit Award. ISMRM, USA
- Brammerloch, M. International Society for Magnetic Resonance in Medicine Quantitative MR Study Group trainee research awards: Second Place. ISMRM, USA

2019

- Brammerloch, M. International Society for Magnetic Resonance in Medicine Summa Cum Laude Merit Award. ISMRM, USA


Our overarching goal is to crack the cognitive code. The fundamental question in cognitive neuroscience—what are the key coding principles of the brain enabling human thinking—still remains largely unanswered. In our long-term aim to tackle this question, we use two model systems: human memory and the neural population code for space, representing the summed activity of neurons while processing an individual’s position in its environment.

The SatNav in the brain. One of the most fascinating discoveries in neuroscience was the Nobel Prize awarded identification of spatially responsive cells in the hippocampal formation (HF). Hippocampal place cells, and grid cells in nearby entorhinal cortex (EC), work in concert with other spatially tuned cell types to signal position, direction, distance and speed. Together, they provide a spatial map, the brain’s SatNav, the most intriguing coding scheme outside the sensory system (O’Keefe & Dostrovsky, 1971, Brain Res, 34(1), 171–5; Hafting, et al., 2005, Nature, 436(7052), 801–6). But what are the corresponding neural coding mechanisms in humans? We have made important steps towards answering this question.

Spatial maps in humans. We have been instrumental, along with others (see Epstein et al, 2017, Nat Neurosci, for a review), in translating neural coding mechanisms underlying wayfinding, from rodent electrophysiology to the systems level in humans. By combining fMRI with virtual-reality (VR), we have demonstrated that similar spatial maps exist in the human brain. Our discoveries include a continuous, grid-like code of space in the human network for episodic memory (Doeller, et al., 2010, Nature, 463, 657–61), the identification of the human homologue of medial EC (Navarro Schröder, et al., 2015, eLife, 4 10.7554), and the grid system breakdown in a human genetic model of Alzheimer’s disease (Kunz, et al., 2015, Science, 350, 430–33). Despite the wealth of studies on spatial coding in the HF, whether similar coding principles support cognitive operations beyond the spatial domain remains one of the most exciting questions in cognitive neuroscience (Tavares, et al., 2015, Neuron, 87, 231-43; Constantinescu, et al., 2016, Science, 352, 1464-8; Aronov, et al., 2017, Nature, 543, 719–22).
From spatial maps to cognitive maps. Is mnemonic information represented in a cognitive space? We have made crucial discoveries and unravelled the neural mechanisms of insight-triggered reconfiguration (Milivojevic, et al., 2015, Curr Biol, 25, 821–30), theta-driven integration (Backus, et al., 2016, Curr Biol, 26, 450-7), and mnemonic scaling of non-spatial mnemonic space (Collin, et al., 2015, Nat Neurosci, 18, 1562-4). We have identified a crucial learning rule of the hippocampus (Doeller, et al., 2008, PNAS, 105, 5909-14; Doeller, et al., 2018, PNAS 105, 5915-20) and provided evidence that memories are not stored in isolation but in hierarchical networks (Collin, et al., 2015, Nat Neurosci 18, 1562-4) and spatio-temporal event maps (Deuker, et al., 2016, eLife e16534). Finally, we have described attractor dynamics (Steemers, et al., 2016, Curr Biol 26, 1750-7) and mnemonic conversion (Backus, et al., 2016, Nat Comm 7:11991) as neural mechanisms for the access of stored information.

Our long-term framework is concerned with the key idea that this navigation system in the brain—potentially as a result of evolution—provides a fundamental neural metric for human cognition. Specifically, we propose that the brain represents our experiences in so-called ‘cognitive spaces’ (Bellmund, et al., 2018, Science, 362, 6415). For illustration, consider the simple example of describing cars, which you might do along two dimensions, their engine power and their weight. Depending on the two features, racing cars, for instance, would occupy a region characterised by high power and low weight, whereas campers comprise low power and high weight. We test the overarching hypothesis that—akin to representing places and paths in a spatial map—similar coding principles are involved in the formation of such cognitive spaces. Importantly, in our experimental framework, we investigate whether these domain-general principles support a broad range of our fundamental cognitive functions ranging from spatial navigation, memory formation, learning, imagination, and perception to time processing, decision making, and knowledge acquisition.

Recently, we have made initial discoveries supporting the concept of cognitive spaces, providing evidence for grid-like coding during mental simulation (Bellmund, et al., 2016, eLife, 5, e17089) and visual exploration (Nau, et al., 2018, Nat Neurosci, 21(2),188–190; see also Nau et al., 2018, Trends Cogn Sci, 22(9), 810–825). We have also found that such coding is reflected in related oscillatory dynamics (Staudigl, et al., 2018, Curr Biol, 28(20), 3325-3329.e1–e4), and the deformation of mnemonic responses in environments with concurrent deformations of the grid code (Bellmund, et al., 2019, Nat Hum Behav). Furthermore, in a series of experiments we have demonstrated spatial coding principles in the HF during the learning of abstract concepts (Theves, et al., 2019, Curr Biol, 29(7), 1226–1231.3) and mapping of temporal aspects of episodic memories in lateral EC (Bellmund, et al., 2019, eLife, e45333).

The tools. Discoveries are only made possible through innovative technologies. Our central research tools are functional magnetic resonance imaging (fMRI) as well as magnetoencephalography (MEG). We further combine neuroimaging with machine learning analysis techniques, informed by artificial intelligence tools, and a wide variety of cognitive tasks.

Neuroimaging. Space-resolved fMRI, as the central, high-throughput research tool, is complemented by time-resolved MEG to take advantage of the high temporal resolution and fine-grained information of multidimensional oscillatory data. High-field, layer-resolved fMRI at 7T is the central tool to understand—on a microarchitectural level—how the specific structure of the brain (e.g. laminar organisation) constrains its functional properties.

Virtual reality and cognitive tasks. To examine cognition in a realistic manner, we leverage virtual reality technology to simulate spatial navigation as well as life-like cognitive tasks. A wide array of cognitive tasks are used, ranging from psychophysics and eyetracking to realistic knowledge acquisition tasks.

Data analyses. Neural as well as behavioural data are analysed with machine learning tools. We use representation-al similarity analysis, a multivariate analysis approach, to quantify properties of representational networks in fMRI as well as multi-sensor time-frequency and source-reconstructed signals from MEG. A key aspect of our framework is the representational architecture of cognitive spaces. Pattern component modelling, multi-dimensional scaling, and graph analyses are used to reconstruct representational spaces. Finally, deep neural networks are applied as discovery tools to neural and behavioural data.

Build-up phase and organisational structure. The Department started its work in September 2018. During the first year, we have recruited the relevant personnel for our team, including a group leader, postdocs, PhD students, administrative and lab technicians, and research assistants. We also started hosting MSc students for their undergraduate projects as well as PhD students from the newly established Max Planck School for Cognition. We have built up the key research lines and setup relevant lab facilities, including behavioural labs, psychophysics labs, and virtual reality. Furthermore, the entire office and lab space on the 3rd floor of the Institute was refurbished and redesigned for our needs.

In addition to the main site of the lab at MPI CBS in Leipzig, we still have significant research activity at the Kavli Institute at NTNU, Trondheim, Norway. While our MPI and Kavli locations focus on distinct research areas (basic cognitive neuroscience at MPI CBS vs translational neuroscience at Kavli), they are complementary, with a multitude of interactions between sites. In the long-term, we plan on maintaining our strong links to translational neuroscience with the world-class Kavli Institute, in par-
ticular with the neurophysiology group of May-Britt and Edvard Moser as well as clinical partners in Norway. This will generate added value for our basic cognitive neuroscience research program at MPI CBS.

We have also integrated the lab well within our own institute. New endeavours have been initiated, such as the lecture series ‘Mind Meeting’, and cooperations started with other Departments and research groups. We now have contact and collaboration with Leipzig University via an Honorary Professorship of Christian Doeller and the teaching activities of Mona Garvert at the University’s Institute for Psychology. We are well integrated within the Max Planck Society, with Christian Doeller being a member of numerous recruitment committees (for new Directors and group leaders), steering committees (Perspective commission) and Graduate Schools. More specifically, Christian Doeller is a faculty member of the Max Planck School of Cognition; International Max Planck Research School on Neuroscience of Communication: Function, Structure and Plasticity; IMPRS NeuroCom; International Max Planck Research School on Computational Methods in Psychiatry and Ageing Research; IMPRS COMP2PSYCH. In addition, Mona Garvert is also Faculty at IMPRS NeuroCom and IMPRS COMP2PSYCH. She also serves as the Institute’s representative at the HSS Section of the Max Planck Society. Our team is highly visible internationally and regularly presents our work at major and specialised international conferences (e.g. twelve presentations at SfN 2019 in Chicago). We also frequently communicate science to the general public, including public lectures and a strong media presence.

In the following section—along the lines of show-case examples of ongoing or recently finished projects—we would like to give an overview of our key research areas including: (1) space, (2) time, (3) memory, (4) knowledge, (5) learning and decision making, and (6) vision. We also include some of our newly developed research methods including: (1) laminar fMRI, (2) MEG & OPM, (3) deep neural networks, and (4) development as a ‘tool’ to examine neural coding.
## Group Leaders

Dr Mona M. Garvert

## Senior Researchers and Postdocs

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## PhD Students

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(89) ZonMw (The Netherlands Organisation for Health Research and Development)  
(90) Samarbeidsorganet Helse Midt-Norge, Stjørdal, Norway  
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As a backbone of the Department’s research activities, we run fundamental studies on spatial navigation and neural coding in the HF. These studies concern, e.g., the following questions: How does spatial coding enable wayfinding? How do spatial representations remap between contexts? How does remapping drive behaviour? Here, we also examine how population activity (e.g. via orientation clustering) is likely to be translated into the hexadirectional, grid-like fMRI signals, distributed within (layers and possibly modules) and across (lateral and medial parts of) EC, and modulated by spatial context.
Remapping and realignment in the human hippocampal formation predicts context-dependent behaviour

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To guide spatial behaviour, the brain must retrieve memories that are appropriately associated with different navigational contexts. Contextual memory may be mediated by cell ensembles in the hippocampal formation that alter their responses to changes in context, processes known as remapping and realignment in the hippocampus and entorhinal cortex, respectively. However, whether remapping and realignment guide context-dependent spatial behaviour is unclear. To address this issue, human participants learned object-location associations within two distinct virtual-reality environments and subsequently had their memory tested during fMRI scanning. Entorhinal grid-cell-like representations showed realignment between the two contexts, and coincident changes in fMRI activity patterns consistent with remapping were observed in the hippocampus. Critically, in a third ambiguous context, trial-by-trial remapping and realignment in the hippocampal-entorhinal network predicted context-dependent behaviour. These results reveal the hippocampal-entorhinal mechanisms mediating human memory-guided behaviour and suggest that the hippocampal formation plays a key role in spatial decision-making under uncertainty.

Figure 4.1.1 Hippocampal and entorhinal context-signals predict behaviour in ambiguous situations. (A) Using a standard virtual-reality object-location memory task, participants learned four object locations in two separate arenas (“Square”, “Circle”). Aerial view schematics of the two arenas are shown. Following training, object location memory was tested in these two arenas while participants (n=24) underwent fMRI scanning. (B) Memory for object locations was also tested in a third, half-square half-circular arena (“Squircle”). The ambiguous Squircle provides a means of assessing the relationship between hippocampal-entorhinal contextual representations and memory-guided spatial behaviour. In particular, for each target object, there were two possible “correct” locations in the Squircle, one more consistent with the location in the Circle, and one more consistent with the location in the Square. Thus, to recall object locations in the Squircle, on each Squircle trial, participants needed to retrieve either Square- or Circle-consistent contextual memories. (C) Across-scan-run similarity of hippocampal activity patterns over time, separately for Sq (red) and Ci (blue) testing trials. Values greater than 0 indicate that an activation pattern is similar to that elicited in the Square across scan runs, whereas values less than 0 indicate that an activation pattern is similar to that elicited in the Circle across scan runs. Hippocampal activity patterns were more similar to those elicited in the same context across scan runs than the opposite context. This is consistent with the existence of reliable remapping of hippocampal contextual representations, complementing previous findings of place cell remapping in rodents. (D) Across-scan-run similarity of hippocampal activity patterns over time, separately for Sq-consistent (red) and Ci-consistent (blue) Squircle trials. Hippocampal activity patterns were more similar to those elicited in the context consistent with spatial memory retrieval than with the inconsistent context. This suggests that trial-by-trial hippocampal remapping supports context-dependent spatial behaviour. (E) We found reliable entorhinal grid-cell-like modulation in the Square and Circle, due to grid-cell-like signals in both the Square and Circle aligned to their respective grid orientations. Yet, grid-cell-like modulation was not observed in either the Square or Circle aligned to the grid orientation from the opposite context. This provides evidence of entorhinal grid-cell-like realignment across the Square and Circle, complementing previous findings of grid-cell realignment in rodents. (F) To test the relationship between grid-cell-like realignment and memory-guided behaviour, two grid-cell-like models were fit to the entorhinal cortex (EC) fMRI signal during Squircle trials. One model assumed the grid orientation (φ) changed on a trial-by-trial basis, consistent with contextual memory (either Square or Circle φ, consistent with (B) i.e. behaviour). The other model assumed φ changed on a trial-by-trial basis but inconsistently with contextual memory. We observed grid-cell-like modulation when the grid orientation switched on a trial-by-trial basis, consistent with spatial behaviour, but not inconsistent with behaviour.
Distorting the coordinate system of cognitive maps

Bellmund, J. L. S. 1, 2, 3, de Cothi, W. 4, Ruiter, T. A. 3, 5, Nau, M. 3, Barry, C. 6, & Doeller, C. F. 1, 3

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Our brain forms cognitive maps of our environment for spatial navigation. Recent advances suggest a central role of the brain’s spatial mapping system for cognitive functions beyond navigation. The regular firing patterns of grid cells in the entorhinal cortex are thought to provide a coordinate system for cognitive maps to encode positions and to compute distances and directions between them. However, studies have demonstrated that grid patterns can be distorted, for example through the geometry of the boundaries forming the environment that the animal navigates. Here, we tested whether spatial memories are systematically distorted when formed in an environment known to deform grid patterns in rodents. In a behavioural experiment, participants navigated a square and a trapezoidal environment using a highly immersive virtual reality system consisting of a head mounted display and a motion platform that translated their physical steps and rotations into virtual movement. In each environment, participants learned the positions of several objects. Participants’ memory for positions in the trapezoid was less precise than in the square. Within the trapezoid, memory was particularly degraded in the narrow end. This memory profile mirrors the severity of grid pattern distortions observed in rodents navigating a trapezoid and was captured by a model grid system based on the successor representation. Further, outside of the virtual trapezoid, we asked participants to estimate the distances between learned positions to test for persistent mnemonic distortions. If positions are encoded using a compressed or stretched grid pattern, then grid patterns change more or less as a function of the distance between two positions. Estimates of the distances between positions, that were encoded using deformed grid patterns, should therefore be distorted outside of the trapezoid environment. Consistent with the predictions of our model grid system, participants estimated identical distances to be longer in the narrow than in the broad part of the trapezoid. We reconstructed the individual positions the participants remembered, from their pairwise distance estimates, to show that these reconstructed mnemonic maps explained object position memory in the trapezoid better than the true object positions. Collectively, the findings from this behavioural experiment suggest that human positional memory is subject to distortions through environmental geometry that can be predicted from a model grid system based on the successor representation. Our findings are in line with the notion that the entorhinal grid system provides a metric for cognitive maps supporting spatial memory and other cognitive functions (Bellmund, et al., 2019, Nat Hum Behav).

Figure 4.1.2. Deforming the metric of cognitive maps distorts memory. The regularity of grid-cell firing patterns is distorted in a trapezoid compared to a square. We model this distortion using the eigenvector grid patterns of the successor representation. In our highly immersive virtual reality setup, participants learned object positions in a square and a trapezoidal environment. Participants made larger errors for objects in the trapezoid compared to the square. Paralleling the distortions of grid patterns, the accuracy of participants’ spatial memory was particularly low in the narrow end of the trapezoid.
Environmental anchoring of grid-like representations minimises spatial uncertainty during navigation behaviour

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Minimising spatial uncertainty is essential for navigation, but the neural mechanisms remain elusive. Here we combine predictions of a simulated grid-cell system with behavioural and fMRI measures in humans during virtual navigation. First, we have shown that polarising cues produce anisotropy in motion parallax. Secondly, we simulated entorhinal grid cells in an environment with anisotropic information and found that self-location was decoded best when grid patterns were aligned with the axis of greatest information. Thirdly, when exposing human participants to polarised virtual reality environments, we found that navigation performance was anisotropic, in line with the use of parallax. Eye movements showed that participants preferentially viewed polarising cues, which correlated with navigation performance. Finally, using fMRI we found that the orientation of grid-cell-like representations in entorhinal cortex were anchored to the environmental axis of greatest parallax information, orthogonal to the polarisation axis. In sum, we demonstrate a crucial role of the entorhinal grid system in reducing uncertainty in representations of self-location and find evidence for adaptive spatial computations underlying entorhinal representations in the service of optimal navigation.

Figure 4.1.3 The grid system minimises spatial uncertainty and optimises behaviour. We found that environmental geometry affects the orientation of grid-like fMRI signals. (A) First-person view of the sparse environment. (B) Red line indicates the polarisation axis of the environment, the blue line the orthogonal directions. (C) Spatial memory performance is anisotropic—larger along the polarisation axis. (D) Grid-like fMRI analysis logic. (E) Grid-like signals were clustered at angles orthogonal to the environmental polarisation axis.
In this research area, we aim to identify how the EC grid code and the HF encode temporal information. We also test whether the processing of space and time converge on the same neural mechanisms.
When did that happen? Mapping the temporal relationships of memories

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Episodic memories are vivid recollections of events that took place at specific moments in time. Typically, we easily remember the chronology of important events. In this experiment, we investigated the question of how the human entorhinal cortex supports our memory of the sequence in which events unfold over time. Participants learned to navigate along a fixed route through a virtual city. Their task was to learn where and when, during the traversal of the route, specific events occurred. Events were defined by the objects encountered along the path. Participants underwent fMRI before and after learning. During these scanning sessions, participants saw the same objects

Figure 4.2.1 Lateral entorhinal cortex maps the temporal structure of events. Participants learned a sequence of events by navigating along a route through a virtual city. Events encountered closely together in time became relatively more similar compared to events far apart in time. This resulted in a negative correlation of representational similarity and temporal distances.
they encountered along the route, but in random order. This enabled us to quantify similarity changes of object representations from before to after learning. Object representations in the entorhinal cortex changed in a way that resembled the sequence in which they were observed in the virtual world. Objects that were encountered in temporal proximity to one another became relatively more similar compared to objects far apart in time. This resulted in a negative correlation between representational change and the temporal distance between the objects in the virtual world. Importantly, this effect was specific to the anterior-lateral entorhinal subregion and to the temporal rather than spatial structure of the event sequence.

Furthermore, we were able to reconstruct the timeline of events from the calculated representational change in MRI activity. Additionally, participants in whom the temporal distance between objects correlated more strongly with representational change tended to successively reproduce objects learned to be nearby in time when trying to recall all objects in a post-scan memory test. Our findings demonstrate that the entorhinal cortex forms a map-like representation of the temporal relationships of events and that the distinctiveness of this representation relates to how we retrieve events from memory (Bellmund, et al., 2019, eLife, 8, e45333).
In the memory domain, research topics include the understanding of how multiple events are integrated into hierarchical, dynamic, mnemonic networks, how episodic information is represented in cognitive spaces, how mnemonic networks are dynamically updated and how novel information is assimilated.
Episodic and spatial memory are two major forms of memory. Episodic memory allows the remembering of events from the past, whereas spatial memory allows the formation of a map-like representation of the environment. Interestingly, these two memory forms are supported by the same brain structure: the hippocampus. However, the exact relationship between episodic and spatial memory processes in the hippocampus remains unclear. In this study we tested two different models, assuming that the hippocampus supports both memory forms either via a parallel processing mechanism or a common coding mechanism, respectively. For this purpose, we conducted an fMRI experiment with a life-simulation task and a virtual reality game to manipulate episodic and spatial relations between objects. In the life-simulation task, subjects watched two different stories whereby regular objects were associated with one or the other (episodic contexts). In the virtual reality game, subjects delivered objects to shops in two different neighbourhoods of a virtual city. Here, regular objects were associated with one of the two neighbourhoods (spatial contexts). Ultimately, this resulted in a 2 × 2 design with pairs of objects sharing both an episodic and a spatial context, pairs of objects sharing only one context (either episodic or spatial) and pairs of objects sharing no context. Subsequently, we presented all objects in picture viewing tasks to assess overlapping neural representations of objects, caused by shared episodic and/or spatial contexts, in cross-stimulus adaptation analyses. Preliminary results show differences between adaptation effects for pairs of objects sharing only an episodic or a spatial context, as well as a trend for an interaction between episodic and spatial context processing in the hippocampus. The interaction was characterised by a stronger adaptation effect for pairs of objects sharing both contexts. This indicates that our experimental approach is powerful enough to induce neural similarity between objects sharing episodic and/or spatial contexts in the hippocampus. Furthermore, our results provide evidence for both, models of parallel processing and a common coding mechanism for episodic and spatial memory in the hippocampus.

Figure 4.3.1 Integrating episodic and spatial context signals in the hippocampus. (A) Experimental timeline. Participants first completed one of two object association tasks in a behavioural session (the spatial task is pictured). Order was counterbalanced across participants. In the scanner, participants completed three tasks: the first picture viewing task (PVT1), the second object association task (here the episodic task...
is pictured), and the second picture viewing task (PVT2). (B) Task design. Both the spatial and episodic tasks were divided into two contexts. Each regular object appeared in both tasks, but only in one episodic and one spatial context (see object A as an example). Each control object appeared only in one task but in both contexts of the given task (see object I as an example). (C) Analysis logic. The distribution of objects over the task contexts resulted in a 2x2 design of object pairs. This design included pairs of objects sharing both an episodic and a spatial context, pairs of objects sharing only one context (either episodic or spatial), and pairs of objects sharing no context. We analysed adaptation effects of these object pairs in the independent PVTs to test hypotheses of two different models of hippocampal involvement in episodic and spatial memory. In brief, the parallel processing model assumes that episodic memory is supported by the anterior and/or left hippocampus whereas spatial memory is supported by the posterior and/or right hippocampus. Therefore, this model predicts a higher adaptation effect in the anterior and/or left hippocampus for pairs of objects sharing an episodic context (in the example in panel C, B-A and C-A) compared to pairs of objects sharing no episodic context (G-A and E-A in panel C). Furthermore, it predicts a higher adaptation effect in the posterior and/or right hippocampus for pairs of objects sharing a spatial context (here in the example, B-A and G-A) compared to pairs of objects sharing no spatial context (C-A and E-A in the example). The common coding model assumes that episodic and spatial memory are processed in the same way in the whole hippocampus (without any subfield differences). Therefore, this model predicts the highest adaptation effect in the hippocampus for pairs of objects sharing both an episodic and a spatial context (in the example B-A). Furthermore, it predicts the second highest adaptation effect for pairs of objects sharing only one (either a spatial context (G-A in the example) or an episodic context (C-A in the example)) and the lowest adaptation effect for pairs of objects sharing no context (E-A in the example). (D) Common coding during PVT2 in the hippocampus ROI. The left bar depicts the contrast estimate of the common coding effect in the hippocampus during PVT2 (T(29) = -2.8820, p = 0.0037). The contrast is based on the common coding model, which predicts an adaptation effect that scales with the context associations between object pairs (no context shared, one (episodic or spatial) context shared, both episodic and spatial context shared). Additionally, the effect is visualised by mean estimates of the different object pair regressors. The adaptation effect for control objects was not significant (T(29) = -0.8025, p = 0.2144). Dots represent single participant values. Error bars are the standard error of the mean. (E) Parallel processing during PVT1 in hippocampal subfields. Depicted are the mean contrast estimates of the shared context vs non-shared context contrast, divided by group (episodic vs. spatial group) and hippocampal subfields. There was no significant interaction between group and either hemisphere and/or axis. Dots represent single participant values. Error bars are the standard error of the mean.
Over the last decades, converging evidence from animal electrophysiology and human neuroimaging studies led to the notion that the hippocampal formation encodes a mental map of the spatial environment (O'Keefe, & Nadel, 1978, Clarendon Press). Recent evidence suggests that the same hippocampal coding principles are also involved in cognitive domains beyond spatial navigation (Nau, et al., 2018, Nat Neurosci, 21(2):188-190; Aronov, Nevers, & Tank, 2017, Nature, 543(7647), 719-722; Constantinescu, O'Reilly, & Behrens, 2016, Science, 352(6292), 1464-1468; Tavares, & et., 2015, Neuron, 87(1), 231-43). Specifically, they might provide a suitable format for neural concept representations, as a map-like organisation of knowledge would allow inference of relations that were not directly experienced and transfer of meaning to novel input. These two processes are critical for the flexible use of knowledge.

We provided first evidence for such a map-like code for concepts, by demonstrating that the hippocampus encodes distances in a multidimensional space spanning continuous feature dimensions that were critical to the acquisition of a novel concept (Theves, Fernandez, & Doeller, 2019, Curr Biol, 29(7), 1226-1231). In a follow-up study, we determined whether the hippocampus maps new information according to all feature dimensions (feature space) or specifically according to conceptually-relevant dimensions (concept space). The critical aspect of a concept space, as opposed to a feature space, is that its structure can be used to transfer meaning to novel information based on generalizable rules. We implemented this via a categorisation task. Specifically, a stimulus was assigned to one of two categories, according to the ratio of values on two of its three feature dimensions. These then defined the axes of the two-dimensional concept space, with the diagonal serving as the category boundary. We found that the hippocampus encodes distances in a space along the two conceptually relevant dimensions, as opposed to distances in the surrounding higher-dimensional feature space defined along all feature dimensions. We ruled out that this result is explained by a difference in complexity between mapping two- versus three-dimensional information.

Together our results provide critical evidence for the view that knowledge is encoded in a map-like format and furthermore propose a domain-general role of the hippocampus in coding information along continuous dimensions, contributing to a general code for cognition.
The hippocampus encodes distances in multidimensional feature space

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The hippocampal formation encodes maps of the physical environment (O’Keefe, & Nadel, 1978, Clarendon Press). A key question in neuroscience is whether spatial coding principles also provide a universal metric for the organisation of non-spatial information. Initial evidence for this comes from studies revealing directional modulation of fMRI responses in humans (Constantinescu, et al., 2016, Science, 352, 1464–1468; Tavares, et al., 2015, Neuron, 87, 231–243) during navigation through abstract spaces and the involvement of place and grid cells in encoding of non-spatial feature dimensions (Aronov, et al., 2017, Nature, 543, 719–722). However, a critical feature of a map-like representation is information about distances between locations, which has yet only been demonstrated for physical space (Morgan, et al., 2011, J Neurosci, 31, 1238–1245; Deuker, et al., 2016, eLife, 5, 5). Here, we probed whether the hippocampus similarly encodes distances between points in an abstract space, spanned by continuous stimulus-feature dimensions that were relevant to the acquisition of a novel concept. We found that, after learning, two-dimensional distances between individual positions in the abstract space were represented in the hippocampal multi-voxel pattern, as well as in the univariate hippocampal signal as indexed by fMRI adaptation. These results support the notion that the hippocampus computes domain-general, multidimensional cognitive maps along continuous dimensions (Theves, et al., 2019, Curr Biol. 29(7), 1226-1231).

Figure 4.4.1 The hippocampus maps distances in multidimensional feature space as a function of concept learning. (A) Design: Via a categorisation task (right), participants acquire a novel concept of two symbol categories (A and B symbols), defined along two continuous stimulus feature dimensions (opacity and size) and further learned to associate objects with specific symbols (left). (B) During object-viewing blocks, subsequent to concept learning in (A), adaptation of the hippocampal BOLD signal scaled with the two-dimensional distance between successively presented objects in concept space.

The hippocampus maps 2D concepts in 3D feature space

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The hippocampal formation encodes maps of space and a key question in neuroscience is whether its spatial coding principles also provide a universal metric for the organisation of non-spatial, conceptual information. Previous work has demonstrated directional coding during navigation through a continuous stimulus-feature space, as well as mapping of distances in a feature space that was relevant for concept learning. Here we provide the first unambiguous evidence for a hippocampal representation of the actual concept space. We show that the hippocampal distance signal selectively reflects the mapping of conceptually-relevant rather than of all feature...
dimensions in feature space. During fMRI scanning, we presented every-day objects, which had beforehand been associated with specific values on three continuous feature dimensions. Crucially, only two dimensions were relevant to concept learning. We found that hippocampal responses to the objects reflected their relative distances in a space defined along conceptually-relevant dimensions as opposed to all task-relevant dimensions. We ruled out that this result could be explained by a difference in complexity between mapping two- versus three-dimensional information. Together, these findings suggest that the hippocampus supports knowledge acquisition by dynamically encoding information in a space spanning the dimensions that define concepts.

Figure 4.4.2  The hippocampus maps 2D concepts in 3D feature space. (A) Design: Participants learn a novel concept of two symbol categories (symbols A and B) via a categorisation task. Only the relation of two of the symbols’ three feature dimensions is relevant for categorisation (opacity and dot frequency, but not stripe frequency). This results in a 2D-concept but 3D-feature space according to which objects could be organised. (B) After learning, the hippocampus represented the 2D conceptual distances between objects but not their 3D feature-based distances. (C) This effect is not driven by differences in dimensionality, as 2D-distance predictions derived from a combination with the conceptually-irrelevant dimension do not reproduce the effect.

4.4.3 Integrating knowledge from physical and abstract spaces

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How do we represent knowledge? One intriguing idea is that our knowledge is stored using a spatial representational format: a cognitive map. Studying spatial navigation has shed light on the underlying neural mechanisms, with recent work suggesting that cognitive map-like coding of physical space might also underlie conceptual knowledge. Examining how spatial and conceptual information is integrated, we created a two-dimensional conceptual space and a corresponding virtual model of a physical space. Space-defining features, such as dimensionality, size, shape and informational content, were carefully matched. Testing object-location memory, participants learned to navigate both spaces using identical egocentric controls and successfully created object-location associations. Further, participants were able to transfer knowledge about object positions from one space to the other. We probed object representations in a passive-viewing fMRI task both before and after learning, allowing us to assess the change in representation. We used multivariate pattern analysis to test if neural similarity, after training, scales with distances between objects and whether this scaling holds for the integrated map of both spaces. Preliminary fMRI analyses have uncovered pattern similarity changes in the hippocampal formation and prefrontal regions following knowledge acquisition in both spaces. Our findings demonstrate a transfer of knowledge between cognitive maps that differ in content, as well as domain. Taken together with findings from a parallel behavioural study using immersive virtual reality, our data highlight potential domain-invariant navigational codes that transcend physical space and help us navigate our knowledge.
Figure 4.4.3 Integrating cognitive spaces. (A-D) experimental design of the behavioural part of the experiment. Participants learned to navigate in a physical space (PS) and a conceptual space (CS). PS was defined by the x- and y-coordinate in a square virtual environment. CS was defined by the number of circles and rectangles shown on the screen. (A) examples of participant’s viewpoints. Left: PS, right: down sampled CS. The triangles in the CS were added as placeholders, so that each position had the same visual complexity. (B) controls the participants used for egocentric navigation through the spaces. The sliders were used to determine the angle. Slider 1 encoded this by choosing the sine of the view-direction (α), while slider 2 used the cosine of α. Sine and cosine of α are directly linked to the rate-of-change of dimensions x and y. ‘Execute’ was used to elicit forward movement in the direction of α. C. link between colour and α. To encode the first-person view in the CS a colour code that mimicked the wall-colours in the PS was adapted. Shapes mapped on the cosine dimension (circles) would receive the corresponding colour shown in (C). Shapes in the sine dimension (rectangles) were treated equally. (D) the integrated map of both spaces. CS and PS were matched in size, complexity and informational content so that the spaces could be integrated. Participants learned to associate objects with the shown positions either in the CS (C numbers) or the PS (P numbers). Object A was present in both spaces at the same position and could be used as an anchor for the integration. (E) behavioural results group level. Black line shows chance level. m-CS/m-PS: mean memory scores for CS or PS objects per participant, t-CS/t-PS: mean transfer score for objects learned in either PS or CS and then tested in the other space. This transfer task was the last experimental task. Participants were generally unaware of the spatial nature of the CS. (F) fMRI paradigm. Participants performed this passive viewing task of the objects associated with the locations before and after memory training. (G) Feature selection was done by training a linear SVM on the trial-wise t-maps for object identity decoding. The top 30% of voxels from each ROI for decoding were chosen to be included in the following representational similarity analysis (RSA). Shown here are hippocampus (HP) and entorhinal cortex (EC) ROIs containing the voxels selected in the analysis. Bright yellow means a voxel was selected in most subjects, darker colours mean a voxel was selected in few participants. (H) representational similarity matrix (RSM) for all objects sorted according to position. The RSM was used to compare to the model RSMs in J and I. (J) context model, testing the idea that objects learned in the same space are more similar than objects learned in different spaces. (I) integrated distance model, testing the idea that objects located close in space are more similar than objects far apart.
Spatial coding in the hippocampal formation has traditionally been studied in the context of navigation. However, recent studies suggest that the hippocampal formation may mediate a diverse range of cognitive functions beyond navigation, including conceptual learning. The hippocampal formation may be involved in concept learning since concepts often are defined based on a set of continuous feature dimensions, akin to the latitude and longitude of navigational space. Importantly, most real-world concepts are defined based on multimodal features. For example, different citrus fruits can be defined by their colour and amount of sweetness, which are derived from visual and gustatory sensory modalities, respectively. Yet, whether the hippocampal formation is involved in learning multimodal concepts is unknown. Our main objective was to develop a multimodal conceptual learning task to investigate hippocampal representations of non-navigational domains. More specifically, are multimodal conceptual spaces represented similarly as navigational cognitive maps? To address this question, we developed a computer-based, multimodal, concept learning task using pitch and colour to create a two-dimensional continuous concept space. In this task, participants were trained to associate specific pitch/colour combinations with distinct symbols. Participants then performed memory tests for these stimulus-symbol associations using a behavioural task, modelled after standard assays of spatial memory during navigation. Preliminary results show that participants were able to successfully manoeuvre around in this multimodal concept space. The results indicate that participants formed an integrated representation of the multimodal space, beyond simply learning the correct stimulus-symbol associations. Follow-up studies are currently exploring whether representations of multimodal space obey the same principles as map-like representations of navigational space. We are also using fMRI to interrogate the role of the hippocampal formation in supporting such representations. Together, this research will reveal how new concepts are learned, and whether similar processes guide conceptual learning and spatial navigation.

Figure 4.4.4 Spatial learning of non-spatial multimodal features. (A) The multimodal space. Desktop-based “navigation” in 2D multimodal space with colour (vision) and pitch (audition) as feature dimensions. Participants learned to associate four unique stimulus combinations (black spots) with Greek symbols. (B) In the target estimation phase (upper figure), the participant pressed a key to create the target combination associated with the Greek symbol. In the target imagination phase (lower figure), the participant was presented with an automatic change in stimulus and had to imagine the continued trajectory before deciding which symbol the final imagined combination would match. (C) Results for the target estimation phase showed a circular response distribution based on participants’ trajectories to the target combinations. This indicates that they used both dimensions in that phase. The star represents all target combinations. (D) Results for the target imagination phase show that participants, throughout the trials, were able to choose the correct symbols, based on their imagined continued trajectories. Their performance was significantly above chance (red line). Together, our results indicate that multimodal, abstract, feature spaces are represented in a manner similar to navigational cognitive maps.
Research Area
LEARNING & DECISION MAKING

Research in this area is expressed along the following lines: How does decision-making organise experiences, according to an internal map-like model of the current task, and thereby structure memory? How does the structure of mental maps contribute to decision-making?
It has been suggested that the brain organises knowledge about the relationships between positions in space and non-spatial regularities in a cognitive map. Such a representation of events and knowledge may facilitate goal-directed behaviour by enabling the generalisation of value or other information across related states. Here, we combined a virtual reality task with computational modelling and functional magnetic resonance imaging (fMRI) to investigate whether humans generalise across related states to infer reward values that were never directly experienced. In this task, spatial relationships between stimuli learned on day 1 predict reward relationships in a choice task on day 2. We found that participants not only update the stimulus-reward associations they experience directly, but they also use their knowledge about the relationships between stimuli to predict values of stimuli that were not directly sampled. This behaviour can be captured by a normative Bayesian model of the believed value distribution, which is updated in accordance with participants’ choices. Relational knowledge organised in cognitive maps can thus be used to extrapolate across related states and thereby facilitate novel inference. Using fMRI, we investigated the neural dynamics underlying the spread of values across cognitive maps in hippocampal-medial prefrontal networks. We found that a hippocampal cognitive map, combined with a prefrontal/striatal value representation, enabled value inference. Together, our approach opens up the possibility to connect seemingly disparate fields of spatial coding, learning, and decision behaviour.

Our experiences are highly complex and unlikely to recur in the same form and context. Nevertheless, we accumulate behavioural repertoires that help us maximise rewards across a wide range of situations. This is possible because our environment is replete with statistical regularities and similar cause-effect relations hold across related experiences. By extracting statistical structure and recombining it in novel ways, the brain can predict states

**Figure 4.5.1** Value generalisation in space. (A) Stimulus arrangement in the arena. (B) Values associated with each stimulus in the two contexts. Two inference objects per context can never be selected in the choice task. (C) True value (left) and inferred value (right) of the inference objects. (D) Final believed peak location in a Bayesian model estimating the value peak. (E) Correlation between distance to real peak and value inference. (F) Representational similarity analysis reveals spatial map in hippocampus and value map in medial prefrontal cortex.
and reinforcements that were never directly experienced. This type of inference requires an organisation of knowledge that enables rapid computations of relationships. In space, this is achieved by representing landmarks in a hippocampal cognitive map. This map provides a coordinate system that can be used to compute distances between landmarks, even if they have never been experienced together. However, despite substantial progress in understanding how the brain stores relational knowledge in cognitive maps, it remains unclear how maps are used for novel inference. Here, we combined a novel virtual reality task with computational modelling to investigate whether humans, using learned knowledge about the relationships between stimuli, infer stimulus-reward associations that were never directly experienced. In this task, the spatial position of stimuli learned by navigating in a virtual arena on day 1 (Fig. 4.5.1A) predicted stimulus values on day 2 (Fig. 4.5.1B). Participants learned two Gaussian distributions of value, centred on a particular peak location in the arena, by repeatedly choosing between pairs of stimuli. We found that updates of stimulus-reward associations in the choice task went beyond directly experienced associations. Rather, they spread across stimuli located nearby in the cognitive map, enabling correct decisions even between stimuli whose values had never been directly experienced. This became particularly evident for two inference objects, which could never be selected during the choice task. Despite the absence of direct experience, participants inferred the corresponding values based on the distance, in space, to other stimuli whose values were known (Fig. 4.5.1C). In most subjects, map-based inference in the choice task was captured well by a Bayesian model, where beliefs about the centre of the value distribution were updated on a trial-by-trial basis, based on the likelihood of observing a choice, given the believed peak location and standard deviation of the distribution (Fig. 4.5.1D, E). Participants whose choice behaviour was well captured by the model were also better at inferring values of the inference objects (Fig. 4.5.1F, G). Relational knowledge organised in cognitive maps can thus be used to extrapolate across related states and facilitate novel inference. Using representational similarity analysis, we found that, in the hippocampus, dissimilarity between stimulus representations scaled with spatial distance in the arena (Fig. 4.5.1F), suggesting that the hippocampus forms a cognitive map of the relationships between stimuli. Pattern similarity in the ventromedial prefrontal cortex and striatum, on the other hand, reflected differences in value between stimuli (Fig. 4.5.1H). Preliminary fMRI results suggest that the hippocampal spatial and prefrontal value information are combined to infer the values of inference objects. Together, we demonstrate that humans combine memory of experienced rewards, with knowledge of relationships between stimuli in space, to infer the value of objects whose values they have never directly experienced. This ability may underlie the remarkable human ability to infer information based on very little data.
How does the brain’s navigation system shape our visual experience? The brain uses sensory information to construct a stable mental model of the environment that guides memory formation and behaviour. This process is called ‘cognitive mapping’ and it engages a large brain network spanning from low-level sensory to high-level memory regions in the medial temporal lobe (Nau, et al., 2018, Trends Cogn Sci, 22, 810–825). In humans, we still know little about cognitive mapping, especially in the light of the behaviour it is thought to support. While traditionally studied in the context of navigation, we recently proposed that encoding in the medial temporal lobe may comprise a more general organisational principle for information in the brain (Bellmund, et al., 2018, Science, 362, eaat6766). To investigate this, we believe that vision and viewing are optimal domains, because they constitute our most prominent means to explore the environment and have a strong and quantifiable impact on our memories. To study the interactions between perception, memory, behaviour, and cognitive mapping, we use a large spectrum of methods that enable a multifaceted and network-level perspective on cognition. These range from computational modelling and machine learning to tightly controlled viewing tasks and naturalistic virtual reality. Our recent work suggests that our brain’s spatial mapping system has adapted to our strong, visually-guided experience and behaviour (Nau, et al., 2018, Nat Neurosci, 21, 188–190) and that our visual and memory networks are indeed strongly intertwined (Bosch, et al., 2014, J Neurosci, 34, 7493–7500). Our work demonstrates that cognitive mapping shapes perceptual processing and behaviour on a large scale (Nau, et al., 2019, bioRxiv, DOI: 10.1101/765800) and suggests that navigation and viewing are guided by a common neural mechanism in the medial temporal lobe (Nau, et al., 2018, Trends Cogn Sci, 22, 810–825). Together, this work aims to answer fundamental questions about human cognition by illuminating how we map our environment using vision, how we plan our behaviour in space, and how this in turn shapes (and is shaped by) our memories.
Hexadirectional coding of visual space in human entorhinal cortex

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Entorhinal grid cells map the local environment, but their involvement beyond spatial navigation remains elusive. We examined human functional MRI responses during a highly controlled visual tracking task and show that entorhinal cortex exhibited a sixfold, rotationally symmetric, signal encoding gaze direction. Our results provide evidence for a grid-like entorhinal code for visual space and suggest a more general role of the entorhinal grid system in coding information along continuous dimensions (Nau, et al., 2018, Nat Neurosci, 21(2),188-190).

A Grid-cell model predicts hexadirectional signal

B Visual tracking & object location memory task

C Human fMRI and eye tracking

Figure 4.6.1 Hexadirectional coding of visual space in human entorhinal cortex (A) Visual grid-cell model: The number of firing fields crossed depends on eye movement direction. More fields are crossed for directions aligned to grid axes (white lines) compared to directions misaligned to it. This relationship translates to hexadirectional biases of putative grid-cell population activity, in turn predicting a stronger fMRI signal for aligned versus misaligned directions. (B) Task: Participants performed a visual tracking and object location memory task while fMRI and eye tracking data were acquired. Participants fixated a moving dot while memorising object locations on the screen. This task tightly controlled the participants’ viewing behaviour and balanced attention and directional sampling. (C) Results: Human entorhinal cortex showed the predicted hexadirectional fMRI-signal. Neither control symmetries, nor other regions of interest showed this effect. These results provide evidence for a grid-like code for visual space and suggest a more general role of the human entorhinal grid system in coding information along continuous dimensions.

Behaviour-dependent directional tuning in the human visual-navigation network

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The brain derives cognitive maps from sensory experience to guide memory formation and behaviour. Despite extensive efforts, it still remains unclear how the underlying neuronal population activity relates to active behaviour and memory performance. Here, we combined 7T-fMRI with a kernel-based encoding model of virtual navigation to map world-centred directional tuning across the human cortex. First, we present an in-depth analysis of directional tuning in visual, retrosplenial, and parahippocampal cortices as well as the hippocampus. Second, we show that the tuning strength, width, and topology of the directional code during memory-guided navigation de-
pends on successful encoding of the environment. Finally, we show that participants’ locomotory state differentially influences directional tuning in sensory and mnemonic regions such as the hippocampus. We demonstrate that locomotion and memory modulate directional tuning in the human brain and that high-level cognitive processes shape environmental coding in the service of behaviour.

Figure 4.6.2 Behaviour-dependent directional tuning in the human visual-navigation network (A) Task: Participants performed a spatial navigation and object location memory task in virtual reality. They memorised and reported the location of objects in the virtual arena by navigating to them. By measuring the Euclidean distance between remembered and true object location, we assessed our participants’ spatial memory performance during this task. (B) Encoding model: We modelled head direction using basis sets of circular-gaussian kernels. We then estimated model weights for each kernel and voxel using cross-validated L2-regularised regression (model training) and used these weights to predict each voxel’s activity time course in independent data (model test). The resulting model performance was converted into Z-scores via bootstrapping, yielding the ‘tuning strength’ of each voxel. By iterating over multiple basis sets of directional kernels differing in kernel width, we also estimated the corresponding ‘directional tuning width’ of each voxel. (C) Results 1: We observed a narrow-to-broad tuning width topology spanning from posterior to anterior parahippocampal cortex. (D) Results 2: Analysing tuning strength as a function of spatial memory performance revealed that network-wide directional tuning topology depends on spatial memory performance and hence, how well the environment has been encoded. (E) Regions of interest: We tested regions involved in deriving cognitive maps from visual experience: Early visual (EVC), retrosplenial (RSC), and posteromedial entorhinal cortices (pmEC), parahippocampal gyrus (PHG), and the hippocampus (HPC). (F) Results 3: Entorhinal and parahippocampal tuning strength as well as retrosplenial tuning width all depended on spatial memory performance. Together, these results reveal directional tuning in the human visual-navigation network, for the first time during active behaviour, and show that a high-level cognitive mapping process influences network-wide environmental processing. By doing so, these results further demonstrate the power of predictive modelling to study the neural underpinnings of human behaviour.
In addition to our ‘traditional’ key research tools of VR, experimental psychology and psychophysics, fMRI and MVPA (see above), we also work with, and further develop, the following new methods:
4.7.1 Research method LAMINAR fMRI

We are interested in structure-function mapping: How do anatomical processing units in the EC and the wider HF relate to cognitive function? This work is concerned with grid coding in EC layers, the modular organisation of spatial and mnemonic modules along the long-axis of the HF, the co-localisation of function and EC patches, and the specialisation of neural processing in lateral vs medial EC, presubiculum, and hippocampal subfields. Looking at brain signals at a layer-specific level is important, as the layers differ with regards to the sources from which they receive input. Studying neural processing and interactions with other regions at the layer-level will hence allow us to develop and refine theories on cognitive function and dysfunction.

4.7.1.1 A laminar triple dissociation for spatial cognition in entorhinal cortex

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Cortical layers are the key processing units in the brain. Single-unit recording studies in freely-moving rodents show that spatially tuned cells are distributed across the multi-layered entorhinal network. However, it is poorly understood how the laminar entorhinal system contributes to spatial cognition in humans. By combining recent advances in ultra-high field 7T fMRI, at submillimetre-resolution, with proxy-measures of entorhinal population activity and functional connectivity analyses, we investigated spatial processing in entorhinal cortex while participants performed a virtual reality task. We found a triple-dissociation of layer-dependent: (1) functional connectivity with cortical regions during navigation, (2) strength of the grid-like hexadirectional fMRI signal, and (3) relationship to spatial behaviour. Cortical regions in the fusiform/para-hippocampal cortex showed strongest functional connectivity with deep entorhinal segments. In contrast, hexadirectional activity was strongest in middle and superficial segments, while spatial memory performance correlated with the coherence of hexadirectional activity in the middle laminar segment. These results provide novel insights into the mesoscopic-level processing of laminar circuits for navigation and their relevance for cognition.

Figure 4.7.1.1 Layer-specific coding of space. We found a laminar network for spatial processing in humans and examine its relevance for behaviour. (A) Object-location memory task. (B) Grid-cell representations are strongest in middle and superficial segments. (C) Spatial memory performance correlates with the coherence of grid-cell representations in the middle layers. (D) Deep segments show highest connectivity with visual movement areas.
Research method MEG & OPM

Our main experimental work with fMRI is complemented by studies leveraging time-resolved MEG measures of oscillatory activity to answer the following questions. Is grid coding related to oscillatory activity in humans? How do neural oscillations support the communication between separate processing units in the HF and beyond?

Hexadirectional modulation of high-frequency electrophysiological activity in the human anterior medial temporal lobe maps visual space

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Grid cells are one of the core building blocks of spatial navigation. Single-cell recordings of grid cells in the rodent entorhinal cortex revealed hexagonal coding of the local environment during spatial navigation. Grid-like activity has also been identified in human single-cell recordings during virtual navigation (Jacobs, et al., 2013, Nat Neurosci, 16, 1188–1190). Human fMRI studies further provide evidence that grid-like signals are also accessi-

Figure 4.7.2.1 Grid-like modulation of broadband high-frequency MEG activity (BHA) during visual exploration. (A) BHA power (60–120 Hz) aligned to the putative grid orientation is significantly higher than misaligned BHA power in the left anterior MTL. (B) 6-fold symmetric modulation of the BHA power, visualising the effect in (A). The x axis depicts the difference between saccade directions and the estimated putative grid orientations. (C) Other rotational symmetries (4-, 5-, 7-, and 8-fold) do not show significant differences between aligned and misaligned BHA power. (D) Putative grid orientations across participants did not show clustering. (E) Whole-brain analysis shows clustering of highest differences (aligned versus misaligned, 60–120 Hz, 6-fold symmetry) in the left temporal lobe. (F) No significant difference between aligned versus misaligned BHA power, in horizontal or vertical electrooculogram (EOG) data (available in 32 participants).
ble on a macroscopic level (Doeller, et al., 2010, Nature, 463, 657–661). Studies in both non-human primates (Kilian, et al., 2012, Nature, 491, 761–764) and humans (Nau, et al., 2018, Nat Neurosci, 21, 188–190; Julian, et al., 2018, Nat Neurosci, 21, 191–194) suggest that grid-like coding in the entorhinal cortex generalises beyond spatial navigation during locomotion. More specifically, there is evidence for grid-like mapping of visual space during visual exploration—akin to the grid-cell positional code in rodents during spatial navigation. However, electrophysiological correlates of the grid code in humans remain unknown. Here, we provide evidence for grid-like, hexadirectional coding of visual space by human high-frequency activity, based on two independent datasets: non-invasive magnetoencephalography (MEG) in healthy subjects and entorhinal intracranial electroencephalography (EEG) recordings in an epileptic patient. Both data sets consistently show a hexadirectional modulation of broadband high-frequency activity (60–120 Hz). Our findings provide the first evidence for a grid-like MEG signal, indicating that the human entorhinal cortex codes visual space in a grid-like manner, and support the view that grid coding generalises beyond environmental mapping during locomotion (Bellmund, et al., 2016, eLife, 5, e17089; Constantinescu, et al., 2016, Science, 352, 1464–1468; Wilming, et al., 2018; eLife, 7, e31745). Due to their millisecond accuracy, MEG recordings allow linking of grid-like activity to epochs during relevant behaviour, thereby opening up the possibility for new MEG-based investigations of grid coding at high temporal resolution.

### 4.7.2.2 Developing a prototype optically pumped magnetometer (OPM) laboratory for magnetoencephalography (MEG) in real-world applications

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MEG provides direct measurements of brain electrophysiology in real time. However, the sensors of conventional MEGs are housed within a liquid helium dewar. The conventional setup constrains the distance between brain sources and sensors to approximately 3 cm in adults. In contrast to conventional MEGs, OPMs are worn on the head, close to the brain sources and subjects are free to move (Boto, et al., 2018, Nature, 555, 657–661). Inspired by the laboratories in Nottingham (Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham) and London (Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology, University College London), we are setting up an OPM laboratory for MEG. The core of our system is an array of 25 OPMs. These sensors are able to measure extremely small magnetic fields in the range of 10 fT/√Hz. However, high sensitivity is only achieved in a small operational range of ±5 nT (Holmes, et al., 2019, Sci Rep, 9(1)). We are developing sophisticated compensation coils to nullify the background magnetic field of the earth, and its gradients, in a 70 cm diameter sphere, in a magnetically shielded room. With our setup, we will be able to measure MEG during more realistic paradigms, where subjects are allowed to move their heads (Boto, et al., 2018, Nature, 555, 657–661).

Figure 4.7.2.2 Pilot work towards OPM Prototype. (A) 1:5 model of an active shielding coil chamber. The coils compensate for a homogeneous field at a target volume in the center of the chamber. (B) Wire paths for compensating the mean and gradient of the field component pointing orthogonal to the figure plane. The design accounts for the shielding effects of the magnetically shielded room and it is optimised for a bi-planar coil setting.

### 4.7.3 Research method DEEP NEURAL NETWORKS

We started using deep neural networks as discovery tools for neural and behavioural data. Deep neural networks were first applied to rodent data. In the future we will work on generalising such findings to human imaging data on spatial navigation and concept spaces.
DeepInsight: A general framework for interpreting wide-band neural activity

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Rapid progress in technologies such as calcium imaging and electrophysiology has seen a dramatic increase in the size and extent of neural recordings, yet their interpretation still depends on time-intensive manual operations. Decoding provides a means to infer the information content of such recordings but typically requires highly processed data and prior knowledge of variables. Here, we developed DeepInsight—a deep-learning-framework able to decode sensory and behavioural variables directly from wide-band neural data. The network requires little user in-
put and generalizes across stimuli, behaviours, brain regions, and recording techniques. Critically, once trained, it can be analysed to determine elements of the neural code that are informative about a given variable. We validated this approach using data from rodent auditory cortex and hippocampus, identifying a novel representation of head direction encoded by CA1 interneurons. Thus, we present a robust, user-friendly tool for characterising and decoding neural recordings.

4.7.4 Research “method” DEVELOPMENT

Examining the development of cognitive and neural processes can provide us with unique insights into basic neural coding principles. In particular, we are interested in how the development of the entorhinal grid system can, within the framework on cognitive spaces, explain qualitative, non-linear jumps in cognitive development.

4.7.4.1 Development of entorhinal grid-cell-like representations of visual space

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It has been proposed that the hippocampal formation supports cognitive map-like representations of both navigational and visual spaces (i.e., where one is looking) (Nau, et al., 2018, Trends Cogn Sci, 22(9), 810–825). This raises the question of whether the same neural mechanisms support both domains. If so, we would expect the visual mapping system to have a long developmental trajectory, as it does in the navigational domain (Julian, et al., 2018, Dev Sci). To address this question, we focused on grid-cell-like representations of visual space in the entorhinal cortex (EC) in a large cohort of children (ages 5-18 years old), for which fMRI data were acquired while they freely viewed a movie (Alexander, et al., 2017, Sci Data). We measured grid-cell-like fMRI responses as a function of gaze movement direction, using an analysis procedure previously used to identify this visual grid signal in adults (Nau, et al., 2018, Nat Neurosci; Julian, et al., 2018, Nat Neurosci). There was significant reliable grid-cell-like modulation in EC as a function of gaze movement direction. Critically, the magnitude of EC visual grid coding increased with age, due to developmental changes in the temporal stability of visual grid-like representations. This change in visual grid coding across the early lifetime could not be explained by developmental changes in eye movement behaviour. Our results support the idea that visual and navigable space are represented using the same neural mechanisms, and help to elucidate how cognitive maps emerge during development.

Figure 4.7.4.1 Developmental trajectory of grid coding. (A) In rodents, grid cells are known to have a relatively long developmental trajectory, compared to other neural components of the hippocampal formation cognitive mapping system. To test whether human grid-cell-like representations also exhibit protracted development, we examined grid-cell-like representations of visual space in the entorhinal cortex (EC) in a large cohort of children (ages 5-18 years old) using a publicly available pediatric neuroimaging database (Alexander et al. 2017, Sci. Data). FMRI data were acquired while the children freely viewed a 10 min. movie clip. (B) We measured grid-cell-like fMRI responses as a function of gaze movement direction during movie watching, the magnitude of split-half reliable EC visual grid coding increased with age, consistent with protracted development of grid cells in humans.
Appendix

Congresses, Workshops, and Symposia

2018

2019

Degrees

Doctoral Theses

2019
- Bellmund, J. L. S. Hippocampal-entorhinal codes for space, time and cognition. Radboud University, Nijmegen, NL.
- Sonntag, H. The effect of uncertainty in MEG-to-MRI coregistrations on MEG inverse problems. Technical University of Ilmenau, Germany.

Appointments

2018
- Kaplan, R. Associate Professor. Kavli Institute for Systems Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway.

2019
- Doeller, C. F. Honorary Professorship for Psychology (Learning and Memory). Faculty of Life Sciences, Leipzig University, Germany.

Awards

2017
- Doeller, C. F. ERC Consolidator Grant. European Research Council (ERC), Brussels, Belgium.

2018
- Julian, J. B. Grid Cell Meeting Travel Award. Sainsbury Wellcome Center, University College London, UK.
- Sonntag, H. Data Analysis Competition #2 Award. 21st International Conference on Biomagnetism (BIOMAG 2018), Philadelphia, PA, USA.

2019
- Polti, I. Norwegian Research School in Neuroscience International Training Grant. Norwegian University of Science and Technology (NTNU), Trondheim, Norway.
- Nitsch, A. Werner-Straub-Prize for outstanding achievements in scientific qualifications. Technical University of Dresden, Germany.
- Schäfer, T. Werner-Straub-Prize for outstanding achievements in scientific qualifications. Technical University of Dresden, Germany.
- Theves, S. Abstract Award. Conference on Concepts, Actions, and Objects, Rovereto, Italy.
Note: These publications include Christian Doeller’s publications since 2017 and publications of the DoellerLab members since 2018 (start of the Department of Psychology at the MPI CBS). Publications of the DoellerLab members at the Kavli Institute in Trondheim are also included as they are highly relevant to our research topics.

**Publications**

**Books and Book Chapters**


**Journal Articles**


**Book Reviews**


**Index of Published Figures**

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*Figure 4.4.1*  

*Figure 4.6.1*  

*Figure 4.7.2.1*  
5
Research Groups
5.1 Minerva Research Group “EGG (Emotions & neuroimaGinG) Lab”

Research Group Leader
PD Dr Julia Sacher

Scientific Assistants
Alyson Buchenau (49) (*)

Technical Assistants
Kirsten Scharr (49) (*)
Ulrike Scharrer

PhD Students
Dr Claudia Barth (*) (PhD since 01/2017)
Carolin A. Lewis (49) (*)
(in cooperation with the University of Tübingen)
Eoin Molloy (49)
Rachel Zsido (11)

MD Students (in cooperation with Leipzig University)
Nathalie Beinhölzl
Matthias Heinrich

Guest Researchers
Esmeralda Hidalgo (63) (*)
(in cooperation with the University of Salzburg, Austria)
Dr Gesa Schaad

Former PhD Students
Dr Claudia Barth
Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway

(Commenced January 2015)

(11) Federal Ministry of Education and Research (BMBF), Germany
(49) Branco Weiss Foundation, Switzerland
(63) Erasmus Mundus Student Exchange Network
(86) German Academic Exchange Service (DAAD)
(92) ERC Starting Grant
(*) Left the Institute during 2017-2019
5.2 Max Planck Research Group “Adaptive Memory”

Research Group Leader
Dr Roland G. Benoit

Postdocs
Dr Ruud Berkers (*)
Dr Heidrun Schultz
Davide Stramaccia, PhD (*)
Dr Angharad Williams

PhD Students
Seyma Bayrak
Aroma Dabas (86)
(in cooperation with Free University Berlin)
Mark Lauckner
Ann-Kristin Meyer
Philipp C. Paulus
Sarah Rösch
Hanna Stoffregen (in cooperation with Leipzig University)

Guest researchers
Zijian Zhu (86) (*)

Technical and Scientific Assistant
Martina Dietrich

Former PhD Students
Dr Ruud Berkers  Vincent van Gogh voor Geestelijke Gezondheidszorg, Venray, NL
Davide Stramaccia, PhD ASkonsulting, Brescia, Italy

(Commenced July 2016)

5.3 Max Planck Research Group “Pain Perception”

Research Group Leader
Dr Falk Eippert

Postdocs
Dr Ulrike Horn (92)
Dr Birgit Nierula

PhD Students
Alice Dabbagh
Merve Kaptan

Technical Assistants
Janek Haschke

Guest Researchers
Dr Johanna Vannesjo

(Commenced June 2018)
5.4 Lise Meitner Research Group
“Cognition and Plasticity”

Research Group Leader
PD Dr Gesa Hartwigsen

Postdocs
Curtiss Chapman, PhD
Dr Jana Klaus (*)
Dr Sabrina Turker
Dr Kathleen Williams

PhD Students
Astrid Graessner
Philipp Kuhnke
Sandra Martin
   (in cooperation with Leipzig University)
Laura Nieberlein
Ole Numssen (14)
Pei-Ju Chien
   (in cooperation with Dept of Neuropsychology)
Anna Rysop (14)

Guest Researchers
Lea-Marie Schmitt   (in cooperation with the University of Lübeck)
Dr Manuela Macedonia (Johannes Kepler University Linz, Austria)
Dr Jens Kreitewolf  (University of Lübeck, Germany)
Dr Sven Paßmann     (University of Fribourg, Suisse)
Maximilian Friehs   (University of Trier, Germany)

(Commenced January 2019)

5.5 Research Group
“Social Stress and Family Health”

Research Group Leader
Professor Dr Veronika Engert

Postdocs
Dr Katrin Preckel
Dr Pascal Vrtička

PhD Students
Mathilde Gallistl
Roman Linz
Lara Puhlmann

Technical and Scientific Assistants
Henrik Grunert
Elisabeth Murzik
Sylvie Neubert
Sylvia Tydecks
Michael Vollmann
Max Planck Research Group “Language Cycles”

Research Group Leader
Dr Lars Meyer

Postdocs
Dr Sabrina Stehwien

PhD Students
Yulia Lamekina
Katharina Menn
   (in cooperation with Dept of Neuropsychology)

Technical Assistants
Monique Horstmann (*)
Lena Henke

(Commenced April 2019)

Guest Researchers
Professor Dr Anne Böckler-Raettig
Department of Psychology, Würzburg University, Germany

Dr Haakon Engen
German Resilience Center (DRZ), University Medical Center of the
Johannes Gutenberg University Mainz

Dr Fynn-Mathis Trautwein
The Edmond J. Safra Brain Research Center, Faculty of Education,
University of Haifa, Israel

Dr Sofie Valk
Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine
University Düsseldorf, Germany, and
Institute of Neuroscience and Medicine (INM-7: Brain & Behaviour), Research
Centre Jülich, Germany

Research Associates
Professor Dr Philipp Kanske
Clinical Psychology and Behavioral Neuroscience, Faculty of Psychology,
Technical University of Dresden, Germany

(Commenced January 2019)
5.7 Minerva Fast Track Group
"Milestones of Early Cognitive Development"

Minerva Fast Track Fellow
Dr Charlotte Grosse Wiesmann

Postdocs
Dr Katrin Rothmaler

PhD Students
Clara Schüler
Marie-Luise Speiger
Anna-Lena Tebbe
Florian Teichmann
(in cooperation with Leipzig University)

(Commenced September 2019)

5.8 Max Planck Research Group
"Vision and Computational Cognition"

Research Group Leader
Dr Martin N. Hebart

PhD Students
Philipp Kaniuth

(Commences February 2020)
The central aim of the research in the Emotion & Neuroimaging (EGG) Lab is to understand how sex hormones affect brain and behaviour across the adult life-span. We investigate the influence of sex and sex hormones on brain states in health and disease, through the use of multimodal neuroimaging techniques (Positron Emission Tomography (PET) & Magnetic Resonance Imaging (MRI)). Our research strives to elucidate the mechanisms underlying the unique vulnerabilities of women to depression and dementia. Our ultimate goal is to improve brain health for both women and men.

We have recently demonstrated novel associations between estradiol, visceral adipose tissue, and structural brain networks: a potential mechanism underlying cognitive decline in women (5.1.1). In other work, we quantify neurochemical changes across the menstrual cycle. We show an increase in serotonin transporter binding in patients with premenstrual dysphoric disorder (5.1.2, Fig. 5.1.2C). This constitutes the first mechanistic biomarker for premenstrual depressed mood in vivo. A second line of work further integrates high-field MRI segmentation of hippocampal subfields. We apply this technique to explore hippocampal structure previously identified to change in synchronisation with the menstrual cycle (5.1.2, Fig. 5.1.2B).

Finally, we study antidepressant effects on reward (5.1.3, Fig. 5.1.3A) and motor learning (5.1.3, Fig. 5.1.3B). Sex and sex hormones are known to affect antidepressant response and sequential motor learning. To overcome this bias, we chose an all-female sample of participants on oral contraceptives. In this homogenous sample, we tested the effects of increased serotonergic signalling on motor learning (5.1.3, Fig. 5.1.3B) and resting state electroencephalography (Fig. 5.1.3C).

Diversity drives scientific discovery. Yet, many scientific discoveries and standards, including in the neurosciences, largely neglect 51% of the population, that is, women. With the male brain still often implicitly employed as the ‘default model’, many basic and clinical neuroscience studies do not include equal numbers of females in their samples. Of the studies that do include equal numbers, many do not consider sex differences as a primary outcome measure, but rather regress sex out as a covariate of no primary interest. We propose and apply the following strategies to overcome this bias: (1) increase numbers of female study participants, (2) consider sex as a primary variable, (3) compare critical hormonal transition phases across the life-span including the menstrual cycle, and when justified, (4) study all-female samples to provide a more in-depth understanding of sex-specific risk trajectories and pathologies.

The EGG lab closely collaborates scientifically with the Department of Neurology (Professor Villringer) and receives valuable support from Maria Paerisch. We also collaborate with the Day Clinic of Neurology (Professor Villringer, Professor Obrig, Professor Schroeter) and with many research groups within the Neurology department (Dr. Gaebler, PD Witte, Professor Nikulin, PD Sehm) and within the MPI-CBS institute (Professor Männel, Professor Möller, Professor Engert). In connection with the several universities we host numerous Bachelor’s and Master’s students who have provided valuable co-supervision experience for our PhD students (e.g. Rachel Zsido, Eoin Molloy, Carolin Lewis). By applying our unique scientific expertise in neuropharmacology, quantitative neurochemical imaging, and sex differences to traditional research questions in the cognitive sciences, we provide novel perspectives on the diversity of human cognition and brain plasticity.
Sex differences in the relationship between abdominal fat and structural brain network integrity: A perimenopausal model of cognitive risk

Zsido, R. G.¹,², Heinrich, M.¹, Slavich, G. M.³, Beyer, F.¹,⁴, Kharabian Masouleh, S.¹, Kratzsch, J.³, Raschpichler, M.⁵,⁶,⁷, Mueller, K.¹, Scharrer, U.¹, Löffler, M.¹,⁴, Schroeter, M. L.¹,⁹, Stumvoll, M.⁴,⁷, Villringer, A.¹, Witte, A. V.¹,¹, & Sacher, J.¹

¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
² Max Planck School of Cognition, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
³ Cousins Center for Psychoneuroimmunology, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles
⁴ Collaborative Research Centre (SFB) 1052 “Obesity Mechanisms,” Leipzig University, Germany
⁵ Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Leipzig University, Germany
⁶ Heart Center Leipzig, Department of Cardiac Surgery, Leipzig, Germany
⁷ Integrated Research and Treatment Center (IFB) Adiposity Diseases Faculty of Medicine, Leipzig University, Germany
⁸ Institute for Medical Informatics, Statistics, and Epidemiology (IMISE), Leipzig University, Germany
⁹ Leipzig Research Center for Civilization Diseases (LIFE), Leipzig University, Germany

Given rising dementia and obesity rates worldwide, the interactions between obesity, accelerated brain atrophy, and unhealthy cognitive aging are critical to understand. Thus, we investigated the links between visceral fat, cognitive function, and brain structure (Zsido et al., 2019). We show sex-specific risk trajectories for brain structure and cognitive function associated with increased visceral fat (Fig. 5.1.1A and 5.1.1B). The study included 974 participants (473 women) distributed across the adult lifespan (19-79 years old). Higher estradiol levels were associated with increased brain network covariance (Fig. 5.1.1C). Furthermore, estradiol seems to protect brain struct-

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Sex differences in visceral adipose tissue (VAT) accumulation: Men show highest VAT-to-age ratio at earlier age, women during midlife.

Sex differences in association between VAT and a brain network critical for memory performance: VAT is associated with compromised brain network structure in both sexes, the association is stronger in men.

Moderation analysis: estradiol seems to mitigate the negative association of visceral adipose tissue on the brain network.

Midlife analyses: Higher estradiol levels are associated with increased memory network covariance and better memory performance in women during perimenopausal years (35-55).

Figure 5.1.1
The influence of ovarian hormone fluctuations on neurochemistry and brain morphology: Implications for depression


1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Max Planck School of Cognition, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
3 Psychosis Research Centre, Institute of Clinical Medicine, University of Oslo, Norway
4 International Max Planck Research School on Neuroscience of Communication, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
5 Integrative Model-based Cognitive Neuroscience Research Unit, Universiteit van Amsterdam, NL
6 Department of Nuclear Medicine, Leipzig University, Germany

Ovarian hormones fluctuate across the female lifespan. These hormone transition periods appear to increase the risk of depression (Fig. 5.1.2A). Previous findings have shown that the magnitude of estradiol fluctuations, around a woman’s own mean, is the strongest predictor of a depressive episode. In the Menstrual Cycle Plasticity Project (Fig. 5.1.2B) we assessed whether physiological fluctuations in endogenous ovarian hormones influence brain morphology. Pioneering longitudinal acquisition of 7T ultra-high field magnetic resonance imaging, across the menstrual cycle, we aim to characterise hippocampal subfield microstructure and structural connectivity in health. In a related, longitudinal neureceptor ligand PET study, we quantified serotonin transporter binding across the menstrual cycle (Fig. 5.1.2C). We found increased serotonin transporter binding in women with Premenstrual Dysphoric Disorder (PMDD). This provides the first mechanistic framework for targeted treatment strategies in women suffering from menstrual cycle-associated mood disturbances.
Villringer, A. (Fig. 5.1.3B), we provide the first empirical evidence on the establishment of feedback (Fig. 5.1.3A). In a second line of work, a single SSRI dose can attenuate the brain response to punishment. Here, we show novel evidence that a single SSRI dose can attenuate the brain response to punishment. How this neurochemical change influences human performance. The current results demonstrate the feasibility of increasing serotonin transporter binding across the menstrual cycle in PMDD patients. This is the first quantitative neurochemical data set in vivo to provide a mechanistic biomarker for a psychiatric disorder newly included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

Figure 5.1.2

Intervention controlled pharmaco-fMRI studies testing serotonergic effects on reward, punishment, and network motor plasticity

Molloy, E. N.1,2, Lewis, C. A.1,2, Zsido, R. G.1,3, Mueller, K.1, Beinhöhlz, N.1, Blöchl, M.1,2,4, Piecha, F.1, Ihle, K.1, Pampel, A.1, Steele, C. J.1,2, Scharrer, U.1, Zheleva, G.1, Regenthal, R.1, Sehm, B.1, Cesnaite, E.1, Nikulin, V. V.1, Möller, H. E.1, Villringer, A.1, & Sacher, J.2

1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 International Max Planck Research School on Neuroscience of Communication, Leipzig, Germany
3 Max Planck School of Cognition, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
4 Department of Psychology, University of Münster, Germany
5 Department of Psychology, Concordia University, Montréal, Canada
6 Rudolf Boehm Institute of Pharmacology and Toxicology, Leipzig University, Germany

The rising use of antidepressants, prescribed to over 30 million adults in the US in 2014 alone (Moore & Mattison, 2017, JAMA Intern Med, 177, 274-275), includes selective serotonin reuptake inhibitors (SSRIs). SSRIs raise extracellular serotonin levels by blocking the serotonin transporter. How this neurochemical change influences human cognition and behaviour, however, is still a matter of intense debate. Here, we show novel evidence that a single SSRI dose can attenuate the brain response to punishment feedback (Fig. 5.1.3A). In a second line of work (Fig. 5.1.3B), we provide the first empirical evidence on the theory of SSRI-induced network plasticity (Castren & Hen, 2013, Trends Neurosci, 36, 259-267). Here, we investigated the combination of SSRI administration and sequential motor learning. Escitalopram, an SSRI, was found to decrease brain responses to external stimuli, possibly reflecting improved neural processing during task performance. The current results demonstrate the feasibility of adapting quality assurance criteria of clinical research to preclinical human study designs. This provides a crucial stepping-stone towards the determination of whether SSRI administration, in combination with experimentally controlled stimuli, can facilitate learning. Future work of our group aims to extend this line of research to cortical...
excitatory and inhibitory states and underlying neurochemical signalling. This will involve using already-acquired resting state electroencephalography (EEG) data and quantitative MR-spectroscopy analysis of glutamate and γ-aminobutyric acid (GABA) levels in primary motor cortex and anterior cingulate cortex (Fig. 5.1.3).

**A**

Acute serotonergic challenge during reward and punishment paradigm:
In a placebo-controlled crossover design, a single 20 mg dose of the selective serotonin reuptake inhibitor (SSRI) escitalopram decreases BOLD response to punishment in subcortical regions, including the thalamus and caudate.

**B**

In the first study in health to combine 1-week SSRI administration with an established motor learning paradigm in a pre-registered design, we test the neuronal network plasticity hypothesis proposed for SSRI-action.

Escitalopram induces decreased BOLD response during sequence specific motor learning, which may reflect increased neural efficiency during motor task performance.

<table>
<thead>
<tr>
<th></th>
<th>Escitalopram</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Dose</strong></td>
<td>Peak region: Left Premotor Cortex</td>
<td>Peak Region: Left Premotor Cortex</td>
</tr>
<tr>
<td><strong>Steady State</strong></td>
<td>Peak Region: Left Posterior Somatosensory Cortex</td>
<td>Peak Region: Left Premotor Cortex</td>
</tr>
<tr>
<td><strong>Single Dose &gt; Steady State</strong></td>
<td>Peak Region: Left Premotor Cortex</td>
<td>No significant change</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td><img src="image" alt="Interaction Image" /></td>
<td><img src="image" alt="Interaction Image" /></td>
</tr>
</tbody>
</table>

**C**

Current EEG and MR-Spectroscopy Analyses:
To investigate underlying changes in the balance between cortical excitation/inhibition following SSRI-administration, we record resting state EEG. Topographical maps of spectral slope reveal a significant increase in excitatory inputs following a single dose of 20 mg escitalopram.

We have acquired MR-spectroscopy data and use Point Resolves Spectroscopy (PRESS, left spectrum) for glutamate (Glu), and MEGA-PRESS (right spectrum) for γ-aminobutyric acid (GABA), to quantitatively measure major excitatory and inhibitory neurotransmitters and investigate potential changes related to motor learning and SSRI kinetics.

![Figure 5.1.3](image)
Congresses, Workshops, and Symposia

2019

2018

2017
- Sacher, J. National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award. Brain & Behavior Research Foundation, USA.
- Sacher, J. American College of Neuropsychopharmacology (ACNP) Associate Membership (by invitation only).

Awards

2019
- Zsido, R. G. Travel Award for the 32nd Annual Meeting European College of Neuropsychopharmacology (ECNP). Copenhagen, Denmark.
- Zsido, R. G. Best Poster Presentation Award at the 8th IMPRS NeuroCom Summer School: Max Planck Institute for Human Brain and Cognitive Sciences, Leipzig, Germany.
- Barth, C. Best Poster Presentation Award at the 32nd Annual Meeting European College of Neuropsychopharmacology (ECNP). Copenhagen, Denmark.
- Heinrich, M. Deutschlandstipendium. Leipzig University, Germany.

2018
- Zsido, R. G. Best Poster Presentation Award at Matariki Winter School and Symposium 2018: Sex Hormones and the Brain. Tübingen, Germany.
- Heinrich, M. Deutschlandstipendium. Leipzig University, Germany.

2017
- Sacher, J. National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award. Brain & Behavior Research Foundation, USA.
- Sacher, J. American College of Neuropsychopharmacology (ACNP) Associate Membership (by invitation only).
- Heinrich, M. Deutschlandstipendium. Leipzig University, Germany.

Degrees

PhD Theses
2017
- Barth, C. Exploring structural and functional brain dynamics across the menstrual cycle. Leipzig University, Germany.


**Publications**

**Books and Book Chapters**


**Journal Articles**


Minerva Research Group “EGG (Emotion & neuroimaGinG) Lab” – Appendix
At the heart of the research in the Adaptive Memory lab is the insight that memory is not merely a passive capacity but a constructive process. On the one hand, memories are malleable to change and disruption. On the other hand, they can be flexibly recombined into simulations of novel experiences. We seek to understand the adaptive nature of memory by focusing on two research areas:

(i) Memory suppression
When people encounter a reminder of an episode that they rather not remember, they often attempt to keep the associated memory out of awareness. We have provided meta-analytical evidence that such suppression induces forgetting, and that it is deficient in individuals experiencing intrusive thoughts (e.g., in anxiety and depression) (5.2.1). Our research examines whether suppression also attenuates the affective component of aversive memories using psychophysiology (5.2.2) and fear conditioning. At the same time, we characterise how it causes forgetting by deteriorating neural memory traces (5.2.2) and scrutinise the contribution of the prefrontal cortex (PFC) using transcranial magnetic stimulation. This research thus contributes to a comprehensive understanding of the mechanisms involved in controlling unwanted memories and intrusive thoughts.

Schemas mediated by the mPFC facilitate episodic simulations. We examine how these simulations convey the anticipated affect of a prospective event and how this experience influences farsighted decisions (Schacter, Benoit & Szpunar, 2017). Our work moreover demonstrates that we learn from such simulations (5.2.3) much in the same way that we learn from real events. By this, episodic simulations can have a profound impact on our models of the world.

Taken together, our research adds to our understanding of the cognitive and neural processes that are fundamentally involved in controlling the contents of our memories and the mental creation of our future.

(ii) Episodic simulation
Our ability to simulate prospective episodes draws on stored details from memory that get recombined into novel events (Schacter, Benoit & Szpunar, 2017). We aim to deconstruct the network supporting episodic simulation and to understand its fundamental functions. For example, we have shown that the medial PFC encodes individual elements of our environment (e.g., familiar people) (5.2.3) and their associations into affective schemas (e.g., of our social network) (5.2.4). Moreover, the mPFC supports the integration of pertinent information that is distributed across the cortex by acting as a hub of brain-wide connectivity.

Schemas mediated by the mPFC facilitate episodic simulations. We examine how these simulations convey the anticipated affect of a prospective event and how this experience influences farsighted decisions (Schacter, Benoit & Szpunar, 2017). Our work moreover demonstrates that we learn from such simulations (5.2.3) much in the same way that we learn from real events. By this, episodic simulations can have a profound impact on our models of the world.

Taken together, our research adds to our understanding of the cognitive and neural processes that are fundamentally involved in controlling the contents of our memories and the mental creation of our future.
Memory suppression and its deficiency in psychological disorders: a focused meta-analysis

Stramaccia, D. F.¹, Meyer, A. K.¹, Rischer, K. M.², Fawcett, J. M.³, & Benoit, R. G.¹
¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
² Université du Luxembourg Maison des Sciences Humaines, Esch-sur-Alzette, Luxembourg
³ Memorial University of Newfoundland, St. John's, Canada

It is hotly debated whether suppressing the retrieval of unwanted memories constitutes a beneficial mechanism that causes forgetting. Here, we scrutinise the evidence for such suppression-induced forgetting (SIF) and examine whether it is deficient in psychological disorders (e.g., anxiety and depression) characterised by intrusive thoughts. Specifically, we performed a focused meta-analysis of studies that have used the Think/No-Think procedure to test SIF in individuals either affected by psychological disorders or exhibiting high scores on related traits. First, our analysis of the control samples (N = 534) indicated that avoiding retrieval indeed leads to reliable forgetting in healthy participants. Overall, the effect size was moderate to small (SMCC = 0.31, 95% CI [0.16, 0.45]) and remained significant after attempting to account for publication bias (Fig. 5.2.1A). However, moderator analy-
Research Groups

5.2.2 Tracking the impact of retrieval suppression on neural memory representations

Meyer, A.-K.¹, & Benoit, R. G.¹

¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

When we experience aversive events, they often turn into unwanted memories. Simple reminders can then trigger their involuntary retrieval and elicit a negative affective response. However, prior evidence indicates that we can intentionally suppress the retrieval of such unwanted memories. This weakens the avoided memories and can eventually lead to forgetting. Here, we test the hypotheses (1) that suppression also attenuates the affective component of aversive memories, and (2) that it weakens memories by deteriorating their neural representations. This deterioration, in turn, would lead to a deficient reinstatement of the representations during subsequent recall attempts. In an fMRI study, participants learned associations between reminders and aversive scenes (Fig. 5.2.2.1A). They then repeatedly suppressed the associated scenes for some reminders, while they recalled the scenes for others. Some reminders were not presented during this period (baseline condition). We assessed how suppression altered participants’ ability to recall the scenes. Supporting (1), suppression led to a stronger reduction in the memo-

A Adapted Think/No-Think procedure

B Suppression renders memories less vivid

C Reduction in vividness is associated with reduction in affective response

Figure 5.2.2.1 (A) Study phase: participants learned associations between neutral objects and pictures of aversive scenes. Pre and post phases: participants recalled the scenes in response to the objects and indicated the vividness of their recollections while their heart rates were being measured. Suppression phase: participants encountered the objects and were cued to either suppress or recall the associated scenes. (B) Previously suppressed memories were recalled less vividly than baseline memories that were not cued during the suppression phase. (C) A greater reduction in vividness (baseline - suppress) was associated with a stronger attenuation of heart rate deceleration (baseline - suppress). We also obtain a significant correlation when combining these data with those of a similar study. Robust spearman skipped correlation. *** p < .001. Affective pictures taken from Lang, Bradley & Cuthbert (2008).
ries’ vividness (compared to baseline) (Fig. 5.2.2.1B), and a stronger reduction in vividness was associated with a greater decline in negative affect (as quantified by heart rate deceleration) (Fig. 5.2.2.1C). To test (2), we estimated – using a linear pattern classifier – the degree to which recall attempts were accompanied by a reactivation of scene information (Fig. 5.2.2.2A). We indeed observed weaker reactivation during the retrieval of formerly suppressed versus baseline memories (Fig. 5.2.2.2C). These results support the hypotheses that suppression deteriorates declarative and affective components of unwanted memories by compromising their neural representations.

Forming attitudes via neural activity supporting affective episodic simulations

Benoit, R. G. 1, Paulus, P. C. 1, & Schacter, D. L. 2

1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Harvard University, Cambridge, USA

Humans have the adaptive capacity for imagining hypothetical episodes. Such episodic simulation is based on a neural network that includes the rostral and ventral medial prefrontal cortex (mPFC). This network draws on existing knowledge (e.g., of familiar people and places) to construct imaginary events (e.g., meeting with the person at that place). This study tests the hypothesis that a simulation changes attitudes towards its constituent elements. Specifically, in two experiments, we demonstrate how imagining meeting liked versus disliked people (serving as unconditioned stimuli; UCS) at initially neutral places (serving as conditioned stimuli; CS) changes the affective value of these places (Fig. 5.2.3A). We further provide evidence that the mPFC codes for representations of those elements (i.e., of individual people and places) (Fig. 5.2.3B-C). Critically, attitude changes induced by the liked UCS are based on a transfer of positive affective value between the representations (i.e., from the UCS to the CS) (Fig. 5.2.3D). Thereby, we reveal how mere imaginings shape real-life attitudes.
Revealing the structure of affective schematic representations in medial prefrontal cortex

Paulus, P. C.1, Charest, I.2, & Benoit, R. G.1

1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 School of Psychology, University of Birmingham, UK

The rostral and ventral medial prefrontal cortex (mPFC) has been proposed to encode memory schemas. Such schemas (e.g., of our social network) are built across series of overlapping experiences and can be understood as network graphs comprising nodes (e.g., individual people) and edges (their relationships). Recently, we have shown that the mPFC encodes representations of individual people and places (i.e., the nodes). Here, we test whether the mPFC also codes for the edges. Specifically, we hypothesized that edges should be stronger for nodes (i) that are more central to their network and (ii) that individuals have encountered more often (i.e., are more familiar with).
Given the mPFC’s role in valuation, we further predicted (iii) stronger edges for nodes with higher affective value. We thus hypothesised that the mPFC encodes affective schematic representations.

Participants provided names of personally familiar people and places, and indicated their centrality, familiarity, and affective value (Fig. 5.2.4A). A principal component analysis confirmed that these variables load on a common factor. This factor quantifies the importance of individual nodes to their schema. If the mPFC encodes affective schemas, we predicted that the importance values explain the strength of the edges. While being scanned with fMRI, participants repeatedly imagined episodes with each person and place, thus reinstating their neural representations. Using representational similarity analysis, we demonstrate that the mPFC codes for the nodes of the graph (Fig. 5.2.4B). Critically, the strength of their edges is indeed best accounted for by the importance of the individual nodes (Fig. 5.2.4C-D). We thus provide evidence that the mPFC encodes affective schematic representations.

Figure 5.2.4 (A) Participants arranged tokens labeled with the names of personally familiar elements (i.e., people and places) to indicate associations between the elements (allowing us to derive each element’s centrality to the network), their familiarity (as a measure of experience), and their liking (as a measure of affective value). Separately for people and places, we extracted a principal component (PC) that indeed correlated with each of these measures. We thus take the PC to quantify the overall importance of the individual elements to the affective schematic representation. (B) Using representational similarity analysis, we demonstrate that representations in the mPFC are more similar whenever an identical element is simulated as compared to when different elements of the same category are simulated. We take this to suggest that mPFC encodes the nodes of affective schemas. (C) Using a region of interest approach, we then examine the structure of the graph. Specifically, we predicted that nodes should exhibit overall stronger edges that are more important to the affective schema (as indexed by the PC). Indeed, representations in the mPFC, but also in the posterior cingulate cortex (PCC) align with the predicted structure of affective schematic representations. (D) Results of a linear mixed model comparison support the hypothesis: the structure of representations in the mPFC - but not in the PCC - is best explained by the predicted structure of affective schematic representations (lower values indicate better fit, relative LER difference > 2 - marked by red dotted line - regarded as decisive). * p < .05, *** p < .001.
Research Groups

Congresses, Workshops, and Symposia

2019


2018

- Benoit, R. G. (May). Voluntary forgetting: basic mechanisms and impact on emotions and mental health, Organizer of the symposium. Annual meeting of the "Biological Psychology and Neuropsychology" section of the German Psychological Society, Gießen, Germany.


- Paulus, P. C. (May). Introduction to Psychophysiological Modelling. Workshop. Young researchers of the unit of "Biological Psychology and Neuropsychology" of the German Society for Psychology (DGPs), Gießen, Germany.

Awards

2019

- Meyer, A.-K. Poster Award DGPs. Annual meeting of the "Biological Psychology and Neuropsychology" section of the German Psychological Society, Dresden, Germany.

2018

- Benoit, R. G. elected into the Memory Disorders Research Society (MDRS).

- Meyer, A.-K. Poster Award IMPRS NeuroCom. 8th IMPRS NeuroCom Summer School, Leipzig, Germany.

2017

- Berkers, R. Memrise Prize. An applied science prize for designing the best method to learn words. Memrise, London, UK.

- Meyer, A.-K. Poster Award IMPRS NeuroCom. 7th IMPRS NeuroCom Summer School, London, UK.

- Paulus, P. C. Experimental design prize. Prize in the experimental design competition at the 7th IMPRS NeuroCom Summer School, London, UK.

Publications

Journal Articles


All preprints are listed as "working papers" on the group's website at https://tinyurl.com/umox86s.
5.3
Max Planck Research Group “Pain Perception”

Pain is an important warning signal of impending or actual tissue damage, yet in its chronic form it is also a source of immense suffering. Importantly, the perception of pain is not a direct reflection of the strength of peripherally received noxious input but is strongly modulated by a plethora of contextual factors, such as our current expectations or our past experience of pain. This argues for a significant involvement of the central nervous system in the construction of the experience of pain.

Accordingly, research in the Pain Perception group is based on the general perspective that perception is not a passively arising response to sensory stimuli, but an active inferential process, in which the central nervous system generates predictions about the inputs it receives and adjusts these predictions in light of new sensory input.

Our research agenda focusses on identifying the neural building blocks involved in this process. Toward this end, we use behavioural recordings in combination with advanced neuroimaging methods at all levels of the nervous system. A special focus is placed on the spinal cord, in order to capture predictive signals of pain processing at the earliest level of the central nervous system, since they are likely to exert a profound effect on processing at higher levels and on the ensuing perceptual experience.

Currently we approach this topic from at least three angles. First, we aim to optimise the acquisition of fMRI data to allow for reliable insights into spinal cord processing (5.3.1). Second, we seek to characterise pain-specific prediction signals in the spinal cord and their behavioural consequences (5.3.2). Third, we are investigating whether it is possible to directly assess spinal cord neuronal processing with non-invasive electrophysiological methods (5.3.3).
Automated slice-specific z-shimming for fMRI of the human spinal cord

Kaptan, M. 1, Vannesjo, J. 2, Mildner, T. 1, Weiskopf, N. 1, Finsterbusch, J. 3, & Eippert, F. 1

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Imaging the human spinal cord comes with many challenges, such as the cord’s small cross-sectional diameter, the prominent influence of physiological noise, and periodically occurring signal drop-out. In this work, we address the latter point, which is due to magnetic field inhomogeneities caused by the repeated occurrence of tissue types with different magnetic susceptibility.

We have previously demonstrated that susceptibility-induced signal drop-out can be largely compensated for using slice-specific z-shimming (i.e. the slice-specific application of a gradient pulse that aims to compensate through-slice signal dephasing; Finsterbusch et al., 2012, Neuroimage 59: 2307-2315). However, this approach comes with the practical drawbacks that it is based on subjective assessment, needs experience-based manual/visual estimation, and is time-consuming. Here, our aim was to improve this approach by developing an automated slice-specific z-shim procedure. We implemented this via a quick and robust automated analysis of a z-shim reference scan (which consists of pre-experimental acquisitions with different z-shims) that resulted in slice-specific z-shim values, which were then fed back into the fMRI protocol.

In a group-study (N=24) we were able to replicate previously observed effects: using a manually determined z-shim, we recovered large parts of the signal (Fig. 5.3.1A,B) and this lead to a 67% reduction in signal variation over slices as well as a 14% increase in signal intensity. Crucially, we achieved nearly identical performance using our automated approach (reduction in signal variation of 64%, increase in signal intensity of 14%) and this held for slices that were either partially or completely affected by signal drop-out (Fig. 5.3.1C). A similar effect was also observed in time-series data (i.e. temporal signal-to-noise ratio), directly highlighting the benefit for fMRI studies.

This work demonstrates that it is possible to carry out slice-specific z-shimming in an automated manner without a performance penalty. This advancement will be important to make spinal fMRI more widely applicable, as it obviates the need for experience in judging image quality in order to obtain z-shims. It will also open the door for longitudinal studies, where z-shims have to be reliably calculated on each scanning day. In ongoing work, we are exploring an alternative approach to automatisation, by calculating z-shims from a concurrently acquired field-map, which would provide a more general platform for obtaining a complete set of x-, y-, and z-shims.

Figure 5.3.1 (A) Mid-sagittal slices through group-averaged EPIs of the spinal cord (vertebrae C2 to T1 in standard space) with either no z-shim correction (red), z-shim correction based on manual selection (blue) or z-shim correction based on automatic selection (green). The black outlines depict the borders of the spinal cord, with the dorsal aspect of the spinal cord being on the left; S: superior, I: inferior. (B) Signal intensity values extracted from each slice of the spinal cord and averaged across the group (error band represents standard error). Note the strongly reduced variation in signal intensity across slices with both z-shim correction methods and their almost identical performance, i.e. the strong recovery of signal drop-out present in the data with no z-shim correction. This pattern can also be seen in the sagittal EPI images in panel A where the uncorrected data (red) show several areas with reduced signal intensity (see arrows), which is much less pronounced in the corrected data (blue and green). (C) Exemplary transversal slices (dorsal aspect of the spinal cord faces the bottom) showing signal drop-out only in the dorsal part of the spinal cord (left column) or in the entire spinal cord (right column); both cases are handled well by the two correction approaches.
The perception of pain is not always a direct reflection of the strength of peripheral input, but can be strongly modified by contextual factors, such as expectations. According to recent thought and experimental evidence (Büchel et al., 2014, Neuron 81:1223-1239; Geuter et al., 2017, eLife 6:e24770) such effects can be readily explained by predictive coding models. These suggest that perception is a dynamic process composed of the predictions our nervous system creates concerning future sensory input, and the mismatch between those predictions and the actual input (i.e. prediction errors). In this project, we aimed at developing a robust paradigm that would allow for a temporal dissociation of pain-specific prediction and prediction error signals. This would enable us to test whether these two parameters are represented in the human spinal cord, the earliest station of central nervous system pain processing.

In two experiments (each: N=24) we used a probabilistic heat-pain paradigm that allowed us to vary the predictive information and nociceptive input on a trial-by-trial basis, while concurrently recording skin conductance and pupil dilation responses. The experiments differed in two aspects: while study 1 was a direct replication of the work of Geuter and colleagues (2017), study 2 used a longer interval for the presentation of the predictive visual cues (to allow for a temporal evolution of prediction signals) and also contained trial-by-trial pain ratings (in order to assess effects on the subjective level).

As expected, we observed that the type of stimulation (painful vs non-painful) had a strong effect on autonomic responses (Fig. 5.3.2.A), as well as on pain ratings, with higher responses for painful stimulation. We also observed an additive effect of cue (high probability of pain vs low probability of pain), with higher autonomic responses for stimuli that had been preceded by the ‘high probability of pain’ cue (Fig. 5.3.2B). This effect was also present in pain ratings. Importantly, we were able to isolate this cue effect in Study 2, where it was evident before the start of thermal stimulation (insets in Fig. 5.3.2.B). Contrary to our expectations, we were not able to find any evidence for prediction error signals (i.e. stronger responses to unexpected vs expected painful stimuli) in autonomic or subjective responses, thus failing to replicate the results from Geuter and colleagues (2017).

In ongoing work, we are following up on the role of two factors that may have led to our replication attempts be-
Assessing the processing of painful stimuli in the human spinal cord is currently only possible via indirect means. One either relies on behavioural read-outs (such as nociceptive reflexes) or acquires hemodynamic signals from the spinal cord with fMRI. While both approaches provide valuable insights, a direct and non-invasive electrophysiological measure of spinal cord nociceptive processing would arguably be desirable. Here, we take a first step in this direction by developing a robust recording and analysis approach for the human spinal cord, using well-established somatosensory evoked potentials (SEPs; Cruccu et al., 2008, Clinical Neurophysiology 119:1705-1719) as a test bed.

In a group study (N=36), we separately stimulated the median and tibial nerves with non-painful electrical impulses and – using surface electrodes – recorded the ensuing responses from the cervical and lumbar spinal cord, as well as peripheral nerves and the brain (Fig. 5.3.3A). In contrast to previous investigations of spinal cord SEPs, we used i) an adequately powered sample, ii) non-sedated participants, iii) a high electrode-density for spinal recordings, and iv) techniques for removal of physiological noise.

Figure 5.3.3 (A) Stimulation and recording set-up. The median and tibial nerves were stimulated at the left wrist and ankle, respectively (yellow rectangles). SEPs were recorded from the brain (64 electrodes; upper rectangle), the cervical spinal cord (18 electrodes; middle rectangle), the lumbar spinal cord (18 electrodes; lower rectangle) and the peripheral nerves (rectangles at biceps and knee). (B) & (C) SEPs to median and tibial nerve stimulation. Top row: early cortical SEPs to median (N20 at electrode CP4, 19ms, -1.3µV) and tibial nerve stimulation (P39 at electrode Cz, 40ms, 1.5µV) as well as corresponding isopotential maps. Middle row: spinal SEPs to median (N13 at electrode over 6th cervical vertebra, 14ms, -1.1µV) and tibial nerve stimulation (N22 at electrode over 1st lumbar vertebra, 23ms, -0.5µV), as well as the corresponding isopotential maps. Bottom row: compound nerve action potentials to median (N6 at biceps electrode, 6ms, -3.1µV) and tibial nerve stimulation (N8 at knee electrode, 9ms, -1.3µV). The large signal around 0ms and the following ramp is an artefact of the electrical stimulation. In all line plots black lines represent the group-averaged response and grey error bands represent the standard error. The scale for all isopotential maps is identical and the data come from a 2ms-window around the peak.
Outside of the spinal cord (first and third row of Fig. 5.3.3B,C), we observed early cortical SEPs with the expected latency and topography to median and tibial nerve stimulation (N20 and P39, respectively; both over primary somatosensory cortex), as well as compound action potentials in the peripheral nerves (N6 at the biceps and N8 at the back of the knee, respectively). In the spinal cord, we observed SEPs to median nerve stimulation at the cervical level (N13 recorded over the 6th cervical vertebra: 14ms, -1.1µV; Fig 5.3.3B) and SEPs to tibial nerve stimulation at the lumbar level (N22 recorded over the 1st lumbar vertebra: 23ms, -0.5µV; Fig. 5.3.3C). The robustness of these responses was established by an odd-even split of the data as well as a replication study. The N13 was maximally expressed over vertebra C4/C5, whereas the N22 had its peak over vertebra L1/L2. In ongoing work, we are aiming to obtain single-trial SEPs (via multivariate techniques) that will also allow us to probe for correlations across levels of the nervous system.

As a whole, this study demonstrates that it is possible to record electrophysiological responses to somatosensory stimulation not only in the human brain, but also in the spinal cord with a considerable level of robustness and topographical specificity. Our next project will extend this approach to investigate electrophysiological responses to natural painful stimuli, which so far have not been recorded in the human spinal cord.
Conferences, Workshops, and Symposia

2019

Awards

2018
- Eippert, F. ERC Starting Grant. European Research Council (ERC), Brussels, Belgium.
- Kapitan, M. Mind and Brain Travel Award, Humboldt University Berlin, Germany.
- Nierula, B. Young Scientist Award. Mind Brain Body Symposium, Berlin, Germany.

Appointments

2018
- Eippert, F. Max Planck Research Group Leader (W2), Max Planck Society, Germany.

Publications

(spanning reporting period, but published prior to joining MPI CBS)

Journal Articles


Cognitive functions are organised in distributed neural networks in the human brain. Flexible interaction within and between different networks is enabled by neural plasticity, key mechanisms that shape brain function throughout life and allow for lifelong learning and adaptation. However, it is not clear how the brain adapts to neuronal challenges. The central aim of our research is to identify generic principles of adaptive plasticity, in the neural networks underlying higher cognitive functions, across the adult lifespan. Specifically, our work looks at the role of neural plasticity during novel cognitive skill acquisition, as an adaptive mechanism for cognitive challenges, in counteracting cognitive decline, and in functional compensation following brain injury. Our overarching hypothesis is that neural networks for cognition can rapidly change the functional weight of participating nodes, enabling flexible compensation after disruption (Hartvigsen, 2018, Trends in Cogn Sci; see Fig. 5.4.). Our research programme has the following specific goals that are exemplified in five abstracts: i) to identify key neural networks for specific cognitive functions and their interactions (5.4.1, 5.4.2); ii) to probe the relevance and specialisation of key nodes for different cognitive functions (5.4.3); iii) to modulate the consolidation of new skills (5.4.4); and iv) to map plasticity-related after-effects of neurostimulation at the neurophysiological and neural network level (5.4.5). A better understanding of these processes will help pave the way for a valid model of adaptive plasticity in neural networks for cognition and future enhancement of recovery after brain injury, such as stroke.

Figure 5.4. A model of flexible compensation in cognitive networks. A (virtual) lesion to a neural key region for a specific cognitive function may decrease the contribution of the specific network. The brain may compensate for the disruption by recruiting alternative networks, including neighboring networks for other specific functions or domain-general networks.
Task-dependent recruitment of modality-specific and multimodal regions during conceptual processing

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2 Department of Psychiatry, Ulm University, Germany

Conceptual knowledge is crucial for many cognitive abilities such as word comprehension. Previous evidence indicates that concepts are, at least in part, composed of perceptual and motor features that are represented in modality-specific brain regions. However, it is unclear to what extent the retrieval of perceptual-motor features and the resulting recruitment of modality-specific regions depend on the task. To address this issue, we measured brain activity in forty healthy participants using fMRI while they performed three different tasks—lexical decision, sound and action judgment—on words that independently varied in their association with sounds or actions. Neural activity for sound or action features was found in modality-specific auditory or motor-related brain regions, respectively, only when they were task-relevant (Fig. 5.4.1.1). Activity in higher-level, multimodal regions was observed during both sound and action feature retrieval (Fig. 5.4.1.2). These findings provide strong evidence for a task dependency of conceptual feature retrieval and recruitment of modality-specific brain regions. Crucially, we show first evidence that not only modality-specific, but also multimodal regions are engaged in conceptual processing in a flexible, task-dependent fashion, responding selectively to task-relevant conceptual features.

Figure 5.4.1.1 (A) Left: Activation overlap (orange) between sound feature retrieval (yellow) and real sound perception (red). Right: Percent signal change in subject-specific functional regions of interest (fROIs) activated for both sound feature retrieval and real sound perception. Different data were used for fROI definition and response estimation. (B) Left: Activation overlap (purple) between action feature retrieval (blue) and movement execution (red). Right: Percent signal change in subject-specific fROIs engaged for both action feature retrieval and movement execution. IFG = inferior frontal gyrus; IPS = inferior parietal sulcus; aIPS = anterior IPS; pIPS = posterior IPS; LTO = lateral temporal-occipital junction; pMTG = posterior middle temporal gyrus; dmPFC = dorsomedial prefrontal cortex; vmPFC = ventromedial prefrontal cortex; PMC = premotor cortex; PMv = ventral PMC; SMA = supplementary motor area; aSMG = anterior supramarginal gyrus. All activation maps were thresholded at q < 0.05 FDR-corrected (extent > 20 voxels).
Differential contributions of left-hemispheric language regions to basic semantic composition

Graessner, A.¹, Zaccarella, E.¹, & Hartwigsen, G.¹
¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Semantic composition, that is, the ability to combine single words to create complex meanings, is a core feature of human language. Despite growing interest in the neural basis of semantic composition, the neural correlates and interactions between semantic-related regions remains a matter of debate. In the present fMRI study, we designed a two-word paradigm in which phrases only differed along the semantic dimension, while keeping syntactic information similar. Healthy participants listened to meaningful phrases (“fresh apple”), anomalous phrases (“awake apple”) and pseudoword phrases (“awake gufl”) and performed a meaningfulness judgement task. We identified distinct neural signatures for two processes during basic semantic composition. The more general phrasal com-

Figure 5.4.2Multimodal conceptual regions. Left: Activation overlap (green) between the retrieval of action features (blue) and sound features (yellow). Activation maps were thresholded at $q < 0.05$ FDR-corrected (extent $> 20$ voxels). Right: Percent signal change in subject-specific FROIs engaged for both action and sound feature retrieval. aIFG = anterior inferior frontal gyrus; pIPL = posterior inferior parietal lobe; pMTG = posterior middle temporal gyrus; dmPFC = dorsomedial prefrontal cortex; vmPFC = ventromedial prefrontal cortex.

5.4.2 Differential contributions of left-hemispheric language regions to basic semantic composition

Semantic composition, that is, the ability to combine single words to create complex meanings, is a core feature of human language. Despite growing interest in the neural basis of semantic composition, the neural correlates and interactions between semantic-related regions remains a matter of debate. In the present fMRI study, we designed a two-word paradigm in which phrases only differed along the semantic dimension, while keeping syntactic information similar. Healthy participants listened to meaningful phrases (“fresh apple”), anomalous phrases (“awake apple”) and pseudoword phrases (“awake gufl”) and performed a meaningfulness judgement task. We identified distinct neural signatures for two processes during basic semantic composition. The more general phrasal com-

Figure 5.4.2.1 (A) Activation overlap of meaningful > pseudowords and anomalous > pseudowords. (B) Activation map for the contrast meaningful > anomalous. All activation maps were thresholded at $q < 0.05$ FDR-corrected. ACC = anterior cingulate cortex, aIFG = anterior inferior frontal gyrus, ATL = anterior temporal lobe, DMPFC = dorsomedial prefrontal cortex; pMTG = posterior middle temporal gyrus, Pa = angular gyrus anterior division, Pg = angular gyrus posterior division, SMG = supramarginal gyrus.

Figure 5.4.2.2 Functional connectivity (PPI) results with Pg as seed region (blue) for the contrast meaningful > pseudowords (thresholded at $p < 0.05$ FWE-corrected at the cluster level). aIFG = anterior inferior frontal gyrus, preSMA = pre supplementary motor area, Pg = angular gyrus posterior division.
position process, which is independent of the plausibility of the resulting phrase, engages a wide-spread, left-hemispheric network comprising both executive semantic control regions as well as general conceptual representation regions (Fig. 5.4.2.1A). Effective connectivity results further showed that meaningful phrasal composition crucially relies on the interaction of the left anterior inferior frontal gyrus and the posterior angular gyrus (Fig. 5.4.2.2). Specific meaningful composition, on the other hand, is guided by the anterior angular gyrus (Fig. 5.4.2.1B). We show that the angular gyrus may be decomposable into two sub-regions for different processes during semantic composition.

Dissociating semantic and phonological contributions of the left inferior frontal gyrus to language production

Klaus, J. 1, & Hartwigsen, G. 1
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While the involvement of the left inferior frontal gyrus (IFG) in language production is undisputed, the role of specific sub-regions at different representational levels remains unclear. Some studies suggest a division of anterior and posterior regions for semantic and phonological processing, respectively. Crucially, evidence thus far comes only from correlative neuroimaging studies. The functional relevance of these sub-regions during a given task remains elusive. In this study, we asked 24 native German-speaking, right-handed participants to perform a rhyme generation task and a category member generation task (Fig. 5.4.3). On each trial, five pulses of 10-Hz repetitive transcranial magnetic stimulation (rTMS) were applied over anterior or posterior IFG (aIFG/pIFG), or vertex as a control site. We found a functional-anatomical double dissociation between tasks and stimulated sub-regions. Naming latencies were significantly delayed in the semantic task when rTMS was applied to the aIFG (relative to pIFG and vertex). In contrast, we observed a facilitation of naming latencies in the phonological task when rTMS was applied to pIFG (relative to aIFG and vertex) (Fig. 5.4.3C). The results provide the first causal evidence for the notion that anterior portions of the IFG are selectively recruited for semantic processing while posterior regions are functionally specific for phonological processing during word production. Thus, the results shed light on the functional parcellation of the left IFG in language production. Moreover, the opposing polarity of the effects provides the first hints of differential mechanisms of TMS relative to the cognitive process at play. We will further investigate this question in a follow-up study.

Figure 5.4.3 (A) Schematic outline of the three-session procedure. Stimulation and task order were counterbalanced across participants. (B) Illustration of a trial in the semantic and phonological task, respectively. (C) Naming latencies aggregated across participants, broken down by task and stimulation site.
Interleaving motor sequence training with high-frequency repetitive transcranial magnetic stimulation facilitates motor consolidation

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2 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

The acquisition of novel motor skills is a fundamental lifelong learning process and crucial for successful everyday behaviour. Performance gains acquired by training undergo a transition from an initially labile state to a state that is progressively more resistant to interference, a phenomenon referred to as motor consolidation. Previous work has shown that the primary motor cortex (M1) is a key neural region for motor consolidation. However, it is not known whether physiological processes underlying post-training motor consolidation in M1 are already active during training or only after the completion of training. We examined whether 10 Hz interleaved repetitive transcranial magnet-

Figure 5.4.4 Experimental Design. (A) Participants performed a different motor sequence in each of two sessions with their left hand. (B) i-rTMS was applied over either the right M1, or the vertex in different sessions. (C) During each session, participants performed 30 training blocks of an explicit motor sequence learning task with their left hand, interleaved by short rest blocks. Offline consolidation of training-induced performance increments was assessed 6 h later with the trained hand, immediately followed by retesting of the mirror-symmetric sequence with the untrained hand. (D) Three trains of i-rTMS were applied during the 8 s rest blocks. (E-F) Behavioural results. (E) Task performance. Performance Index (PI) measures across blocks of training, delayed retesting of the trained hand, and delayed retesting of the untrained hand. Vertical bars represent standard error of the mean (SEM). (F) Consolidation. Columns represent the mean of normalised PI measures across the 8 blocks of delayed retesting (retest PI changes relative to the individual end-of-training performance). Bars represent SEM. (*) indicates significant difference of consolidation following i-rTMS directed to M1 relative to i-rTMS directed to vertex.
ic stimulation (i-rTMS) of M1 during rest periods between active motor training in an explicit motor learning task affects post-training offline consolidation. We hypothesised that stimulation during rest blocks, following active training, may have effects on motor consolidation that could be dissociated from the effects of stimulation on active motor training. Twenty-four healthy volunteers underwent two sessions of a motor-sequence learning task with i-rTMS applied to the hand area of M1 or the vertex (control region). Relative to the vertex, i-rTMS of M1 facilitated post-training consolidation assessed 6 hours after training without affecting training. This facilitatory effect generalised to delayed performance of the mirror-symmetric sequence with the untrained hand. These findings indicate that post-training consolidation can be facilitated independently of training-induced performance increments and suggest that consolidation is already initiated during offline processing in short rest periods between active training phases. These results may have implications for our understanding of the mechanisms underlying motor consolidation and stimulate novel therapeutic strategies in motor rehabilitation.

10 Hz transcranial alternating current stimulation over the prefrontal cortex induces plastic after-effects on phonological word decisions

Moliadze, V., Sierau, L., Lyzhko, E., Stenner T., Werchowski, M., Siniatchkin, M., & Hartwigsen, G.

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Department of Neuropediatrics, University Medical Center Schleswig Holstein, Kiel University, Germany
Department of Mathematical Problems of Biology RAS, Pushchino, Moscow Region, Russia
Clinic for Child and Adolescent Psychiatry and Psychotherapy, Medical Center Bethel, Bielefeld, Germany
Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Previous studies in the language domain have shown that "virtual lesions" of the left or right posterior inferior frontal gyrus impaired phonological decision-making, arguing for a causal contribution of these areas to phonological processing. However, the neurophysiological correlates of these effects are unclear. The present study addressed
the question of whether neural activity in the prefrontal cortex could be modulated by 10 Hz transcranial alternating current stimulation (tACS) and how this would affect phonological decisions. In three sessions, 24 healthy participants received tACS at 10 Hz, at 16.18 Hz (control frequency), or sham stimulation over the bilateral prefrontal cortex. Stimulation occurred before the task. Thereafter, participants performed a syllable judgment task while EEG was recorded. Relative to sham stimulation, 10 Hz tACS significantly facilitated phonological response speed. This effect was task-specific as tACS did not affect a simple decision making task. Moreover, 10 Hz tACS significantly increased theta power during phonological decisions. The individual increase in theta power was positively correlated with the behavioural facilitation after 10 Hz tACS. The observed phonological facilitation after 10 Hz tACS might indicate that tACS increased task-related activity in the stimulated area to a level that was optimal for phonological performance. The significant correlation with the individual increase in theta power suggests that the behavioural facilitation might be related to increased theta power, likely indicating increased working memory efficiency. These results indicate that offline tACS provides a powerful tool to modulate task-related activity and behaviour beyond the period of stimulation.
Congresses, Workshops, and Symposia

2019
- Kuhnke, P., Numssen, O., Rysop, A., & van der Burght, S. (June). Hands-on TMS workshop. 9th IMPRS NeuroCom Summer School, Leipzig, Germany.

2018
- Kuhnke, P., Numssen, O., Rysop, A., & van der Burght, S. (June). Hands-on TMS workshop. 9th IMPRS NeuroCom Summer School, Leipzig, Germany.

2017
- Bergmann, T. O., & Hartwigsen, G. (June). Transcranial brain stimulation in psychology: from neural mechanisms to cognitive function. Annual Meeting of the German Society for Psychology, Section Biopsychology and Neuropsychology, Trier, Germany.

Appointments

2018

Awards

2019
- Hartwigsen, G. Visiting Fellowship. Queensland University of Technology, Institute of Health and Biomedical Innovation. Brisbane, Australia.
- Martin, S. First prize in Science Slam at Annual Symposium of German Association of Speech-Language Pathology (dbs), Halle, Germany.

Publications

(spanning reporting period, published during or prior to group’s commencement, hence partly overlapping with Dept of Neuropsychology)

Journal Articles


Index of Published Figures

Figure 5.4

Figure 5.4.3
Figure adapted from Klaus, J., & Hartwigsen, G. (2019). Dissociating semantic and phonological contributions of the left inferior frontal gyrus to language production. Human Brain Mapping, 40(11), 3279-3287. doi:10.1002/hbm.24597.

Figure 5.4.4

Figure 5.4.5
Figure adapted from Weise, K.*, Numssen, O.*, Thielscher, A., Hartwigsen, G.# & Knoeschke, T.R.# (in press). A novel approach to localize cortical recruitment of modality-specific and multimodal regions during conceptual processing. Cerebral Cortex.


The World Health Organization has declared stress one of the major health risks of the 21st century. They predict that every second sick call in the year 2020 will be due to stress. It is our tendency to mount a stress response for psychosocial reasons that leads to chronic stress exposure and stress-related disease in modern society. Stress reactivity in the social context and how social factors and training techniques can be used to decrease stress reactivity, are important topics of the Social Stress and Family Health Research Group.

A central topic that we are currently investigating concerns the interactions of different stress- and health-related biomarkers. Here we focus both on situations of acute challenge and on basal states. We thus gain a fundamental understanding of how different adverse and protective factors contribute to stress-related vulnerability and stress resilience. Above and beyond learning about the physiological stress reaction per se, this work informs our hypotheses on how mental training interventions may reduce stress and improve health and wellbeing. Recent work in this context has focused on interactions of cortisol and the brain-derived neurotrophic factor (BDNF; 5.5.1) and on interactions of leukocyte telomere length and cortical thickness (5.5.2).

A second focus of the group lies within the social neuroscience of human attachment. In this context we assess the psychological, biological, and brain bases of interpersonal relationships within families. When humans communicate, they unconsciously synchronise their behaviour, and even their brain and peripheral physiological activity. This empathic ability of tuning in to one another seems to be an important aspect of successful social interaction and understanding. In studying social interactions between children and parents in a dyadic setting, our work examines the role of human attachment in behavioural and neural synchronisation (5.5.3).

Data in our group are collected using advanced methods of social neuroscience, including functional magnetic resonance imaging and functional near-infrared spectroscopy. These data are combined with peripheral physiological biomarkers such as cortisol, pro-inflammatory cytokines and brain-derived neurotrophic factor, self-report questionnaires, and semi-structured narrative interviews derived from attachment theory.
Acute psychosocial stress increases serum BDNF levels: An antagonistic relation to cortisol but no group differences after mental training

Linz, R. 1, Puhlmann, L. M. C. 1, Apostolakou, F. 2, Mantzou, E. 3, Papassotiriou, I. 2, Chrousos, G. P. 4, Engert, V. 1, 5, †, & Singer, T. 6, †

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3 First Department of Pediatrics, School of Medicine, University of Athens, "Aghia Sophia" Children's Hospital, Athens, Greece
4 First Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, Greece
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6 Social Neuroscience Lab, Max Planck Society, Berlin, Germany
† Joint last authors

Brain-derived neurotrophic factor (BDNF) facilitates neuronal plasticity and can thus counteract the adverse effects of excessive cortisol signaling on neuronal integrity. While this long-term antagonism of BDNF and cortisol is well documented during chronic stress, here we investigated their relationship during an acute laboratory stress paradigm (the Trier Social Stess Test, TSST) in a large sample of 301 healthy participants.

We show that BDNF is stress-reactive, characterised by a significant increase in serum BDNF levels in response to the TSST, and a significant decline after a recovery phase (Figure 5.5.1 A). Our results indicate an antagonistic association of BDNF and cortisol during acute stress. Specifically, higher BDNF peaks after stress were associated with a faster cortisol recovery while a higher increase in cortisol after stress was associated with a faster decrease in BDNF (Figure 5.5.1B). Mental training did not modulate the found alterations.

This work demonstrates in a large healthy adult population that serum BDNF levels are stress-sensitive. It also provides novel evidence for the dynamic short-term interaction of BDNF and cortisol, which is consistent with the proposed long-term antagonism of the two agents. These findings contribute to our understanding of how stress responses, mediated by both cortisol and BDNF, may turn from adaptive to pathologic. Moreover, they highlight the critical need to explore involved molecular mechanisms in order to obviate stress chronification and its consequential health risks.

Figure 5.5.1 (A) Brain-derived neurotrophic factor (BDNF) measures (ln) collected at −50 min (baseline), +15 min (post-stress) and +60 min (recovery) relative to Trier Social Stress Test (TSST) onset at 0 min. (B) Higher serum BDNF levels at post-stress (+20 min) were associated with a steeper cortisol recovery (p < .001).
Association of short-term change in leukocyte telomere length with cortical thickness and outcomes of mental training among healthy adults. A randomised clinical trial

Puhlmann, L. M. C. 1, Valk, S. L. 2,3, Engert, V. 1,4, Bernhardt, B. C. 5, Lin, J. 6, Epel, E. S. 7, Vrtička, P. 1,†, & Singer, T. 8,†

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4 Institute of Psychosocial Medicine and Psychotherapy, Jena University Hospital, Friedrich-Schiller-University Jena, Germany
5 Montreal Neurological Institute, McGill University, Montreal, Canada
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The length of telomeres, i.e. protective chromosomal caps, is associated with the development of age-related diseases and structural differences in multiple brain regions (King et al., 2014, JAMA Neurology 71:1247-1254). It remains unclear, however, whether change in telomere length is also linked to brain structure change. In this study, we first investigated whether there is evidence for such a dynamic association between leukocyte telomere length (L TL) and cortical thickness (CT). Second, we examined whether LTL is affected by a longitudinal contemplative mental training intervention. Mindfulness-based mental training has been found to reduce several psychological strains that are associated with shorter telomeres, including loneliness and stress (e.g. Epel et al., 2004, PNAS 101:17312-17315). As a final analysis, we planned to assess whether potential training-related changes in LTL are mirrored by CT change in the regions identified in our first analysis. LTL and CT were measured four times over nine months as part of the ReSource Project (Singer et al., 2016, Max Planck Institute for Human Cognitive and Brain Sciences). Training cohort participants completed three modules cultivating interoception and attention and interoception (Presence module), compassion (Affect module), or perspective taking (Perspective module) (Figure 5.5.2A).

Our first research question was tested in a retest control cohort who underwent all testing but no training. In this subsample, naturally occurring LTL change was related to CT change in the left precuneus extending to the posterior cingulate cortex (Figure 5.5.2B). Telomere shortening was related to cortical thinning and telomere lengthening to cortical thickening. The training had no effect on LTL (Figure 5.5.2C). The findings of this trial indicate an association between short-term change in LTL and concomitant change in plasticity of the left precuneus extending to the posterior cingulate cortex. This result contributes to the evidence that LTL changes more dynamically on the individual level than previously thought. No effect of contemplative mental training was noted in what may be, to date, the longest intervention with healthy adults.

Figure 5.5.2. (A), Study design of the ReSource Project. (B), Positive association between change in leukocyte telomere length and change in cortical thickness of the left precuneus/posterior cingulate cortex (mean $t_{161} = 3.22; P < .001; r = 0.246$). (C), Model-estimated change in leukocyte telomere length by training module, error bars representing 95% CIs.
Inter-brain synchrony in mother-child dyads during cooperation: An fNIRS hyperscanning study

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† Joint first authors

During or shortly after social interaction, increased bio-behavioural synchrony can be observed on several levels of the human organism (behaviour, physiology, endocrinology, and brain activity). Bio-behavioural synchrony seems to be strongest for social interactions between close and intimate interaction partners, particularly within parent-child dyads. We hypothesised, however, that bio-behavioural synchrony and especially inter-brain coherence in parent-child dyads would depend on inter-individual differences in relationship quality. To investigate such association, we relied upon the comprehensive psychological framework of attachment theory and predicted that more secure mother-child dyads would display higher inter-brain coherence during social interaction.

Figure 5.5.3 (A) fNIRS optodes and regions of interest. The estimated average location of source (red circles) and detector (blue circles) optodes based on 3D digitizer data and plotted in MNI space. Regions of interest (ROIs) were established a priori for the right inferior (yellow triangle), right dorsolateral (red triangle), right superior (green triangle), and right frontopolar prefrontal cortex (purple triangle), as well as right temporoparietal cortex (blue rectangle). (B) Left panel: experimental setup (depicted is an identical setup in an adult-adult dyad due to data protection issues — taken from Xu et al., 2012); right panel: trial stimulus sequence, screenshots of the ready signal, “go” signal to initiate mother and child response, and feedback window. (C) Left panel: overall inter-brain coherence during cooperative versus independent button presses (F(1, 27) = 7.47, p = .011, partial η² = .22); right panel: overall inter-brain coherence split into the five a priori ROIs, with significant (uncorrected) effects in the dorsolateral (t(27) = 2.15, p = .041, pFDR = .103, red) and right frontopolar prefrontal cortex (t(27) = 2.62, p = .014 pFDR = .070, purple). (D) Significant gender-effect (F(1, 25) = 7.57, p = .010, partial η² = .24) in overall inter-brain coherence, driven by differential coherence in mother-son dyads only. (E) Negative association between right frontopolar prefrontal cortex inter-brain coherence increase during cooperative (versus independent) button presses and avoidant child attachment towards the mother (r = -.39, p = .038 – uncorrected). * = p < .05; † = p < .10, error bars +/- 1 S.E.M.
Inter-brain coherence data acquired by dual functional near-infrared spectroscopy (fNIRS) in five regions of interest spanning the right prefrontal and lateral temporal cortex (Figure 5.5.3A) was available from N = 28 mother-child dyads (15 girls; child age M = 11.17, SD = 1.27; mother age M = 45.93, SD = 3.76). We contrasted two interaction conditions during a computerised button-press task (Figure 5.5.3B), either requiring dyads to press a button as simultaneously as possible (cooperation) or as fast as possible regardless of the other dyad partner’s response (independent). Child attachment towards the mother was acquired with a child version of the Experiences in Close Relationships Questionnaire (revised version; ECR-RC). Findings revealed overall increased inter-brain coherence during cooperative versus independent button presses, particularly in the dorsolateral and frontopolar prefrontal cortex (Figure 5.5.3C). Interestingly, there was a gender-effect in overall inter-brain coherence in that only mother-son dyads showed a differential coherence pattern for cooperative versus independent button presses (Figure 5.5.3D). Finally, we found preliminary evidence for an influence of attachment of the child towards the mother, because inter-brain coherence increases during cooperative versus independent button presses in the frontopolar prefrontal cortex was less pronounced the higher children scored on attachment avoidance (Figure 5.5.3E). However, the latter association did not survive correction for multiple comparisons (number of ROIs, attachment anxiety, child age, and gender). More research is needed to better understand the potential role of overall inter-brain coherence in mother-child cooperation and the potential link between inter-brain coherence and attachment.
Conferences, Workshops, and Symposia

2019

- Engert, V. (August). Stress reduction after contemplative mental training: Involvement of plasma oxytocin? 49th International Society for Psychoneuroendocrinology, Milan, Italy.

Appointments

- Engert, V. Research Group Leader (W2), Max Planck Society, Germany.
- Engert, V. Professor of Social Neuroscience, Institute of Psychosocial Medicine and Psychotherapy, Jena University Hospital, Friedrich-Schiller-University Jena, Germany.

Publications

Journal Articles


Language comprehension is mostly effortless. However, difficulty may arise when speakers speak too fast or too slowly, or give too much information in too little time. Whilst we may be flexible, our comprehension abilities are still limited.

Language Cycles looks for electrophysiological properties of the human brain that limit our verbal processing abilities: Does our preferred speed of talking depend on the brain’s pace of processing? How much information can we process within a given time window, and how long are the time windows that our brain uses to sample and process language? Are endogenous language-sampling time windows of the human brain the reason that all languages of the world serve information in units of certain durations (e.g. words, phrases, and sentences)?

In electrophysiological terms, our working hypothesis is that oscillatory activity with periods in the range of seconds underlies linguistic information sampling. Our research combines classical psycholinguistic experiments, methods from cognitive neuroscience (e.g. electro- and magnetoencephalography (M/EEG), transcranial magnetic stimulation), computational linguistics (e.g. annotated cross-linguistic corpora, parsing algorithms, information theory), and artificial intelligence.

The combination of psycholinguistic and neuroscientific methodology enables us to characterise the electrophysiological time windows that determine our pace and limits of linguistic information sampling. Our experimental workhorse are ambiguous sentence stimuli that have multiple readings: For instance, in *The client sued the murderer with the corrupt lawyer.*, participants’ decision on whether *The client* or *the murderer* hired the corrupt lawyer indicates directly at which pace they sample information units from speech (i.e. they either terminate or continue a unit at the offset of *the murderer*). Likewise, in *Max saw John and Jim smiled.*, an erroneous sampling of *John and Jim* as a single unit of information triggers a processing breakdown at *smiled*, which can be used to study the underlying reason for the erroneous sampling, that is, the endogenous limit of information sampling.

Our hypothesis is not only directed at the brain, but also the possible implications concerning our understanding of language cycles.
of language as a cultural system: If endogenous electro-physiological cycles temporally constrain linguistic information sampling, could (all) human languages not have evolved to serve information in units that fit these cycles in duration? To address this hypothesis, we will quantify the size of information units in the languages of the world, employing large-scale cross-linguistic text corpora. To explain the observed linguistic units from cyclic electrophysiological activity, we will acquire cross-linguistic resting-state and event-related EEG data. We then aim to link the linguistic and electrophysiological data in the frequency domain, using methods from computational linguistics and artificial intelligence.

Our inter-disciplinary research has the potential to explain the shape of human language by the processing cycles of the human brain—the Language Cycles.

![Language Cycles Map](image_url)

**Figure 5.6.B** Large-scale corpora annotated for linguistic information units are available for 50+ languages, allowing for typologically representative cross-linguistic analyses. For a sub-sample of these languages, EEG data will be acquired and linked to the corpus-linguistic results.
5.6.1 Linguistic bias modulates interpretation of speech via neural delta-band oscillations

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Language comprehension requires that single words be grouped into syntactic phrases, as words in sentences are too many to memorise individually. In speech, acoustic and syntactic grouping patterns mostly align. However, ambiguous sentences allow for alternative grouping patterns (e.g. The client sued the murderer with the corrupt lawyer, where the corrupt lawyer could either belong to The client or the murderer). In such situations, comprehenders may form phrases that contradict speech prosody. In the example, comprehenders tend not to group with the corrupt lawyer with the murderer, even if there is no prosodic boundary that interrupts this grouping pattern. While delta-band oscillations are known to track prosody, we hypothesised that linguistic grouping bias can modulate the interpretational impact of speech prosody in ambiguous situations, which should surface in delta-band oscillations when grouping patterns chosen by comprehenders differ from those indicated by prosody. In our auditory electroencephalography study, the interpretation of ambiguous sentences depended on whether an identical word was either followed by a prosodic boundary or not, thereby signaling the ending or continuation of the current phrase. Delta-band oscillatory phase at the critical word should reflect whether participants terminate a phrase despite a lack of acoustic boundary cues. Crossing speech prosody with participants’ grouping choice, we observed a main effect of grouping choice—indeed of prosody. An internal linguistic bias for grouping words into phrases can thus modulate the interpretational impact of speech prosody via the delta-band oscillatory phase. This is evidence that delta-band oscillations do not only passively follow speech prosody, but also have an active and potentially constraining role in the internal formation of linguistic information units.

Figure 5.6.1 (A) In no-boundary sentences (left), den Mörder (the murderer) and mit dem korrupten Anwalt (the corrupt lawyer) form one single syntactic phrase (blue). In boundary sentences (right), mit dem korrupten Anwalt forms a distinct syntactic phrase (red), interpreted as linking to Der Klient (the client); conditions are distinguished prosodically. Participants indicated their grouping choice via a button press (bottom). (B) Participants can distinguish the conditions acoustically, but are biased to assume a syntactic phrase boundary (i.e. more two-phrase choices for two-phrase sentences than one-phrase choices for one-phrase sentences). (C) Delta-band phase differs between two-phrase and one-phrase choices, orthogonal to speech prosody. (D) When a syntactic phrase boundary is assumed, EEG coherence with speech prosody reduces, predicting individual bias.
Perturbation of left posterior prefrontal cortex modulates top-down processing in sentence comprehension

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Communication is an inferential process. In particular, language comprehension constantly requires top-down efforts, as multiple interpretations are often compatible with a given sentence. To assess top-down processing in the language domain, our experiment employed ambiguous sentences that allow for multiple interpretations (e.g. The client sued the murderer with the corrupt lawyer, where the corrupt lawyer could either belong to The client or the murderer). Interpretation thus depended on whether participants chunked the words of the sentence into short or long syntactic phrases. In principle, bottom-up acoustic information (i.e. the presence or absence of an intonational phrase boundary at the offset of the murderer) indicates one of the two possible interpretations. Yet, acoustic information often indicates interpretations that require words to be chunked into overly long phrases that would overburden internal processing constraints, such as working memory capacity. Processing is biased against these demands, reflected in a top-down preference to chunk words into short rather than long phrases. It is often proposed, but also debated, that the ability to chunk words into short phrases is subserved by the left inferior frontal gyrus (IFG). Here, we employed focal repetitive transcranial magnetic stimulation to perturb the left IFG, which resulted in a further decrease in the aptitude to tolerate long phrases, indicating the inability of the left IFG to assist the chunking of words into phrases. In contrast, auditory information processing was not affected. Our findings support a causal top-down role of the left inferior frontal gyrus in chunking words into phrases, which poses an endogenous constraint on grouping words into larger units of information.

Figure 5.6.2  (A) In no-boundary sentences (left), den Mörder (the murderer) and mit dem korrupten Anwalt (with the corrupt lawyer) form one single syntactic phrase (blue); in boundary sentences (right), mit dem korrupten Anwalt forms a distinct syntactic phrase (red), interpreted as linking to Der Klient (the client); conditions are distinguished prosodically; participants indicated their grouping choice via a button press (bottom); (B) participants can distinguish the conditions acoustically, but are biased in assuming a syntactic phrase boundary (i.e. more two-phrase choices for two-phrase sentences than one-phrase choices for one-phrase sentences); (C) rTMS over the left IFG, normalised to sham stimulation, significantly reduces participants’ aptitude to generate a long syntactic phrase, even if prosodic cues do not indicate phrase termination.
Synchronous, but not entrained: Exogenous and endogenous cortical rhythms of speech and language processing

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Research into speech processing often focuses on a phenomenon termed **entrainment**, whereby the cortex shadowed rhythmic acoustic information with oscillatory activity. Entrainment has been observed in a range of acoustic rhythms that are physically present in speech. In addition to acoustic rhythms, synchronicity with abstract information (e.g. syntactic structures) has recently been observed. Current accounts of entrainment face two major challenges. First, speech is not precisely rhythmic, leaving it unclear whether speech acoustics are a plausible cause for associated rhythmic electrophysiological activity or not. Second, electrophysiological synchronicity with abstract linguistic representations that lack a clear acoustic counterpart has recently been described; this synchronicity can, in principle, not have been caused by physical features of the speech stimulus. In the current opinion article, we propose that apparent entrainment does not always result from acoustic information. Rather, internal oscillatory rhythms may have self-contained functionalities in the generation of abstract representations and predictions. While acoustics may often provide punctate opportunities for entrainment, internal rhythms may also have self-contained functionalities in the inference and prediction of information, leading to intrinsic synchronicity—not to be counted as entrainment. Our proposal may open up new research avenues in the psycho- and neurolinguistic study of language processing and language development.

![Figure 5.6.3](image)

(A) Entrainment of neural oscillations by a rhythmic exogenous acoustic stimulus (e.g. a regular tone sequence). Rhythmic edges or peaks in the amplitude envelope of the stimulus synchronise neural oscillation at stimulation frequency. (B) Entrainment is impossible in cases of non-rhythmic amplitude cues in speech stimulus. (C) Intrinsic synchronicity of neural oscillations to a non-rhythmic acoustic stimulus (e.g. speech). Inferred and predictive linguistic knowledge (e.g. of abstract syntactic structure or predicted words) deployed by endogenous signals (i.e. local-field potentials or slower-frequency neural oscillations) establishes continued oscillatory rhythmicity disguised as entrainment, in spite of lacking acoustic cues.
In auditory neuroscience, synchronisation of electrophysiological oscillations to low-level acoustic and high-level linguistic features is a well-established phenomenon, but its functional purpose for verbal information transmission is unclear. Here, we hypothesised that the synchronisation of electrophysiological responses at delta-band frequency (i.e. < 4 Hz) to the speech stimulus serves to implicitly align neural excitability with syntactic information. This hypothesis rests on two prior findings. First, the phase of an oscillation recorded at the scalp is often taken to be a mirror of neuronal excitability, and thus receptiveness on the neuronal level. Second, auditory task performance, and thus information processing, was previously observed to depend on delta-band oscillatory phase. The experimental paradigm of our auditory electroencephalography study uniformly distributed morpho-syntactic violations across syntactic phrases of natural sentences, such that violations would occur at points differing in syntactic information content. In support of our hypothesis, we found behavioural responses to morpho-syntactic violations to increase with decreasing syntactic information—in significant correlation with the delta-band phase, which we found to be synchronised to our speech stimuli.

Our findings indicate that rhythmic electrophysiological synchronisation to the speech stream is a functional mechanism that may serve to align neural excitability with linguistic information content, optimising the uptake of syntactic information during language comprehension.
Conferences, Workshops, and Symposia

2017


Appointments

2018


Publications

(spanning reporting period, published during or prior to group's commencement, hence partly overlapping with Dept of Neuropsychology)

Journal Articles


- Meyer, L. (May/June). Advances in Language Electrophysiology: from Auditory Processing to Sentence Comprehension. Symposium at Psychologie und Gehirn, Giessen, Germany. (Chair together with Caroline Beese)
Index of Published Figures

Figure 5.6.1

Figure 5.6.2

Figure 5.6.3

Figure 5.6.4
Infants have remarkable social abilities. From very early in life, they have a preference for social over non-social stimuli, are guided by the attention and actions of others when encoding the world, and develop sophisticated expectations of others’ actions within the first year of life. It is not before the age of 4 years, however, that children are traditionally thought to begin to reason about others’ minds. This ability, referred to as Theory of Mind (ToM), is characteristic of the complex social interaction that occurs between us humans. Similarly, while infants from their first year of life have some form of representation of their own body and actions, it is only by the age of 2 years that children recognise themselves in the mirror. Finally, by 4 years of age, children begin to reason about their own thoughts and beliefs, in parallel with those of others. Our research group is guided by the question: How do children come to understand themselves and others as thinking agents in the world?

(i) Understanding others - A new account of Theory of Mind development
The traditional account that ToM develops late, relies on language, and is uniquely human has been questioned by novel, non-verbal ToM paradigms. These paradigms show that preverbal infants, and even apes, take into account others’ beliefs in their expectations of the other’s actions (e.g., Onishi & Baillargeon, 2005, Science, 308, 255-8; Krupenye et al., 2016, Science, 354, 110-4). In our previous work, we have shown a dissociation between these early ToM-like action expectations and later-developing, verbal ToM reasoning on the behavioural and neural levels (Grosse Wiesmann et al., 2017, Dev Science, 20, 1-15; Grosse Wiesmann et al., 2017, Nature Comm, 8, 1-10; Grosse Wiesmann et al., under revision). A core objective of our group is to understand the cognitive and neural structure of the processes that guide infants’ non-verbal, ToM-like behaviour, as opposed to a mature, verbal ToM.

(ii) The neural networks of verbal and non-verbal Theory of Mind
We have shown that the emergence of verbal ToM reasoning in children relies on the maturation of the same brain regions that are also involved in ToM in adults (Grosse Wiesmann et al., 2017, Nature Comm, 8, 1-10; Grosse Wiesmann et al., under revision). Moreover, the maturation of a dorsal nerve fibre bundle, connecting temporoparietal and inferior-frontal brain regions, played a crucial role for the emergence of verbal ToM (Grosse Wiesmann et al., 2017, Nature Comm, 8, 1-10). Non-verbal ToM-like behaviour, in contrast, was supported by the maturation of the inferior parietal lobe (Grosse Wiesmann et al., under revision) in a region ventrally connected to the anterior insula. Along with fMRI data from adults, these findings hint at a dual-pathway model of ToM, with a dorsal connection for verbal ToM reasoning, and a ventral connection for non-verbal ToM-like processes. Our research group seeks to uncover the functional and structural neural networks involved in verbal and non-verbal ToM processes in children and adults.

(iii) Understanding the self
A third objective of our group is to get a better understanding of the gradual emergence of a mature self-concept and its relation to the development of ToM. We investigate the hypothesis that early ToM-like behaviour is based on a strong orientation towards others. Only when a self-concept emerges and children learn to distinguish self from other, can a mature verbal ToM develop.

With a combination of behavioural and neurocognitive methods, including eye-tracking, fNIRS, EEG, and MRI, we aim to clarify the cognitive and neural basis of understanding self and others, in early childhood.
Congresses, Workshops, and Symposia

2019
- Grosse Wiesmann, C. (March) Far from a consensus – On
  the developmental continuity of implicit and explicit Theory
  of Mind. Symposium at the International Conventions for
  Psychological Science (ICPS), Paris, France. (together with
  Josef Perner, Beate Sodian, Daniela Kloo and Diane Poulin-
  Dubois)

- Grosse Wiesmann, C. (October) The development of
  understanding self and other. Workshop at University of
  Copenhagen, Denmark. (Organizer and Chair together with
  Dora Kampis & Victoria Southgate)

Appointments

2019
- Minerva Fast Track Fellow, Max Planck Society, Germany.

Publications

Books and Book Chapters
- Grosse Wiesmann, C. (2018). The emergence of Theory of
  Mind: Cognitive and neural basis of false belief understanding
  Cognitive and Brain Sciences, Leipzig.
- Grosse Wiesmann, C., & Southgate, V. (in press). Early theo-
  ry of mind development: Are infants inherently altercentric? In
  K. Ochsner, & M. Gilead (Eds.), The neural basis of mentalizing.
  Springer Nature.

Journal Articles
- Grosse Wiesmann, C., Friederici, A. D., Disla, D., Steinbeis, N.,
  & Singer, T. (2018). Longitudinal evidence for 4-year-olds’ but
  not 2- and 3-year-olds’ false belief-related action anticipation.
  cogdev.2017.08.007.
- Grosse Wiesmann, C., Schreiber, J., Singer, T., Steinbeis, N., &
  Friederici, A. D. (2017). White matter maturation is associated
  with the emergence of Theory of Mind in early childhood. Nature
  Communications, 8: 14692. doi:10.1038/ncomms14692.
- Grosse Wiesmann, C., Friederici, A. D., Singer, T., & Steinbeis, N.
  (2017). Implicit and explicit false belief development in preschool
  desc.12445.
Humans are remarkably accurate at perceiving the visual world around them and can effortlessly interact with it in a meaningful manner. Despite the apparent simplicity of visual perception, it has remained challenging to understand how we are able to extract meaningful information from ever-changing visual input. A major component of this challenge lies in the sheer complexity of the visual world. While we are experts in visual perception, there are thousands of different objects we can identify and categorise, despite dramatic changes in position, size, illumination, color, shape, or texture. Further, there are an abundance of possible features – or dimensions – of an object that may be key to their recognition and categorisation. Many of those dimensions often co-occur in the real world, making it difficult to identify their role in visual perception. For example, two common dimensions of artificial objects are “being made of metal” and “having sharp edges”, but their co-occurrence may make it difficult to identify the importance of either of those dimensions for object recognition.

The long-term goal of the “Vision and Computational Cognition” group is to gain a mechanistic understanding of the processes underlying visual perception, from early cortical processing to high-level visual recognition. To achieve this goal, our group departs from traditional experimental approaches in two critical ways. First, we use a large-scale, data-driven approach to identify the key components, or “dimensions”, underlying computations at different visual and cognitive processing stages in humans. In particular, we seek to identify interpretable dimensions from behaviour, brain data, and computational models of vision and semantics that may form the basis for our mental and neural representations of the visual world. By acquiring and analysing large behavioural and neuroimaging datasets (millions of behavioural trials, dense sampling of individual brains), we aim at (1) identifying the unique contribution of different object dimensions to explaining the observed patterns of data, and (2) elucidating their predictive power for other object-related behaviour.

Complementing this data-driven approach, we use a model-driven computational approach. This approach is based on recent developments in artificial intelligence, such as deep convolutional neural networks and semantic embeddings, which have revolutionised the fields of computer vision and natural language processing. We plan to study emergent properties of these models depending on the goal – or objective function – they were trained for. For example, how does a model architecture change when training a model not to categorise objects, but to grasp them? This approach may provide critical insight into our understanding of the role of these properties in visual perception. Finally, we aim at building better computational models of human perception and cognition by improving the correspondence between those computational models and the human brain, with the goal of bringing us closer to a computational understanding of visual processing in humans.
Appointments

2019

- Hebart, M. *Faculty member of the International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity (IMPRS NeuroCom).* Max Planck Institute for Human Cognitive and Brains Sciences, Leipzig, Germany.

- Hebart, M. *Max Planck Research Group Leader (W2), Max Planck Society, Germany.*

Publications

(spanning reporting period, but published prior to joining MPI CBS)

**Journal Articles**


Methods & Development Groups
**6.1 Methods and Development Group “Nuclear Magnetic Resonance”**

**Head**
Professor Dr Harald E. Möller

**Senior Researchers and Postdocs**
Anna Bujanow  
Dr Kristin Ihle (*)  
Dr Anna Kosatschek (*)  
Dr Lorenz Lemcke  
Dr Jöran Lepsien  
Dr Toralf Mildner  
Professor Dr Karsten Mueller  
Dr habil. André Pampel  
Fabian Piecha (*)  
Dr Robert Trampel (joint position, shared with Dept of Neurophysiology)

**PhD Students**
- Ratnamanjuri Devi  
- Richard Gast (80)  
- Jakob Georgi (*)  
- Dimitrios Gkotsoulias (78)  
- Dr Maria Guidi (8, 37) (*) (PhD since 02/2018)  
- Dr Ahmad Seif Kanaan (37) (*) (PhD since 07/2017)  
  - (in cooperation with Hannover Medical School)  
- Dr Tobias Lenich (37) (*) (PhD since 12/2018)  
- Dr Kathrin Lorenz (*) (PhD since 02/2018)  
  - (in cooperation with Leipzig University)  
- Henrik Marschner (37) (*)  
- Dr Miguel Martinez-Maestro (37) (*) (PhD since 03/2019)  
- Dr Riccardo Metere (8) (*) (PhD since 03/2018)  
- Renzo Torrecuso

**Secretarial and Technical Staff**
- Nancy Muschall  
- Manuela Hofmann  
- Mandy Jochemko  
- Anke Kummer  
- Roland Müller  
- Nicole Pampus  
- Torsten Schlumm  
- Simone Wipper
## Visiting Research Fellows and Guest Researchers

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Dr Ondřej Bezdíček</td>
<td>Center for Interventional Therapy of Movement Disorders, Department of Neurology, 1st Faculty of Medicine and General University Hospital, Charles University Prague, Czech Republic</td>
</tr>
<tr>
<td>Dr Pavel Dušek</td>
<td>Center for Interventional Therapy of Movement Disorders, Department of Neurology, 1st Faculty of Medicine and General University Hospital, Charles University Prague, Czech Republic</td>
</tr>
<tr>
<td>Professor Dr G. Allan Johnson</td>
<td>Center for In Vivo Microscopy, Department of Radiology, Duke University Medical Center, Durham, NC, USA</td>
</tr>
<tr>
<td>Tomáš Pšorn</td>
<td>Institute of Scientific Instruments of the Czech Academy of Sciences, Brno, Czech Republic</td>
</tr>
<tr>
<td>Dr Filip Růžička</td>
<td>Center for Interventional Therapy of Movement Disorders, Department of Neurology, 1st Faculty of Medicine and General University Hospital, Charles University Prague, Czech Republic</td>
</tr>
<tr>
<td>Kadir Şimşek</td>
<td>Department of BioMedical Research (DBMR), Faculty of Medicine, University of Bern, Switzerland</td>
</tr>
<tr>
<td>Dr Petra Štofaniková</td>
<td>Center for Interventional Therapy of Movement Disorders, Department of Neurology, 1st Faculty of Medicine and General University Hospital, Charles University Prague, Czech Republic</td>
</tr>
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## Former Researchers

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Dr Kristin Ihle</td>
<td>Department of Anaesthesia, Pain Medicine and Emergency Medicine, imland Klinik Rendsburg, Germany</td>
</tr>
<tr>
<td>Dr Anna Kosatschek</td>
<td>Clinic for Neurology, kbo-Inn-Salzach-Klinikum gemeinnützige GmbH, Wasserburg/Inn, Germany</td>
</tr>
<tr>
<td>Fabian Piecha</td>
<td>Clinic for Neurology, Klinikum Altenburger Land GmbH, and Section of Psychoneurobiology, University of Lübeck, Germany</td>
</tr>
</tbody>
</table>

## Former PhD Students

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Jakob Georgi</td>
<td>SLG Prüf- und Zertifizierungs GmbH, Hartmannsdorf, Germany</td>
</tr>
<tr>
<td>Dr Maria Guidi</td>
<td>Zanichelli editore S.p.A., Bologna, Italy</td>
</tr>
<tr>
<td>Dr Ahmad Seif Kanaan</td>
<td>AbbVie Inc., North Chicago, IL, USA</td>
</tr>
<tr>
<td>Dr Tobias Lenich</td>
<td>unkown</td>
</tr>
<tr>
<td>Dr Kathrin Lorenz</td>
<td>unkown</td>
</tr>
<tr>
<td>Henrik Marschner</td>
<td>Hamilton Medical AG, Bonaduz, Switzerland</td>
</tr>
<tr>
<td>Dr Miguel Martínez-Maestro</td>
<td>unknown</td>
</tr>
<tr>
<td>Dr Riccardo Metere</td>
<td>Donders Institute, Radboud University Nijmegen, NL</td>
</tr>
</tbody>
</table>

(8) European Union 7th Framework Programme
(37) Helmholtz Association, Germany
(78) EU H2020
(80) Studienstiftung des deutschen Volkes
(*) Left the Institute during 2017–2019
6.2 Methods and Development Group “Brain Networks”

Heads
Professor Dr Thomas R. Knösche
Dr Burkhard Maess

Senior Researchers and Postdocs
Dr Helmut Schmidt (14)
Dr Peng Wang
Dr Konstantin Weise
(in cooperation with Ilmenau University of Technology)

PhD Students
Ole Bialas (69)
(in cooperation with Leipzig University)
Vincent Chien
Jae-Hyun Cho (*)
Richard Gast (80)
Dr Mirco Fuchs (21) (*) (PhD since 08/2017)
Ruxue Gong
Dr Seung-Goo Kim (*) (PhD since 01/2017)
Dr Tim Kunze (*) (PhD since 12/2018)
Dr Hermann Sonntag (**) (PhD since 12/2019)

Secretarial and Technical Staff
Nancy Muschall
Yvonne Wolff-Rosier

Visiting Research Fellows and Guest Researchers
Dr Kateřina Chládková Institute of Psychology, Leipzig University, Germany
Professor Dr Jens Haueisen Institute of Biomedical Engineering and Informatics, Ilmenau University of Technology, Germany
Dr Björn Herrmann Brain and Mind Institute, The University of Western Ontario, Canada
Stella M. Sánchez School of Exact and Natural Sciences, University of Buenos Aires, Argentina
Narjes Soltani Institute for Cognitive & Brain Sciences, Shahid Beheshti University, Teheran, Iran
Dr Alessandro Tavano Max Planck Institute for Empirical Aesthetics, Frankfurt/Main, Germany
Dr Hiroki Watanabe NARA Institute of Science and Technology (NAIST), Japan

Former PhD Students
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Dr Mirco Fuchs Laboratory for Biosignal Processing, Forschungszentrum Life Science & Engineering, Leipzig University of Applied Sciences (HTWK), Germany
Dr Seung-Goo Kim Department of Psychology and Neuroscience, Duke University, NC, USA
Dr Tim Kunze Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany
Dr Hermann Sonntag Department of Psychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
6.3 Methods and Development Group “Databases and IT”

Heads
Dr Roberto Cozatl (DB) (*)
Dr Mathias Goldau (DB)
Dr Helmut Hayd (IT)

Secretarial and Technical Staff
Nancy Muschall
Stefan Bunde (DB) (84)
Frank Burkhardt (IT)
Heiko Korsawe (IT)
Hagen Lipka (IT)
Elke Maess (DB)
Stephan Moeller (IT)
Karin B. Rudisch (DB)
Markus Then (IT)
Alexander Tyapkov (DB) (84)

Former Head
Dr Roberto Cozatl
University and State Library Saxony-Anhalt, Martin Luther University Halle-Wittenberg, Germany

(*) Left the Institute during 2017–2019
(**) Left the group during 2017–2019
6.1
Methods and Development Group “Nuclear Magnetic Resonance”

Our group is engaged in the development of magnetic resonance (MR) methods to study brain anatomy, metabolism, and function. This ranges from radiofrequency (RF) hardware to MR pulse sequences and image analysis procedures. Another research theme relates to the biophysics underlying image contrast and the quantitative characterisation of tissue composition or physiology, particularly in the context of water relaxation. As in previous years, we have benefitted from cooperations within and outside the Max Planck Society, of which some are exemplarily highlighted below. Other established and new partnerships included Hannover Medical School; Leiden, Maastricht, Berne, Bristol, and Duke University; as well as the Donders Centre and CNR.

Concerning actual development, a novel coil feeding concept was introduced to improve RF transmission at high field. It is based on a passive RF current mirror and robustly achieves equal currents in different coil elements. Custom-made RF coils are instrumental in experiments in fixed specimens to understand how tissue structure impacts imaging results. An example of this line of work is the role of the extracellular matrix, performed collaboratively with Leipzig University’s Paul Flechsig Institute for Brain Research and Felix Bloch Institute for Solid-State Physics. Interactions of an electromagnetic field (EMF) and a biological object were evaluated, in the numerical domain, for RF safety assessment of multi-modal imaging scenarios or the development of subject-specific human body models (6.1.1). Encouraging results were obtained with pseudo-continuous arterial spin labelling (pCASL) through detailed analyses of spin inversion (6.1.2). Meanwhile, our sequence implementation is routinely being used in a clinical setting at Leipzig University Hospital’s Department of Nuclear Medicine on a PET-MR hybrid scanner. A novel editing procedure referred to as PROBE improved the robustness and flexibility of chemical exchange saturation transfer (CEST) MR imaging (MRI) and was tested at the

Figure 6.1
(A) The magnet’s patient end after removal of the covers, patient bed, and cold heads.
(B) Service end of the magnet with installed transport bungs; also visible are the partly dismantled Faraday cage, the massive iron shield (362 tons), and the prepared removal path.
Center for Stroke Research Berlin (6.1.3). Indubitably, echo planar imaging (EPI) will continue to be the workhorse in the majority of the Institute’s MR experiments. Here, a novel deconvolution technique for distortion correction yielded promising performance. Different flavours of “high resolution” were important in applications of resting-state functional MRI (fMRI). Recordings of the fluctuation amplitude, at submillimetre spatial resolution, were targeted at a calibration of blood oxygenation level-dependent (BOLD) fMRI and removal of some of the venous bias in the BOLD response. Achieving a high temporal resolution (order of 300 ms) was crucial in studies—performed jointly with Oxford University—of cardiac pulsatility in the cerebral microstructure. Compared to these examples, resolution was rather coarse (order of centimetres and minutes) in functional MR spectroscopy (fMRS), but allowed comparisons of metabolic changes during activation and inhibition (6.1.4). Activation patterns evoked by finger tapping in Parkinson’s patients were studied together with Charles University in Prague, hinting at different baseline conditions of the motor network in relation to the presence of levodopa (6.1.5).

Considerable effort resulted from damage to our Connectom scanner’s gradient coil, probably related to an undocumented resonant mode. A look-ahead evaluation of the acoustic spectrum of arbitrary MR sequences was therefore established, based on earlier work the context of echo-planar spectroscopic imaging. Last but not least, the requirement to remain at the forefront of imaging technology led to the decision to replace our 7T scanner after twelve years of extensive operation (some 35,000 hours of scanning) with extraordinary results (order of 100 publications). Following de-installation (Fig. 6.1), a MAGNETOM Terra is expected to be up and running in March 2020.
Semi-automated generation of individual computational models of the human head and torso

Kalloch, B.1,2, Bode, J.1,3, Kozlov, M.1, Pampel, A.1, Hlawitschka, M.2, Sehm, B.1, Villringer, A.1, Möller, H. E.1, & Bazin, P.-L.1,4,5

1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Leipzig University of Applied Sciences, Germany
3 Department of Engineering Physics, Münster University of Applied Sciences, Germany
4 Netherlands Institute for Neuroscience, Amsterdam, NL
5 Spinoza Centre for Neuroimaging, Amsterdam, NL

Computational modelling of the interaction of an EMF with the human body is important for MRI safety assessment and RF coil design. As anatomical differences impact the results, there is a need for subject-specific models. We developed a pipeline (released on figshare) for creating surface-based human models with a high level of automation from gradient-echo MRI data. It performs atlas-based segmentation, mask generation, and triangulation of the boundaries between adjacent structures (Fig. 6.1.1). Inter-subject differences are well reproduced, and the models are suitable for EMF simulations of the RF magnetic field ($B_1^+$) and the specific absorption rate (SAR) using finite element method software.

Simulation-based optimisation of pCASL and experimental validation

Lorenz, K.1,2, Mildner, T.1, Schlumm, T.1, & Möller, H. E.1

1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Faculty of Physics and Earth Sciences, Leipzig University, Germany

Currently, pCASL is the recommended choice for non-invasive measurements of cerebral blood flow (CBF). We optimised such acquisitions through simulations of the labelling efficiency ($\alpha$). A large parameter space was considered, comprising pulse-sequence and physiological variables. Results obtained in silico were validated in vivo in the human internal carotid artery employing a fast echo planar-imaging protocol at 3T. Choice of a labelling...
In CEST experiments, information on metabolites is obtained through their influence on the ubiquitous water signal. This requires multiple acquisitions with different saturation frequencies. However, unspecific molecular contributions produce a background that confounds the detection of metabolite peaks. The PROBE saturation scheme compensates for unwanted contributions through a bespoke variation of the saturation power yielding a flat baseline (Fig. 6.1.3). Metabolite peaks not considered in the power optimisation procedure are enhanced as distinct perturbations of the baseline. For experimental verification, mapping of the lactate concentration in the presence of bovine serum albumin was performed in vitro at 7T. The concept was also applied in a clinical setting with excellent background compensation.
Dynamic metabolic changes in cortical regions with positive and negative BOLD response

Martínez-Maestro, M.¹, Labadie, C.², & Möller, H. E.¹

¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
² Berlin Center for Advanced Neuroimaging, Charité University Medicine Berlin, Germany

We used fMRS to study metabolic changes during sustained stimulation of human primary visual cortex. Two established paradigms were employed to generate widespread areas of positive or negative BOLD responses (Fig. 6.1.4). Glutamate concentrations increased during activation and decreased during deactivation. These changes were positively correlated with the BOLD response and probably reflect tricarboxylic acid cycle...
Levodopa-induced pattern of putamen activity in Parkinson’s disease

Mueller, K.¹, Holiga, Š., Möller, H. E.¹, Růžička, P.²,³, Roth, J.²,³, Schroeter, M. L.¹,⁴, Růžička, E.², & Jech R.²,³

¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
² Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, Czech Republic
³ Na Homolce Hospital, Prague, Czech Republic
⁴ Clinic for Cognitive Neurology, University Hospital Leipzig, Germany

There are discrepancies between previous studies concerning the role of the putamen in levodopa-related brain activity changes in Parkinson’s disease (PD). To address these, we performed fMRI in 32 patients (advanced akinetic-rigid type of PD) on and off medication using a motor paradigm. A differential pattern of levodopa-related putamen activity was obtained depending on the experimental condition (Fig. 6.1.5). Activity increased during finger tapping and strongly decreased during rest. This pattern was associated with an interaction between medication and experimental condition. That is, on levodopa the putamen was underactive at rest but increased during tapping whereas off of levodopa it was increased at rest and was absent during tapping. This suggests a fundamental difference of the involvement of the resting and active motor network, depending on the basal ganglia dopamine level.

Figure 6.1.5 Cross-sectional brain slices showing a differential pattern of brain activity change (consecutive blocks of finger tapping and rest) with levodopa medication (p < 0.05, family-wise error correction at the voxel level). Putamen activity was increased with levodopa during tapping (“TAP”; (A, C)) but decreased during the resting phase (“REST”; (B, C)). A significant interaction between the factors experimental condition (TAP/REST) and medication (ON/OFF) was observed in the left and right putamen (A–B). In contrast, we did not find any brain activity differences between the OFF and ON states in the primary motor cortex (D).
Conferences, Workshops, and Symposia

2017

2018

Degrees

Doctoral Theses

2017
- Kanaan, A. S. Elemental and neurochemical based analysis of the pathophysiological mechanisms of Gilles de la Tourette syndrome. Hannover Medical School, Germany.

2018
- Guidi, M. Depth-dependent physiological modulators of the BOLD response in the human motor cortex. Leipzig University, Germany.
- Lenich, T. Development and application of an NMR metabolic imaging technique based on CEST/NDE. Leipzig University, Germany.

2019
- Martínez-Maestro, M. Functional magnetic resonance spectroscopy (fMRS) for the investigation of brain metabolism during neural activation at 3T and 7T. Leipzig University, Germany.

Awards

2017
- Georgi, J. Summa cum Laude Merit Award. International Society for Magnetic Resonance in Medicine (ISMRM), Honolulu, HI, USA.
- Georgi, J. Trainee Award. International Society for Magnetic Resonance in Medicine (ISMRM), Honolulu, HI, USA.
- Guidi, M. Trainee Award. International Society for Magnetic Resonance in Medicine (ISMRM), Honolulu, HI, USA.
- Kanaan, A. S. Trainee Award. International Society for Magnetic Resonance in Medicine (ISMRM), Honolulu, HI, USA.
- Metere, R. Investigating brain tissue microstructure using quantitative magnetic resonance imaging. Leipzig University, Germany.
Publications

Books and Book Chapters


Journal Articles


## Patents


## Index of Published Figures

**Figure 6.1.1**


**Figure 6.1.2**


**Figure 6.1.3**


**Figure 6.1.4**


**Figure 6.1.5**

Our work focuses on the identification and mechanistic modelling of functional and structural networks in the brain, based on experimental data from EEG/MEG, functional MRI, diffusion MRI, and non-invasive brain stimulation. For this task, we use a combined bottom-up and top-down approach. Using biologically realistic computational modelling, we explore the dynamics and the functional repertoire of neuronal circuits. We developed biologically plausible models of canonical microcircuits and metacircuits that implement basic building blocks of cognition, such as input gating, memory, structure building, priming, and change detection, and demonstrated how such microcircuits can be combined to support complex cognitive tasks, such as sentence processing (6.2.1).

In addition, we develop and refine methods to link extracranial measurements and stimulation to the activity of neural populations. In particular, we developed techniques to relate non-invasive electrical and magnetic brain stimulation to observable behavioural and physiological effects (6.2.2). Furthermore, we are working on quality assessment of our experimental recordings and data analysis methods. As a first step, we investigated the role of the coregistration between MEG data and MR models of the brain (6.2.3). Importantly, in order to facilitate dissemination of our results and collaboration with other researchers, the developed methodology has been implemented in publicly available and open source software toolboxes.
Neural mass modelling – Cortical microcircuits as building blocks of cognition

Knösche, T. R. 1,2, Kunze, T. 1, Gast, R. 1, Schmidt, H. 1, Rose, D. 1, Haueisen, J. 2, Peterson, A. 3, Weiskopf, N. 1, Möller, H. E. 1, & Maess, B. 1
1 Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
2 Ilmenau University of Technology, Germany
3 University of Melbourne, Australia

The relative uniformity of local cortical wiring lends support to the connectionist's notion that cognitive function arises from a distributed network of a large number of relatively simple and uniform elements (Douglas & Martin, 2007, Neuron, 56, 226–238). We show that a simple neural mass model of a local cortical microcircuit can provide basic functionality, such as input-dependent gating and memory, tunable by top-down input and neuromodulation (Kunze, Peterson, Haueisen, & Knösche, 2017, PLOS One, 12(12): e0188003). We further demonstrate how cooperation between microcircuits implements more complex functionality, such as transient structure building, priming (Fig. 6.2.1) (Kunze, Haueisen, & Knösche, 2019, Biol. Cybern., 113, 273–291), and change detection (Chien, Maess, & Knösche, 2019, Biol. Cybern., doi:10.1007/s00422-019-00804-x).

When connecting local microcircuits to larger networks, long-range connectivity through axon bundles becomes relevant. Different transmission speeds due to varying axon diameters and myelination, as well as ephaptic coupling between axons, govern dispersion and synchronisation of transmitted information. We developed a semi-analytic axon model, which explains key experimental findings (Schmidt, & Knösche, 2019, PLOS Comp. Biol., 15(10): e1007004). This allows one to incorporate potentially measurable parameters, such as axon diameter and g-ratio.

To facilitate the study of neural mass models, we developed the Python based toolbox PyRates (Gast, Rose, Möller, Weiskopf, & Knösche, in press, PLOS One), which allows for fast and flexible implementation as well as efficient exploration of brain network models.

Figure 6.2.1 Principle mechanism of priming with two coupled cortical microcircuits $A_1^*$ and $A_2^*$ each comprising pyramidal cells (Py), excitatory interneurons (EIN), and inhibitory interneurons (IIN). (A) A target stimulus applied to $A_2^*$ is too weak to produce an output. (B) A stronger priming stimulus produces output at $A_2^*$ which is fed into $A_1^*$ such that it enters the upstate (memorises the input). The output of $A_2^*$ is fed back as top-down input to the pyramidal cells of $A_2^*$ and changes the functional fingerprint of that circuit. (C) A weaker target stimulus now produces a signal at the output of $A_2^*$. (D) Time courses of the stimulation. (E) Output signal of both microcircuits.
Field prediction and functional mapping in non-invasive brain stimulation

Weise, K.¹,², Numssen, O.¹, Hartwigsen, G.¹, Madsen, K. H.³, Thielscher, A.³, Saturnino, G. B.³, & Knösche, T. R.¹,²

¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
² Ilmenau University of Technology, Germany
³ Hvidovre Hospital, University of Copenhagen, Denmark

Electric field modelling is important to determine where and how neural populations are affected by transcranial magnetic or electrical stimulation (TMS, TES), which depends on uncertain head tissue conductivities. We developed the Python based toolbox pyGPC, implementing non-intrusive generalised polynomial chaos, and used it to quantify the reliability of the field estimates and identify the most influential parameters (Saturnino, Thielscher, Madsen, Knösche, & Weise, 2019, NeuroImage, 188, 821–834; Fig. 6.2.2.1).

Due to its focality, TMS can identify brain structures underlying behavioural or physiological effects. This mapping procedure normally involves exhaustive scanning of the coil position, orientation, and stimulation strength. We developed a novel method with far fewer experiments and higher accuracy (Weise, Numssen, Thielscher, Hartwigsen, & Knösche, in press, NeuroImage). This is based on the unique relationship between field strength and observable effect, quantified by the congruence factor. We used this method to localise the cortical generators of motor evoked potentials in the hand muscles (Fig. 6.2.2.2).

![Figure 6.2.2.1](image_url) Some results showing the uncertainty and sensitivity analysis for TMS and TES (tDCS) field calculation. (Column 1) Schematic stimulation configurations. (Column 2) Mean and relative standard deviation (RSD) of the electric field on the cortical surface under the assumption of the conductivity uncertainties taken from the literature. While significant uncertainty only occurs at locations with low field strength (sulci) for TMS, tDCS field calculations are uncertain everywhere. (Columns 3–5) Relative contributions of different tissue types to the uncertainty. While TMS is somewhat influenced by grey matter (GM) and white matter (WM), but not at locations with a strong field (gyral crowns), tDCS is strongly impacted by GM, compact bone (CB), and scalp (S), and moderately impacted by WM and cerebrospinal fluid (CSF). Spongy bone (SB) has little influence.
For high precision in source reconstruction of magnetoencephalography (MEG) data, high accuracy of the coregistration of sources and sensors is mandatory, because the numerical model of the head is derived from a different modality, namely magnetic resonance imaging (MRI). In our recent paper, we suggest using target registration error (TRE) as criterion for the quality of coregistrations (Sonntag, Haueisen, & Maess, 2018, Phys. Med. Biol., 63(7): 075003). TRE measures the effect of uncertainty in coregistrations at all points of interest. In total, 5,544 datasets with sensor-to-head and 128 head-to-MRI coregistrations, from a single MEG laboratory, were analysed.
An adaptive Metropolis algorithm was used to estimate the optimal coregistration and sample the coregistration parameters (rotation and translation). We found an average TRE between 1.3 and 2.3 mm at the head surface. Furthermore, we observed a mean absolute difference in coregistration parameters between the Metropolis and iterative closest point algorithm of $(1.9 \pm 1.5)^\circ$ and $(1.1 \pm 0.9)$ mm. The sampled parameters allowed for computation of TRE on the entire grid of the MRI volume. Hence, we recommend the Metropolis algorithm for head-to-MRI coregistrations.

Figure 6.2.3 Target registration error (TRE) plotted as overlay onto the corresponding MRI slices. The RMS of TRE is computed for all samples of all grid points. Black lines indicate the slices in Freesurfer MRI coordinates. The yellow crosshairs indicate the estimated minimum of TRE. With respect to axes orientation, (A) refers to anterior, (P) to posterior, (I) to inferior, (S) to superior, (R) to right, and (L) to left. On the left and right sides, the coronal and sagittal cuts at slices 110 and 100 are plotted, respectively.
Congresses, Workshops, and Symposia

2018

2019
- Haueisen, J., & Knösche, T. R. (September). EEG/MEG– Spatial Filters and Uncertainty Analysis. Tutorial. 4th International Conference on Basic and Clinical Multimodal Imaging (BaCI), Chengdu, China.
- Haueisen, J., & Knösche, T. R. (September). Non-invasive brain stimulation—how modeling can deal with targeting and dosing. Symposium. 4th International Conference on Basic and Clinical Multimodal Imaging (BaCI), Chengdu, China.
- Schneider, T., Wolters, C., & Knösche, T. R. (September). New methods and experimental results for optimized multi-channel tES. Oral Session. 13th International Conference on Complex Medical Engineering (CME), Dortmund, Germany.

Degrees

Doctoral Theses

2017
- Dannhauer, M. Evaluation of forward modeling inaccuracies and spatio-temporal source reconstruction for EEG/MEG data analysis in human brain research. Leipzig University, Germany.
- Fuchs, M. The smoothness constraint in spatially informed minimum norm approaches for the reconstruction of neuro-electromagnetic sources. Technical University of Ilmenau, Germany.

2018
- Kunze, T. How models of canonical microcircuits implement cognitive functions. Technical University of Ilmenau, Germany.
- Kim, S.-G. Myeloarchitecture and intrinsic functional connectivity of auditory cortex in musicians with absolute pitch. Leipzig University, Germany.
- Sevgi, M. Mechanistic models of reward based learning and decision making for clinically motivated problems. Technical University of Ilmenau, Germany.

2019
- Sonntag, H. The effect of uncertainty in MEG-to-MRI coregistrations on MEG inverse problems. Technical University of Ilmenau, Germany.

Appointments

2018
- Knösche, T. R. Honorary Professorship of Imaging and Modelling in the Neurosciences. Ilmenau University of Technology, Germany.

Awards

2017
- Schmidt, H. Best Poster Award. Computational Neurology 2017, Newcastle upon Tyne, UK.

2018
- Sonntag, H. Data Analysis Competition #2 Award. 21st International Conference on Biomagnetism (BIOMAG 2018), Philadelphia, PA, USA.
- Weise, K. Best Poster Award. 4th International Conference on Basic and Clinical Multimodal Imaging (BaCI), Chengdu, China.

2019
- Schmidt, H. Poster Award. 28th Annual Computational Neuroscience Meeting (CNS*2019), Barcelona, Spain.
Publications

Books and Book Chapters


Journal Articles


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**Figure 6.2.1**

**Figure 6.2.2.1**

**Figure 6.2.2.2**
Figure modified from Weise, K., Numssen, O., Thielischer, A., Hartwigsen, G., & Knösche, T. R. (in press). A novel approach to localize cortical TMS effects. *NeuroImage*.

**Figure 6.2.3**
6.3
Methods and Development Group “Databases and IT”

Adaptations to GDPR and BDSG, and software development for Castellum

Goldau, M. ¹
¹ Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

The 2018 amendment of general data protection regulations (GDPR) by the European Union and its implementation in Germany by the Bundesdatenschutzgesetz (BDSG) has considerably strengthened the rights of subjects in the processing of their personal data. For our institute, which conducts extensive research with human subjects, this change entailed considerable adjustments, particularly in the areas of legal bases (declarations of consent), data information, and restrictions on processing. Because many participants are naturally interested in their brain scans, there is an increased number of requests to retrieve such data. In this context, tools and processes were developed to effectively implement subjects’ rights regarding their data, whilst allowing flexibly to the changing legal situation and to scale well with data volume and inquiries. Implementing these processes with free software was a strong focus. At the same time, an inter-institutional project of the Max Planck Society (MPS) was started to create a generic database for test subjects.

Four research facilities are involved in the Castellum project: the Max Planck Institute for Human Development (MPI-B) in Berlin, which leads the project; the Max Planck Institute for Psychiatry (MPI-P) in Munich; the Max Planck Computing and Data Facility (MPCDF) in Munich; and the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig. The Max Planck Institute for Empirical Aesthetics (MPI-eA) in Frankfurt/Main was added later in an advisory capacity.

Different self-developed software solutions have been employed previously at the individual institutes, which are mostly tailored to the prevailing workflows. The project is scheduled to run for three years (from 2018) and will deliver generic open-source software for subject management to the Max Planck Society and its institutes. Castellum faces the significant challenge of meeting the very specific requirements of the institutes, whilst also finding a holistic solution. For example, it is currently being deployed at the MPI-B in a pilot phase, whereas the features presently implemented remain inadequate for the other participating institutes. To help address this, stronger modularisation was encouraged by us and has now concluded. This makes it possible to selectively add, remove, replace, or reuse single modules.

Whilst our current self-developed database system is very flexible, it is not adequately prepared for the challenges of data protection and technological change. In addition, our current database management system is based on expiring technology, so that a change is imminent for our institute in the medium term.

Castellum offers our institute the opportunity to replace our database management system and prepare for new technological challenges. Digitisation, data protection, mobile devices, or self-management of the test subjects are only a few such challenges that could be addressed adequately and holistically with a new technological fundament.
File Service Solution
Over the past few years ZFS has become a well-established component of our file service solution. It offers different levels of data loss prevention and performance. NFSv4.2 allows the sharing of ZFS datasets with the reliable authentication and authorisation of Kerberos. Our latest ZFS file server has a gross capacity of more than 1 PB (88 hard disks). The segmentation of the stored data, in blocks, ensures the horizontal scalability and manageability for the future. Usually, a block consists of the data from a project or a study. A set of internally developed scripts makes the management of the blocks (e.g. context aware movement to another server, archiving, or handling of orphaned files) easy and less error-prone. This set was completed by a graphical user interface for the user self-service. The underlying script allows the defining of the access-control list, to apply for disk space, the archiving.

Remote Access
For remote access to our Linux servers we have set up a new NoMachine server with GPU-accelerated 3D rendering and H.264 encoding and decoding. This channel into the institute is much more secure than any VPN tunnel. This is because it only allows the transfer of pixels and signals from the input devices and not file transfer (originating from malware on the client). A two-factor authentication additionally increases the security.

Singularity
We are introducing Singularity in connection with Gitlab and its DevOps tools. Singularity is a free, cross-platform, and open-source software for containerisation of user programmes or even complete software environments. Singularity brings reproducibility to scientific computing. The development of the containers will be tracked by git. Any change of the definition file of a container starts a rebuild of the container using the DevOps tools of Gitlab and makes the new version available in a public download area.

Pap2Com
We have developed a solution, called Pap2Com, to incorporate information on paper into an electronic workflow. It consists of a consumer scanner, a Raspberry Pi (a pocket-sized computer), and a collection of open source programmes integrated in a self-developed Python framework. At the time of writing we have already digitised more than 150 thousand pages.
Publications

Journal Articles


7

Former Groups
7.1 Max Planck Research Group
“Neural Mechanisms of Human Communication”

Research Group Leader
Professor Dr Katharina von Kriegstein (*)

Postdocs
Dr Louise Kauffmann (77) (*)
Dr Corrina Maguinness (77) (*)
Dr Brian Mathias (14) (77) (63) (*)
Dr Paul Glad Mihai (77) (*)
Dr Alejandro Tabas (77) (*)
Dr Nadja Tschentscher (77) (*)

PhD Students
Kamila Borowiak (77) (14) (*)
(in cooperation with Berlin School of Mind and Brain)
Lisa Jeschke (77) (*)
Christa Müller-Axt (14) (77) (*)
Claudia Roswandowitz (*)
Stefanie Schelinski (77) (*)
Lena Schliephake (77) (*)

MD Students in cooperation with Leipzig University
Carolin Otto (*)
Leona Sureth (*)
Andrea Klingebiel (*)

Guest Researchers
Dr Nicole Altvater-Mackensen
(University of Göttingen)
Dr Manuela Macedonaha
(Johannes Kepler University Linz, Austria)

(01.08.2009–30.09.2017)

Technical and Administrative Assistants
Martina Dietrich (77) (**) 
Liane Dörr (77) (*)
Claudia Pelke (*)

(*) Left the Institute during 2017–2019
(**) Left the group during 2017-2019
7.2 Max Planck Research Group
"Neuroanatomy & Connectivity"

Research Group Leader
Dr Daniel S. Margulies (*)

Postdocs
Dr Marcel Falkiewicz (*)

Personal and Scientific Assistant
Dr Natacha Mendes (**)

Guest Researchers
Aman Preet Badhwar (25) (*)
Leonardo Cerliani (93) (*)
Chris Foulon (93) (*)
Dr Franziskus Liem (*)

PhD Students
Blazej Baczkowski (**)
Seyma Bayrak (**)
Philipp Haueis (*)
Julia M. Huntenburg (43) (*)
Mark E. Lauckner (**)
Katharina Ohmberger (*)
Sabine Olschläger (*)

(in cooperation with Berlin School of Mind and Brain)
(in cooperation with Leipzig University)

7.3 Otto Hahn Research Group
"Neural Bases of Intonation in Speech and Music"

Research Group Leader
PD Dr Daniela Sammler (**)  

Postdocs
Dr Sven Passmann (*)

PhD Students
Pei-Ju Chien (**)
Maria Dotzer (*)
Katarzyna Gugnowska (94) (**)
Nele Hellbernd (*)
Natalie Kohler (**)

Guest Researchers
Dr Eleanor Elizabeth Harding

(01.07.2013–30.06.2019)
7.4 Max Planck Research Group “Early Social Cognition”

Research Group Leader
Professor Dr Stefanie Hoehl (*)

Postdocs
Dr Christine Michel
Ezgi Kayhan, PhD (14) (*)
Jing Jiang (*)

PhD Students
Miriam Langeloh
Hanna Schleihauf (14) (*)

Technical Assistants
Ulrike Barth (**)
Daniel Matthes (*)

Guest Researchers
Dr Moritz Köster (*) (FU Berlin)

(01.01.2017–28.02.2019)

(14) German Research Foundation (DFG)
(*) Left the Institute during 2017–2019
7.1
Max Planck Research Group “Neural Mechanisms of Human Communication”

Degrees
PhD Theses
2017
- Jiang, J. Neural mechanisms of turn-taking and eye contact in social communication. Humboldt University Berlin, Germany.
- Roswandowitz, C. Voice-identity processing deficits: The cognitive and neural mechanisms of phonagnosia. Humboldt University Berlin, Germany.

2018
- Schelinski, S. Mechanisms of voice processing: Evidence from autism spectrum disorder. Humboldt University Berlin, Germany.

Appointments
2017
- Von Kriegstein, K. Professor of Cognitive and Clinical Neuroscience, Faculty of Psychology, TU Dresden, Germany.

Publications
Books and Book Chapters
Journal Articles


7.2
Max Planck Research Group
"Neuroanatomy & Connectivity"

Degrees

PhD Theses
2017
- Huntenburg, J.M. A core organizing axis of the human cerebral cortex. Free University of Berlin, Germany.

Appointments
2018
- Margulies, D.S. Chargé de recherche, Centre national de la recherche scientifique (CNRS), Paris, France.

Publications
Books and Book Chapters
Journal Articles


7.3
Otto Hahn Research Group “Neural Bases of Intonation in Speech and Music”

Degrees

Habilitation Theses
2018
- Sammler, D. The Melodic Mind: Neural bases of intonation in speech and music. Leipzig University, Germany.

PhD Theses
2017
- Bianco, R. Principles of action planning in music production: Evidence from fMRI and EEG studies in professional pianists. Leipzig University, Germany.

Publications

Books and Book Chapters

Journal Articles


7.4
Max Planck Research Group “Early Social Cognition”

Degrees
PhD Thesis
2018
- Schleihauf, H. Why do we imitate nonsense? The underlying motivations of overimitation. Heidelberg University, Germany.

Appointments
2017
- Hoehl, S. Full Professor of Developmental Psychology, Faculty of Psychology, University of Vienna, Austria.
- Hoehl, S. Full Professor (W3) of Developmental and Educational Psychology, University of Bremen, Germany (declined)
- Hoehl, S. Professor (W2) of Psychology with a Focus on Neurocognitive Development and Self-Regulation, School of Education, Bergische Universität Wuppertal, Germany (declined)

Publications
Books and Book Chapters

Journal Articles


The International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity (IMPRS NeuroCom) is an interdisciplinary PhD programme. The school is based at the MPI CBS and Leipzig University (LU) and also involves the Max Planck Institute for Evolutionary Anthropology (MPI EVA), also in Leipzig, and the Institute of Cognitive Neuroscience (ICN) at University College London in the UK. The IMPRS NeuroCom is funded by the Max Planck Society, the MPI CBS, and the LU. Currently the school is in its second funding period (2015-2021). We receive about 300 applications yearly, from which we select 15-20 outstanding doctoral researchers. The graduate school strengthens the already-existing, close working relationship between the participating institutions.
PhD students and projects

Module I: Language and Communication

<table>
<thead>
<tr>
<th>Student</th>
<th>Project</th>
<th>Project Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamson, Helyne</td>
<td>Understanding mechanisms of brain plasticity using multimodal imaging to assess brain structure changes during L2 learning</td>
<td>progressed</td>
</tr>
<tr>
<td>Dr Beese, Caroline</td>
<td>The effects of neurocognitive aging on sentence processing</td>
<td>completed</td>
</tr>
<tr>
<td>Dr Bianco, Roberta</td>
<td>Principles of action planning in music production: evidence from fMRI and EEG studies</td>
<td>completed</td>
</tr>
<tr>
<td>Carthaus, Anna</td>
<td>Neural segregation of syntax and semantics in healthy individuals and epilepsy patients</td>
<td>left the Institute during 2017–2019</td>
</tr>
<tr>
<td>Cheung, Ka-Ming</td>
<td>Predictive processes in musical syntactic cognition</td>
<td>final</td>
</tr>
<tr>
<td>Chien, Pei-Ju</td>
<td>Neural networks for lexical tone and intonation in Mandarin Chinese: a cross-linguistic perspective</td>
<td>progressed</td>
</tr>
<tr>
<td>Girlich, Sarah</td>
<td>Verb Acquisition in German-speaking children – evidence from various methods</td>
<td>progressed</td>
</tr>
<tr>
<td>Goranskaya, Dariya</td>
<td>Neural basis of grammar learning</td>
<td>final</td>
</tr>
<tr>
<td>Graessner, Astrid</td>
<td>Interactions in the cortical language network for basic semantic composition</td>
<td>progressed</td>
</tr>
<tr>
<td>Gugnowska, Katarzyna</td>
<td>Neural bases of interpersonal coordinated behaviour during music performance</td>
<td>progressed</td>
</tr>
<tr>
<td>Hellbernd, Nele</td>
<td>The tone of voice conveys speakers’ intentions: Acoustics, perception and neural bases of intentional prosody</td>
<td>final</td>
</tr>
<tr>
<td>Kohler, Natalie</td>
<td>Neural bases of joint action in music</td>
<td>progressed</td>
</tr>
</tbody>
</table>

* We differentiate between the following project stages: Orientation: PhD student has recently started the PhD project and is in the process of finding a PhD topic; Progressed: PhD student is planning/running studies and writing papers; Final: PhD student is writing up the thesis; Submitted: PhD student has submitted the thesis at University and is waiting for the defense; Completed: PhD student has successfully defended the thesis between 2017–2019.
<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Krause, Carina Denise</td>
<td>Syntactic complexity and verbal working memory load in sentence comprehension</td>
<td>final</td>
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<tr>
<td>Dr Kroczek, Leon</td>
<td>The impact of speaker information on language processing</td>
<td>completed</td>
</tr>
<tr>
<td>Lisanik, Martin</td>
<td>Functional correlates of second language acquisition: A longitudinal fMRI study on second language processing in comparison with first language</td>
<td>left the Institute during 2017–2019</td>
</tr>
<tr>
<td>Maran, Matteo</td>
<td>The implementation of the syntactic merge mechanism in the cortical language network: causal neuronal indexes of grammatical category access and hierarchization</td>
<td>progressed</td>
</tr>
<tr>
<td>Dr Marzecová, Anna</td>
<td>How prediction and attention jointly shape visual processing: a predictive coding view</td>
<td>completed</td>
</tr>
<tr>
<td>Menn, Katharina</td>
<td>The role of top-down information for speech entrainment during early language acquisition</td>
<td>orientation</td>
</tr>
<tr>
<td>Numssen, Ole</td>
<td>Functional segregation in the default mode network: The left and right TPJ in attention, semantic and social processing</td>
<td>left the graduate school during 2017–2019</td>
</tr>
<tr>
<td>Papitto, Giorgio</td>
<td>Broca’s area in the neural networks of language and action</td>
<td>progressed</td>
</tr>
<tr>
<td>Qi, Ting</td>
<td>The structure of the brain during language development: associations between brain structure and sentence comprehension in children</td>
<td>final</td>
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<tr>
<td>Roho, Inès</td>
<td>Relation of vocal production and white matter connectivity in the chimpanzee's brain</td>
<td>orientation</td>
</tr>
<tr>
<td>Dr Roswandowitz, Claudia</td>
<td>Voice-identity processing deficit. The cognitive and neural mechanisms of phonagnosia</td>
<td>completed</td>
</tr>
<tr>
<td>Rysop, Anna</td>
<td>Modulating the neural network dynamics of auditory speech comprehension - the role of the angular gyrus</td>
<td>progressed</td>
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<tr>
<td>Schell, Marianne</td>
<td>Neuroanatomical correlates for syntactic and semantic composition on a fundamental level</td>
<td>final</td>
</tr>
<tr>
<td>Schliephake, Lena</td>
<td>The role of the lateral geniculate nucleus in autism spectrum disorder</td>
<td>left the Institute during 2017–2019</td>
</tr>
</tbody>
</table>

© Thomas Abé: Fotografie
<table>
<thead>
<tr>
<th>Student</th>
<th>Project</th>
<th>Project Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroën, Joëlle</td>
<td>The chronometry of semantic processing in the brain</td>
<td>orientation</td>
</tr>
<tr>
<td>Stuckenbg (née Erfort), Maria</td>
<td>Bimodal interaction mechanisms</td>
<td>final</td>
</tr>
<tr>
<td>Trettenbrein, Patrick Christian</td>
<td>Modality (in-)dependence of syntactic processing</td>
<td>progressed</td>
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<tr>
<td>Tu, Hsing-Fen</td>
<td>Modulation of visual search performance by auditory stimulations in early childhood</td>
<td>final</td>
</tr>
<tr>
<td>Vassileiou, Benedict</td>
<td>Description of the spatiotemporal network dynamics subserving working memory resources involved in sentence comprehension</td>
<td>progressed</td>
</tr>
<tr>
<td>Wei, Xuehue</td>
<td>The language connectome: plasticity in second language acquisition</td>
<td>progressed</td>
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<tr>
<td>Winkler, Marina</td>
<td>Learning complex grammar from simple tones: young infants’ and adults’ processing of nested dependencies measured by EEG and fNIRS</td>
<td>progressed</td>
</tr>
<tr>
<td>Dr Xiao, Yaquiong</td>
<td>Resting-stage functional connectivity in the brain and its relation to language development in preschool children</td>
<td>completed</td>
</tr>
</tbody>
</table>

**Module II: Cognitive and Affective Neuroscience**

<table>
<thead>
<tr>
<th>Student</th>
<th>Project</th>
<th>Project Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deilmann, Felix</td>
<td>Mnemonic decision making: replay and preplay as a mechanism for generalizing knowledge</td>
<td>progressed</td>
</tr>
<tr>
<td>Gallistl, Mathilde</td>
<td>Investigation of social processes and physiological stress resonance in dyads</td>
<td>orientation</td>
</tr>
<tr>
<td>Kaniuth, Philipp</td>
<td>Identifying core dimensions underlying human object recognition</td>
<td>orientation</td>
</tr>
<tr>
<td>Karew, Artem</td>
<td>Development of grid cells and their effect on cognition in children</td>
<td>progressed</td>
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<tr>
<td>Langeloh, Miriam</td>
<td>Neural correlates of imitation in infancy</td>
<td>final</td>
</tr>
<tr>
<td>Lewis, Carolin</td>
<td>Hormonal modulation of reward processing and mood in women</td>
<td>progressed</td>
</tr>
<tr>
<td>Linz, Roman</td>
<td>The mind-brain-body triad in healthy humans: exploring interactions of subjective experience, neural and endocrine biomarkers within the framework of stress</td>
<td>final</td>
</tr>
<tr>
<td>Dr Lumma, Anna-Lena</td>
<td>The integration of first- and third-person methods in the context of meditation practices and the self</td>
<td>completed</td>
</tr>
<tr>
<td>Meyer, Ann-Kristin</td>
<td>Examining the disruption of suppressed memory representations</td>
<td>progressed</td>
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<tr>
<td>Molloy, Eoin</td>
<td>Functional, network, and metabolic alterations in neural responses during sequence motor learning in response to escitalopram</td>
<td>progressed</td>
</tr>
<tr>
<td>Nitsch, Alexander</td>
<td>Coding principles for value-based decision making</td>
<td>progressed</td>
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<tr>
<td>Oligschläger, Sabine</td>
<td>Gradients of connectivity distance in the primate cerebral cortex</td>
<td>final</td>
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<tr>
<td>Paulus, Philipp</td>
<td>Affective representations in medial prefrontal cortex</td>
<td>progressed</td>
</tr>
</tbody>
</table>
Neuroscience of Communication: Function, Structure, and Plasticity

For reasons of faculty member retirement or relocation, the structure and research focus of Module II, in particular, has changed considerably. Formerly named "Social, Cognitive and Affective Neuroscience", it is now named "Cognitive and Affective Neuroscience".

Module III: Basic and Clinical Neuroscience

<table>
<thead>
<tr>
<th>Student</th>
<th>Project</th>
<th>Project Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albrecht, Franziska</td>
<td>Neural correlates of parkinsonian syndromes</td>
<td>completed</td>
</tr>
<tr>
<td>Baczkowski, Blazej</td>
<td>Integrating pavlovian conditioning with relational knowledge for adaptive threat (fear) memory</td>
<td>final</td>
</tr>
<tr>
<td>Ballarini, Tommaso</td>
<td>Magnetic Resonance Imaging biomarkers for clinical symptoms and therapy in parkinson's disease</td>
<td>submitted</td>
</tr>
<tr>
<td>Belger, Julia</td>
<td>Application of Virtual Reality in the assessment of visuospatial neglect after stroke</td>
<td>progressed</td>
</tr>
<tr>
<td>Bialas, Ole</td>
<td>The cortical encoding of sound source elevation</td>
<td>progressed</td>
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<tr>
<td>Blöchl, Maria</td>
<td>Vascular risk and disease as cause of depressive symptoms during lifespan</td>
<td>progressed</td>
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<tr>
<td>Braga, Alessandro</td>
<td>Motor driven predictive processes in the auditory cortex</td>
<td>progressed</td>
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<tr>
<td>Dabbagh, Alice</td>
<td>Spinal cord imaging and pain perception</td>
<td>orientation</td>
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<tr>
<td>Dermody, Nadene</td>
<td>Neural correlates of frontotemporal lobar degeneration (FTLD)</td>
<td>left the Institute during 2017–2019</td>
</tr>
<tr>
<td>Gippert, Magdalena</td>
<td>Motorical learning</td>
<td>orientation</td>
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<tr>
<td>Student</td>
<td>Project</td>
<td>Project Stage</td>
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<tr>
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<tr>
<td>Gong, Ruxue</td>
<td>Development of a framework for treating Parkinsonian motor symptoms by brain state-dependent transcranial magnetic stimulation</td>
<td>progressed</td>
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<tr>
<td>Grigoryan, Khosrov</td>
<td>Neural correlates of brain-computer interface-based post-stroke motor rehabilitation</td>
<td>progressed</td>
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<tr>
<td>Dr Hardikar, Samyogita</td>
<td>Taste perception in obesity</td>
<td>completed</td>
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<tr>
<td>Herzog, Nadine</td>
<td>Working memory updating and maintenance in obesity: bridging fMRI, EEG, and dopamine</td>
<td>progressed</td>
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<tr>
<td>Hofmann, Simon</td>
<td>Understanding deep learning to model the brain and mind</td>
<td>progressed</td>
</tr>
<tr>
<td>Dr Jacobsen, Estrid N.</td>
<td>Sub-dividing Broca's region based on functional connectivity: New methods for individual level in vivo cortical parcellation</td>
<td>completed</td>
</tr>
<tr>
<td>Kandia, Dimitra-Maria</td>
<td>Effects of early music experience on language development</td>
<td>progressed</td>
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<tr>
<td>Kaptan, Merve</td>
<td>Functional imaging of the spinal cord: methodological and anatomical aspects</td>
<td>progressed</td>
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<tr>
<td>Morozova, Maria</td>
<td>Microstructural properties of long fibre connections in the human central nervous system</td>
<td>progressed</td>
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<tr>
<td>Ruthig, Philip</td>
<td>Comparative microanatomy of mammalian auditory brain areas orientation</td>
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<tr>
<td>Dr Sarrou, Mikaela</td>
<td>Auditory motion: perception and cortical response</td>
<td>completed</td>
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<tr>
<td>Schaare, Herma Lina</td>
<td>The relationship between blood pressure, vascular disease and the brain: a neuroimaging approach</td>
<td>submitted</td>
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<tr>
<td>Schulz, Charlotte</td>
<td>Effects of child maltreatment on adolescent brain structure, function and psychopathology: roles of threat and deprivation</td>
<td>progressed</td>
</tr>
<tr>
<td>Shih, Pei-Cheng</td>
<td>The effects of aging and stroke on bilateral coordination</td>
<td>final</td>
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<tr>
<td>Stephani, Tilmann</td>
<td>Probing instantaneous cortical states with neuronal oscillations and stimulus-evoked responses</td>
<td>progressed</td>
</tr>
<tr>
<td>Uhlig, Marie</td>
<td>Effect of diurnal rhythm and its disruptions by acute stress on grey matter volume</td>
<td>progressed</td>
</tr>
<tr>
<td>Waltmann, Maria</td>
<td>Neurocognitive mechanism of maladaptive decision making in binge eating disorder and obesity</td>
<td>progressed</td>
</tr>
</tbody>
</table>

**Module IV: Neuroimaging Physics and Signal Processing**

<table>
<thead>
<tr>
<th>Student</th>
<th>Project</th>
<th>Project Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brammerloh, Malte</td>
<td>Biophysical modeling of iron-induced MRI contrast in the human brain</td>
<td>progressed</td>
</tr>
<tr>
<td>Chien, Shih-Cheng</td>
<td>Brain network dynamics in deviance response and auditory perception</td>
<td>submitted</td>
</tr>
<tr>
<td>Name</td>
<td>Project</td>
<td>Status</td>
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<tr>
<td>Devi, Ratnamanjuri</td>
<td>Magnetic resonance investigations of physiological effects related to functional inhibition</td>
<td>progressed</td>
</tr>
<tr>
<td>Gast, Richard</td>
<td>Modeling phase transitions in neural motor circuits in health and disease - a combined experimental and computational approach</td>
<td>progressed</td>
</tr>
<tr>
<td>Georgi, Jakob</td>
<td>Quantitative characterization of nerve fibers</td>
<td>left the Institute during 2017-2019</td>
</tr>
<tr>
<td>Dr Guidi, Maria</td>
<td>Depth-dependent physiological modulators of the BOLD response in the human motor cortex</td>
<td>completed</td>
</tr>
<tr>
<td>Haenelt, Daniel</td>
<td>Submillimetre fMRI - which MR sequence yields the best results?</td>
<td>progressed</td>
</tr>
<tr>
<td>Jamshidi Idaji, Mina</td>
<td>Multivariate methods for quantification of nonlinear interactions in human brain</td>
<td>progressed</td>
</tr>
<tr>
<td>Kalloch, Benjamin</td>
<td>Individualised therapy through computer simulation - prediction and optimization of the effects of transcranial direct current stimulation on sensorimotor deficits after a stroke</td>
<td>final</td>
</tr>
<tr>
<td>Dr Kanaan, Ahmad Seif</td>
<td>Elemental and neurochemical based analysis of the pathophysiological mechanisms of Gilles de la Tourette Syndrome</td>
<td>completed</td>
</tr>
<tr>
<td>Dr Kim, Seung-Goo</td>
<td>Myeloarchitectonic and functional organizations of auditory cortex in musicians with absolute pitch</td>
<td>completed</td>
</tr>
<tr>
<td>Dr Lorenz, Kathrin</td>
<td>Optimization of the labeling efficiency of pseudo-continuous Arterial Spin Labeling (pCASL) for the measurement of cerebral perfusion</td>
<td>completed</td>
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<tr>
<td>Dr Metere, Riccardo</td>
<td>Investigating brain tissue mMicrostructure using quantitative magnetic resonance imaging</td>
<td>completed</td>
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<tr>
<td>Movahedian Attar, Fakhereh</td>
<td>Identification and characterization of superficial white matter structures using non-invasive MRI</td>
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<tr>
<td>Rose, Daniel</td>
<td>Informing neural mass models</td>
<td>progressed</td>
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<tr>
<td>Podranski, Kornelius</td>
<td>Improved processing of high-resolution multi parameter maps</td>
<td>progressed</td>
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<tr>
<td>Schmidt, Jochen</td>
<td>Quantitative transverse relaxation mapping at ultra high field in human subcortical, grey matter and white matter structures.</td>
<td>orientation</td>
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<tr>
<td>Vaculciakova, Lenka</td>
<td>Ultra high resolution mapping of cortical myelination using quantitative MRI</td>
<td>orientation</td>
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<tr>
<td>Waschke, Johannes</td>
<td>Analysis of histological data</td>
<td>orientation</td>
</tr>
<tr>
<td>Zarubin, Georgy</td>
<td>Development of a tACS-EEG closed loop system in order to understand and utilize the neuromodulatory role of tACS</td>
<td>final</td>
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<td>Zoraghi, Mahsa</td>
<td>Modeling and characterization of the cortical layer geometry using neo-hookean hyperelastic theory</td>
<td>progressed</td>
</tr>
</tbody>
</table>
## Faculty

### Module I: Language and Communication

<table>
<thead>
<tr>
<th>Faculty Member</th>
<th>Position</th>
<th>Department</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor A. D. Friederici</td>
<td>Since 2009</td>
<td>MPI CBS, Dept of Neuropsychology</td>
<td>Professor A. D. Friederici (since 2009)</td>
</tr>
<tr>
<td>PD Dr. G. Hartwigsen</td>
<td>Since 2016</td>
<td>MPI CBS, LMRG &quot;Cognition and Plasticity&quot;</td>
<td>PD Dr. G. Hartwigsen (since 2016)</td>
</tr>
<tr>
<td>Professor J. Jescheniak</td>
<td>Since 2009</td>
<td>LU, Dept of Cognitive Psychology</td>
<td>Professor J. Jescheniak (since 2009)</td>
</tr>
<tr>
<td>Dr. C. Maennel</td>
<td>Since 2019</td>
<td>MPI CBS, Dept of Neuropsychology, RG &quot;Early Language Acquisition&quot;</td>
<td>Dr. C. Maennel (since 2019)</td>
</tr>
<tr>
<td>Dr. L. Meyer</td>
<td>Since 2018</td>
<td>MPI CBS, MPRG &quot;Language Cycles&quot;</td>
<td>Dr. L. Meyer (since 2018)</td>
</tr>
<tr>
<td>Professor D. Saur</td>
<td>Since 2016</td>
<td>LU, Dept of Neurology</td>
<td>Professor D. Saur (since 2016)</td>
</tr>
<tr>
<td>Professor E. Schröger</td>
<td>Since 2009</td>
<td>LU, Dept of Cognitive and Biological Psychology</td>
<td>Professor E. Schröger (since 2009)</td>
</tr>
<tr>
<td>Dr. M. A. Skeide</td>
<td>Since 2019</td>
<td>MPI CBS, Dept of Neuropsychology</td>
<td>Dr. M. A. Skeide (since 2019)</td>
</tr>
<tr>
<td>Dr. L. Meyer</td>
<td>Since 2018</td>
<td>MPI CBS, MPRG &quot;Language Cycles&quot;</td>
<td>Dr. L. Meyer (since 2018)</td>
</tr>
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</table>

### Module II: Cognitive and Affective Neuroscience

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<th>Faculty Member</th>
<th>Position</th>
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</thead>
<tbody>
<tr>
<td>Dr. R. G. Benoit</td>
<td>Since 2016</td>
<td>MPI CBS, MPRG &quot;Adaptive Memory&quot;</td>
<td>Dr. R. G. Benoit (since 2016)</td>
</tr>
<tr>
<td>Professor C. F. Doeller</td>
<td>Since 2018</td>
<td>MPI CBS, Dept of Psychology</td>
<td>Professor C. F. Doeller (since 2018)</td>
</tr>
<tr>
<td>Professor V. Engert</td>
<td>Since 2016</td>
<td>MPI CBS, Dept of Social Neuroscience</td>
<td>Professor V. Engert (since 2016)</td>
</tr>
<tr>
<td>Dr. M. Garvert</td>
<td>Since 2018</td>
<td>MPI CBS, Dept of Psychology</td>
<td>Dr. M. Garvert (since 2018)</td>
</tr>
<tr>
<td>Professor D. Haun</td>
<td>Since 2016</td>
<td>MPI EVA, Dept of Comparative Cultural Psychology</td>
<td>Professor D. Haun (since 2016)</td>
</tr>
<tr>
<td>Dr. M. N. Hebart</td>
<td>Since 2019</td>
<td>MPI CBS, MPRG &quot;Vision and Computational Cognition&quot;</td>
<td>Dr. M. N. Hebart (since 2019)</td>
</tr>
<tr>
<td>Professor K. Musholt</td>
<td>(2018)</td>
<td>LU, Dept of Philosophy</td>
<td>Professor K. Musholt (since 2018)</td>
</tr>
<tr>
<td>PD Dr. J. Sacher</td>
<td>(2016)</td>
<td>MPI CBS, Minerva/Branco Weiss Fellowship Group EGG (Emotions &amp; neuroimaGinG)-Lab</td>
<td>PD Dr. J. Sacher (since 2016)</td>
</tr>
<tr>
<td>Professor M. L. Schreiter</td>
<td>(2012-2018)</td>
<td>UL, Day Clinic of Cognitive Neurology, and MPI CBS, Dept of Neurology</td>
<td>Professor M. L. Schreiter (since 2012)</td>
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</table>
### Module III: Basic and Clinical Neuroscience

<table>
<thead>
<tr>
<th>Professor I. Bechmann (since 2012)</th>
<th>Professor R. Rübsamen (2009-2018)</th>
</tr>
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<tbody>
<tr>
<td>LU, Institute for Anatomy</td>
<td>LU, Dept of General Zoology and Neurobiology</td>
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<table>
<thead>
<tr>
<th>Professor J. Classen (since 2012)</th>
<th>Professor M. Schönwiesner (since 2016)</th>
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<tr>
<td>LU, Dept of Neurology</td>
<td>LU, Dept of General Zoology and Neurobiology</td>
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<tr>
<th>Dr F. Eippert (since 2018)</th>
<th>Professor P. Schönknecht (2009-2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI CBS, MPRG “Pain Perception”</td>
<td>LU, Clinic and Polyclinic of Psychiatry</td>
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<tr>
<th>PD Dr S. Geyer (since 2009)</th>
<th>Professor A. Villringer (2009)</th>
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<tbody>
<tr>
<td>MPI CBS, Dept of Neurophysiology, RG</td>
<td>MPI CBS, Dept of Neurology</td>
</tr>
<tr>
<td>&quot;Anatomical Analysis of the Organization of the Human and Non-Human Primate Brain&quot;</td>
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<tr>
<td>LU, Clinic and Polyclinic of Psychiatry</td>
<td>LU, Clinic and Polyclinic of Children and Youth Psychiatry</td>
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<tr>
<th>Professor H. Obrig (since 2009)</th>
<th>PD Dr A. V. Witte (since 2018)</th>
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<td>LU, Day Clinic of Cognitive Neurology, and MPI CBS, Dept of Neurology</td>
<td>MPI CBS, Dept of Neurology</td>
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<table>
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<tr>
<th>Professor P. Ragert (since 2016)</th>
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<tr>
<td>LU, Dept of Movement and Training</td>
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### Module IV: Neuroimaging Physics and Signal Processing

<table>
<thead>
<tr>
<th>Professor M. Bogdan (since 2012)</th>
<th>Professor H. E. Möller (since 2009)</th>
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<tr>
<td>UL, Dept of Computer Engineering</td>
<td>MPI CBS, &quot;Nuclear Magnetic Resonance&quot; Unit</td>
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<table>
<thead>
<tr>
<th>Professor J. Haase (since 2009)</th>
<th>Professor K. Mueller (since 2009)</th>
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<tbody>
<tr>
<td>UL, Dept of Magnetic Resonance of Complex Quantum Solids</td>
<td>MPI CBS, &quot;Nuclear Magnetic Resonance&quot; Unit</td>
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</table>

<table>
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<tr>
<th>Professor M. Hlawitschka (since 2012)</th>
<th>PD Dr V. Nikulin (since 2017)</th>
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<tr>
<td>HTWK, Computer Graphics</td>
<td>MPI CBS, Dept of Neurology, RG &quot;Neural Interactions and Dynamics&quot;</td>
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<tr>
<th>Dr E. Kirilina (since 2018)</th>
<th>Professor G. Scheuermann (2009)</th>
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<tr>
<td>MPI CBS, Dept of Neurophysics</td>
<td>UL, Dept of Image Processing</td>
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<tbody>
<tr>
<td>MPI CBS, &quot;Brain Networks&quot; Unit</td>
<td>UL, Felix Bloch Institute für Solid State Physics</td>
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<table>
<thead>
<tr>
<th>Dr B. Maess (since 2009)</th>
<th>Professor N. Weiskopf (since 2016)</th>
</tr>
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<tbody>
<tr>
<td>MPI CBS, &quot;Brain Networks&quot; Unit</td>
<td>MPI CBS, Dept of Neurophysics</td>
</tr>
</tbody>
</table>

Please note: MPRG = Max Planck Research Group, LMRG=Lise Meitner Research Group
Structure of the Graduate School

The International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity (IMPRS NeuroCom) focuses on the functional, structural, and neural plasticity foundations of the neuroscience of human communication, through an integrative and interdisciplinary approach. The overriding goal of this programme is to train doctoral researchers in the multidisciplinary aspects of cognition, psychology, neuroscience, computer science, and neurophysics.

The school offers an innovative, interdisciplinary, and international research environment. Besides introducing behaviour methodology, the programme draws on powerful modern neuroimaging techniques such as functional and structural magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS), and transcranial magnetic stimulation (TMS). The breadth of these tools works toward our aim of understanding the brain in all its complexity and functionality. There is a strong interaction between doctoral projects focusing on neuroscientific methodologies and those focusing on cognitive science, which is supported by the school’s infrastructure and facilities.

Research Topics

Research projects and teaching are assigned to four modules:

1. Language and Communication
2. Cognitive and Affective Neuroscience
3. Basic and Clinical Neuroscience
4. Neuroimaging Physics and Signal Processing

Fundamental knowledge covering all four modules is imparted in the form of lecture series, courses, and seminars. This provides a comprehensive foundation for conducting doctoral research in neuroscience, and opens up horizons for potential interdisciplinary approaches. The curriculum not only includes lectures, courses, and seminars, but also colloquia, an annual summer school, and an exchange program in the final year.

Admission to the School

Every year new doctoral researchers with a variety of professional backgrounds are recruited. In the context of each recruitment period we receive about 300 applications, of which ca. 7% get admitted to the graduate school. This rate illustrates that admission to the school is highly competitive. Doctoral researchers, who hold a PhD position with one of the faculty members, can also apply to IMPRS NeuroCom throughout the year. As with all candidates, students entering via this route must pass an admission interview, attended by at least three faculty members.

Coordination Team

Spokesperson
Professor Arno Villringer
(since 2013)
Director, Department of Neurology
Email: villringer@cbs.mpg.de

Coordinator
Dr Veronika Krieghoff
Email: vkrieghoff@cbs.mpg.de

International Office
Susann Glasewald
Email: glasewald@cbs.mpg.de
Teaching Curriculum

Lecture Series
The PhD curriculum combines opportunities for outstanding research with excellent teaching to ensure that doctoral researchers are highly qualified for a successful career in relevant areas of Neuroscience. Courses held in 2017–2019 included modules on Basic and Clinical Neuroscience, Physics of Neuroimaging, Language and Communication, Neuroplasticity, Social, Cognitive, and Affective Neuroscience, and Advanced Statistics. Lecture series were conducted by members of the IMPRS faculty from all involved institutions in Leipzig as well as by external guest speakers. In addition, several workshops on Matlab took place.

IMPRS NeuroCom Summer School
As a special highlight of our graduate program, IMPRS NeuroCom offers an annual Summer School. Every third year this event is hosted by our partner institute, the Institute of Cognitive Neuroscience at University College London. During the other years the Summer School takes place in Leipzig at MPI CBS. The main topic of the most recent Summer School, which took place from 16-19 June 2019 at MPI CBS in Leipzig, was Sex Differences and the Brain. Further topics included: Language and Communication, Cracking the Code of Cognition, and Computational Neuroscience. On the one hand, the summer school offers theoretical input through lectures taught by internationally renowned speakers. On the other hand, students are provided many opportunities for direct exchange with the speakers, for example, during a panel discussion or the ‘meet the speakers’ lunch, which are offered for each session. In addition, junior scientists had the chance to present their research in the form of posters. The latest program was rounded off by several hands-on workshops, social activities, and the award of the poster prize.

Transferable Skills Training
In order to assist students in developing and broadening essential research skills, the IMPRS NeuroCom offered transferable skills seminars. These have included the annual workshop for new doctoral researchers on Time and Project Management, as well as an annual workshop on Good Scientific Practice. Further workshop topics were Scientific Writing, Grant Proposal Writing and Career Planning. Together with the other IMPRSs from Leipzig, IMPRS NeuroCom hosted a workshop on Mental Strategies for doctoral researchers conducted by Techniker Health Insurance. As IMPRS NeuroCom is a recognised graduate school at Research Academy Leipzig (ral), the umbrella organisation of all graduate schools at Leipzig University, our doctoral researchers have the possibility to attend further transferable skills courses there. Furthermore, international students were encouraged and financially supported to participate in German language courses.

Retreat
Supported with a grant from the Max Planck Foundation, IMPRS NeuroCom had its first retreat in May 2018. This three-day-event took place at the Harnack House in Berlin and was attended by one faculty member of each IMPRS module, the IMPRS spokesperson, the IMPRS co-ordinator as well as by most doctoral researchers of IMPRS NeuroCom. The junior researchers presented their work in the form of talks and posters. In addition, alumni of IMPRS and MPI CBS presented their career pathways and chatted with current IMPRS doctoral researchers in a speed meeting event. The IMPRS retreat was so well received by the IMPRS doctoral researchers that we decided to have an IMPRS NeuroCom Retreat again this year (November 2019, Weimar).
9

The Max Planck School of Cognition (MPS Cog)
MPS Cog: A Brand New Doctoral Programme in Germany

In the international competition for the most high caliber doctoral students, several German research institutions are in very good standing. However, some of the leading US and UK universities such as Harvard, Princeton, Oxford, or Stanford still have advantages due to their considerably larger faculties and regular entry at Bachelor level. Thus, to overcome this drawback the president of the Max Planck Society, Martin Stratmann, suggesting creating nationwide joint schools which integrate all leading experts across Germany in certain fields from Max Planck institutes, universities, and other non-university research institutions. Together with the former Federal Research Minister Johanna Wanka and the former President of the German Rectors’ Conference Horst Hippler, the concept was further developed and a competitive call was initiated for the foundation of three pilot schools. Arno Villringer was the leading PI for the proposed “Max Planck School of Cognition”, formed the school’s faculty, and finally presented the proposal, which was selected as one of the three pilot schools. MPS Cog is funded during the five-year pilot phase by the German Federal Ministry of Education and Research (BMBF) in collaboration with the Max Planck Society.

MPS Cog is an interdisciplinary and bespoke doctoral programme that offers exceedingly bright doctoral candidates the tools to gain a superior grasp on the different methods and approaches used in the rapidly evolving field of cognition. Our programme is characterised by the passion to better understand both human and animal cognition, and “mental phenomena” potentially occurring in non-biological systems and agents (artificial intelligence). The official inauguration of the Max Planck Schools and welcoming of the first doctoral candidates took place on 11 September 2019 in Berlin. The event was supported by the presence of the Federal Minister for Education and Research, Anja Karliczek, former president of the German Rectors’ Conference Horst Hippler, the President and the Vice President of the Max Planck Society Martin Stratmann and Ferdi Schüth, respectively, Nobel Prize winner Stefan Hell, world-leading pioneers in functional neuroimaging Bruce Rosen and Jonathan Cohen, as well as members of various institutions across a wide range of career stages.

Main Goals

MPS Cog bundles the best cognition researchers from 14 different universities (in addition to University College London as our international partner) and scientific organisations in a unique setting, thereby 1) providing doctoral candidates with a sophisticated repertoire of different methods and approaches used in the rapidly evolving field of cognition; 2) preparing the next generation of leading researchers in the interdisciplinary field of cognition; 3) developing new ways of defining cognition, philosophy, and artificial intelligence, fostering a new language of cognition and intelligence across many different disciplines; and 4) drawing more international talent to Germany as well as convincing outstanding German researchers to study at home.

MPS Cog Faculty

MPS Cog is comprised of an outstanding and world renowned cluster of approximately 50 fellows from diverse scientific backgrounds but with overlapping research interests. Our fellows come from 29 partner organisations including Max Planck institutes, universities, the Helmholtz Association and Fraunhofer-Gesellschaft.

Fellows

| Professor Katrin Amunts |
| Heinrich Heine University Düsseldorf & Forschungszentrum Jülich, Germany |
| Professor Hans-Jochen Heinze |
| Otto von Guericke University, Magdeburg, Germany |

| Professor Elisabeth Binder |
| Max Planck Institute of Psychiatry, Munich, Germany |
| Professor Ralph Hertwig |
| Max Planck Institute for Human Development, Berlin, Germany |

| Professor Nicole Boivin |
| Max Planck Institute for the Science of Human History, Jena, Germany |
| Professor Jürgen Jost |
| Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany |

<p>| Professor Michael Brecht |
| Bernstein Center for Computational Neuroscience, Humboldt University Berlin &amp; Charité University Medicine Berlin, Germany |
| Professor Gerd Kempermann |
| Technical University of Dresden &amp; German Center for Neurodegenerative Diseases, Dresden, Germany |</p>
<table>
<thead>
<tr>
<th>Professor Name</th>
<th>Institution and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Christian Büchel</td>
<td>University Medical Center Hamburg-Eppendorf, Germany</td>
</tr>
<tr>
<td>Professor Peter König</td>
<td>Osnabrück University, Germany</td>
</tr>
<tr>
<td>Professor Peter Dayan</td>
<td>Max Planck Institute for Biological Cybernetics, Tübingen, Germany</td>
</tr>
<tr>
<td>Professor Arthur Konnerth</td>
<td>Technical University of Munich, Germany</td>
</tr>
<tr>
<td>Professor Christian Doeller</td>
<td>MPI CBS, Leipzig, Germany</td>
</tr>
<tr>
<td>Professor Ulman Lindenberger</td>
<td>Max Planck Institute for Human Development, Berlin, Germany</td>
</tr>
<tr>
<td>Professor Emrah Düzel</td>
<td>Otto von Guericke University Magdeburg &amp; German Center for Neurodegenerative Diseases, Magdeburg, Germany</td>
</tr>
<tr>
<td>Professor Nikos Logothetis</td>
<td>Max Planck Institute for Biological Cybernetics, Tübingen, Germany</td>
</tr>
<tr>
<td>Professor Isabel Dziobek</td>
<td>Humboldt University Berlin, Germany</td>
</tr>
<tr>
<td>Professor Antje S. Meyer</td>
<td>Max Planck Institute for Psycholinguistics, Nijmegen, NL</td>
</tr>
<tr>
<td>Professor Simon B. Eickhoff</td>
<td>Heinrich Heine University Düsseldorf &amp; Forschungszentrum Jülich, Germany</td>
</tr>
<tr>
<td>Professor Klaus-Robert Müller</td>
<td>Technical University of Berlin, Germany</td>
</tr>
<tr>
<td>Professor Christoph Engel</td>
<td>Max Planck Institute for Research on Collective Goods, Bonn, Germany</td>
</tr>
<tr>
<td>Professor Michael Pauen</td>
<td>Berlin School of Mind and Brain &amp; Humboldt University Berlin, Germany</td>
</tr>
<tr>
<td>Professor Peter Falkai</td>
<td>Ludwig Maximilian University Munich, Germany</td>
</tr>
<tr>
<td>Professor Michael Petraglia</td>
<td>Max Planck Institute for the Science of Human History, Jena, Germany</td>
</tr>
<tr>
<td>Professor Simon E. Fisher</td>
<td>Max Planck Institute for Psycholinguistics, Nijmegen, NL</td>
</tr>
<tr>
<td>Professor David Poeppel</td>
<td>Max Planck Institute for Empirical Aesthetics, Frankfurt/ Main, Germany</td>
</tr>
<tr>
<td>Professor Angela D. Friederici</td>
<td>MPI CBS, Leipzig, Germany</td>
</tr>
<tr>
<td>Professor Brigitte Röder</td>
<td>University of Hamburg, Germany</td>
</tr>
<tr>
<td>Professor Pascal Fries</td>
<td>Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with the Max Planck Society, Frankfurt/ Main, Germany</td>
</tr>
<tr>
<td>Professor Caroline Rowland</td>
<td>Max Planck Institute for Psycholinguistics, Nijmegen, NL &amp; University of Liverpool, UK</td>
</tr>
<tr>
<td>Professor Russell Gray</td>
<td>Max Planck Institute for the Science of Human History, Jena, Germany</td>
</tr>
<tr>
<td>Professor Caroline Scharff</td>
<td>Free University Berlin, Germany</td>
</tr>
<tr>
<td>Professor Onur Güntürkün</td>
<td>Ruhr University Bochum, Germany</td>
</tr>
<tr>
<td>Professor Klaus Scheffler</td>
<td>Max Planck Institute for Biological Cybernetics, Tübingen, Germany</td>
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<tr>
<td>Dr Philipp Gunz</td>
<td>Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany</td>
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<tr>
<td>Professor Erich Schröger</td>
<td>Leipzig University, Germany</td>
</tr>
<tr>
<td>Professor Patrick Haggard</td>
<td>University College London, Institute of Cognitive Neuroscience, UK</td>
</tr>
<tr>
<td>Professor Arno Villringer</td>
<td>MPI CBS, Leipzig, Germany</td>
</tr>
<tr>
<td>Professor Peter Hagoort</td>
<td>Max Planck Institute for Psycholinguistics, Nijmegen, NL</td>
</tr>
<tr>
<td>Professor Melanie Wald-Fuhrmann</td>
<td>Max Planck Institute for Empirical Aesthetics, Frankfurt/ Main, Germany</td>
</tr>
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</table>
MPS Cog offers a four-year doctoral programme. The programme begins with an orientation year (first year) to equip the doctoral candidates (hereafter candidates) with necessary interdisciplinary knowledge and hands-on research lab experience via three rotations in partnering laboratories. The orientation year will also aid candidates to make an informed decision about which faculty researcher(s) they would like to pursue their research questions with for the following three years. Given the collaborative and interdisciplinary nature of the MPS Cog doctoral programme, candidates are encouraged to select fellows with complementary research fields as co-supervisors.

During the first year, there is also an essential emphasis on teaching. Candidates attend online courses during which the fundamentals on the following topics are covered: Cognitive Science, Functional Neuroanatomy and Neurophysiology, Clinical Neuroscience, Artificial Intelligence and Intelligent Systems, Philosophy of Mind and Ethics, Methods in Cognitive Neurosciences, Basics in Molecular Neurobiology and Genetics, Experimental Design and Statistics. To further elaborate on these online courses, candidates attend Cognition Academies (i.e., classroom weeks) in which these topics are presented in greater detail. There are three of such academies in the first year, two academies in the second to third years, and a final academy in the fourth year. All academies will have a duration of two weeks, except for the Welcome Academy in the first year that has a duration of one week. The Welcome Academy that took place in Berlin from 9–12...
September 2019 included presentations from several outstanding MPS Cog fellows, two exceptional international guests, Professor Bruce Rosen and Professor Jonathan Cohen, as well as presentations by the candidates along with soft skill trainings. The first year ends with an evaluation of the students that will determine if they can advance to the doctoral research phase (i.e., second to fourth year). This evaluation will consider several points: confirmation of three lab rotations, final evaluation of each of those rotations by the respective fellow, final assessment of performance in each of the online courses by the respective tutor, and the commitment from a fellow(s) who agrees to (co-)supervise the doctoral work of the student.

First Cohort of Doctoral Candidates & Zero-Year Students/Mentors

In the first recruitment phase (October–December 2018), a total of 171 applications were received. From those, 39 applicants were invited for interviews with fellows in Berlin. A total of thirteen candidates (8 male and 5 female) from eight different countries were admitted to the first cohort of the MPS Cog doctoral programme. Doctoral candidates receive a generous stipend for the first year and will receive a full-time contract for the remaining three years of the programme. All thirteen candidates have started their first lab rotation in October 2019. The second lab rotation will start at the end of January 2020 and the third one in May 2020. Each rotation will take an average of three months.

List of doctoral candidates and respective research background

<table>
<thead>
<tr>
<th>Doctoral candidates (Surname, name)</th>
<th>Research Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassam, Hassan</td>
<td>Modelling Biological Complexity/Mathematics</td>
</tr>
<tr>
<td>Chormai, Pattarawat</td>
<td>Data Science</td>
</tr>
<tr>
<td>Contier, Oliver</td>
<td>Psychology</td>
</tr>
<tr>
<td>Coy, Nina</td>
<td>Psychology</td>
</tr>
<tr>
<td>Dörfler, Montz</td>
<td>Mind and Brain</td>
</tr>
<tr>
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* Candidate who entered the doctoral programme with a bachelor degree. This candidate will perform all academic requirements from MPS Cog first year and simultaneously finish his master at the Berlin School of Mind and Brain, Humboldt University Berlin.
MPS Cog has also appointed 16 zero-year students (i.e., doctoral candidates at the end of their research phase) and three mentors (i.e., early postdoctoral researchers). These, nominated by MPS Cog fellows, help us to set up specific aspects of the school and the doctoral programme. Their tasks are to provide advice on how to improve the quality of the (e-)courses, to personally welcome and orient the candidates to the respective institutes or universities and city during a lab rotation, to encourage prospective students to apply via advertisement at conferences and workshops, and to discuss academic and non-academic topics with candidates.

Application

During recruitment phase, candidates can apply with a Bachelor’s or a Master’s degree in areas related to cognition such as artificial intelligence, (cognitive) neuroscience, genetics, linguistics, mathematics, neurobiology, neurology, philosophy, psychiatry, and psychology.
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